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Over-the-counter products for insomnia in adults: A scoping review of randomised controlled trials

Adriana Salame [a], Silvy Mathew [b], Cini Bhanu [b,c], Juan Carlos Bazo-Alvarez [b], Sukvinder Kaur Bhamra [d], Michael Heinrich [e], Kate Walters [b], Rachael Frost [b,f,*]

[a] Division of Medicine, University College London, London, United Kingdom
[b] Department of Primary Care and Population Health, University College London, London, United Kingdom
[c] Escuela de Medicina, Universidad Cesar Vallejo, Trujillo, Peru
[d] Medway School of Pharmacy, University of Kent, Medway, United Kingdom
[e] School of Pharmacy, University College London, London, United Kingdom and China Medical University, Taichung, Taiwan
[f] School of Public and Allied Health, Liverpool John Moores University, Liverpool, United Kingdom

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ABSTRACT

Background: Insomnia is highly prevalent and poses significant personal and socio-economic challenges. While the National Institute for Health and Care Excellence (NICE) recommendations define possible medical approaches, over-the-counter products are commonly used to self-manage insomnia symptoms. This scoping review aims to determine the size and scope of the evidence-base regarding the effectiveness and safety of over-the-counter products for insomnia symptoms in adults.

Methods: The electronic databases of CENTRAL, MEDLINE, EMBASE, PsycINFO, and AMED were searched from inception to December 19th, 2022, for all randomised controlled trials evaluating over-the-counter products compared to placebo, in adults aged 18–65 with insomnia symptoms. Results were synthesised descriptively.

Results: 51 randomised controlled trials were included, evaluating herbal products (n = 34), dietary supplements (n = 15), herbal-dietary combinations (n = 4), and over-the-counter medicines (n = 2). Sample sizes ranged between 10 and 405 participants. Eleven studies were conducted in participants with co-morbidities. Interventions were most frequently given as monotherapy and compared against placebo. Most studies (n = 41) demonstrated interventions' positive effects on insomnia symptoms. Among the most studied products, valerian and melatonin have substantial evidence to demonstrate their effectiveness and safety. Promising products demonstrating benefits compared with prescription medication alone included: valerian; lemon balm and fennel; and valerian, hops, and passionflower. Intervention-related side effects were mostly mild and transient. No serious adverse events were reported across all studies.

Conclusions: Over-the-counter products show promising, but inconclusive findings in alleviating insomnia symptoms in adults. Future research should focus on investigating products currently used in real life, consider economic evaluations, and be evaluated in populations with co-morbidities and ethnic minorities, to better guide clinical advice.

1. Introduction

1.1. Insomnia: definition, prevalence, and impact

Insomnia is a sleep disorder defined by a) difficulty in initiating, maintaining, and/or consolidating sleep, and b) its impact on well-being and daytime functioning. The clinical diagnosis is based on the presence of these symptoms for at least three nights per week, for at least three months [1,2]. Globally, insomnia is highly common, with symptoms affecting one in three adults in Western countries, and a formal diagnosis being attributed to ~10 % of the general population [1,3]. While surveys suggest that insomnia's prevalence is gradually rising [4–8], particularly in working middle-aged adults, the condition also showed a marked increase during the Covid-19 pandemic [9]. Reasons for this increase are unclear and may include greater awareness and reporting, and modern lifestyles. Stressful life-events, including a change in work

* Corresponding author. Tithebarn Building 312, 82 Tithebarn Street, Liverpool, L2 2ER, United Kingdom.
E-mail address: r.h.frost@ljmu.ac.uk (R. Frost).

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circumstances, health, or physiological factors altering sleep patterns, such as pregnancy and ageing, usually precipitate the onset of insomnia [1,10]. Consequently, insomnia is likely to persist into a chronic condition [11–13], perpetuated by factors including anxiety around sleep, changes in sleep behaviour, and sensitivity to sleep-regulating mechanisms [13].

Given its high reported prevalence, insomnia has widespread and impactful consequences to individuals' physical and mental health, and well-being [14]. Critically, difficulty in falling asleep is associated with all-cause and cardiovascular disease mortality [15], and insomnia demonstrates strong associations with myocardial infarction incidence [16]. A considerable body of research has demonstrated a bidirectional link between the risk of metabolic syndrome [17,18] and its core components, including obesity, hypertension, and diabetes [19–23], and insomnia. From a mechanistic perspective, alterations in the neuroendocrine control of appetite, including reduced leptin, increased ghrelin [24], and increased cortisol [25], may contribute to changes in energy intake and dietary patterns [26,27]. Moreover, a bi-directional relationship exists between insomnia and musculoskeletal complaints, which appears to be driven by tension and sympathetic nervous system activation [28,29]. Insomnia is also a strong risk factor for developing depression, anxiety, alcohol misuse, and dementia in older age [30,31]. Finally, the condition has a debilitating impact on daytime functioning and quality of life [32–34], not least in the experience of fatigue, emotional dysregulation, and presenteeism at work [35,36]. Altogether, insomnia and poor health are strongly linked, and directly influence the socio-economic system.

The economic burden of insomnia is well-documented, and aggregates the costs of healthcare use and services, work unproductivity, and increased accident risk [37–39]. In Canada, total annual costs of insomnia symptoms were estimated at $1.9 billion [40], and appear to be mainly driven by work absences and presenteeism [41]. A 5 % decrease in insomnia symptoms in Canada was estimated to save $353 million annually [40]. In the United States, untreated insomnia costs $100 billion per year [37], and in Australia, a total of $21,982 per adult, annually [42]. Finally, in the UK, over 1.65 million work hours are lost due to insufficient sleep annually, costing an estimated $50 billion [43]. Hence, insomnia and its pervasive consequences at the individual and socio-economic level, require addressing as a public health problem.

1.2. Insomnia management: recommendations and real-life practice

In Germany, preparations for use in insomnia are commonly dispensed by community pharmacists based on approved exempt standard formulations (Standardzulassungen) which are produced on site [44]. In the UK clear and up-to-date National Institute for Health and Care Excellence [NICE] guidelines for insomnia management in adults advise on several treatment options, for short- and long-term insomnia [45]. In the short-term, guidelines recommend using benzodiazepines and z-drugs to alleviate symptoms for a maximum of 3–7 days, and only if sleep hygiene interventions have failed [45], due to the risk of drug tolerance and dependence and the association with health risks such as road accidents, dementia, cancer, and increased mortality [46–49]. Despite this, these drugs are routinely used in general practice for chronic insomnia management [50,51], with approximately 300,000 adults in the UK taking benzodiazepines or z-drugs for 1 year or longer [52].

In the long-term, NICE guidelines recommend cognitive behavioural therapy for insomnia [CBT-I] as the first-line treatment in adults [45], which has substantial evidence of cost-effectiveness [53,54]. However, it is rarely, or never, offered in UK general practices [50,51,55], and digital CBT-I services such as Sleepio [56,57], which is endorsed by NICE, may have awareness or accessibility barriers [58].

Current NICE guidance generally advises against over-the-counter products' use for insomnia [45], based on 2017 guidelines describing only a few studied supplements, namely valerian and melatonin, and recommendations of limited certainty [59,60]. Such guidelines present a major discrepancy with the ever-growing sales in over-the-counter sleep aids in the UK, exceeding £60 million in 2021 [61], and increased research in the field in the past 5 years. Although no studies were found investigating the prevalence of over-the-counter sleep aids use in the UK, evidence from other countries suggests this lies between 7.2% and 18.5 % in young adults [62–64]. From a qualitative perspective, people living with insomnia often express hopelessness and dissatisfaction in the face of current treatments, but feel satisfied and empowered when they are able self-manage their insomnia symptoms, including through using over-the-counter products [62,65–68]. Furthermore, there is an increasing role for pharmacists' supply and advice-giving on over-the-counter products for insomnia [69–72]. From an economic perspective, this has the potential to reduce general practitioners' time pressure and consultations, and NHS costs, and aligns with existing UK policy such as the NHS "Stay Well Pharmacy" campaign [73]. Still, pharmacists have voiced the need for an increase in sleep health awareness within the healthcare system, and targeted education for pharmacists to better provide clinical advice [69]. Other healthcare professionals such as dietitians also often get asked for advice on supplements, and advocate additional professional education opportunities [74–76].

1.3. Over-the-counter products: definitions, current knowledge, and research gaps

A diversity of over-the-counter products is available, including medicines, dietary supplements, and herbal and homeopathic products. In the UK, a medicinal product is defined as 'any substance or combination of substances presented as having properties for treating or preventing disease in human beings' (p. 6) [77]. Food supplements are defined as 'foodstuffs the purpose of which is to supplement the normal diet, and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect … ' (p. 18) [77]. Moreover, the term 'over-the-counter' refers to all general sale and pharmacy medicines, distinguished as being purchasable without requiring a prescription [78]. Accordingly, it is worth highlighting that over-the-counter products' regulatory framework markedly differs across countries and regions [79]. For example, melatonin is sold as an over-the-counter dietary supplement in the United States, whereas it has been approved only as a prescription medicine in other regions, including the UK, Canada, Japan, and Australia [80]. Similarly, kava, a plant preparation from *Piper methysticum G.* Forst, known for its anxiolytic properties [81], is available as a dietary supplement in Australia and the United States, while its sale is restricted in many countries, including the UK [82] due to safety concerns raised in the first decade of this century, which are now considered less of a concern [83]. Critically, whilst medicines are tightly regulated globally, the classification of many products as 'dietary supplements' implies these may not undergo quality control or rigorous safety testing, particularly in developing countries [84]. Overall, this presents significant challenges to research and quality control, regarding both products' effectiveness and safety [85].

Currently, a multitude of over-the-counter products have been explored for their potential in managing insomnia, some of which have demonstrated notable performance. In fact, recent meta-analyses concluded that across dietary supplements, amino acids and vitamin D may significantly improve sleep quality [86,87], and melatonin may prove beneficial specifically in sleep disorders [88], while magnesium, zinc, resveratrol and nitrate may play a potential role [89]. Considering herbal products, valerian, lavender and chamomile, amongst others, have shown a clinically meaningful impact, whilst being generally safe and well tolerated [90–92]. In fact, certain herbal products have been used for centuries to treat sleep problems [93], such as lettuce seed and jujube seed in Traditional Persian and Chinese medicines, respectively [94,95]. Finally, diphenhydramine is an over-the-counter antihistamine medicine commonly used to treat insomnia, with few adverse effects

[96], despite limited research examining its effectiveness.

Nonetheless, clear research gaps on the effectiveness and safety of over-the-counter products hinder the development of clinical recommendations. Indeed, systematic reviews and meta-analyses are often on single products, and report variations in the number and quality of studies [86,87,91,97]. Focussing on trials across products allows emerging products with a small amount of promising effectiveness to be highlighted for future research. Additionally, many herb and supplement reviews e.g. Refs. [88–92] contain other study types in addition to high quality RCTs, focus on sleep quality rather than people with insomnia symptoms, and/or the effects of single doses in addition to the continuous usage likely in insomnia patients, all of which are likely to obscure findings regarding effectiveness and safety. A large, comprehensive scope of the literature using consistent criteria relevant to people with insomnia symptoms is required to fully understand and map the evidence base regarding OTC products. Additionally, to assess the generalisability of trial findings, it is important to understand participants' characteristics in trials, particularly their health status and presence of co-morbidity, and the potential for adverse effects. As patients and healthcare professionals often lack reliable information sources and knowledge of OTC [98–101], there is a clear need to map and evaluate the evidence for the wide range of products used for insomnia, to inform future research and clinical decision making.

1.4. Aims and objectives

This review aims to determine the size and scope of the evidence base regarding the effectiveness and safety of over-the-counter products for symptoms of insomnia in adults, specifically to map over-the-counter products evaluated in trials for reducing insomnia symptoms in adults aged 18–60 years, and to outline the characteristics of the evidence for each product, including its effectiveness and safety.

2. Methods

This scoping review was carried out as part of a larger project, investigating the effectiveness and safety of over-the-counter products for symptoms of insomnia, depression, and anxiety in adults and older adults. The final registered protocol is available at https://osf.io/rkm57/, Due to the large volume of studies found across all conditions (n = 403), studies were synthesised separately for each condition, and this synthesis addresses aim #3. Research was also divided by age group given that older adults may have differing sleep needs and safety considerations (risk of interactions, greater risk of adverse effects) [102]. This review follows the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) [103] and uses the methodological framework described by Arksey and O'Malley [104].

2.1. Inclusion criteria

The inclusion criteria were: randomised controlled trials, including crossover, cluster and parallel-group, and economic evaluations, of over-the-counter oral medications, herbal and homeopathic products, and dietary supplements, to improve insomnia symptoms in community-dwelling adults aged 18–60 years old. Participants needed to be living with symptoms (as measured by a questionnaire) or a diagnosis of insomnia for inclusion. Studies were required to have a measure of insomnia at baseline and after the intervention. Treatment duration was required to be $\geq$ 1 week. Traditional Chinese herbal preparations were excluded, as these are not easily available online or over the counter in the UK, and individualised prescription may be required to use some preparations. Other study types, individualised approaches, and studies where participants had insomnia as part of a mix of symptoms [e.g., in menopause or addiction] were excluded unless symptoms met a minimum specified threshold for insomnia.

2.2. Search strategy

The search strategy was completed as part of the overarching scoping review including all ages and depression and anxiety. A systematic literature search was conducted in the electronic databases of CENTRAL, MEDLINE, EMBASE, PsycINFO and AMED, inception to December 19th, 2022. Boolean operators were used to combine terms in the following clusters: over the counter products AND depression, anxiety and insomnia AND trials terms, using filters where they are available. Reference lists of eligible studies and 10 % of review articles were also searched. Trial registries were searched within the CENTRAL search for ongoing or completed trials, and these were followed up until May 22nd, 2023. No language or publication date restrictions were applied. See Appendix A for the MEDLINE search strategy, reproduced from the scoping review's paper in older adults [105].

2.3. Study selection

Studies were included using a two-step process, as presented in the PRISMA flowchart (Fig. 1). First, two reviewers (in pairs of RF and SU, SM and AS, and SM and VT) independently screened 10 % titles and abstracts, using an online collaboration tool (Rayyan, Rayyan Systems Inc, Cambridge, Massachusetts, USA). Paired reviewers discussed disagreements and planned ways forward, and the remaining titles and abstracts (90 %) were single screened. The same process was followed for full texts. Any remaining disagreements were discussed with a third reviewer. Studies in foreign language were screened using Google translate, and eligible papers were extracted using basic translation tools, with any unclear data checked by multi-lingual members of the research team.

2.4. Data extraction

Data for this section of the review were extracted by one reviewer (AS) into a standardised spreadsheet. Data extraction included: study details (authors, journal, year of publication), country and setting, target condition, participant characteristics (age, gender, ethnicity), comorbid conditions, inclusion and exclusion criteria, product type and characteristics (including brand and common name, manufacturer, product characteristics, ingredients, dosage, duration of administration, processing methods, quality assurance data, batch number), comparator(s), outcomes measured (grouped according to symptoms, remission, quality of life, functioning, adherence, adverse events, serious adverse events, study withdrawal), and results by outcome.

2.5. Data synthesis

Given the heterogeneity in study inclusion criteria, interventions, insomnia questionnaires, and outcomes, quantitative analysis was not appropriate beyond descriptive statistics. Both study characteristics and a summary of findings of individual studies were tabulated, and results were summarised descriptively using narrative synthesis.

2.6. Consultation

Two patient and public involvement members participated in the project's conceptualisation, and choosing the products to be included, and outcomes to focus on. They were involved at all review stages (including protocol, search development and dissemination), through attending regular team meetings with researchers.

3. Results

3.1. Literature search and study characteristics

The literature search (Fig. 1) yielded 23,993 abstracts, and after

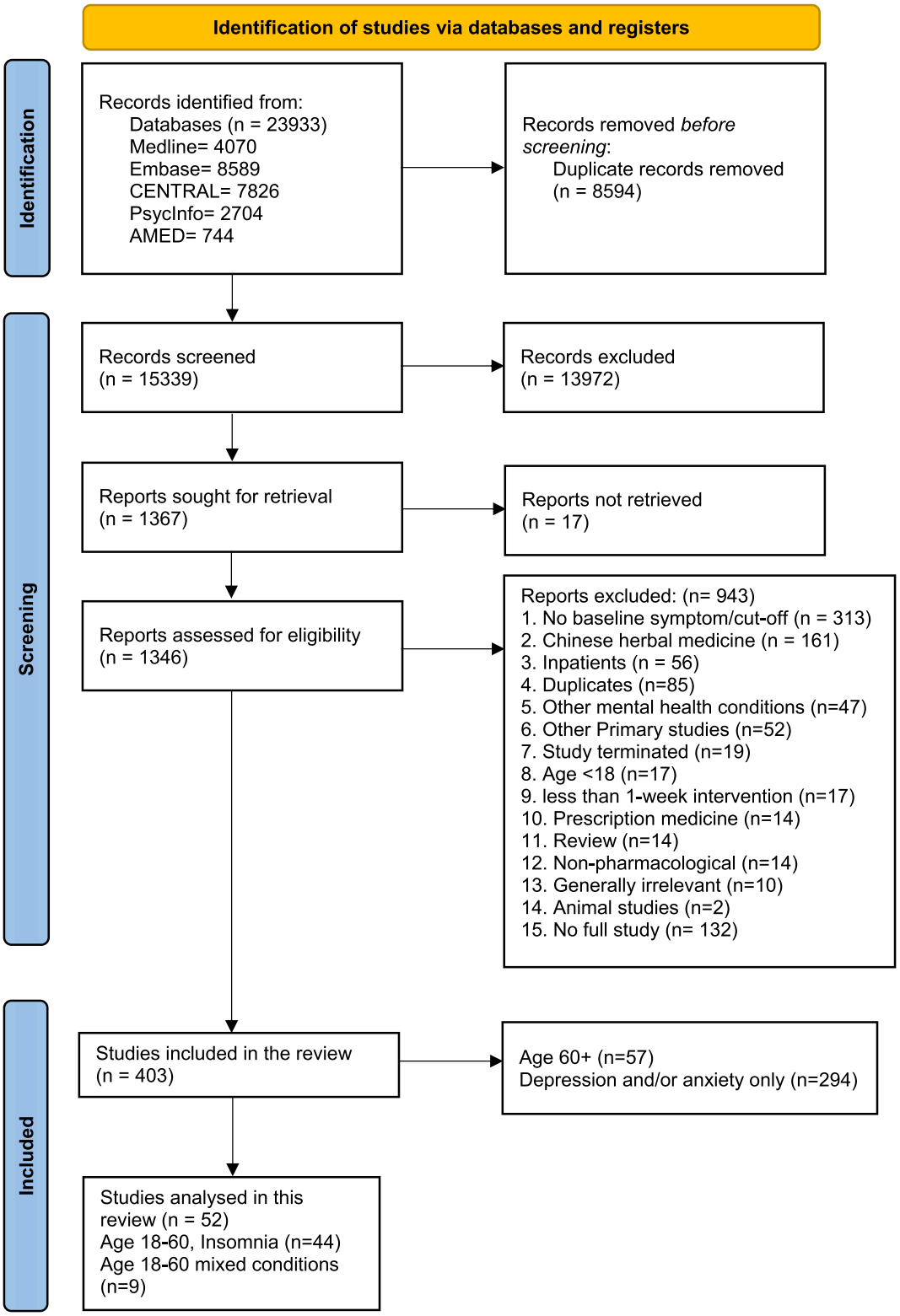

Fig. 1. Flowchart of the literature search results.

deduplication 15,339 abstracts were screened. 1346 full texts were selected for review and 403 studies were included in the scoping review, of which 52 were analysed separately in this review's subsection.

Most studies were conducted in Iran [n = 12, 23.5 %], followed by the United States [n = 8, 15.7 %], Germany [n = 5, 9.8 %], Australia [n = 4, 7.8 %], India [n = 3, 5.9 %] and Japan [n = 2, 3.9 %], South Korea [n = 2, 3.9 %], and Taiwan [n = 2, 3.9 %], and a study each was conducted in Belgium, China, Finland, France, Mexico, New Zealand, Norway, Russia, Spain, Thailand and the UK.

Chronological trend in types of products studied is presented in Fig. 2, and showed a general increase over time, particularly in studies on herbal and dietary supplements.

Sample sizes varied between 10 and 405 participants, with a mean of 81 participants and a total of 4192 participants. The mean age ranged

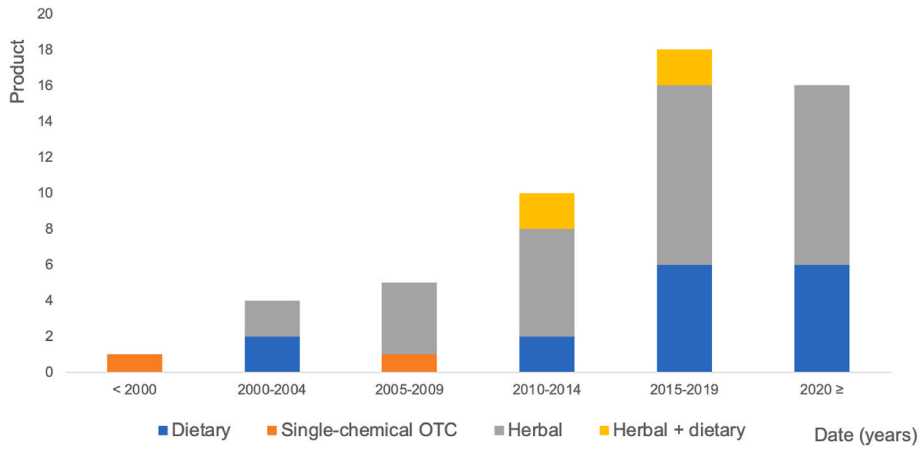

Fig. 2. Chronological trend in types of products studied.

from 26 to 59 years. The percentage of women in the studies ranged from 0 to 100 %. Nine out of 52 [17 %] studies reported on participants' ethnicity, which was predominantly White [106–112] or all White [113, 114]. In terms of participants' health information, 42 studies [81 %] included participants without co-morbidities. In 12 studies, participants had accompanying conditions including anxiety [106,107,114–117], depression [116,118,119], breast cancer [120], multiple sclerosis [121], overweight/obesity [119] and traumatic brain injury [122,123]. One study was conducted during pregnancy [124] and two studies post-partum [125,126]. Study details are presented in Table 1.

Studies used varied baseline measures of insomnia and scales, which included.

- Meeting official diagnostic criteria [e.g., International Classification of Diseases, International Classification of Sleep Disorders, Diagnostic and Statistical Manual of Mental Disorders] [n = 16] [112, 116,119,123,127–138].
- Pittsburgh Sleep Quality Index [n = 20] [107,110,111,113,114,117, 121,123,124,128,129,131,139–146], with cut-offs ranging from ≥3 to >20
- Insomnia Severity Index [n = 7] [121,127,128,133,147–149], with cut-offs ranging from >7 to >14
- Others [n = 19]: self-reported sleep/insomnia complaints [106,108, 109,118,120,122,150–156]; postpartum sleep quality scale ≥16 [n = 2] [125,126]; diagnosis/meeting diagnostic criteria [n = 2] [109, 157]; rating of at least 2 points ['moderate'] on Hamilton Anxiety Rating Scale item 'insomnia' [n = 1] [115]; Bergen Insomnia Scale cut-off [n = 1] [158]; carer-assessed [n = 1] [159].

3.2. Interventions

Most studies [n = 48] evaluated a single intervention, and four studies each evaluated two interventions. In most studies [n = 43], interventions were given as monotherapy. In two studies, participants were allowed to resume previous prescription medicine for insomnia, in one study participants followed a weight reduction diet, and in six studies the type of therapy was not reported. Most studies evaluated products in the form of capsules [n = 27], followed by tablets [n = 14], pills [n = 2], syrup [n = 2], teabags [n = 2] and powder [n = 1]. Four studies did not report the form of products. The control groups were given placebo [n = 42], active drug [Oxazepam; Zolpidem] [n = 2], placebo and active drug [Citalopram; Zolpidem] [n = 2], non-prescription drug [Spikenard rhizome; Combination of fibre, acacia gum, maltodextrin, cocoa powder, and riboflavin powder] [n = 2], no treatment [n = 3], and one study did not report the control group treatment.

3.3. Herbal products

Thirty-three studies were identified evaluating a total of 34 herbal products in insomnia. Studies evaluated: valerian (*Valeriana officinalis* L.; n = 5), lavender (*Lavandula angustifolia* Mill.; n = 4), valerian and hops (*V. officinalis/Humulus lupulus* L.; n = 2), saffron (*Crocus sativus* L.)/ crocetin (isolated from *Gardenia jasminoides* Ellis n = 4), lettuce seed (*Lactuca sativa* L.) n = 2), lemon verbena (*Aloysia citrodora* Paláu; n = 2), kava (*P. methysticum*; n = 2), German chamomile (*Matricaria chamomilla* L.; n = 2), and one study each on water hyssop (*Centella Asiatica* L. *Urb*); passionflower (*Passiflora incarnata* L.); black seed (*Nigella sativa* L.); citron leaf (*Citrus Medica Linn.*); jujube seed (*Ziziphus jujuba* Mill.); ashwagandha root (*Withania somnifera* L. *Dunal*); lemon balm and valerian (*Melissa officinalis/V. officinalis*); lemon balm and lavender (*Melissa officinalis/Lavandula angustifolia)*; lemon balm and fennel (*Melissa officinalis* L./*Foeniculum vulgare* L.); valerian, passionflower and hops (*V. officinalis/P. incarnata/H. lupulus*) combination; and a poly-herbal formulation containing saffron, lettuce seed, opium poppy, frankincense, agarwood, and sugarcane (*Crocus sativus* L./*Lactuca sativa* L./*Papaver Somniferum* L./*Boswellia Spp./Aquilaria* agallocha Roxb./ Saccarum officinarum L.) (Table 1).

3.3.1. Valerian

Five studies (sample sizes 30–405) investigated valerian as a single botanical drug/extract, with daily doses of 500–640 mg for four weeks in four studies, and two weeks in one study. In three studies, valerian was found to have a significant benefit compared to placebo [143,145], or a comparable effect to an active drug [132], on sleep parameters. Two studies investigating the effects of valerian found no significant beneficial effects on sleep parameters compared with placebo [106,153]. All studies considered adverse events, with one study reporting mild-moderate gastrointestinal symptoms that were probably related to valerian [106].

3.3.2. Lavender

Four studies were available and investigated lavender as a single botanical drug/extract, in the form of lavender essential oil (80 mg daily for 10 weeks) [107,114], flower powder (1000 mg daily for 8 weeks) [140] and 2g tea for two weeks [126]. Sample sizes ranged from 76 to 212. In two studies, a significant benefit on sleep quality of lavender extract compared with placebo was found [107,140]. One study found no benefits of lavender tea [126]. One study did not report sleep outcomes independently, and the combined effect on anxiety or sleep did not reach statistical significance [114]. Adverse events were considered across all studies, of which two reported gastrointestinal side effects related to interventions [107,114].

Table 1
Characteristics of included studies on herbal products.

First author, year published Country Study type	Population Male/Female Age [y] Patient health information [co-morbidities/ pregnancy]	Intervention [s]	Control	Effectiveness reported on sleep outcomes	Adverse events
Valerian					
Dorn, 2000 [132] Germany RCT Controlled Double-blinded	N = 65 Men and women Age: 52 ± 12 y	Valerian; 2x tablets of 300 mg daily for 4 weeks	Oxazepam for 4 weeks	Yes, for 8 out of 9 parameters; No significant difference compared with oxazepam for all outcomes.	Adverse events occurred and were comparable between groups. No serious adverse events occurred.
Jacobs, 2005 [106] United States RCT Placebo-controlled Double-blinded	N = 391 Men and women Age: 41 ± 10 Anxiety	Valerian; 2x capsules of 320 mg daily for 4 weeks	Placebo for 4 weeks	No beneficial effects in 1 out of 1 parameter	Adverse events occurred in both groups. Diarrhoea was more frequent in valerian group.
Koetter, 2007 [153] Germany RCT Placebo-controlled Double-blinded	N = 30 Men and women Age: 38 ± 14	Valerian; 500 mg daily for 4 weeks	Placebo for 4 weeks	No beneficial effects in 8 out of 8parameters	No adverse events were reported by participants.
Oxman, 2007 [143] Norway RCT Placebo-controlled Double-blinded	N = 405 Men and women Age: 44 ± 13	Valerian; 3x tablets of 200 mg every night for 2 weeks	Placebo for 2 weeks	Yes, for 1 out of 6 parameters	No significant differences between groups and no serious adverse events reported by participants.
Taavoni, 2011 [145] Iran RCT Placebo-controlled Double-blinded	N = 100 Women only Age: 53 ± 3	Valerian; 2x capsules of 530 mg daily for 4 weeks	Placebo for 4 weeks	Yes, for 1 out of 1 sleep parameter	No adverse events reported by participants
Lavender					
Chen, 2015 [126] Taiwan RCT	N = 76 Women only Age: 32 ± 4 Post-partum	Lavender; 1 cup of tea made from 2g infusion before bedtime for 2 weeks	No treatment for 2 weeks	No beneficial effects for 1 out of 1 parameter	No side effects reported by participants
Kamalifard, 2018 [140] Iran RCT Placebo-controlled Double-blinded	N = 156 Women only Age: 53 ± 4	Lavender; 2x capsules of 500 mg daily for 8 weeks for 8 weeks	Placebo for 8 weeks	Yes, for 1 out of 1 parameter	Mild and transient adverse events, comparable with placebo group.
Kasper, 2010 [107] Germany RCT Placebo-controlled Double-blinded	N = 212 Men and women Age: 46 Anxiety	Lavender; 1x capsule of 80 mg essential oil daily for 10 weeks	Placebo for 10 weeks	Yes, for 1 out of 1 parameter	Adverse events reported, only gastrointestinal disorders were attributable to intervention used.
Kasper, 2015 [114] Germany RCT Placebo-controlled Double-blinded	N = 139 Men and women Age: 48 Anxiety	Lavender; 1x capsule of 80 mg essential oil daily for 10 weeks	Placebo for 10 weeks	No relevant effectiveness outcomes reported	Adverse events reported, only gastrointestinal disorders were attributable to intervention used. No serious adverse events were reported.
Saffron/crocetin					
Kuratsune, 2010 [142] Japan Cross-over RCT Placebo-controlled Double-blinded	N = 21 Men only Age: 44 ± 9	Crocetin; 1 capsule of 7.5 mg daily for 2 weeks	Placebo for 2 weeks	Yes, for 1 out of 5 parameters	Adverse events noted but deemed unrelated to the intervention by the study physicians.
Lopresti, 2020 [148] Australia RCT Placebo-controlled Double-blinded	N = 55 Men and women Age: 50	Saffron; 2 × 14 mg daily for 4 weeks	Placebo for 4 weeks	Yes, 3 out of 8 parameters	No significant adverse events were reported by participants.
Pachikian, 2021 [149] Belgium RCT Placebo-controlled Double-blinded	N = 59 Men and women Age: 45 ± 14	Saffron; 15.5 mg pr day for 6 weeks	Placebo for 6 weeks	Yes, 6 out of 18 parameters.	One case of palpitations leading to termination. No difference in other adverse events reported between groups. No serious adverse events reported.
Umigai, 2018 [156] Japan Cross-over RCT	N = 24 Men and women Age: 51 ± 7	Crocetin; 7.5 mg daily for 2 weeks	Placebo for 2 weeks	Yes, for 3 out of 11 parameters	Adverse events noted but deemed unrelated to the intervention by the study physicians.

(*continued on next page*)

Table 1 (*continued*)

First author, year published Country Study type	Population Male/Female Age [y] Patient health information [co-morbidities/ pregnancy]	Intervention [s]	Control	Effectiveness reported on sleep outcomes	Adverse events
Placebo-controlled Double-blinded					
Chamomile					
Chang, 2016 [125] Taiwan RCT	N = 72 Women only Age: 33 Post-partum	Chamomile; 1 cup of tea made from 2g infusion before bedtime for 2 weeks	No treatment for 2 weeks	Yes, for 1 of 2 sub-parameters in 1 out of 1 sleep parameter	No side effects reported by participants.
Zick, 2011 [112] United States RCT Placebo-controlled Double-blinded	N = 34 Men and women Age: 42 ± 14	Chamomile; 6x capsules of 90 mg daily for 4 weeks	Placebo for 4 weeks	Yes, for 2 out of 8 parameters	No significant difference between groups
Kava					
Jacobs, 2005 [106] United States RCT Placebo-controlled Double-blinded	N = 391 Men and women Age: 41 ± 10 Anxiety	Kava; 3x capsules of 100 mg kavalactones daily for 4 weeks	Placebo for 4 weeks	No beneficial effects on 1 out of 1 parameter	Similar between kava and placebo groups
Lehrl, 2004 [115] Germany RCT Placebo-controlled Double-blinded	N = 45 Men and women Age: 52 Anxiety	Kava; 2x capsules of 70 mg kavalactones daily for 4 weeks	Placebo for 4 weeks	Yes, for 4 out of 5 parameters	No adverse events in the treatment group
Lemon verbena					
Afrasiabian, 2019 [131] Iran RCT Placebo-controlled Double-blinded	N = 101 Men and women Age: 41 ± 12	Lemon verbena; 10 cc syrup daily, containing 1.66 mg essential oil for 4 weeks	Placebo for 4 weeks	Yes, for 6 out of 6 parameters	Mild and transient side effects reported
Martinez-Rodriguez, 2022 [117] Spain RCT Placebo-controlled Double-blinded	N = 40 Men and women Age: 39 ± 12 Anxiety	Lemon verbena; 1x pill of 400 mg daily for 8 weeks	Placebo for 8 weeks	Yes, for 2 out of 7 parameters. Effects were more pronounced in women.	Not reported.
Lettuce seed					
Mosavat, 2021 [120] Iran RCT Placebo-controlled Double-blinded	N = 43 Women only Age: 48 Breast cancer	Lettuce seed; 2 × 5 ml syrup daily for 4 weeks	Placebo for 4 weeks	Yes, for 5 out of 8 parameters	Mild reflux and dyspepsia in the intervention group, no major side effects.
Pour, 2018 [124] Iran RCT Placebo-controlled Double-blinded	N = 70 Women only Age: 29 ± 5 Pregnancy	Lettuce seed; 1 × 1000 mg capsule daily for 2 weeks	Placebo for 2 weeks	Yes, for 1 out of 1 parameter	No side effects reported were attributable to the intervention used. Neonatal adverse events reported, however were not attributable to the intervention used.
Valerian and hops					
Koetter, 2007 [153] Germany RCT Placebo-controlled Double-blinded	N = 30 Men and women Age: 38 ± 14	Valerian and hops; 500 mg valerian and 120 mg hops daily for 4 weeks	Placebo for 4 weeks	Yes, for 3 out of 8 parameters	No adverse events were reported by participants.
Morin, 2005 [154] United States RCT	N = 184 Men and women Age: 44 ± 10	Valerian and hops; 2x tablets of 187 mg valerian and 41.9 mg hops daily for 4 weeks	Placebo for 4 weeks	No significant effects for 7 out of 7 parameters	No significant difference between groups. No serious adverse events were reported.
Others					
Asadi, 2020 [151] Iran RCT Placebo-controlled Double-blinded	N = 60 Women only Age: 54 ± 4	Nigella sativa; 600 mg daily for 8 weeks	Zolpidem 5 mg, or placebo for 8 weeks	No significant benefits in 1 out of 1 parameter.	No adverse events reported by participants.
Langade, 2021 [130] India RCT Placebo-controlled Double-blinded	N = 37 Men and women Age: 37 ± 6	Ashwaganda root; 2x capsules of 300 mg daily for 8 weeks	Placebo for 8 weeks	Between-group statistics were not reported.	No adverse events reported by participants

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Table 1 (*continued*)

First author, year published Country Study type	Population Male/Female Age [y] Patient health information [co-morbidities/ pregnancy]	Intervention [s]	Control	Effectiveness reported on sleep outcomes	Adverse events
Lee, 2020 [134] South Korea RCT Placebo-controlled Double-blinded	N = 84 Men and women Age: 40 ± 11	Passionflower; 60 mg daily for 2 weeks	Placebo for 2 weeks	Yes, for 1 out of 11 parameters	No adverse effects were reported in the intervention group. No serious adverse effects were reported.
Lopresti, 2021 [158] Australia RCT Placebo-controlled Double-blinded	N = 89 Men and women Age: 50	Waterhyssop; 150 mg twice daily for 4 weeks	Placebo for 4 weeks	No significant benefits in 7 out of 7 parameters	No significant differences between groups. No significant adverse events reported.
Mahmoudi, 2020 [141] Iran RCT Placebo-controlled Double-blinded	N = 96 Women only Age: 58 ± 6	Jujube seed; 2x tablets of 250 mg daily for 3 weeks	Placebo for 3 weeks	Yes, for 1 out of 1 parameter	Digestive problems reported.
Maroo, 2013 [133] India RCT Double-blinded	N = 78 Men and women Age: 49 ± 15	Valerian, passionflower, and hops; 1x tablet of 300 mg valerian, 80 mg passionflower, 30 mg hops daily for 2 weeks	Zolpidem, 10 mg for 2 weeks	Yes, in 4 out of 5 parameters, but was not superior to comparator drug	Adverse events reported; but were not significantly different between groups. No serious adverse events were reported.
Panara, 2017 [135] India RCT Open-labelled	N = 62 Men and women Age: 20-70	Citron leaf; 3g daily before bedtime for 4 weeks	Spikenard rhizome, 3g for 4 weeks	Yes, for 3 out of 5 parameters, but was not superior to comparator drug.	No adverse effects were noted by participants in both groups.
Poursaleh, 2022 [136] Iran RCT Placebo-controlled Double-blinded	N = 52 Men and women Age: 42 ± 13	Polyherbal formulation of containing saffron, lettuce seed, opium poppy seed, frankincense, agarwood, and sugar; 4x capsules of 690 mg daily for 8 weeks	Placebo for 8 weeks	Yes, for 7 out of 8 parameters	Mild and transient gastrointestinal symptoms, which were resolved after taking the medicine in divided doses.
Ranjbar, 2018/2018 [116,147] Iran RCT Placebo-controlled Double-blinded	N = 45 Mostly women Age: 39 ± 11 Depression and anxiety in the second study	Lemon balm and Persian lavender; 3x capsules containing a total of 1000 mg lemon balm and 400 mg Persian lavender for 4 weeks	Placebo for 4 weeks	Yes, for 9 out of 9 parameters	One case of unbearable itching, three with agitation and intensifying anxiety that improved after few days of treatment.
Shirazi, 2016/2021 [144,160] [a] Iran RCT Controlled Double-blinded	N = 60 Women only Age: 51 ± 6	Lemon balm and fennel; 1 equal combinatorial capsule of 600 mg daily for 8 weeks in the first paper, and 500 mg daily for 8 weeks in the 2021 paper[a]	Citalopram, 20 mg then increased to 30 mg, or placebo for 8 weeks	Yes, for 1 out of 1 parameter in the first paper. No relevant effectiveness outcomes reported in the second paper.	Not reported in the first paper. No adverse events reported in the treatment group in the second paper.
Taavoni, 2013 [146] Iran RCT Placebo-controlled Double-blinded	N = 100 Women only Age: 53 ± 6	Lemon balm and valerian; 2x capsules of 160 mg of essence of Valerian officinalis and 80 mg of lemon balm daily for 4 weeks	Placebo for 4 weeks	Yes, for 1 out of 1 parameter	No adverse effects were reported during or after the study period.

[a] [144,160]; papers were both identified with an identical clinical trial code https://irct.behdasht.gov.ir/trial/13828 and had identical demographics, but the recruitment period and dosages differed. Given this conflict, it was assumed that both texts refer to the same study reporting on different outcomes.

3.3.3. *Saffron/crocetin*

Two studies (sample sizes 21 and 24) investigated the effects of crocetin extract (7.5 mg daily for 2 weeks), an important carotenoid constituent of saffron, but was derived in these studies from *Gardenia jasminoides* Ellis, a more accessible source. They found significant benefits to wake episodes [142], delta power (measure of homeostatic sleep drive), improvement in sleepiness on rising, and feeling refreshed after sleep [156].

Two studies explored the effects of saffron on sleep. Lopresti et al. [148] investigated the effects of Affron, a saffron extract (28 mg daily for 4 weeks), and found significant improvement in insomnia severity, sleep quality and restorative sleep, compared with placebo. Pachikian et al. [149] found that, relative to placebo, time in bed and sleep duration significantly improved in the saffron group (15.5 mg/day for 6 weeks). Sample sizes were small (55 and 59).

Adverse events were reported by all studies. In two studies, adverse events were considered to be unrelated to the study interventions [142, 156], in one study adverse events were not significantly different between groups, except for one case of palpitations [149], and one study observed no significant adverse events [148].

3.3.4. *Chamomile*

Two studies (sample sizes 34 and 72) were available for German chamomile. Chang et al. [125] found a benefit of chamomile tea [2g infusion for 2 weeks] compared to no treatment in the physical-symptom-related sleep inefficiency in postpartum women. Zick et al. [112] carried out a pilot study and found moderate effect sizes in favour of chamomile extract (540 mg/day for 4 weeks) on sleep latency

and number of night-time awakenings, and on total sleep time in favour of placebo; All outcomes did not reach statistical significance. Risk of bias was noted in the lack of participant blinding in one study [125].

3.3.5. Kava

Two studies were available for kava and investigated its effects on insomnia and anxiety. Lehrl et al. (n = 45) found significant beneficial effects of kava extract (standardised to 70 mg kavalactones twice daily for 4 weeks) on quality of sleep, recuperative effect after sleep, psychic exhaustion, and psychosomatic symptoms during sleep [115]. In an internet-based study by Jacobs et al. (n = 391), Kava [three capsules standardised to 100 mg kavalactones daily for 4 weeks] was not found beneficial in 319 participants on insomnia severity [106].

3.3.6. Lemon verbena

Of the two studies on lemon verbena, Afrasiabian et al. [131] found that lemon verbena syrup (10 cc per day for 4 weeks, n = 101) was significantly beneficial in improving sleep quality, daytime dysfunction, sleep latency, habitual sleep efficiency and insomnia severity in 101 participants with insomnia. Martinez-Rodriguez et al. [117] found significant benefits of lemon verbena (400 mg daily for 8 weeks, n = 40) to sleep quality and percentage REM sleep. A quality concern was noted in one study which did not report adverse events [117].

3.3.7. Lettuce seed (Lactuca sativa L)

Lettuce seed was evaluated in two studies. Mosavat et al. [120] recruited 43 participants living with breast cancer. They found that lettuce seed syrup (10 ml daily for 4 weeks), but not placebo, significantly improved sleep quality, sleep duration, habitual sleep efficiency, and sleep disturbance. However, between-group analyses did not reveal statistical significance. A study by Pour et al. [124] also investigated lettuce seed (1000 mg capsule daily for 2 weeks), and reported a statistically significant improvement in sleep quality in pregnant women compared with placebo (n = 70). Mild gastrointestinal side effects were more prevalent in the lettuce seed group compared with placebo in one study [120], and no adverse events or neonatal adverse events were attributable to the intervention used in the other one [124].

3.3.8. Valerian-hops combination

A combination of valerian and hops was tested in two four-week studies, and compared with placebo. One study [153] found significant differences in 30 participants for sleep latency, and sleep stages 3 and 4 at the end of treatment with 500 mg valerian and 120 mg hops daily. In comparison, a second study [154] of 374 mg valerian and 83.8 mg hops daily found no benefits of valerian-hops combination on sleep parameters, compared with placebo, in 184 participants. Adverse events were either not observed for valerian-hops treatment [153] or not significantly different between groups [154].

3.3.9. Single-study herbal products

A total of 11 studies were available, with 42–100 participants, each singly investigating a product. Six products, including passionflower, jujube seed, valerian, hops and passionflower, lemon balm and valerian, lemon balm and lavender, lemon balm and fennel, and a traditional Persian polyherbal combination containing saffron, lettuce seed, opium poppy, frankincense, agarwood, and sugarcane, were found to have significant benefits on sleep outcomes [116,133,134,136,141,146,160]. Two studies, each investigating nigella sativa and water hyssop, found no benefits on sleep parameters compared with the control groups [151,158]. One study [135] compared the effects of citron leaf to spikenard rhizome in participants with primary insomnia, and found that citron leaf had a benefits to sleep outcomes, but that spikenard had superior effects on all outcomes. One study by Langade et al. [130] investigated ashwagandha root. They did not report between-group statistical comparisons, and quality concern was noted in terms of selective outcome reporting.

All studies investigated adverse events; In five studies [130,134,135,146,151] and one paper [144], no adverse events to the interventions used were reported and in two studies there were no significant differences between intervention and control groups [133,158]. In three studies, adverse events were related to interventions used (jujube seed, a traditional Persian polyherbal formulation, and combination of lemon balm and lavender) [116,136,141], of which two studies reported resolution of symptoms, after few days of treatment [116] and splitting the treatment dosages [136]. The other paper by Shirazi et al. did not report on adverse events [160].

3.4. Dietary supplements

Sixteen studies were identified evaluating dietary supplements in insomnia (Table 2), including studies on: melatonin (n = 10) and a study each on bitter orange, *Lactobacillus plantarum* PS128, a polyphenol blend, rice bran extract, vitamin E, and a magnesium-melatonin-vitamin B complex.

3.4.1. Melatonin

In seven out of ten studies on melatonin, it was found to be beneficial, with statistically significant differences in sleep efficiency [122,123] sleep quality [119,123], total sleep time [121], number of night-time awakenings, daytime sleepiness [122], and early awakening [138] compared with placebo. Doses used in all ten studies ranged from 0.3 mg to 6 mg daily, for between one and 12 weeks. A pilot study by Roth et al. [109] investigated 13 participants with total blindness and non-24 sleep wake disorder, and found a clinically significant benefit of melatonin to total sleep duration and sleep latency, but these did not reach statistical significance. Laakso et al. [159] investigated participants with developmental brain disorders and found a significant improvement in the fragmentation of the rest–activity rhythm, day/-night ratio of activity and onset of rest period with melatonin, compared with placebo. Three studies [118,137,152] demonstrated no benefits of melatonin on sleep parameters. Sample sizes in all studies were relatively small [range 10–107].

Seven studies [109,118,119,123,137,138,159] reported adverse events which were comparable to placebo groups, and 1 study [121] observed no adverse events in all participants. Two studies did not report adverse events [122,152].

3.4.2. Single-study dietary supplements

A total of six studies (sample sizes 40 to 160) individually exploring a dietary supplement were identified, all of which reported statistically significant improvements in sleep parameters for each of their products, which included: a magnesium-melatonin-vitamin-B complex, Lactobacillus plantarum PS128, bitter orange, a polyphenol blend, rice bran, and vitamin E [111,128,129,139,140,157]. All products were compared with placebo, except for 1 study where the control group treatment was not reported [157]. Another concern noted was the lack of reporting adverse events in three studies [111,140,157]. Across the other three studies, adverse events were comparable [140], or not significantly different between groups [139], or no serious adverse events were raised [129].

3.5. Single chemical over-the-counter medicines

Two studies were identified evaluating over-the-counter medicines in insomnia, both diphenhydramine compared with placebo (Table 3). Morin et al. [154] investigated 184 participants with mild insomnia, and reported a significantly greater impact of diphenhydramine on sleep efficiency and insomnia severity, compared with placebo, after two weeks. Rickels et al. [108] investigated 96 participants with mild-moderate insomnia, and found significant beneficial effects of diphenhydramine on sleep latency, night-time awakenings, time awake in bed, total sleep time after one week, perception of sleep improvement,

Table 2
Characteristics of included studies on dietary supplements.

First author, year published Country Study type	Population Male/Female Age [y] Patient health information [co-morbidities/ pregnancy]	Intervention [s]	Control	Effectiveness reported on sleep outcomes	Adverse events
Melatonin					
Akhondzadeh, 2022 [119] Iran RCT Placebo-controlled Double-blinded	N = 43 Women only Age: 37 ± 10 Depression and overweight/obesity	Melatonin; 0.3 mg daily for 12 weeks	Placebo for 12 weeks	Yes, for 1 out of 1 parameter	Mild adverse events and similar in both groups. No serious adverse events were reported.
Almeida, 2003 [139] Mexico Cross-over RCT Placebo-controlled Double-blinded	N = 10 Men and women Age: 50 ± 13	Melatonin; 0.3 mg or 1 mg for 1 week	Placebo for 1 week	No beneficial effects	No differences in side effects reported in the study.
D'Ambrosio, 2001 [152] United States RCT Placebo-controlled Double-blinded	N = 19 Men and women Age: 59 years	Melatonin; 0.3 mg daily in the morning for 4 weeks	Placebo for 4 weeks	No beneficial effects across outcomes	Not reported.
Grima, 2018 [123] Australia Cross-over RCT Placebo-controlled Double-blinded	N = 107 Men and women Age: 37 Post- traumatic brain injury	Melatonin; Prolonged release, 1x capsule of 2 mg daily for 4 weeks	Placebo for 4 weeks	Yes, for 2 out of 4 parameters	No serious adverse events reported. Symptoms more frequently reported in the placebo treatment.
Hsu, 2021 [121] United States Cross-over RCT Placebo-controlled Double-blinded	N = 30 Men and women Age: 47 ± 2 Multiple sclerosis	Melatonin; 0.3 mg daily, then increased to 3 mg if no effects for 2 weeks	Placebo for 2 weeks	Yes, for 1 out of 5 parameters	No side effects reported by participants.
Ivanova, 2014 [122] Russia RCT	N = 60 Men and women Age: 50 Mild traumatic brain injury	Melatonin; 3 mg once before bedtime for 2 weeks	No treatment for 2 weeks	Yes, for 3 out of 7 parameters.	Not reported.
Laakso, 2017 [159] Finland Cross-over RCT Placebo-controlled Double-blinded	N = 17 Men and women Age: 37 ± 12 Developmental brain disorders	Melatonin; Fast release; 1 x tablet of 1, 3, and 6 mg daily, each for 4 weeks	Placebo for 3 × 4 weeks	Yes, for 3 out of 6 parameters. Higher doses [3 and 6 mg] were not more effective than the lowest dose of 1 mg.	Adverse events reported but similar between groups. In the 6 mg melatonin period, one case of extreme tiredness and one of increased seizure frequency.
Roth, 2015 [109] United States RCT Placebo-controlled Double-blinded	N = 13 Men and women Age: 54 Total blindness	Melatonin; Prolonged release, 2 mg once daily for 6 weeks	Placebo for 6 weeks	Yes, for 2 out of 2 parameters with reported statistics, although these did not reach statistical significance.	Mild adverse events and similar in both groups. No serious adverse events were reported.
Serfaty, 2010 [118] United Kingdom RCT Placebo-controlled Double-blinded	N = 31 Men and women Age: 40 Depression	Melatonin; Slow release; 6 mg daily before bedtime for 4 weeks	Placebo for 4 weeks	No beneficial effects in 8 out of 8 parameters	Adverse events reported and were similar in both groups.
Xu, 2020 [138] China RCT Placebo-controlled Double-blinded	N = 61 Men and women Age: 57	Melatonin; Fast release, 1x tablet of 3 mg daily for 4 weeks	Placebo for 4 weeks	Yes, in 1 out of 11 parameters	No significant difference in adverse events between groups. No serious adverse effects were reported.
Others					
Djokic, 2019 [157] RCT	N = 60 Men and women Age: 48 ± 15	Magnesium, melatonin, and vitamin B; 1× capsule of 175 mg magnesium, 10 mg Vit B6, 16 µg vit B12, 1 mg melatonin, 600 µg 5methyltetrahydrofolate once daily before sleep, for 3 months	Not reported	Yes, for 1 out of 1 parameter	Not reported.
Ho, 2021 [128] Taiwan RCT Placebo-controlled Double-blinded	N = 40 Mostly women Age: 26	Lactobacillus plantarum PS128; 2x capsules of 3 × 1010 colony-forming units of PS128 daily, for 1 month	Placebo, for 1 month	Yes, in 2 out of 26 parameters	Not reported.
Kamalifard, 2018 [140] Iran	N = 156 Women only Age: 53 ± 4	Bitter orange; 2x capsules of 500 mg daily, for 8 weeks	Placebo for 8 weeks	Yes, for 1 out of 1 parameter	Mild and transient adverse events, comparable with placebo group

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Table 2 (*continued*)

First author, year published Country Study type	Population Male/Female Age [y] Patient health information [co-morbidities/ pregnancy]	Intervention [s]	Control	Effectiveness reported on sleep outcomes	Adverse events
RCT Placebo-controlled Double-blinded					
Tubbs, 2021 [111] United States RCT Placebo-controlled Double-blinded	N = 89 Men and women Age: 31 ± 8	Polyphenol blend; 485 mg dose containing >120 mg polyphenols [and >65 mg rosmarinic acid and epigallocatechin gallate] for 1 month	Placebo for 1 month	Yes, in 2 out of 12 parameters.	Not reported.
Um, 2019 [139] South Korea RCT Placebo-controlled Double-blinded	N = 42 Men and women Age: 44 ± 14	Rice bran extract; 1000 mg daily for 2 weeks	Placebo for 2 weeks	Yes, in 4 out of 10 parameters	Adverse events reported but were not significantly different between groups; No serious adverse events were reported.
Thongchumnum, 2023 [129] Thailand RCT Placebo-controlled Double-blinded	N = 160 Women only Age: 56	Vitamin E; 400 units of mixed tocopherol daily for 1 month	Placebo for 1 month	Yes, for 1 out of 1 parameter	No serious adverse events were reported.

Table 3
Characteristics of included studies on over-the-counter medicines.

First author, year published Country Study type	Population Male/Female Age [y] Patient health information [co-morbidities/ pregnancy]	Intervention [s]	Control	Effectiveness reported on sleep outcomes	Adverse events
Morin, 2005 [154] United States RCT Placebo-controlled	N = 184 Men and women Age: 44 ± 10	Diphenhydramine; 2x tablets of 25 mg each night for 2 weeks	Placebo for 4 weeks	Yes, in 2 out of 7 parameters	Adverse events were significantly greater in diphenhydramine vs valerian-hops group. There was no significant difference between valerian and placebo groups. No serious adverse events were reported. No difference in next-day residual effects.
Rickels, 1983 [108] United States Cross-over RCT Placebo-controlled Double-blinded	N = 96 Mostly women Age: 45 ± 13	Diphenhydramine; 2x tablets of 25 mg before sleep for 1 week	Placebo 1 week	Yes, for 8 out of 8 parameters	Drowsiness, dizziness, grogginess, and tiredness more frequent in intervention group.

deep sleep, sleep quality and feeling rested in the morning. Both uses doses of 50 mg per day.

Both studies reported more frequent adverse events in the diphenhydramine treatment; Morin et al. did not describe the adverse events, and Rickets et al. reported symptoms of drowsiness, dizziness, tiredness, and grogginess.

3.6. Combination of dietary and herbal products

Four studies (n = 17 to 171) were identified each evaluating a different combination of herbal and dietary supplements in insomnia [110,113,127,155] (Table 4). Three studies [110,113,155] found significant benefits of the interventions used on sleep outcomes, compared with placebo, which included: a micronutrient blend containing choline, DL-phenylalanine, citrus bioflavonoids, inositol, L-Glutamine, L-Methionine, grape seed, gingko biloba, germanium, boron, vanadium, and nickel; a combination of alpha-s1 casein hydrolysate, sour date, hops, magnesium, and vitamin B6; and an amino acid-based formula containing choline, Griffonia, GABA, grape seed, hydrolysed whey protein, valerian, ginkgo biloba, glutamic acid, and cocoa. One study [127] found no benefit of a combination of polyunsaturated fatty acids and hops against placebo on sleep outcomes.

Adverse events were investigated by all studies, with three studies reporting mild intervention-related adverse events, including gastrointestinal symptoms and headaches [110,113,127], and one study observing no adverse events in all participants [155].

No studies investigating the costs and cost-effectiveness of products were identified.

4. Discussion

This scoping review's aim is to determine the size and scope of the evidence on the effectiveness and safety of over-the-counter products for insomnia symptoms in adults. We provided a comprehensive summary of the clinical trial evidence base available for OTC products targeted at people with insomnia symptoms or diagnosis. Our review showed increasing trials of OTC products for insomnia over time, and the evidence base was primarily concentrated upon herbal products, although included a wide range within this.

Table 4
Characteristics of included studies on herbal and dietary supplement combinations.

First author, year published Country Study type	Population Male/Female Age [y] Patient health information [co-morbidities/ pregnancy]	Intervention [s]	Control	Effectiveness reported on sleep outcomes	Adverse events
Carley, 2017 [113] New Zealand RCT Placebo-controlled Double-blinded	N = 17 Men and women Age: 48 ± 10	Blend containing Choline, DL-phenylalanine, citrus Bioflavonoids, Inositol, L-Glutamine, L-Methionine, Grape seed, Gingko biloba, Germanium, Boron, Vanadium and Nickel; Titrated up to 8x capsules per day, for 8–10 weeks.	Placebo, for 5, 9 or 14 days	Yes, for 1 out of 1 parameter.	Mild and transient events possibly related to the intervention; mainly included headaches and gastrointestinal disturbances.
Cornu, 2010 [127] France RCT Placebo-controlled Double-blinded	N = 101 Men and women Age: 41	Polyunsaturated fatty acid and hop; 2x capsules of 260 mg soya oil, 173 mg cade oil and 50 mg hop before sleep for 1 month	Placebo; 2x capsules of olive oil before sleep for 1 month	No beneficial effects in 5 out of 5 parameters	Minor adverse events reported in both groups, including headache.
Scholey, 2017 [110] Australia RCT Placebo-controlled Double-blinded	N = 171 Men and women Age: 30 ± 10	Lactium [α-casozepine], jujube, hops, magnesium and vitamin B6; 2x tablets of 75 mg lactium, 4.5 g jujube, 500 mg hops, 52.5 mg magnesium, 8.23 mg vitamin B6 daily for 2 weeks	Placebo for 2 weeks	No beneficial effects in 5 out of 5 parameters	Gastrointestinal symptoms were related to study medication, with two cases leading to discontinuation. No serious adverse events were reported.
Shell, 2010 [155] RCT Placebo-controlled Double-blinded	N = 18 Men and women Age: 18-65	Amino acid-based formula containing choline bitartrate, griffonia extract, GABA, grape seed, hydrolysed whey protein, valerian, ginkgo biloba, glutamic acid, and cocoa; 2x capsules containing 2000 mg in the evening, for 1 week.	Placebo for 1 week	Yes, in 4 out of 6 parameters	There were no adverse events reported by either placebo or treatment groups.

4.1. Herbal products

Thirty-four herbal products have been studied for their potential to improve insomnia in adults. Valerian was the most studied botanical drug/extract, and based on vote counting showed mixed results with slightly more positive than null studies, including comparable effects to oxazepam. It is hypothesised to work through its bio-active substances' hypnotic and anxiolytic effects, particularly valerenic acid [92]. Lavender and saffron/crocetin were the following most studied products, which reflects the literature highlighting their promising role in improving sleep problems [97,161]. Interestingly, these herbal products' promising effects in other mental health conditions [92,162,163], questions whether they may be more effective in people living with insomnia as well as anxiety/depression, which commonly co-occur [164,165].

Highly promising herbal products with a performance at the minimum equal to prescription medication alone, are valerian [132], lemon balm and fennel [160], and valerian, hops and passionflower [133]. The benefits of herbal combinations compared with prescription drugs is notable, while one study demonstrated superior effects of a valerian-hops combination compared with valerian [153]. This pre-supposes whether herbal mixtures may provide a potentiated effect which is not attainable by their individual constituents, and warrants further comparative trials. Herbal products with one or two studies, and promising benefits to insomnia symptoms included chamomile, kava, lemon balm and fennel, lemon verbena, lettuce seed, jujube seed, passionflower, citron leaf, and a polyherbal Persian formulation, justifying further clinical trials, and comparison against conventional treatment. Worthy of note, many of these herbs have shown plausible mechanisms of action in insomnia, which include agonist activity on $GABA_A$ receptors [93].

Side effects possibly related to the interventions were mainly mild gastrointestinal symptoms, and no serious events were reported across all studies, which is promising evidence on products' safety. For example, regulated valerian products are generally considered to have a reasonable safety level [166]. Interestingly, in comparison to prescription hypnotics being mostly contraindicated in pregnancy [167], lettuce seed extract, used in traditional Persian medicine, was found to have no maternal or neonatal adverse events while incurring sleep benefits. Similarly, post-partum women drinking lavender and chamomile teas reported no adverse effects. Notwithstanding, case reports of herb toxicity, such as kava's risk of hepatoxicity [168], have resulted in its ban in several markets [169] which has now been lifted in many countries [83]. This highlights the challenges in assessing the safety of herbal medicines, and the crucial need for thorough safety assessment and active pharmacovigilance systems [84,85]. Nevertheless, within this review most studies were carried out for only short periods (commonly 4 weeks), and so the long term safety and potential for tolerance and/or dependency remains to be explored.

4.2. Dietary supplements

In this review, melatonin was the most studied supplement, and using vote counting more studies showed effects than not on insomnia symptoms, when compared against placebo/no treatment [170]. Hence, the literature on melatonin's performance reflects the international expert consensus on its use in sleep disorders [171]. In particular, melatonin has shown benefits in conditions with circadian rhythm

disruption, including sleep-onset difficulties, developmental brain disorders, total blindness, and post-traumatic brain injury [172,173], This not only emphasizes its mechanism of action as a physiological regulator of the sleep/wake cycle [174], but also its potential in treatment. All single-studied supplements improved insomnia symptoms. While most supplements [175,176], but not all [177], lack clear understanding into their mechanism of action, further research into their effectiveness and mechanistic pathways is vindicated.

Considering safety, no adverse events were referrable to the study interventions, and no serious adverse events were reported. Eminently, melatonin's well-evidenced short-term safety in adults [178], alongside its established effectiveness, justifies the evaluation of its safety for long-term use [179]. Preliminary evidence on other dietary supplements' safety, at their administered doses, provides limited basis for conclusions on their safety, and most dietary supplement trials only had short intervention periods. Indeed, despite common beliefs on the safety of 'natural' products, the risks of dietary supplements are increasingly appreciated [180–182]. For example, bitter orange extract has sympathomimetic effects which may pose safety concerns [183]. Also, while polyphenol dosages are shown to be safe up to 250 mg, the risk associated with overconsumption [184,185] justifies further trials prior to using higher doses.

4.3. Over-the-counter medicines

Diphenhydramine was the only over-the-counter medicine, and was found to alleviate insomnia symptoms in the two studies. Interestingly, despite its widespread, unrestricted use and purported effectiveness [67,186], diphenhydramine has relatively limited research to support its use. In this review, diphenhydramine's adverse events were mainly unwanted residual effects, such as dizziness and drowsiness [187], and these were only captured over 1–4 weeks. However, in recent years, safety concerns for its use in adults have been identified, including the risk of misuse, abuse and dependence [188–190], drug interactions [191], and dementia risk associated with long-term usage [192]. Hence, given the unrestricted and common usage of diphenhydramine, it is essential to increase awareness of its risks among healthcare professionals and the general population, and establish preventative measures [193], as well as collecting long term effectiveness and safety data.

4.4. Combinations of herbal and dietary products

Amongst all single-studied products, a micronutrient blend and amino-acid based formula were effective in alleviating insomnia symptoms. While mechanisms of action remain largely unclear, certain nutrients and herbal extracts used in these preparations, such as glutamine, magnesium, and ginkgo biloba, are suggested to influence the synthesis of neurotransmitters involved in sleep regulation [175,194,195]. Three out of four studies reported intervention-related adverse events, including mostly headaches and gastrointestinal disturbances of varying intensity, while no serious adverse events were reported. Importantly, while the safety evaluation of a single compound alone is challenging, that of a combination of several products may be far more difficult, and resource-intensive [84,85], not least in the multiplying number of bioactive substances, but also in their interactions. This underlines again the importance of safety research, particularly in herbal combinations, and developing current pharmacovigilance systems [196].

4.5. General practical considerations

4.5.1. Quality control and regulatory framework

Discrepancies in over-the-counter herbal and dietary products' effectiveness and safety outcomes, in this review and the wider literature, may be importantly accounted for by their classification, and accordingly, countries' regulatory framework. Indeed, while a UK Traditional Herbal Registration license requires an over-the-counter herbal medicine to meet certain standards of safety, quality, and efficacy [197], similarly in the European Union [198], this is not the case in many parts of the world. In the United States, herbal products are mostly legally classified as dietary supplements, which allows them to be sold without first proving efficacy or safety [199]. A study by Erland et al. in Canada provides a significant example of the resulting poor quality control, whereby the content of melatonin in supplements varied between −83 % to +478 % of their labelled content, and supplements were contaminated with serotonin [200].

Similarly, some of the most popular herbal products, including milk thistle and coneflower, were found to have compromised quality, namely adulteration, when sold as a dietary supplement in the UK [201]. Critically, the latter example highlights that certain products are purchasable online in the UK without being licensed under the Traditional Herbal Registration scheme. Overall, the efficacy and safety of consuming herbal and dietary products may be significantly compromised by a lack of suitable quality control, resulting in adulteration and contamination with toxic agents [85,202,203] or in the use of inactive adulterants [204]. Meanwhile, lacking patient information may lead to misuse and drug interactions. As the global market of over-the-counter products continuing to grow, it will prove important to strengthen and harmonise global policies on herbal medicines to ensure safety, quality, and efficacy, while supporting professionals and patients' education, and safeguard public health [84].

4.5.2. Concordance with real-life use

A mismatch between over-the-counter products investigated in trials, and their use in real-life settings [67], underlines the importance of linking research and practice [205,206]. In this review, studies have explored products which are commonly used to self-manage insomnia, including valerian, lavender, chamomile, kava, lemon balm, hops, herbal teas, melatonin, and to a lesser extent, vitamins, and minerals [64–66,68,207–209]. However, there is scarce to no evidence for other commonly used products. Indeed, magnesium supplements are highly popular and increasingly used [210,211], while it has been investigated for sleep mostly in healthy volunteers [212]. Similarly, St John's Wort is commonly used in insomnia self-management [64,65], whereas no evidence was found for its benefits in insomnia patients, but these preparations could have indirect effects in reducing symptoms of mild to moderate depression.

Notwithstanding, while people living with insomnia often simultaneously use over-the-counter sleep aids and/or prescription drugs [62,213,214], only two studies in this review allowed participants to resume previous sleep medication. Therefore, the external validity of the effectiveness and safety findings is limited. Finally, only 11 studies included participants with co-morbidities, therefore findings may be cautiously considered in people living with co-morbidities [215]. However, there was a tendency for products to demonstrate significant benefits in people living with co-morbid conditions, with mild to no intervention-related side effects, which merits further research in these populations, to whom drug interactions present a greater safety concern [216–218]. Ethnicity was rarely reported. Whilst studies were carried out in a range of countries with differing majority ethnic groups, better reporting of ethnicity is needed to understand the generalisability of trial results [219]. Altogether, future work may benefit from conducting preliminary research to identify products commonly used and their mode of usage, and explore these amongst different populations, to promote findings' generalisability, and better inform clinical practice.

4.5.3. Economic impact

In this review, no studies carried out an economic evaluation of their product. Considering the cost-of-living crisis in the UK and globally [220], understanding cost implications prior to implementing health interventions is crucial. Particularly, out-of-pocket payments may lead to unmet health needs in the most vulnerable groups, including individuals of low socioeconomic status and with multimorbidity [221,

222], while these two populations may be most affected by poor sleep [223,224]. Notwithstanding, there is evident potential for over-the-counter products to enhance the management of insomnia, which mediates the relationship between low socioeconomic status and ill health [225]. Additionally, UK policy, through the 'NHS Stay Well Pharmacy' campaign [73] is directing people to seek support in pharmacies. It remains unclear whether self-management of insomnia with OTC products leads to lower, similar or increased used of primary and secondary health care. Hence, future research may benefit from investigating the cost-effectiveness of over-the-counter products for insomnia, and the overall implications on healthcare spending [226].

4.6. Strengths and limitations

This review has strengths, including its compliance with established methodological and reporting guidelines [103,104], a comprehensive and thorough search of the literature and screening of studies, and inclusion of titles without any language or date restrictions. We focussed on insomnia symptoms rather than sleep quality to provide a clearer picture than other previous reviews, which have included studies assessing sleep quality in healthy people or those with other health conditions, and only randomised trials. Due to the quality of studies not being assessed, conclusions on products' effectiveness or safety may not be confidently stated. Nonetheless, this scoping review's purpose was rather to map and point towards promising products to guide future studies in the field. Due to the large volume of articles found, only 10 % of titles, abstracts and full-texts were double-screened, which was limited by the review's available resources. For the same reasons, only 10 % of review articles' references were screened for potentially relevant articles. The review also relied on vote counting of significant results within and across studies; due to a lack of consideration of study quality to contextualise this effectiveness and safety conclusions should be considered preliminary and not definitive. Finally, it was beyond the scope of this review to comprehensively explore the potential mechanisms of action behind over-the-counter products' effectiveness, although future work investigating this topic is warranted.

4.7. Conclusions

In conclusion, there is promising evidence for over-the-counter products in the management of insomnia disorder in adults. In particular, valerian and melatonin are well-studied products, which appear safe and show effectiveness in more trials than not. Alternatively, promising products with fewer studies merit further investigation, for example lemon balm & fennel and valerian, hops & passionflower showed similar effects to prescription drugs. A number of supplements and herbal products with single trials also showed promising effects versus placebo. Large-scale trials, assessing the cost-effectiveness and safety of products in the context of real-life use, are warranted to form the basis for robust clinical recommendations [45]. This review contributes to the evidence-base by mapping over-the-counter products investigated to alleviate insomnia symptoms in adults, and the characteristics of the evidence, which may usefully guide future work in the field. The need to fill the gaps in research is evident, with a particular emphasis on over-the-counter products already used in real-life settings, and relative cost-effectiveness and safety in diverse populations.

CRediT authorship contribution statement

Adriana Salame: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Silvy Mathew:** Verity Thomas, Validation, Investigation, Funding acquisition, Data curation. **Cini Bhanu:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Data curation. **Juan Carlos Bazo-Alvarez:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Sukvinder Kaur Bhamra:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization, Sayem Uddin, Validation, Investigation, Data curation. **Michael Heinrich:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Kate Walters:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Rachael Frost:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

None.

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Appendix A

MEDLINE search log

1 (anxi* or (anxiety adj1 disorder) or (stress* adj1 (psychological or emotional)) or panic attack or depress* or mental health or dysthymia or (panic adj1 disorder) or (sleep adj1 disorder) or insomnia or (mood adj1 disorder) or (psychological adj1 distress)). ti,ab,kw.
2 mental health/or anxiety disorders/or mood disorders/or Anxiety/or exp Depression/or exp "Sleep Initiation and Maintenance Disorders"/
3 1 or 2
4 ("Over-the-counter" or OTC or (over the counter adj1 (medic* or drug or product)) or "General sales" or "pharmacy only" or Non-prescription or Self-medication or Self-prescription or antihistamines or (botanical or herb* or "medicinal plant" or fungus or medicinal mushroom or herbal tea or plant extract or flower extract or root extract or seed extract or "bach flower" or "natural product" or CBD or cannabidiol) or ("nutritional supplement" or "dietary supplement" or vitamins or minerals or "amino acids" or "essential fatty acids" or "omega-3 fatty acid" or 5-Htp or 5-Hydroxytryptophan or tryptophan or probiotic or prebiotic or melatonin) or ((Traditional adj1 medicine) or (Chinese adj1 medicine) or ayurv* or homeopathy or "homeopathic medicine" or phytotherap* or nutraceutical or "herbal medicine")). ti,ab,kw.
5 exp Nonprescription Drugs/or plant extracts/or teas, herbal/or Plants, Medicinal/or Cannabidiol/or Dietary Supplements/or exp Vitamins/or Vitamin D/or Vitamin E/or Folic Acid/or magnesium compounds/or minerals/or zinc compounds/or amino

acids/or Tryptophan/or Fatty Acids/or homeopathy/or exp medicine, traditional/or Melatonin/
6 4 or 5
7 exp animals/not humans. sh.
8 (randomised controlled trial or controlled clinical trial). pt. or randomised. ab. or placebo. ab. or clinical trials as topic. sh. or randomly. ab. or trial. ti.
9 8 not 7
10 (cost-effectiveness or (cost adj1 effectiveness adj1 analysis) or (cost adj1 benefit adj1 analysis) or "economic evaluations"). ti,ab, kw.
11 Cost-Benefit Analysis/
12 9 or 10 or 11
13 3 and 6 and 12
14 limit 13 to humans

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