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Does valerian work for insomnia? An umbrella review of the evidence

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ABSTRACT

Valerian is one of the most used herbal agents (phytotherapeutics) to manage sleep disturbances, in particular, sleep-onset difficulties in young adults. However, the evidence based on primary studies and systematic reviews that supports its use in this domain is weak or inconclusive. In the current study, an umbrella review was performed on the efficacy of valerian for sleep disturbances with a focus on insomnia. As such, only systematic reviews (with or without meta-analysis) were considered for this study. Systematic searches in PubMed, Web of Science, Scopus, Cochrane Database of Systematic Reviews, PROSPERO and CNKI databases retrieved 70 records. Only 8 articles were considered eligible for qualitative analysis. Overall, data suggested that valerian has a good safety profile, however, the results showed no evidence of efficacy for the treatment of insomnia. Moreover, valerian appears to be effective concerning subjective improvement of sleep quality, although its effectiveness has not been demonstrated with quantitative or objective measurements. Despite its widespread use and prescription by general practitioners, psychiatrists and other professionals, valerian does not have empirical support for insomnia. Further studies, in particular high quality randomized controlled trials, are highly recommended since there are scarce studies and the existing ones are quite heterogeneous and with low methodological quality. The implications of our findings for clinical practice are critically discussed.

1. Introduction

Sleep is an essential physiological and behavioral process for homeostatic regulation, contributing to physical and psychological well-being, quality of life and longevity. Poor sleep is reported in approximately 30–35 % of the general population (Liu et al., 2016). Decreased sleep quality (SQ), sleep deprivation or restriction are all risk factors for the development of several diseases being associated with the emergence of cardiovascular problems, hypertension, metabolic and neurocognitive dysfunction, obesity, oncological pathology, and mental disorders such as anxiety and depression, leading to an increase in mortality (Morin et al., 2015; Roach et al., 2020). Insomnia disorder, the most common sleep disorder, characterized by dissatisfaction with sleep quality or quantity and with significant distress and inability to restore normal levels of energy and wakefulness, is known to affect between 3.9 and 22.1 % of the population (Morin et al., 2015).

Traditionally, treatments for insomnia can be divided into three major classes: nonpharmacological, pharmacological, and complementary and alternative medicine. Prescription pharmacotherapy remains the most frequently used intervention in the treatment of insomnia although guidelines from the American academy of sleep medicine (AASM), the American college of physicians (ACP) and the European sleep research society (ESRS) strongly recommend cognitive-behavioral therapy for insomnia (CBT-I) as the first-line treatment for chronic insomnia in adults of any age, as well as several systematic reviews (Dujardin et al., 2018; Edinger et al., 2021; Qaseem et al., 2016; Riemann et al., 2023). As to pharmacological treatment of insomnia, several psychotropic drugs are available, including: benzodiazepines (BZDs) (e.g., diazepam, lormetazepam, oxazepam) (Dujardin et al., 2018; Frase et al., 2018; Roach et al., 2020; Riemann et al., 2023; Walsh and Roth, 2016); benzodiazepine receptor agonists (BZRAs) or "Z" drugs (e.g., zolpidem, zaleplon, zopiclone) (Dujardin et al., 2018; Riemann et al., 2023: Walsh and Roth, 2016); orexin receptor antagonists (e.g., suvorexant and lemborexant); "off-label" medication such as sedative

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antidepressants (e.g., agomelatine, trazodone, mianserin, doxepine), atypical antipsychotics (e.g., quetiapine, chlorprothixene, melperone); and over-the-counter (OTC) medication/supplements (e.g., valerian, melatonin, doxylamine) (Dujardin et al., 2018; Morin and Espie, 2004; Riemann et al., 2023; Roach et al., 2020; Sateia et al., 2017). Nevertheless, the medications come with a series of adverse effects that are worth mentioning, such as tolerance, dependence, drowsiness, occurrence of rebound insomnia, cognitive impairment of memory, learning, concentration and attention as well as depression (Dujardin et al., 2018; Frase et al., 2018; Hassinger et al., 2020; Morin and Espie, 2004; Riemann et al., 2023; Roach et al., 2020; Sateia et al., 2017; Walsh and Roth, 2016). Several meta-analyses demonstrated a substantial placebo effect in the treatments for insomnia, whether pharmacologic or behavioral (Dujardin et al., 2018; Riemann et al., 2023; Winkler and Rief, 2015; Yeung et al., 2018).

As such, the quest for other treatment options for sleep disturbances, namely insomnia, remains pressing especially for food supplements such as herbal products. Nevertheless, there are limited data regarding the efficacy of OTC medications currently available, namely melatonin, cannabinoids and valerian (Valeriana officianalis) (Dujardin et al., 2018; Frase et al., 2018; Krystal, 2017; Morin and Espie, 2004; Sateia et al., 2017).

Extracts of the roots of valerian (Valeriana officianalis), a flowering plant native to Europe and Asia, are widely used for the treatment of anxiety and for inducing sleep and improving sleep quality being known for its sedative, hypnotic, and anxiolytic properties (Harris and Nikles, 2018; Spinella, 2006; Zhang et al., 2022). Valerian is widely available in a variety of commercial preparations and is among the top-selling herbs in the US being recognized since the 18th century in Europe to improve sleep disturbances (Donald & Farzanech, 2007; Spinella, 2006). Indeed, valerian is commonly used by young people, particularly college students (Silva et al., 2021). Nevertheless, both AASM and ESRS guidelines suggest that clinicians should not use valerian as a treatment for sleep onset or sleep maintenance disturbances due to poor evidence of its effectiveness (Riemann et al., 2023; Sateia et al., 2017). High doses of valerian can produce headache, gastrointestinal symptoms, feelings of uneasiness, dizziness, and heart rate changes (Spinella, 2006).

Scientific evidence regarding the efficacy of valerian is inconclusive. Valerian has been reported to reduce subjective sleep latency (SL) and reduce slow wave sleep at a dose of 300 mg per day for two weeks (Donath et al., 2000). Ziegler et al. (2002) published the longest trial of valerian, administering the herb to patients diagnosed with non-organic insomnia over a six-week period (dose 600 mg/die). They demonstrated that it produced similar results to oxazepam (short to intermediate-acting benzodiazepine), with both agents improving patient reported sleep quality from baseline. A study from Taavoni et al. (2011) concluded that valerian improved sleep quality in post-menopausal women with insomnia. However, Oxman et al. (2007) found that valerian does not improve sleep quality with comparable improvements between valerian treatment and placebo (29 % improvement in valerian group versus 21 % in placebo group). Also, Diaper and Hindmarch (2004) conducted a randomized controlled trial and have investigated the acute effects (one day) of valerian at a dose of 300 mg and 600 mg compared to placebo, and showed that valerian is ineffective at improving any sleep electroencephalogram (EEG), mood or psychometric measure. Taibi et al. (2009) also reported, in a randomized controlled trial, no difference in a range of sleep measures, including SL, wake after sleep onset and SQ, between single dose valerian (600 mg), two weeks valerian treatment or placebo groups in women with insomnia aged between 55 and 80.

Still, some systematics reviews (SRs) on the efficacy of valerian on sleep have been performed, but they reached different conclusions (Bent et al., 2006; Fernández-San-Martín et al., 2010; Leach and Page, 2015; Shinjyo et al., 2020; Stevinson and Ernst, 2000; Taibi et al., 2007; Taslaman, 2014). As the evidence demonstrates, systematic reviews and meta-analyses can also present biases and discrepant conclusions. While long considered at the top of the hierarchy of evidence, systematic reviews and meta-analyses could only provide a comprehensive overview of an intervention (Aromataris et al., 2020). According to Murad et al. (2016), systematic reviews may be seen not as a separate level of evidence but a way of looking (i.e., a lens) at the evidence. This, coupled with the existence of multiple systematic reviews on the same topic or question, often leaves the researcher and the clinician with difficulties in assimilating the findings, especially when the results and conclusions from systematic reviews are discrepant (Aromataris et al., 2020). Consequently, a logical and appropriate next step is to carry out an umbrella review, allowing the findings of separate systematic reviews to be compared and critically assess the quality and availability of the evidence (Tsagris and Fragkos, 2016).

Thus, our aim was to conduct an umbrella review to summarize all available systematic reviews and meta-analyses investigating the efficacy and safety of valerian concerning to sleep problems, namely insomnia. To our knowledge, no such study has been performed so far. Taking into account the weak / inconclusive results and conclusions related to the impact of valerian on sleep between different systematic reviews and meta-analysis, we reviewed those published studies to evaluate the strength and potential bias of evidence concerning the role of valerian on insomnia.

2. Methods

2.1. Search strategy

Firstly, an informal survey was conducted to check the feasibility of conducting an umbrella review on the topic. No umbrella review was identified. The protocol for the present study was pre-registered at PROSPERO's International Prospective Register of Systematic Reviews (Reg. number: CRD42022365334). The present review was reported in accordance with 1) the 2020 PRISMA statement (Page et al., 2021) which assists review authors in reporting of their systematic review and/or meta-analysis and 2) the guidelines from the Joanna Briggs Institute (JBI) Evidence Synthesis Manual developed by Aromataris et al. (2020). We established systematic document retrieval on PubMed, Web of Science, Scopus, Cochrane Database of Systematic Reviews, PROSPERO and CNKI from inception to September 2022 for eligible studies. The references section of selected reviews was carefully checked to look for additional records. All search fields were considered regardless of the language of publication. The following terms were used in all searches except for Scopus database: ("systematic review" OR "meta-analysis") AND ("valerian*") AND ("sleep" OR "insomnia"). Concerning Scopus search, the following terms were used: (("systematic review" OR "meta-analysis") AND "valerian*" AND ("sleep" OR "insomnia")) AND (LIMIT-TO (DOCTYPE, "re")).

2.2. Study screening and selection

We investigated the impact of valerian on insomnia by looking for systematic reviews, with or without meta-analysis (MAs), which included randomized controlled trials (RCTs) and observational studies, which evaluated the efficacy and/or safety of valerian for the management of insomnia. Original studies, case reports, clinical guidelines, letters and research protocols, studies conducted in animals and studies that included valerian preparations combined with other substances, such as valerian with hops were excluded. The selection criteria for this review were based on participant, intervention, comparison, outcome (PICO) criteria. *Participants*: any human population of any age as the population diagnosed with insomnia disorder and comorbid insomnia according to DSM-5 and ICD-10 diagnostic criteria or with clinically significant insomnia symptoms; *Interventions*: trials using orally administered mono-preparations of valerian, of any dose, form and duration; *Control group*: studies that compared valerian against a placebo or control group. The control group could receive no intervention, treatment as

usual, another active or passive treatment or placebo; *Outcome*: any objective/subjective sleep-related measure, such as polysomnography, actigraphy, visual analog scale (VAS), sleep diary and Pittsburgh Sleep Quality Index. As secondary outcomes, safety and adverse effects of valerian.

Two independent reviewers (VV and DRM) performed the search strategy. The *Rayyan* QCRY (Ouzzani et al., 2016) application was used as a support tool for the duplicate records elimination and article selection phase, namely for the inter-rater agreement. Article selection and data extraction was performed by two researchers in an independently way in order to reduce the bias and subjectivity of the article search. More specifically, two reviewers (VV and DM) conducted the title and abstract screening. Disagreements were resolved by a third reviewer (DRM). The full text of relevant reviews was then independently evaluated by two reviewers (VV and SJ) to finalize its eligibility. Disagreements between the reviewers were resolved during a consensus session with a third reviewer (DRM). Furthermore, for each step, interrater reliability was computed.

2.3. Data collection and data summary

For included studies, data were extracted by two independent reviewers (VV and DM), and disagreement was resolved by consensus. Authors of papers were contacted for clarification when data was missing or unclear. The extracted study characteristics included qualitative summaries of (1) authors' country; (2) journal where the article was published and respective impact factor; (3) inclusion criteria; (4) search strategies; (5) appraisal of primary studies; (6) patients demographics; (7) intervention protocol; and (8) main outcome measures. The extracted quantitative variables included (1) year of publication; (2) number of included studies; (3) sample size (*N* summed across included studies); and (4) declared any conflicts of interest. The extracted study results/findings included summaries of (1) qualitative main results and, in particular, whether there was a statistically significant improvement in total sleep time (TST), SQ and SL; (2) type of review, in particular if meta-analyses were conducted or not; (3) qualitative and/or quantitative heterogeneity reports; (4) main conclusions; and (6) principal limitations.

2.4. Assessment of methodological quality/critical appraisal

AMSTAR 2. Two authors (VV and DM) independently assessed the quality of included reviews. The methodological quality was evaluated through the Assessment of Multiple Systematic Reviews - AMSTAR 2 tool (Shea et al., 2017). This instrument, includes 16 domains in total (e.g., "Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?"; "Did the review authors perform data extraction in duplicate?") and generates an overall rating based on the scores in these domains. The possible ratings are: High, Moderate, Low, and Critically Low (Shea et al., 2017).

2.5. Assessment of risk of bias (RoB)

ROBIS. Although commonly confused, methodological quality analysis and risk of bias analysis are different concepts. Therefore, for each analysis there are distinct assessment tools (Perry et al., 2021). Two independent authors (VV and DRM) assessed the RoB of included reviews with the Risk of Bias in Systematic Review (ROBIS), and disagreements were resolved by discussion (Whiting et al., 2016). Despite some overlap between AMSTAR-2 and ROBIS in terms of the critical questions, AMSTAR-2 is an effective tool at assessing quality and ROBIS is an effective tool for assessing RoB (Perry et al., 2021). ROBIS is divided into three distinct phases, including assessing relevance, identifying concerns with the review process, and judging risk of bias (Whiting et al., 2016). Firstly, there is an optional phase to assess if participants, interventions, comparators and outcomes match the research question of interest. The answers are "yes", "no", "partial", and "uncertain". We started our analyses with phase two that includes four domains with 20 items in total: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; 4) synthesis and findings (Whiting et al., 2016). Each domain has signaling questions as "yes", "probably yes", "no" and "no information", and ends with a judgement of bias associated to each domain (low, high or unclear). Phase three, consisted of three signaling questions (e.g., "did the interpretation of findings addressed all the concerns identified in domains 1 to 4?"), to enable an overall risk of bias in the systematic reviews (low, high or unclear). ROBIS has a vast application and is aimed at assessing effectiveness (Whiting et al., 2016).

2.6. Assessment of corrected covered area (CCA)

Overlaps should be reported by default in overviews/umbrella reviews and CCA is the most adequate measure. This assessment prevents reporting, without proper discussion, biased results due to high levels of overlap. Degree of overlap (CCA) is computed by dividing the frequency of repeated occurrences of the index publication in other reviews by the product of index publications and reviews, being this product reduced by the number of index publications. CCA can be interpreted as the area that is covered after eliminating the inclusion of all primary publications the first time they are counted. A CCA value lower than 5 can be considered as slight overlap, between 6 and 10 can be considered moderate overlap, 11 to 15 can be considered as a high overlap and greater than 15 is regarded as very high overlap (Pieper et al., 2013).

3. Results

3.1. Review selection

In current review, eight studies were included involving a total of 15,716 participants. The total number of participants that inform the outcomes relevant to the umbrella review question, from all studies included, is 9706. Searches performed in Pubmed, Web of Science, Scopus, Cochrane and CNKI yielded a total of 70 articles after screening and removal of duplicates. A further 50 records were excluded as they had the wrong publication type; were conducted in animals; or were excluded for an unspecified reason. Of the 20 full-text articles assessed, 14 were excluded for the following reasons: 7 papers used a wrong intervention (e.g., valerian preparation combined with hops), 3 had wrong publication type (e.g., narrative reviews), 2 had inappropriate study design (e.g., no relevant outcomes), 1 had insufficient data to be included and 1 was not available (cf. Fig. 1). For the screening of title and abstract, we obtained a value of $k = 0.72$ (89 % agreement) and for the evaluation of the full text we obtained a value of $k = 0.78$ (90 % agreement). Kappa statistic values between 0.80 and 0.90 are considered strong values with very good agreement between reviewers (McHugh, 2012).

3.2. Characteristics of included reviews

Out of the eight systematic reviews included, five of them performed meta-analysis (Bent et al., 2006; Fernández-San-Martín et al., 2010; Leach and Page, 2015; Shinjyo et al., 2020; Zhang et al., 2023) and all eight included RCTs and observational studies. Two systematic reviews/meta-analyses were published by authors from the USA (Bent et al., 2006; Taibi et al., 2007); two systematic reviews/meta-analysis were published by authors from Australia (Leach and Page, 2015; Taslaman, 2014); one systematic review was published in United Kingdom (Stevinson and Ernst, 2000), one meta-analysis in Spain (Fernández-San-Martín et al., 2010), one meta-analysis in Japan (Shinjyo et al., 2020) and another meta-analysis in China (Zhang et al., 2023). The systematic reviews were published from 2000 to 2023. Most of them

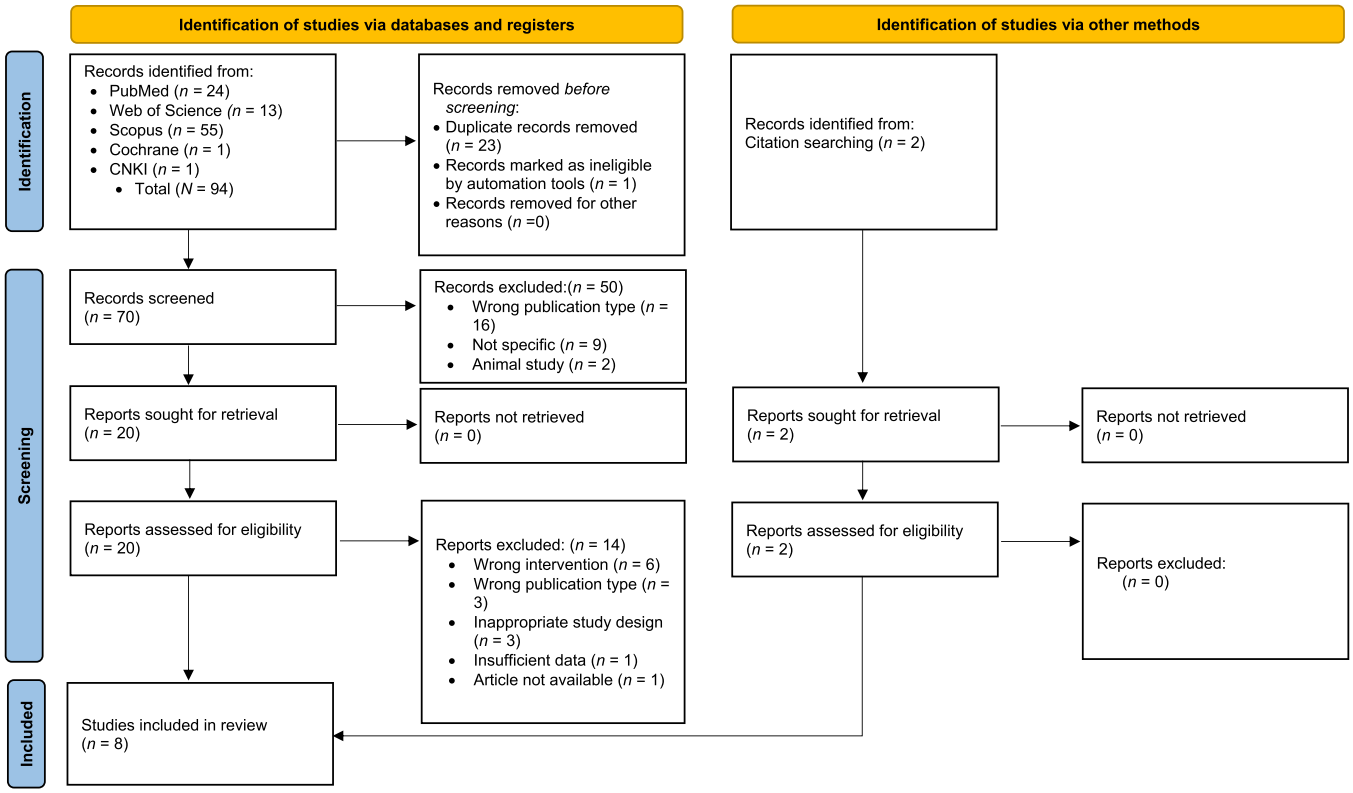

Fig. 1. PRISMA 2020 flow diagram.

have no restriction on age, but two systematic reviews included only adults. The sample size from the included systematic reviews ranged from 390 to 1539 subjects, and the number of primary studies included in each of the systematic reviews ranged between 5 and 22 studies. The studies involved patients with sleep disturbances, sleep problems, sleep complaints, intellectual deficits and sleep disturbances, post-menopause women with sleep disturbances, geriatric inpatients with sleep disturbances, patients that took benzodiazepines for sleep disturbances and healthy volunteers. One study (Leach and Page, 2015) included only adults with insomnia (not comorbid or secondary insomnia), as defined by established diagnostic criteria, standardized instruments or medical diagnosis. The intervention content was mainly based on different preparations of valerian with doses ranging from 6.4 to 6000 mg and administered for between 1 day to 5 months. One study (Taibi et al., 2007) compared the results of the valerian intervention according to three different valerian preparations: ethanolic and aqueous valerian extracts and valepotriate preparations. There were a variety of measures used to determine the outcome of the reviews, but a majority of the studies used self-reported SL, SQ and TST as measures to determine drug efficacy. Other measures such as sleep efficiency (SE), polysomnography (PSG), Actigraphy and wakefulness after sleep onset (WASO) were also used. Six systematic reviews/meta-analysis used the Jadad scale to evaluate the quality of the trials (Bent et al., 2006; Fernández-San--Martín et al., 2010; Taibi et al., 2007; Shinjyo et al., 2020; Stevinson and Ernst. 2000; Zhang et al., 2023). Two systematic reviews used the Cochrane's Risk of Bias tool (Leach et al., 2015; Zhang et al., 2023) and another systematic review did not perform quality appraisal of primary studies (Taslaman, 2014). The heterogeneity of meta-analysis data estimated by I^2 ranged from 0 % to 93 %. Table 1 summarizes the study characteristics of the reviews for Valerian.

3.3. Findings of reviews

Total sleep time (TST). One meta-analysis (Zhang et al., 2023) reported longer self-perceived sleep duration measured with sleep questionnaires and PSQI in participants in valerian group (450–1060 mg/d before bed time during 5 days or 4 weeks, respectively) compared with those receiving placebo. One systematic review (Stevinson and Ernst, 2000) partially reported some significant statistical results for improved TST measured with validated questionnaires and a sleep rating scale. Sleep duration improved in chronically ill patients in geriatric hospitals administered aqueous valerian extract (3 × 2 capsules *Baldrian Dispert®* daily, two weeks) compared with placebo. Four meta-analyses (Bent et al., 2006; Fernández-San-Martín et al., 2010; Leach and Page, 2015; Shinjyo et al., 2020) have not reported statistically significant objective/subjective results for improved TST. Furthermore, the same systematic review (Stevinson and Ernst, 2000) investigated objective improvement for TST with PSG sleep recordings and wrist actigraphy but showed no significant groups differences in this outcome between valerian and placebo group. Even so, findings of the primary studies from this systematic review were contradictory and there was great inconsistency between trials. Two systematic reviews (Taibi et al., 2007; Taslaman, 2014), have not reported statistically significant objective/-subjective results for improved TST (cf. Table 2).

Sleep quality (SQ). The findings of three meta-analyses suggested that valerian might improve SQ (Bent et al., 2006; Fernández-San-Martin et al., 2010; Shinjyo et al., 2020). Bent et al. (2006) used a dichotomous measure of SQ (sleep quality improved or not) and founded that patients taking valerian (range 90 mg to 600 mg/ 1 day to 1 month) had an 80 % greater chance of reporting improved sleep compared with patients taking placebo, the use of valerian almost double the chance of sleeping better when compared with placebo; one review (Fernández-San-Martin et al., 2010) used SQ improvement (yes/no) and SQ improvement quantified through visual analogic scales to evaluate the effectiveness of valerian for insomnia, the results from qualitative dichotomous analyses suggested that valerian (range 6.4 mg to 600 mg/ 4–43 days) improved subjective reports of SQ, although its effectiveness has not been demonstrated with quantitative or objective measurements (EEG).

Table 1
Characteristics of the included reviews.

First author (year) [Country]	Journal (current IF / 5-year IF)	Inclusion criteria	Search strategy (nr. of databases) Date range of search	Nr. of RCT/OS (participants) [Date range of included studies]	Appraisal of primary studies	Patients/Interventions/Outcomes measures	Conflict of Interest
Stevinson et al. (2000) [United Kingdom]	Sleep Medicine (4.842/5.593)	No age restriction; No language restriction	Medline, Embase, Biosis, The Cochrane Library, Current Contents (5) Till 1999	9 ($N = 390$) [1982–1996]	Jadad scale Median score: 2 out of 5	*Patients* Mild/non-organic insomnia; sleep difficult; healthy *Interventions* Valerian 400–900 mg; 3–28 days *Outcomes* SQ: PSG/self-reported; Activity meter	NR
Bent et al. (2006) [USA]	American Journal of Medicine (5.928/-)	No age restriction; No language restriction	Pubmed, Embase, Ibids, Biosis, Cochrane Library (5) Till 2005	16 ($N = 1093$) [1977–2005]	Jadad scale Median score: 3 out of 5 Funnel plots Publication bias may be present Kendall's tau Positive for bias ($p = 0.03$)	*Patients* Chronic/non-organic/not well-defined insomnia; self-reported sleep problems; sleep disturbance; mild sleep complaint; intellectual deficits and sleep disturbances; healthy volunteers *Interventions* Valerian 225–1215 mg per day; 1 day to 1 month *Outcomes* VAS, dichotomous of sleep quality, sleep-onset latency	NR
Taibi et al. (2007) [USA]	Sleep Medicine Reviews (11.401/-)	No age restriction; No language restriction	Pubmed, Cochrane Central Register of Controlled Trials, Embase, PsychINFO, Cinahl, International Pharmaceutical Abstracts, Dissertation Abstracts (7) No date range of search	21 ($N = 1460$) [1977–2003]	Jadad scale Median score: 3 out of 5 Criteria of Stevinson and Ernst Publication bias	*Patients* Insomnia; self-reported sleep problems; mild sleep complaints; sleep disturbance; healthy volunteers *Interventions* Valerian 6.4–1215 mg, per day; 1–42 days *Outcomes* SQ and SL: PSG/actigraphy/self-reported; VAS	NR
Fernández-San-Martín et al. (2010) [Spain]	Sleep Medicine (4.842/5.593)	No age restriction; No language restriction	Medline, Cochrane Library, Embase, Biosis (4) Till 2008	18 ($N = 1317$) [1982–2009]	Jadad scale Median Score: 3 out of 5 Funnel plots No publication bias	*Patients* Insomnia; chronic/light insomnia; self-reported sleep problems; mild sleep complaint, disturbed sleep; sleep disturbance; sleep problems and intellectual deficits; healthy *Interventions* Valerian 6.4–900 mg; 4–56 days *Outcomes* SQ and SL: PSG/self-report; VAS	NR
Taslaman (2014) [Australia]	Australian Journal of Herbal Medicine (0.10/-)	Adults; No language restriction	Pubmed, Cochrane Collaboration, Cinahl, EBSCO, Medline, Science direct, Scopus, Google Scholar (8) 2003–2014	5 ($N = 757$) [2003–2008]	–	*Patients* Primary/chronic insomnia; anxiety and insomnia, mild sleep complaint; *Interventions* Valerian 6.4–600 mg; 6–44 days *Outcomes* SQ and SL: PSG/self-report; VAS, WASO, home recordings (wrist autography and sleep diaries). safety	NR
Leach et al. (2015) [Australia]	Sleep Medicine Reviews (11.401/-)	Adults; English Language	Academic Search Premier (EbscoHost), AMED (Ovid), CAM on PubMed, CINAHL (EbscoHost), EMBASE (Ovid), EThOS Beta, Health Source: Nursing/ Academic Edition (EbscoHost), Informit, International Pharmaceutical Abstracts (Ovid), MEDLINE (Ovid), Natural medicines comprehensive database, ProQuest (Dissertations and theses), ProQuest (Conference proceedings), Psychological and Behavioural Sciences	11 ($N = 1326$) [1994–2012]	Cochrane's ROB tool Unclear risk of bias for most of the included studies Funnel plots Due to insufficient studies, unable to assess Chi-squared and the I^2 statistic Due to insufficient	*Patients* Insomnia; primary/psycho-physiological/ chronic insomnia; self-reported sleep problems; sleep disturbances; sleep disorders *Interventions* Valerian 300–3645 mg; 1–42 days *Outcomes* PSG, Actigraphy, SF-A, SQ, VAS, Sleep diary, ISI, LSEQ, Sleep quality and sleep improvement ratings, sleep quality (VAS), 4-point symptom rating scales, sleep quality (VAS)	No

(*continued on next page*)

Table 1 (*continued*)

First author (year) [Country]	Journal (current IF / 5-year IF)	Inclusion criteria	Search strategy (nr. of databases) Date range of search	Nr. of RCT/OS (participants) [Date range of included studies]	Appraisal of primary studies	Patients/Interventions/Outcomes measures	Conflict of Interest
			Collection (EbscoHost), PsycINFO (EbscoHost), The Cochrane Library, and Web of Science (Web of Knowledge). (17) Till 2014		studies, unable to assess		
Shinjyo et al. (2020) [Japan]	Journal of Evidence-Based Integrative Medicine (0.453/-)	No age restriction; English Language	Pubmed, Science direct, Cochrane Library (3) Date range of search varied between databases	23 (N = 1930) [1982–2017]	Jadad Scale Median score of: 4 out of 5 Funnel plots I^2=85.33 %	*Patients* Insomnia; chronic/ psychophysiological/ non-organic insomnia; self-reported sleep problems; mild sleep disturbance; sleep disturbance; sleep disorders; RLS patients; healthy subjects *Interventions* Valerian 6.4–1600 mg; 5 days to 8 weeks *Outcomes* PSG, Wrist actigraphy, sleep dairy, the reduction of initially prolonged sleep latency, sleep EEG, LSEQ, SQ, Objective SE, SL, NREM, REM, SWS, subjective sleep quality (VAS), sleep quality and latency (self-assessment), severity of stress and sleep disturbance (subjective), subjective sleepiness scales (Karolinska Sleepiness Scale), PSQI, sleep disturbances (PSQI and ESS), severity of RLS, sleep latency, time spent awake during the night and sleep quality (VAS), total sleep time, sleep efficiency, number of arousals, WASO.	No
Zhang et al. (2023) [China]	Current Sleep Medicine Reports (0.43/-)	No age restriction; No Language restriction	Pubmed, Cochrane Library-Trails, Web of Science, Embase, CNKI, VIP, WangFang (7) From inception to December 29, 2021	21 (N = 1433) [1985–2019]	Jadad Scale Median score of: 4 out of 5 Funnel plots Chi-squared and I^2 Due to insufficient studies, unable to assess	*Patients* Self-reported/parent-rated insomnia questionnaires or scales; established insomnia diagnostic classification; subjects with no reported sleep disturbance. *Interventions* Valerian 6.4–6000 mg; 5 days to 5 months *Outcomes* PSG, Wrist actigraphy, sleep dairy, sleep EEG, LSEQ, SQ, PSQI, sleep disturbances (PSQI and ESS), sleep questionnaire, Transportable home recorder system (QUISI), self-rated sleep, VAS, WASO, NREM, REM, ISI.	No

Note. NR-no register.
Abbreviations: EEG=electroencephalogram, ESS=Epworth Sleepiness Scale, ISI= Insomnia Severity Index; LSEQ= The Leeds Sleep Evaluation Questionnaire, NREM=Non-rapid eye movement sleep; OS=observational studies, PSG=Polysomnography; PSQI=Pittsburgh Sleep Quality Index, QUISI=Transportable Home Recorder System, RCT=Randomized controlled trial, REM=rapid eye movement sleep, RLS=Restless Legs Syndrome, SF-A-Spindle Frequency Activity, SL=sleep latency, SQ=sleep quality, SWS=Slow-wave sleep, VAS=visual analog scale, WASO=Wakefulness After Sleep Onset.

Shinjyo et al. (2020) also suggested that valerian may be useful to improve subjective SQ, but studies with repeated administration are required to obtain reliable and generalizable data. And specifically, *V. edulis* and valepotriates from *V. wallichii* (20 mg/kg for two weeks), improved SQ in children with intellectual deficits and primary sleep problems (e.g., initiating and maintaining sleep, long sleep latencies, problematic bad-time behaviour) measured with VAS. Furthermore, one systematic review (Taibi et al., 2007), reported improved SQ (PSG, VAS, sleep questionnaires and sleep diaries) ratings in: geriatric patients; persons withdrawing from benzodiazepines and persons reporting disturbed sleep, taking aqueous valerian extracts (90 mg of Valdispert ®/ *3 days for two weeks) or valepotriate preparations (60 mg to 120 mg of *V.edulis* for 1 night; 100 mg of V. *wallichi*/ 3*day for 15 nights), respectively, compared to placebo. Also, ethanolic extracts of *V.officinalis* (600 mg for 14 nights) improved subjective SQ ratings, measured by sleep questionnaire, in a manner equivalent to benzodiazepines (10 mg Oxazepam for 42 nights) under the assumption that the benzodiazepines tested were superior to placebo. Nonetheless, another review (Leach and Page. 2015) evaluated the effectiveness of valerian (range 100 mg to 530 mg administrated by tablets noctes or softgel capsules; 30 to 60 min before bed; for 2 to 6 weeks) in patients with insomnia (different diagnostic criteria) and found no significant difference in SQ (measured not defined) between valerian and placebo and between valerian and oxazepam (cf. Table 2).

Table 2
Results of the reviews.

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
Stevinson et al. (2000)	Three trials investigated the effect of valerian following repeated administration: one study found improvements in a number of sleep-related parameters between 2 and 4 weeks; another study reported superior SL and duration by 2 weeks; another study suggested an increase in slow wave sleep after 1 and 8 days of valerian, but other polysomnographic and subjective measures did not show any improvements. Six trials investigated responses to single doses of valerian, three reported positive results and three show no difference compared to placebo. Side effects: scarce reports; mild side effects and similar to those experienced with placebo.	PY	N	–	PY	–	Inconsistencies between trials in experimental design; heterogeneity in samples, daily dose treatment; outcomes measures; methodological quality.	Contradictory findings. Results of some trials suggested that valerian may have both acute and cumulative effects on sleep, but not all studies have produced positive findings. The evidence for valerian as a treatment for insomnia is inconclusive.	Conflicting results and small sample sizes; poorly defined samples; lack of control over confounding variables; use of non-validated outcome measures.	
Bent et al. (2006)	From 7 studies that used a visual analog scale to assess change in SQ, 5 studies reported no statistically significant improvement in the valerian group compared to placebo; two studies noted improvements but they were not statistically significant. Pool data from dichotomous outcome of SQ proved that valerian almost	N/Y	Y	1.8 (1.2–2.9)	PY	–	*P* value for heterogeneity = 0.3 Valerian doses, preparations and length of treatment	Valerian might improve SQ without producing side effects. Patients taking valerian had an 80 % greater chance of	Methodological flaws led to invalid results in individual studies: small sample sizes; most studies did not describe the process of identifying,	Seven studies used a visual analog scale to assess change in SQ among participants and the statistical presentation

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	double the chance of sleeping									
Bent et al. (2006)	better when compared with placebo (1.8, 95 % *CI*, 1.2 to 2,9). Two studies reported significant improvements in subjective SL of 16.7 min. Five of the included studies used polysomnographic sleep recordings and there were no statistically significant changes in any outcome measures. Side effects: Only one study reported a statistically significant increase in any adverse event (diarrhea), in 18 % of patients in the valerian group compared with 8 % of patients in the placebo group ($p = 0.02$).						varied considerably.	reporting improved sleep compared with patients taking placebo; there was evidence of publication bias and methodological problems of the included studies.	recording, or analyzing adverse events. The statistical presentation of the data did not allow pooling of some outcome measures.	of the data did not allow pooling of this outcome measure. Same for subjective sleep onset latency outcome.
Taibi et al. (2007)	The studies of highest quality did not find valerian (ethanolic extracts) to be significantly superior to placebo for improving outcomes in insomnia. Studies that investigated Ethanolic extracts of *V.officinalis*, several of which using rigorous studies designs, not showed significantly affect objective or subjective sleep outcomes in comparison to placebo in subjects with or without insomnia.	N/PY	N	–	PY	–	Considerable variation among the studies in duration, design, and herbal preparation.	No significant differences between valerian and placebo either in healthy individuals or in persons with general sleep disturbance or insomnia.	Variability in the research quality of the studies; Failure in control pre-bedtime variables;	
Taibi et al. (2007)	These preparations improved subjective SQ ratings in a manner equivalent to benzodiazepines under						Differing characteristic of the samples studied (healthy versus insomnia).	Improvement of sleep over time but insufficient to exclude the possibility of	Variation among the studies in sample sizes and characteristics, duration, design and	

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	the assumption that the benzodiazepines tested were superior to placebo; Studies testing the effects of *aqueous valerian extracts* produced mixed results. In older persons with sleep disturbance, one study reported that a significant proportion of the sample reported "better" sleep. Another study did not show significant effects on either objective or subjective sleep outcomes. Short-term supplementation (one to four nights) of valerian was not shown to affect PSG or subjective sleep outcomes in subjects without known sleep complaints, but valerian reduce subjective SL and WASO with sleep onset insomnia; Findings from 5 studies suggested that *valepotriate preparations* may mildly reduce sleep disturbances. Compared to placebo, studies reported significantly improved sleep quality ratings in persons withdrawing from benzodiazepines and persons reporting disturbed sleep. One of these studies also reported reduced awakening versus baseline but used no placebo control. Side effects: no serious adverse effects. Mild neurological symptoms							placebo effects or to conclude that the valerian is effective. Valerian is a safe herb associated with only rare adverse events.	herbal preparation; Failure to ensure that the placebo and valerian were adequately masked.	

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	(dizziness, headache, drowsiness) and gastrointestinal symptoms (nausea, diarrhea); no evidence of hepatic symptoms, changes in liver function and cognitive impairment.									
Fernández-San-Martín et al. (2010)	Ten studies evaluated the effect of valerian compared with the placebo in terms of SL and no significant improvement was found: 0.70 min (95 % *CI* −3.44 to 4.83; $p = 0.013$; $I^2 = 57$ %); Seven studies compared the SQ improvement (measured with the visual analogic scale) between the valerian group and the placebo group and no statistically significant improvements was found: −0.02 (95 % *CI*, −0.35 to 0.3; $p = -0.01$; $I^2 = 62$ %). A non-significant negative effect of valerian in the SQ was found when the analyses were restricted to studies with a greater methodological rigor subgroup (Jadad ≥4). Also, the greater methodological rigor subgroup turned out to be homogenous ($I^2 = 0$ %); Six studies compared the SQ of the group undergoing treatment with valerian with the control group and treatment with valerian showed a risk ratio of SQ improvement of 1.37 (95 % *CI*, 1.05–1.78; *p*	N/PY	Y	-/1.37 (1.05–1.78)	N	0.70 (3.44–4.84)	*p* for the heterogeneity ranged from 0.013 to 0.03; I^2 ranged from 57 % to 60 %; The majority of studies had small sample sizes, different settings, a wide range of dosages and types of valerian, variable follow-up times, lack of standardized sleep quality measurements. Differing characteristic of the samples studied (healthy versus sleep problems).	The qualitative dichotomous results suggested valerian effective for a subjective improvement of insomnia, although its effectiveness has not been demonstrated with quantitative or objective measurements; clinical trials of high methodological quality and sufficient sample size were not conclusive;Valerian use can be considered for some patients given its safety.	Clinical trials tended not to fulfil pre-specified quality criteria; Eligibility of the studies in the systematic evaluation was limited to published reports; The majority of the studies had inadequate presentations of fata and limited evaluations of adverse effects. Future studies should investigate insomnia with other more promising substances.	When estimated the risk ratio in the subgroup of studies with a greater degree of quality, the improvement was maintained and statistical heterogeneity was decreased; Two studies used validated questionnaires in order to evaluated sleep improvement, the rest obtained responses from the patients through questions designed by authors. No significant publication biases were found in the analyses that are different from the estimate made in the meta-analysis of (Bent et al., 2006).

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	$= 0.03$; $I^2 = 60$ %) in comparison with the placebo group. When the analysis was restricted to studies with greater methodological rigor (Jadad ≥ 4), the efficacy of valerian in SQ was at the limit of significance; All analysis of sensitivity didnt show substantial modifications in the estimators; Side effects: gastrointestinal effects and central nervous system effects are usually low intensity and no different from those seen with the placebo. Exception for diarrhea, more frequent in patients taking Valerian (18 %) in comparison with placebo (8 %, $p = 0.02$).									
Taslaman (2014)	All five RCTs conducted on valerian for the treatment of insomnia disorder in adults have not reached statistically significant scoring for either subjective or objective primary outcomes measures. Improvements in the valerian group were noted in some trials with the majority of evidence remaining either inconclusive or unsupportive for the efficacy of valerian for sleep problems. One study did not reach statistical significance from primary measures, although were observed modest	N/PY	N	–	N	–	Variation in research methodologies regarding: dosage, sample size, treatment duration, preparation, and possible cofounding factors due to various exclusion/ inclusion criteria.	Valerian was found to have a good safety profile but the results demonstrate no efficacy for the treatment of insomnia; the results do not support valerian use as a solo treatment; there questions about the adequacy of the dosage and quality of valerian used in the trials reviewed.	Discrepancies amongst the trials with highly variable research methodologies: small sample size, lack of control over confounding variables (stimulants use and inadequately screened patients with co-morbidities); the methodological quality of the studies was not evaluated.	

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	improvements favoring the valerian group for number of night awakenings and sleep duration. A secondary measure, the global self-assessment question for perceived "better-sleep", reached statistical significance ($p = 0.04$). No statistical differences between the treatment group and placebo in four studies. One of these studies reported a decrease in SL in both groups indicating a placebo effect. Increased nocturnal wakefulness was noted in the valerian group compared to placebo, indicating a negative outcome. Side effects: One study reported mild side effects, some moderate and few severe, experienced by both groups: headache, nervousness, restlessness, and some gastro-intestinal complaints.									
Taslaman (2014)	Other study found the difference in the proportion of participants experiencing side effects in both the run-in period and treatment period for both groups to be statistically significant suggesting the effects (reduced concentration, drowsiness, tiredness, headache, dizziness, irritability and trembling) were more						.			

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	likely to be symptomatic of insomnia.									
Leach et al. (2015)	In four trials, mean differences in SL (minutes) between, valerian an placebo, and in one trial between, *V.edulis* and *V.officinalis* were not statistically significant: 9.17 (95 % *CI*, −2.50 to 20.84; $p = 0.12$) and −0.65 (95 % *CI*, −7.55 to 6.25; $p = 0.85$), respectively. Three trials reported no statistically significant differences in TST, (minutes) between valerian and placebo and one trial, between *V.edulis* and *V. officinalis*: −1.15 (95 % *CI*, −17.49 to 15.20; $p = 0.89$) and −6.47 (95 % *CI*, −31.27 to 18.32; $p = 0.61$), respectively. Four trials reported no statistical significance in sleep efficiency (%) between, valerian and placebo, and one trial between, *V.edulis* and *V. officianalis*: 0.59 (95 % *CI*, −3.53 to 4.70; $p = 0.78$) and −1.17 (95 % *CI*, −6.30 to 3.96; $p = 0.65$), respectively. One trial reported no statistical significance between valerian and placebo on daytime functioning: 0.00 (95 % *CI* −18.28 to 18.28; $p = 1.00$).	N	Y	−1.15 (−17.49–15.20)/ 0.29 (−0.52–1.09)	N	9.17 (−2.50–20.84)	I^2 ranged from 0 % to 90 %; Chi-squared ranged from 0.33 to 19.89; Tau^2 ranged from 0.00 to 59.78.	Insufficient evidence to conclude that valerian is of any benefit to adults suffering from insomnia.	Language and publication bias; poor or uncertain methodological quality (with unclear risk of bias) of included studies.	One trial assessed sleep onset latency using a 7-point categorical scale, the difference in SL between valerian and placebo was marginally significant: 0.27 (−0.01–0.55). $p = 0.06$.
Leach et al. (2015)	Four trials reported no statistically significance difference in SQ between, valerian and placebo, and one									

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	trial between, valerian and oxazepam: 0.29 (95 % *CI*, −0.52 to 1.09; $p =$ 0.48), there was considerable heterogeneity: I^2=90 % between studies; and 0.13 (95 % *CI*, −0.16 to 0.42; $p = 0.37$), respectively. Two trials reported no statistically significance in WASO between valerian and placebo: −0.41 (95 % *CI*, −1.53 to 0.72; $p =$ 0.48), there was a substantial level of heterogeneity: I^2=63 %). One trial reported no statistical significance in total wake time (mean difference in minutes) between treatment groups: 5.48; 95 % *CI*, −19.15 to 30.10; $p =$ 0.66); One trial compared the frequency of nocturnal awakenings between valerian and placebo, and found no statistically significant difference between groups: 0.06 (95 % *CI*, −0.16 to 0.28; $p =$ 0.59). Side effects: 561 adverse events were reported in 422 participants (1.3 events/person) assigned to valerian, and 489 events in 421 participants (1.2 events/person) assigned to placebo. One study reported a significantly greater incidence of *diarrhea* in the valerian-treated									

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
Leach et al. (2015)	group (i.e., 18 % [valerian] vs. 8 % [placebo], $p = 0.02$). In seven studies no statistically significant differences were observed between valerian and placebo treated subjects in the type or severity of adverse events. The number of participants experiencing adverse events (as opposed to the total number of events recorded) was reported in only one trial; a total of three participants reported adverse events among 16 participants randomized to valerian, compared to 11 in 16 participants randomized to placebo. The difference between groups was statistically significant (OR 0.10; 95 % *CI* 0.02 to 0.54; $p = 0.007$; 32 participants; 1 trial).									
Shinjyo et al. (2020)	Eight studies used hydroalcoholic extracts of valerian. As a single dose, *V. officianalis* hydroalcoholic extracts did not improved SQ, however improved REM sleep was observed in insomnia patients. Repeated administration of hydroalcoholic extracts also led to inconsistent outcomes: SQ was improved in 4 studies using 600 mg (2 to 6 weeks), whereas 3 studies using 300–600 mg (5 days to 4 weeks) found no improvement.	N/PY	Y	-/0.36 (−0.08–0.81)	PY	–	I^2= 85.33 % Considerable variation in research methodologies regarding dosage, sample size, treatment duration, preparation, and possible cofounding factors due to various exclusion/ inclusion criteria.	Valerian may be useful to improve subjective SQ and repeated administration is required to obtain significant effects; valerian could be a safe and effective herb to promote sleep. Due to the presence of multiple active constituents	The study reviewed the effectiveness of valerian without specifying target populations; potential differences in the outcomes depending on the target populations;	

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First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	One of the studies found improved SL and deep sleep, after two weeks, while no improvement was observed after a single dose; Among the tree studies using aqueous extracts, two studies with single dose found improved subjective SQ and SL in healthy volunteers, while there was no significant difference in polysomnography.									
Shinjyo et al. (2020)	Three studies using extracts using unspecified solvents found inconsistent outcomes: negative outcomes for two studies and positive for an observational study; All five studies using herbal substance (the whole root/rhizome) showed that the interventions led to improved sleep at least in 1 subgroup. Subgroup analysis for the whole root and the extract revealed that the combined effect size for the whole root was considerable higher 0.83(95 % *CI*: 0.03 to 1.62), compared to the extract 0.10 (95 % *CI*: −0.02 to 0.22). *V. edulis and* valepotriates from *V. wallichii* reduced SL, improved SQ in children with intellectual deficit and primary sleep problems, increased REM sleep, reduced the number of awaking in								and relatively unstable nature of some of the active constituents, it may be necessary to revise the quality control processes, including standardization methods and shelf life.heterogeneity in the outcome measures limited the number of data sources for meta-analysis, which in turn limits the generalizability of the results.	

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	insomnia patients, and improved SQ in insomnia patients, respectively. Side effects: There were no serious adverse events reported in the studies included in the review. Agitation and restlessness were experienced only in minority. Mild adverse events were reported in RLS patients (vivid dreams and fatigue), arthritis patients with sleep disturbance (dizziness and sleepiness), sleep-disturbed subjects (drowsiness), insomnia patients (gastrointestinal symptoms), and outpatients with stress-induced									
Shinjyo et al. (2020)	insomnia (vivid dreams, drowsiness, heavy dream and depression), however there was no clear association with the treatments. No significant results for potential drug interaction effects.									
Zhang et al. (2023)	The results from the meta-analysis for six RCTs showed statistically significant reductions in the PSQI score in the groups receiving valerian in comparison to placebo −1.21(95 % *CI:* −1.92 to −0.51; $p = 0.0007$)*)* and significant interstudy heterogeneity (I^2= 93 %). Four studies showed that participants receiving	PY/Y	Y	1.27 (1.02-1.48)/−1.37 (−1.13- −1.68)	N	–	I^2 ranged from 0 % to 93 %; Chi-squared ranged from 0.07 to 107.60.	The qualitative dichotomic results suggest that valerian would have a small to moderate effect on the improvement of subjective sleep, although its effectiveness has been limitedly demonstrated with one quantitative or objective measurement; valerian is safety.	Methodologic flaws in the studies included may lead to invalid results of different sleep outcomes; Discrepancies of eligibility criteria; the study does not report how treatment effects were maintained at follow-ups; studied only effect sizes on sleep/insomnia; lack of control over	

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Table 2 (*continued*)

First author (year)	Main Results	Is there a statistically significant improvement in TST/SQ	Meta-analysis	TST/SQ-WMD (95 % CI) (mins)	Is there a statistically significant improvement in SL?	SL-WMD (95 % CI) (mins)	Heterogeneity	Conclusions	Limitations	Other comments
	valerian had significant improvement in the SQ compared to the placebo (*RR*=1.37; 95 % *CI*: 1.13 to 1.68; p = 0.002). Two studies showed longer self-perceived sleep duration compared with placebo 1.27(95 % *CI:* 1.02 to 1.48; p = 0.03). Five studies investigated objective improvement for SL and TST with PSG sleep recordings and wrist actigraphy but showed no significant groups differences in these outcomes between valerian and placebo groups. Three studies showed significantly increased time of non-REM stage 3 four those receiving valerian compared to placebo 0.89(95 % *CI:* 0.35 to 1.43; p = 0.001, while no significant differences were found in other non-REM stages between participants of two groups. Three and four studies investigated the effect of valerian on REM sleep-onset latency and REM sleep duration, respectively, and time differences were nonsignificant between the valerian and placebo groups (−0.27, 95 % *CI*: −0.65 to o.10 and −0.03, 95 % *CI*: −0.45 to 0.39, respectively). Side effects: not consistently assessed or reported.								confounding variables; High heterogeneity between studies.	

Note: Y=yes, PY=partial yes, *N*=no.

Abbreviations: CI=confidence interval, PSG=polysomnography, RCT=Randomized Controlled Trials, REM=rapid eye movement sleep, RLS=Restless Legs Syndrome, SL=sleep latency, SQ=sleep quality, TST=total sleep time, WMD=Weighted Mean Difference.

Sleep latency (SL). Four meta-analysis / systematic reviews reported significant results for improved sleep latency (Bent et al., 2006; Taibi et al., 2007; Shinjyo et al., 2020; Stevinson and Ernst, 2000). Shinjyo et al. (2020) meta-analysis reported that: a) repeated administration of valerian hydroalcoholic extract (600 mg/d before bed time) improved objective SL after two weeks of administration, while no improvement was observed after a single dose; b) healthy volunteers who received a single dose of valerian aqueous extract (450 or 900 mg before bed time) had a reduced SL measured with sleep questionnaires and self-rating scale, while there was no significant difference in objective sleep (Polysomnogram). *V.edulis* administration (20 mg/kg for 2 weeks) in children with intellectual deficit and primary sleep problems, also reduced SL measured by VAS. However, in Shinjyo et al. (2020) meta-analysis there is considerable heterogeneity among the included primary studies, and no meta-analysis was carried out for the SL outcome. Bent et al. (2006) meta-analysis and Stevinson and Ernst (2000) systematic review reported significant improvements in subjective sleep-onset latency (validated sleep questionnaire) of 16.7 min for valerian administration (320 mg/4 days) compared to placebo and superior SL (validated sleep questionnaires and sleep rating scale) by two weeks of valerian administration (3 × 2 capsules *Baldrian Dispert* ®) compared with placebo, respectively. Nonetheless, the findings of the primary studies were contradictory and there was great inconsistency between trials included in the reviews. The systematic review by Taibi et al. (2007) reported that short-term supplementation (one to four nights) of valerian reduced subjective SL in patients with sleep onset insomnia. Three meta-analyses (Fernández-San-Martin et al., 2010; Leach and Page, 2015; Zhang et al., 2023) evaluated the effect of valerian compared with placebo and no significant improvement was found for neither objective (PSG, EEG, wrist actigraphy) nor subjective (sleep questionnaires) SL. Furthermore, a systematic review (Taslaman, 2014), reported that valerian for the treatment of insomnia disorder in adults did not reached statistical significance (cf. Table 2).

Side effects. As to safety and side effect profile, all eight studies reported valerian as a safe herb with no serious adverse events (Bent et al., 2006; Fernández-San-Martín et al., 2010; Leach and Page, 2015; Shinjyo et al., 2020; Stevinson and Ernst, 2000; Taibi et al., 2007; Taslaman, 2014; Zhang et al., 2023). Five meta-analyses (Bent et al., 2006; Fernández-San-Martín et al., 2010; Leach and Page, 2015; Shinjyo et al., 2020; Zhang et al., 2023) and three systematic reviews (Stevinson and Ernst, 2000; Taibi et al., 2007; Taslaman, 2014), reported mild neurological/central nervous system symptoms (e.g., dizziness, headache, drowsiness) and mild gastrointestinal symptoms (i.e., nausea, diarrheia). Only for diarrhea, did three studies report higher frequencies in patients taking valerian. However, Fernández-San-Martin et al. (2010) and Stevinson and Ernst (2000), found no difference between these mild adverse events from those seen with placebo. Also, Shinjyo et al. (2020) found no clear associations between the mild side effects with the valerian treatment, and Taslaman's (2014) systematic review results suggested that mild side effects were more likely to be symptomatic of insomnia. (cf. Table 2).

3.4. Methodological quality of included reviews

Based on the AMSTAR 2 scale (cf. Table 3), 7 of the reviews (87.5 %) were rated as critically low and 1 review (12.5 %) rated as low. When analyzing a single risk area for bias, most systematic reviews have reported weaknesses: not providing a complete list of exclusions and reasons (88 %), not explaining their selection of the studies design for inclusion in the review (100 %), not establishing acceptable research protocols (100 %), and not including gray literature. Some systematic reviews (Shinjyo et al., 2020; Taslaman, 2014) also do not assess, or partially assess, research quality on outcomes; or do not provided analysis of heterogeneity and do not assess publication bias. Also, most systematic reviews do not reported sources of funding for the primary studies included in the review nor the review authors reported any potential sources of conflict of interest when conducting the review.

3.5. Risk of bias assessment

The ROBIS tool was used to assess the RoB of the included systematic reviews. The results of phase 2 were as follows. Domain one, assessed the studies' eligibility criteria. Five articles were ranked with high bias due to inappropriate and ambiguous eligibility criteria. Domain two, assessed the risk of bias of the methods used for studies identification and selection. Three articles were rated as high risk of bias due to limiting the language retrieval to English in included systematic reviews, non-use of adequate terms and search strategy structures to retrieve as many eligible studies as possible. Three reviews were rated as uncertain because they did not report how the selection of studies was carried out. Domain three, assessed the risk of bias on data collection and study appraisal. Five articles were rated as unclear risk of bias because they did not report if the process of data collection and risk of bias assessment involved one or more reviewers. Domain four, assessed the appropriateness of data synthesis methods, and all reviews were rated as unclear risk of bias for this domain due to lack of protocols to confirm appropriateness. Overall, all the eight articles had high risk of bias according to the results of phase three of ROBIS (cf. Table 4 and Fig. 2).

3.6. Corrected covered area (CCA) for valerian systematic reviews

Pertaining to the studies included in the review, the degree of overlap (CCA) was 0.32, which can be considered high overlap. This means a high overlap of the primary studies reviewed among the selected systematic reviews, especially between the oldest reviews and between the two most recent reviews from 2020 to 2023 (Shinjyo et al., 2020; Zhang et al., 2023) (cf. Table S1).

4. Discussion

In our review, evidence on the efficacy and safety of valerian on insomnia was synthesized from 8 SRs/MAs. Overall, the existing evidence suggests no efficacy of valerian for the treatment of insomnia but data suggested that it has a good safety profile with no reported adverse events and mild side effects at the doses investigated (up to > 3000 mg). However, based on all the review papers included, some results were inconsistent. While one meta-analysis and three systematic reviews found no or inconclusive evidence for valerian as a treatment for insomnia, four meta-analysis found that valerian may be useful to improve subjective sleep quality. This is important as the diagnosis of insomnia is based on sleep reported sleep and does not rely on objective measures (Riemann et al., 2023). However, the efficacy of valerian has not been demonstrated using quantitative or objective measurements. Heterogeneity in experimental designs, such as heterogeneity in sample sizes, daily vs. single dosing, dose levels, herbal preparation and outcomes measures, in addition with the poor overall methodological quality, led the authors of most SRs/MAs not to draw firm conclusions. Furthermore, according to the assessment of results of the AMSTAR-2, the included SRs/MAs appear quite heterogeneous and with low methodological quality. Seven (87.5 %) of the eight reviews were rated as critically low and one review (12.5 %) was rated as low. None of the SRs/MAs had registered a preliminary design protocol, which may have led to an increased risk of bias and affecting the rigor of the SRs/MAs. In the case of SRs/MAs, a protocol should be designed and recorded in advance to ensure that the study execution process is methodical. Only the review from Stevinson and Ernest (2000) provided a complete list of excluded studies and justify the exclusions. The remaining SRs/MAs do not provide a complete list which may affect the reliability of the results. Five SRs/MAs (Bent et al., 2006; Fernández-San-Martín et al., 2010; Stevinson and Ernst, 2000; Taibi et al., 2007; Taslaman, 2014; Zhang et al., 2023) did not report any potential sources of conflict of interest,

Table 3
Results of the AMSTAR 2 checklist.

Studies	Q1	Q2*	Q3	Q4*	Q5	Q6	Q7*	Q8	Q9*	Q10	Q11*	Q12	Q13*	Q14	Q15*	Q16	Overall quality
Stevinson et al. (2000)	Y	N	N	PY	N	N	Y	Y	Y	N	–	–	Y	Y	–	N	Low
Bent et al. (2006)	Y	N	N	PY	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Critically Low
Taibi et al. (2007)	N	N	N	PY	N	N	N	Y	Y	N	–	–	Y	Y	–	N	Critically Low
Fernández-San-Martín et al. (2010)	Y	N	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Critically Low
Taslaman (2014)	Y	N	N	PY	N	N	N	Y	N	N	–	–	N	Y	–	N	Critically Low
Leach et al. (2015)	Y	N	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically Low
Shinjyo et al. (2020)	N	N	N	PY	N	N	N	Y	PY	N	N	N	N	N	Y	Y	Critically Low
Zhang et al. (2023)	N	N	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically Low

Note: * AMSTAR 2 critical domains.
Y: yes; PY: partial yes; N: no.
Q1: Did the research questions and inclusion criteria for the review include the components of PICO?.
Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?.
Q3: Did the review authors explain their selection of the study designs for inclusion in the review?.
Q4: Did the review authors use a comprehensive literature search strategy?.
Q5: Did the review authors perform study selection in duplicate?.
Q6: Did the review authors perform data extraction in duplicate?.
Q7: Did the review authors provide a list of excluded studies and justify the exclusions?.
Q8: Did the review authors describe the included studies in adequate detail?.
Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?.
Q10: Did the review authors report on the sources of funding for the studies included in the review?.
Q11: If meta-analysis was performed, did the review author use an appropriate methods for statistical combination of results?.
Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of meta-analysis or other evidence synthesis?.
Q13: Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?.
Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?.
Q15: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?.
Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?.

including any funding they received, which may increase the reporting bias of the study, since the results of company-funded studies may be biased toward the funder. Furthermore, the results of bias assessment showed that all eight articles had high risk of bias. The sources of bias mainly come from study eligibility criteria, identification and selection of studies, study synthesis and findings. The assessment results demonstrates that researchers should use more appropriate study eligibility criteria and data synthesis methods in future systematic reviews.

Heterogeneity. Conflicting findings and inconsistencies between the SRs/MAs lead to a high uncertainty regarding the efficacy of valerian in improving sleep.

Firstly, there is considerable heterogeneity between the reviews: 1) Populations studied ranged from primary to comorbid insomnia, other sleep disturbances, self-reported sleep problems, and varied on intellectual ability. Age groups included in each review varied markedly as well, with some restricted to adults while others had no age restriction and included elderly and children which can present with highly differential complaints. The inclusion of patients with sleep disorders and comorbidities or patients diagnosed with secondary insomnia, involving other etiologies that may not be taken into account with valerian acting only in one of the many pathways involved in sleep regulation. This is the case of primary insomnia with comorbid anxiety, that influence each other, making it difficult to stabilize the effects of valerian on sleep, since it is also used for anxiety disorders, due to its anxiolytic properties

Table 4
Risk of bias assessment.

Review	Phase 2				Phase 3
	Domain 1: study eligibility criteria	Domain 2: identification and selection of studies	Domain 3: data collection and study appraisal	Domain 4: synthesis and findings	Risk of bias in the review
Stevinson et al. (2000)	☹	?	?	?	☹
Bent et al. (2006)	☹	☹	?	?	☹
Taibi et al. (2007)	☺	☹	?	?	☹
Fernández-San-Martín et al. (2010)	☹	☺	☺	?	☹
Taslaman (2014)	☹	?	?	?	☹
Leach et al. (2015)	☺	☹	☺	?	☹
Shinjyo et al. (2020)	☹	?	?	?	☹
Zhang et al. (2023)	☹	☺	☺	?	☹

☺ = low risk; ☹ = high risk; ? = unclear risk

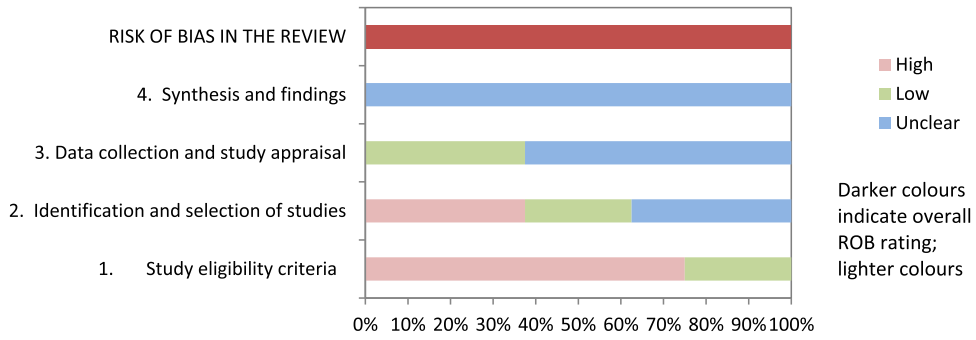

Fig. 2. Results of bias assessment.

(Becker et al., 2014). Furthermore, different diagnosis and different definition of insomnia between studies may also cause clinical heterogeneity. Also, since studies do not differentiate between different types of insomnia symptoms, it is not possible to understand the effectiveness of valerian for sleep initiation versus sleep maintenance symptoms; 2) The dose of valerian administered ranged from 6.4 to 3645 mg and the treatment duration ranged from 1 day to 8 weeks. No current standards exist for an ideal dose or recommended duration of treatment. However, it is commonly recommended that at least two weeks of valerian treatment is required for effects to manifest, but this recommendation has not been specifically investigated (Houghton, 1999). Included SRs/MAs used various types of valerian products (e.g. *V.officianalis, V.edulis*, and *V.wallichi*). The chemical constituents in valerian products vary according to species and extraction methods (Bos et al., 1997; Upton et al., 1999). Valepotriates are common among all three species, suggesting that valepotriates may contribute at least in part to the sleep-promoting activity of valerian, while valerenic acids are specific to *V. officianalis,* but also considered one of the most biologically active constituents of valerian (Bos et al., 1998; Rotblatt and Ziment. 2002). Scientific research suggests that the type of extraction solvent used could have a direct impact on the rate of activity of a metabolizing enzyme, leading to potential differential effects on sleep outcomes (Awad et al., 2007); 3) Outcomes differed between included SRs/MAs. Some reviews used objective measures and other subjective measures to assess the same sleep parameter. In addition, some reviews utilized non validated sleep questionnaires and data resulting from them may be biased, making it difficult to compare the results of different reviews. SQ, SL, and TST were the most frequently evaluated sleep outcomes. Conclusions concerning many other parameters, such as sleep efficiency, wake after sleep onset, and sleep stages, have not been determined. In addition, failure to control confounds, such as pre-bedtime caffeine use or exercise may have enabled such factors to impact results, confounding any possible effects of valerian on sleep.

Secondly, placebo or comparator drugs varied between included SMr/MAs. The review from Taibi et al. (2007) reported no differences between placebo and valerian. As valerian has a very characteristic odor, failure to adequality mask the valerian treatment or "odorize" the comparison treatment may have increased patient expectations that valerian would be effective. Recently, research has shown that several factors can influence the placebo effect, including, for example, the size of the placebo pill, the larger the pill the greater the expectancy effect (Guevarra et al., 2020; Robson, 2022). Furthermore, even an "honest placebo" can produce effects and even valid benefits (Guevarra et al., 2020; Robson, 2022; Eccles, 2007). Stevinson and Ernst (2000) found no difference between the mild adverse events seen with valerian preparations from those seen with placebo. One possible explanation is that people who take placebos not only feel the benefits of the medicine they think they are receiving, but can also report side effects, the so-called "nocebo effect" (Robson, 2022).

Implications of findings. We believe that the practical and clinical value of this umbrella review goes beyond a summary of valerian's effectiveness for sleep, given the importance and relevance of valerian in primary health care and child psychiatry. The results of our review meet the recommendations and conclusions of AASM and ESRS guidelines: valerian does not have support for sleep disturbances, in particular, insomnia. Even so, valerian continues to be often prescribed by general practitioners, psychiatrists and even by pediatricians, since sleep problems are quite prevalent in children, adolescents and young adults (Silva et al., 2021). According to a national sample of psychiatrists, members of the American Academy of Child and Adolescent Psychiatry, 96% responded that they recommended at least one prescription medication to children and adolescents for the treatment of insomnia in a typical month, and 88% recommended at least one OTC medication. These recommendations were self-reported as part of the clinician's routine practice (Badin et al., 2016). Furthermore, the demand for herbal medicines has increased drastically in the last few years, leading the pharmaceutical industry and the world market for such medicines to reach $60 billion USD (Kartal, 2007). Valerian is commonly marketed as a dietary supplement, not requiring a medical prescription or being subject to the same rigorous safety controls or pharmacovigilance to get regulatory / FDA approval. These factors are certainly at the base of the constant dissemination and commercialization of valerian for sleep, despite their apparent ineffectiveness, and also contribute to the lack of investment and interest from pharmaceutical companies, in carrying out stringent studies, especially RCTs, given the high cost involved and the uncertainty of return on investment (Anquez-Traxler, 2011). Future studies should address the need to investigate dietary supplements such as valerian in order to understand the effects of each of the constituents, their efficacy, appropriate dosage and safety.

Strengths and Limitations. One of the strengths of our paper is that it summarizes existing data on the effect of valerian on insomnia. Furthermore, the methodology of our study was based on the guidelines provided by PRISMA and JBI and on relevant umbrella reviews that served as a model (Low et al., 2020; Moncrieff et al., 2022). A careful review of the primary papers included in the reviews was performed in order to define the real number of participants that inform the outcomes relevant to our umbrella review question. Further, we independently assessed included reviews for both risk of bias and methodological quality (Perry et al., 2021).

Limitations of this umbrella review can be divided in two major classes. First, limitations partially justified with methodological constraints of an umbrella review. Even though an umbrella review has a lot of potential through its ability to provide a summary of existing research syntheses, it is still exposed to weaknesses that derive essentially from a lack of clarity in approaching heterogeneity amongst the included reviews such as inconsistencies in outcomes, interventions and methods. Because of the high heterogeneity between the included SRs/MAs and since there are no specific statistical tools to quantify heterogeneity in an umbrella review, we did not perform quantitative synthesis/meta-analysis. Nevertheless, "the principle focus of an Umbrella Review is to provide a summary of existing research syntheses related to a given topic or question and not to re-synthesize, for example, the results of

existing reviews or syntheses with meta-analysis or meta-synthesis" (Aromataris. 2020). Furthermore, how to deal with the overlapping of primary studies between included SRs/MAs, is a remaining question, even though we have performed the CCA calculation to ascertain the actual degree of overlap in our overview, as recommended (Pieper et al., 2014).

Secondly, limitations arising from low quality studies and heterogeneity. Only eight SRs/MAs were included and had small sample sizes, yet, relevant umbrella reviews, published in peer-reviewed journals, included fewer than eight papers for analysis (Drozd et al., 2022; Huang et al., 2020). Also, based on the AMSTAR 2 scale, 7 (87.5 %) of 8 reviews were rated as "critically low" and 1 review (12.5 %) rated at "low". Further, results from ROBIS assessment showed high risk of bias in all SRs/MAs. Nevertheless, even though the studies may be of low quality, we use the best available evidence on the subject, while warning of serious flaws in the literature on this topic. Furthermore, the included reviews suffer from wide heterogeneity such as small sample sizes, different experimental design, subjective data, different duration, preparation and dosage of treatment and limiting clinical applicability of the results.

5. Conclusion

In summary, valerian seems not have support for insomnia even though it may be considered safe. Yet, one should note that there is very low quality evidence to suggest no effect of valerian on sleep outcomes Moreover, valerian appears to have some limited efficacy for subjective improvement of sleep quality, although its effectiveness has not been demonstrated with objective measurements. Further studies, in particular RCTs, are highly recommended since there are scarce studies and the existing ones are quite heterogeneous and with low methodological quality. We consider that this umbrella review has a great practical potential in the case of clinical practice, in which all disease management options need to be considered before making a decision, providing a summary of the breadth of relevant research on valerian for sleep and possible reasons for the contradictory findings between included SRs/MAs (Tsagris and Fragkos, 2016). A consensus on the pertinent outcome measures and the best way to define them with operationalized criteria would be informative for future studies. Future valerian efficacy studies need to consider the type of valerian products, dosage and treatment duration in improving sleep parameters in addition to the importance of confounding factors.

CRediT authorship contribution statement

Valéria Valente: Formal analysis, Investigation, Data curation, Writing – original draft. **Daniela Machado:** Validation. **Susana Jorge:** Validation. **Christopher L. Drake:** Writing – review & editing. **Daniel Ruivo Marques:** Conceptualization, Methodology, Writing – original draft, Supervision.

Declaration of competing interest

None.

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Supplementary materials

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