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THE EFFECT OF HERBAL SUPPLEMENTS ON THE SEVERITY OF ANXIETY AND INSOMNIA SYMPTOMS IN ADULTS WITH GENERALIZED ANXIETY DISORDER OR INSOMNIA: A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS

by

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Author's Contribution Statement

I certify that I am the author of this thesis and that any assistance I have had in its preparation is fully acknowledged and referenced in the following text. I have also cited any sources from which I have used data, ideas or words, whether they are quoted exactly or paraphrased. I also certify that this thesis was prepared by me personally specifically for the requirements of obtaining a Master's degree in Lifestyle Medicine by the University of Thessaly. I declare that I will respect co-authorship rights in any linked scientific publication and/or presentation stemming from this thesis, in accordance to my signed affirmation, and in respect of the principles of ethics in research. Likewise, I declare I will recognize any funding sources and will acknowledge my affiliation to the University of Thessaly during the preparation of this work in any future presentation.

Razan Abou Assaf

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Abstract

Introduction: This systematic review aimed to study the effect of different types and dosages of herbal supplements on the severity of anxiety and insomnia symptoms in adults with clinical diagnosis of either Generalized Anxiety Disorder (GAD) or Insomnia.

Aims: This systematic review aims to investigate the effects of various herbal supplements on the severity and frequency of anxiety and insomnia symptoms in adults diagnosed with GAD or insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria as determined by clinicians. By examining the current literature, this review seeks to provide a comprehensive overview of the potential benefits and limitations of herbal supplements as an alternative treatment option for these common mental health disorders, by assessing randomized control trials (RCTs) that assess the effect of herbs on GAD and insomnia to provide insight for future research in this field.

Methodology: A comprehensive search of the PubMed database was conducted from inception to May 2024, focusing on randomized clinical trials (RCTs) that examined the effects of herbal supplements on GAD and insomnia. Studies were included if they assessed herbal treatments versus placebo or conventional medications, with outcomes measured using clinical scales like the Hamilton Anxiety Scale (HAM-A) and polysomnography. The risk of bias was evaluated using the Cochrane risk of bias tool.

Results: Thirteen RCTs were included, comprising studies on Passionflower, German Chamomile, Galphimia Glauca, Lavender, Ashwagandha, Valerian, and Kava. Findings indicated that Passionflower improved total sleep time and sleep efficiency in insomnia patients, but subjective measures showed no significant difference from placebo. German Chamomile reduced HAM-A scores in GAD patients, but other anxiety measures were not significantly affected. Galphimia Glauca has a comparable efficacy to lorazepam in reducing anxiety with fewer side effects. Lavender showed potential benefits in improving sleep parameters and reducing postmenopausal symptoms. Ashwagandha significantly improved sleep and reduced anxiety in both healthy individuals and those with insomnia. Valerian demonstrated anxiolytic effects like diazepam, with good tolerability. And Kava reduced anxiety symptoms comparable to conventional medications like Buspirone and Opipramol, though further research is needed to confirm long-term efficacy and safety.

Discussion: According to the comprehensive analysis, herbal treatments show potential as alternative treatments for anxiety and insomnia, with some demonstrating efficacy

comparable to conventional medications, and high tolerability rate. However, limitations such as small sample sizes and methodological variations necessitate further rigorous research to establish their clinical utility and safety profiles.

Keywords: anxiety, anxiolytic, insomnia, sedative, “herbs scientific names”, “herbs common names”

Abstract [Arabic]

مقدمة: تهدف هذه المراجعة المنهجية إلى دراسة تأثير الأنواع والجرعات المختلفة للأعشاب على شدة أعراض القلق والأرق لدى البالغين الذين يعانون من التشخيص السريري لاضطراب القلق العام (GAD) أو الأرق.

الأهداف: تهدف هذه المراجعة المنهجية إلى دراسة آثار المكملات العشبية المختلفة على شدة وتواتر أعراض القلق والأرق لدى البالغين الذين تم تشخيصهم باضطراب القلق العام أو الأرق وفقًا لمعايير الدليل التشخيصي والإحصائي للاضطرابات العقلية (DSM) على النحو الذي يحدده الأطباء. تسعى هذه المراجعة إلى تقديم نظرة شاملة عن الفوائد والقيود المحتملة للمكملات العشبية كخيار علاج بديل لهذه الاضطرابات الصحية العقلية الشائعة، من خلال تقييم التجارب العلمية (RCTs) التي تقيم تأثير الأعشاب على القلق والأرق لتوفير نظرة ثاقبة للبحث المستقبلي في هذا المجال.

المنهجية: تم إجراء بحث شامل في قاعدة بيانات PubMed منذ البداية وحتى مايو 2024، مع التركيز على التجارب العلمية السريرية العشوائية (RCTs) التي فحصت آثار المكملات العشبية على اضطراب القلق العام والأرق. تم مقارنة الدراسات إذا قاموا بتقييم العلاجات العشبية مقابل العلاج الوهمي أو الأدوية التقليدية، مع قياس النتائج باستخدام المقاييس السريرية مثل مقياس هاملتون للقلق (HAM-A) وتخطيط النوم. تم تقييم خطر التحيز باستخدام أداة كوكرين لخطر التحيز.

النتائج: تم تضمين ثلاثة عشر تجربة، تشمل دراسات على passionflower، والبابونج الألماني، Galphimia Glauca، واللافندر، ashwagandha، valerian، kava. أشارت النتائج إلى أن passionflower تحسن إجمالي وقت النوم وكفاءة النوم لدى مرضى الأرق، لكن التقييم الذاتي لم تظهر أي اختلاف كبير عن العلاج الوهمي. قلل البابونج الألماني من درجات HAM-A لدى مرضىGAD ، لكن المقاييس القلق الأخرى لم تتأثر بشكل كبير. يتمتع Galphimia Glauca بفعالية مماثلة Lorazepam في تقليل القلق مع آثار جانبية أقل. أظهر اللافندر فوائد محتملة في تحسين معايير النوم وتقليل أعراض ما بعد انقطاع الطمث. تحسنت ashwagandha بشكل كبير من النوم وتقليل القلق لدى الأفراد الأصحاء والذين يعانون من الأرق. أظهر نبات valerian تأثيرات مزيلة للقلق مشابهة diazepam، مع قدرة تحمل جيدة. وقد خفضت kava أعراض القلق مقارنة بالأدوية التقليدية مثل Buspirone وOpipramol، على الرغم من أن هناك حاجة إلى مزيد من الأبحاث لتأكيد فعاليتها وسلامتها على المدى الطويل.

المناقشة: وفقا للتحليل الشامل، تظهر العلاجات العشبية إمكانية استخدامها كعلاجات بديلة للقلق والأرق، مع إظهار بعضها فعالية مماثلة للأدوية التقليدية، ومعدل تحمل مرتفع. ومع ذلك، فإن القيود مثل أحجام العينات الصغيرة والاختلافات المنهجية تتطلب المزيد من البحث الدقيق لتحديد فائدتها السريرية وملامح السلامة.

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List of abbreviations

GAD: Generalized Anxiety Disorder

TST: Total Sleep Time

DSM: Diagnostic and Statistical Manual of Mental Disorders (DSM)

IG: Intervention Group

PSG: Polysomnography

ISI: Insomnia Severity Index

PSQI: Pittsburgh Sleep Quality Index

SE: Sleep Efficiency

WASO: wake after sleep onset

CES-D: Center for Epidemiologic Studies Depression Scale

BAI: Beck Anxiety Inventory

GARS: Global Assessment of Recent Stress Scale

HAM-A: Hamilton Anxiety Rating Scale

DSM; SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders

PGWBI: Psychological General Well-Being Index

GAD-7: Generalized Anxiety Disorder Assessment

CGI-I: clinical global impression – improvement scale

PGE: Patient Global Evaluation

HAM-D: Hamilton Depression Scale

MADRS: Montgom-ery–Asberg Depression Rating Scale

MINI: The Mini-International Neuropsy-chiatric Interview

SIGH-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale

PSWQ: Penn State Worry Questionnaire

WHOQOL: World Health Organization Quality of Life

K-10: Kessler Psychological Distress Scale

ASEX: Arizona Sexual Experiences Scale

BOEAS: Boerner Anxiety Scale

SAS: Self-Rating Anxiety Scale

Bf-S: Self-rating scale for well-being

SF-B: Sleep questionnaire

1. Introduction

In modern society, people suffer from various psychiatric disorders, particularly anxiety and insomnia, which have profound effects on both individuals and society. Generalized Anxiety Disorder (GAD) and insomnia are two of the most prevalent mental health disorders affecting the adult population. According to the American Psychiatric Association, "Generalized anxiety disorder involves persistent and excessive worry that interferes with daily activities. This ongoing worry and tension may be accompanied by physical symptoms, such as restlessness, feeling on edge or easily fatigued, difficulty concentrating, muscle tension or problems sleeping. Often the worries focus on everyday things such as job responsibilities, family health or minor matters such as chores, car repairs, or appointments" (American Psychiatric Association, 2022). While health professionals define insomnia as "trouble falling asleep, staying asleep, or getting good quality sleep" (National Heart, 2022), which significantly impacts daily functioning and overall quality of life. Evidence suggests that each condition can make the other worse, and there is a well-established link between GAD and insomnia. This bidirectional relationship can lead to a vicious cycle where anxiety increases sleep disturbances, and poor sleep further heightens anxiety levels (Cox & Olatunji, 2016). Conventional medications for GAD and insomnia, such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs), are generally effective but are often associated with significant side effects and the risk of dependency (Baldwin et al., 2013). As a result, there has been a growing interest in complementary and alternative medicine (CAM), including herbal supplements. These supplements are gaining attention due to their lower cost, natural origins, and perceived minimal side effects compared to traditional pharmaceuticals. Herbal supplements such as valerian root, kava, lavender, and passionflower have been traditionally used to alleviate symptoms of anxiety and insomnia. However, the scientific evidence supporting their efficacy and safety remains underexplored. This systematic review aims to investigate the effects of various herbal supplements on the severity and frequency of anxiety and insomnia symptoms in adults diagnosed with GAD or insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria as determined by clinicians. By examining the current literature, this review seeks to provide a comprehensive overview of the potential benefits and limitations of herbal supplements as an alternative treatment option for these common mental health disorders, by assessing randomized control trials (RCTs) that assess the effect of herbs on GAD and insomnia to provide insight for future research in this field.

2. Aims – Significance

The primary aim of this systematic review was to evaluate the effectiveness of herbal supplements in alleviating symptoms of anxiety and insomnia in adults diagnosed with Generalized Anxiety Disorder (GAD) or Insomnia. Several systematic reviews studied the effect of herbs on anxiety and insomnia, but to date, no review was conducted to investigate the effect of herbal treatment on clinically diagnosed patients with GAD or insomnia exclusively, which will help health providers to access evidence-based data to recommend herbal treatments. The review focuses on herbal treatments as potential alternatives to pharmaceutical interventions. The study aims to provide valuable insights into the efficacy of natural remedies in managing these common mental health conditions. The research questions guiding this systematic review include: What types of herbal supplements show promise in reducing symptoms of anxiety and improving sleep quality in individuals with GAD or Insomnia? How do herbal treatments compare to traditional pharmaceutical interventions in terms of effectiveness and safety for managing anxiety and insomnia? What gaps exist in the current literature regarding the use of herbal supplements for mental health conditions, and what recommendations can be made for future research in this area?

Through a comprehensive analysis of randomized controlled trials (RCTs) meeting predefined inclusion criteria, this review aims to synthesize existing evidence on the efficacy of herbal treatments, particularly in comparison to standard pharmaceutical approaches in patients diagnosed with GAD and insomnia according to DSM criteria for mental health conditions. By examining objective outcomes such as anxiety levels measured by the Hamilton Anxiety Rating Scale (HAMA) and objective sleep assessments using polysomnography.

In conclusion, the findings of this review could inform clinical practice by guiding healthcare providers in recommending evidence-based treatments for patients with GAD or Insomnia, where healthcare providers may be able to offer cost-effective and potentially safer treatment options for individuals. This approach could help reduce the financial burden associated with long-term medication use and minimize the risk of dependency on conventional drugs, which may contribute to improving the overall quality of life for patients with fewer side effects offering patients a holistic approach to managing their mental health conditions, potentially leading to enhanced well-being and improved daily functioning.

3. Literature Review

Generalized anxiety disorder (GAD) and insomnia are prevalent mental health issues affecting millions worldwide. Traditional pharmacological treatments often come with side effects, leading to a growing interest in alternative therapies, particularly herbal remedies due to their perceived safety and effectiveness. Systematic reviews and meta-analyses literature on the use of herbal remedies for sleep, insomnia, and anxiety have generated a considerable body of literature. Despite this, the heterogeneity of herbal treatments and the generally small sample sizes of the studies limit the conclusiveness of these reviews. This underscores the necessity for further research, particularly focused on the effects of herbs on clinically diagnosed generalized anxiety and insomnia according to international criteria such as DSM. Clinical diagnoses provide greater precision compared to self-reported episodic or situational anxiety or sleep disturbances, which are often prone to misdiagnosis, potentially being incorrectly labelled as insomnia or anxiety disorders. Therefore, rigorous studies employing clinical settings and objective measurements of sleep and anxiety are essential to yield more reliable conclusions about the efficacy of herbal treatments in these specific contexts. Among the herbal treatments that have been subjected to systematic reviews to evaluate their efficacy is Passionflower (Passiflora incarnata), Passionflower has been traditionally used for its sedative and anxiolytic properties. A systematic review of clinical trials investigating Passionflower's efficacy in anxiety and sleep disorders (Miroddi et al., 2013)concluded that Passionflower showed significant anxiolytic and sedative effects in addition of having a goof safety profile, However, the review highlighted the limitations observed in the clinical trials studying passionflower efficacy like undefined drug extract ratio, limited sample size, unclear blinding and randomisation procedure, unknown placebo, and lack of proper analysis of the outcome. In a recent review studying the effects of ashwagandha on stress and stress related neuropsychiatric disorders including anxiety and insomnia, the results showed that there is numerous animal models and clinical studies demonstrating the remarkable anti-stress and anti-anxiety activity of extracts derived from ashwagandha leaf or root, with few studies reflecting positive effects on sleep quality (Speers et al., 2021). However, the limitations addressed in this review, was that the severity of the conditions that respond to ashwagandha has not yet been determined, nor has the best extraction technique and dosage to treat any or all these disorders, suggesting further studies to be conducted on the relationship between chemical content and biological activity and mechanism of

ashwagandha. On the other hand, Valerian treatment has been proposed that it may help with subjective sleep quality and that more than one dose is needed to produce noticeable results (Shinjyo et al., 2020), and the findings indicated that more consistent results could be anticipated from the entire root or rhizome. Moreover, therapeutic benefits may be enhanced when valerian is combined with other herbal supplements, in addition of showing no severe adverse events, which appears to be a safe and effective herb for improving sleep quality and preventing related disorders. However, given the multiple active constituents of valerian herb and the unstable nature of some of these compounds, more studies should investigate the quality control of this herbal treatment including standardization methods and shelf-life assessment. Melissa officinalis, commonly known as lemon balm, has been extensively studied for its therapeutic potential. In a systematic review and meta-analysis for randomized controlled trials assessing the efficacy of lemon balm in alleviating anxiety and depression (Ghazizadeh et al., 2021), reveals through meta-analysis that lemon balm significantly improved mean anxiety and depression scores compared to placebo, without serious adverse effects. However, the study faced high risk of heterogeneity and included data from a limited number of clinical trials, indicating a need for further research with larger and more homogeneous sample sizes. A recent systematic review and meta-analysis investigated several medicinal herbs for the treatment of anxiety, and a total of 29 trials were reviewed to compare 12 medicinal herbs (Zhang et al., 2022). Lavender herbal treatment known as Silexan showed a significant effect on anxiety, and possibly benefitted the treatment of insomnia. In addition to Kava, prepared from the root of Piper methysticum, showed efficacy and more tolerability compared with a placebo and standard treatments, with a moderate number of samples of patients suffering from anxiety. However, compared to placebo, Kava efficacy was not statistically significantly in patients with generalized anxiety disorder or diagnosed anxiety. Conducting a conclusive systematic review of herbal treatments for generalized anxiety disorder (GAD) and insomnia presents significant challenges. Many clinical trials, including randomized controlled trials (RCTs), exhibit a high risk of bias due to numerous limitations. Common issues include incomplete randomization and blinding data, undefined placebo controls, and variability in dosage regimens for herbal interventions. These deficiencies complicate the analysis and interpretation of study outcomes. The variability in dosage and duration of herbal treatments remains a critical area underexplored in the existing literature. This inconsistency hinders the establishment of standardized treatment protocols and limits the generalizability of findings. Additionally,

the pharmacokinetics and pharmacodynamics of many herbal compounds are not well understood, further complicating dosage optimization. To address these limitations, there is an urgent need for more rigorously designed RCTs. Future studies should emphasize transparent reporting of randomization and blinding processes, clearly define placebo controls, and establish standardized dosages and treatment durations. Such measures will enhance the reliability of the data and facilitate more robust conclusions regarding the efficacy of herbal treatments for GAD and insomnia. Moreover, exploring the long-term effects and safety profiles of these interventions is crucial for their potential integration into clinical practice.

In psychiatric research, structured or semi-structured diagnostic interviews, such as the Composite International Diagnostic Interview (CIDI) or the Structured Clinical Interview for DSM-5 (SCID), are considered the "gold standard" for determining disorder diagnoses. However, because clinical trials aim for large sample sizes, researchers often prefer self-reporting data over clinical interviews or clinical diagnosis procedures, which are expensive and time-consuming (Davies et al., 2022). This results in the use of self-reported questionnaires, which are less expensive and time-efficient but have a high risk of bias and less reliable outcome measurements. These methods often yield inconclusive results that cannot be classified as evidence-based data. One study addressed some of these limitations by evaluating the comparability of commonly used remote diagnostic methods for depression and anxiety disorders in research. It revealed that, for anxiety disorders, most participants were classified as having GAD based on self-reported diagnoses, while symptom-based diagnoses distributed participants more evenly across the anxiety disorders (Davies et al., 2022). Additional verification using gold standard metrics is necessary to ensure the validity and reliability of these findings. Another study, aimed at studying the relationship between objective and subjective sleep measurements, comparing polysomnography measurements to self-reporting questionnaire, and the study highlights a significant discrepancy between self-reported and objectively measured sleep times. It reveals that individuals tend to overestimate their total sleep times both habitually and after a polysomnography (PSG) session. While estimates of Sleep Onset Latency (SOL) are somewhat more accurate, discrepancies are still present. This suggests that subjective assessments of sleep times may not align well with objective measurements, indicating that studies relying solely on self-reported data may not be directly comparable to those using objective methods (Silva et al., 2007).

In conclusion, while self-reported data in mental health research offers practical benefits, it is crucial to acknowledge its limitations. The discrepancies between self-reported and objective measures underscore the importance of using validated diagnostic methods and objective assessments to ensure the reliability and accuracy of research findings.

4. Methodology

4.1. Searching and Selection Processes

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Cochrane Library handbook. Studies were identified using PubMed, and by examining the references listed in the relevant papers to identify additional studies that may have been missed during the initial database searches. The database was thoroughly scanned for studies from all available years up to May 2024. A systematic search of human trials using the terms: "(Passionflower or Passiflora incarnata) OR (ashwagandha or withania somnifera) OR (Rhodiola or Rhodiola rosea) OR (Tulsi Holy Basil or Ocimum tenuiflorum) OR (Schisandra or Schisandra chinensis) OR (Siberian Ginseng or Eleutherococcus senticosus) OR (Skullcap or Scutellaria lateriflora) OR (Ginkgo or Ginkgo biloba) OR (Bacopa or Bacopa monnieri) OR (Lemon Balm or Melissa officinalis) OR (German Chamomile or Matricaria recutita) OR (Lavender or Lavandula angustifolia) OR (Gotu Kola or Centella asiatica) OR (Rosemary or Rosmarinus officinalis) OR (Blue Vervain or Verbena hastata) OR Motherwort or Leonurus cardiaca) OR (Hops or humulus lupulus) OR (Kanna or Sceletium tortuosum) OR (Galphimia or Galphimia glauca) OR (Saffron or Crocus sativus) OR (Curcumin or Curcuma longa) OR (St. John's wort or Hypericum perforatum) OR (Valerian or Valeriana officinalis) OR (Californian poppy or Eschscholzia californica) OR (Magnolia Bark or Magnolia Officinalis) OR (Lotus or Nelumbo nucifera) OR (Drumstick tree or Moringa oleifera) OR (KAVA KAVA or Piper methysticum) OR (Yuan Zhi or Polygala tenuifolia) OR (Bitter Orange or Citrus aurantium), AND (Anxiety OR Anxiolytic OR Sedative OR Insomnia OR Restlessness).

4.2. Study Inclusion and Exclusion Criteria

This systematic review included any interventional randomized clinical trials assessing the efficacy of the above-mentioned herbal treatment versus placebo or other pharmaceutical treatments or medications for generalized anxiety disorder or Insomnia in human adults diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), and who completed pre- and post-intervention outcome measures. The effectiveness of the herbal treatments should be measured using clinical outcome measures such as Hamilton Anxiety Scale (HAM-A) for anxiety and polysomnography for insomnia as primary outcome. Exclusion criteria included any type of study other than RCTs, any other language than English, and studies that measures anxiety or insomnia in

subjective scales as primary outcome. The eligibility criteria for participant inclusion in this systematic review were defined according to the PICOS framework as follows: The population/problem (P) includes both female and male individuals of all races and ethnicities, aged between 18 and 70 years, who had received a clinical diagnosis of Generalized Anxiety Disorder or Insomnia based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. The intervention/exposure (I) under investigation was herbal treatment, while the comparison/control (C) group included individuals receiving a placebo, medication, or pharmaceutical treatment. The primary outcome (O) measures included the Hamilton Anxiety Rating Scale (HAMA) and objective assessments such as Polysomnography or actigraphy, with secondary outcomes involving self-reporting questionnaires to evaluate sleep quality and anxiety levels. Lastly, the study design (S) focused exclusively on Randomized Control Trials (RCTs) to ensure rigorous methodology and reliable data analysis in assessing the efficacy of herbal treatments for Generalized Anxiety Disorder and Insomnia.

4.3. Materials

4.3.1. Risk of bias assessment

The revised Cochrane Collaboration's risk of bias tool (RoB 2) was used to assess the risk of bias for the included randomized controlled trials studies (Sterne et al., 2019).The domains assessed through this tool are: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective reporting. For randomization, blinding, and allocation concealment, the word "randomization" or "double-blinded" mentioned in the title or abstract without elaborating in the study protocol was considered of high risk of bias in that domain.

4.3.2. Data Extraction Strategy

In this systematic review, data were extracted from interventional studies, specifically randomized controlled trials (RCTs), that satisfied the predefined inclusion criteria. The primary focus was on adult participants diagnosed with insomnia or generalized anxiety disorder (GAD) as per DSM criteria, both male and female subjects. The interventions under consideration included herbal treatments compared to pharmaceutical treatments,

medications, or placebo. The data extraction process involved the comprehensive collection of study characteristics (title, authors, publication year, country of study), participant demographics (number of participants, age, diagnostic criteria), details of the interventions (type of herbal treatment, type of pharmaceutical treatment or medication, placebo details), and outcome measures. The primary outcomes were objective assessments of anxiety using the Hamilton Anxiety Rating Scale (HAMA) and polysomnography for insomnia. Secondary outcomes included subjective scales evaluating anxiety and insomnia. Data sources were confined to published articles retrieved from PubMed. The search strategy was formulated using appropriate keywords and Boolean operators (“AND” "OR" "NOT") to ensure a comprehensive search. The data extraction process followed a systematic approach: an initial search on PubMed using predefined keywords, identifying potential studies, followed by a screening of titles and abstracts to assess relevance based on the inclusion criteria. Full texts of articles eligible studies were then retrieved and subjected to another review to confirm adherence to the inclusion criteria. Articles with undefined or unclear protocols, such as unknown placebos, were excluded from the review. Studies meeting all inclusion criteria were incorporated into the final analysis.

4.3.3. Data Synthesis and Presentation

Due to the heterogeneous nature of the interventions, encompassing various types of herbs and dosages, data pooling was unfeasible. Consequently, data were synthesized by summarizing and categorizing the studies according to intervention type and measured outcomes to facilitate comprehension of the interventions, as illustrated in Table 1.

4.3.4. Evidence of Effectiveness

The evaluation of the certainty of the evidence should consider several factors: the precision of the synthesis findings which includes confidence intervals if available, the total number of participants and number of studies, the consistency of effects across studies, the risk of bias within the studies, the directness of the studies in addressing the population, intervention, comparator, and outcome (PICO), and the risk of publication bias. GRADE (Grading of Recommendations, Assessment, Development and Evaluations) is the most widely utilized framework for assessing certainty, as outlined in the Cochrane Handbook. However, conducting a GRADE analysis would have been

challenging for the following reasons, first reason for not employing GRADE in this review is the limited number of studies available for each herbal supplement. GRADE analysis benefits from a substantial body of evidence, where findings can be compared and synthesized to provide robust estimates of effect. However, this systematic review included only thirteen randomized clinical trials (RCTs) across several different herbal treatments. For most individual herbs, the number of studies was too small to facilitate meaningful comparison and synthesis required for GRADE (Guyatt et al., 2008) Heterogeneity of Studies is another reason, since there was considerable heterogeneity in the types of herbal interventions, dosages, and outcome measures. This variability makes it difficult to combine results and assess overall evidence quality systematically. For GRADE, consistency across studies is crucial, and the heterogeneity observed here undermines this requirement (Guyatt et al., 2011). And inadequate statistical reporting in many studies, such as risk ratios, confidence intervals, or relative effect sizes, are crucial for GRADE assessment. The absence of detailed statistical reporting and the reliance on p-values without comprehensive descriptive statistics hinders the ability to accurately assess the precision and consistency of the evidence (Balshem et al., 2011).

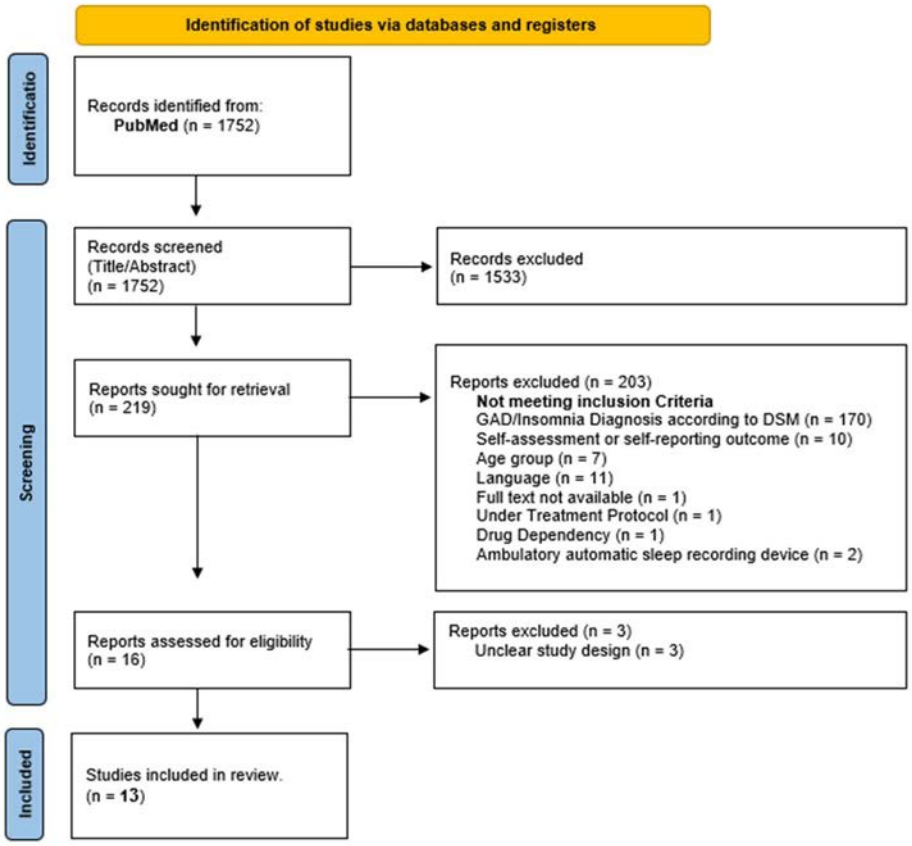
Given the above limitations, the narrative data synthesis approach was a more suitable method for summarizing and interpreting the diverse and limited evidence available. This approach allows for a more qualitative and context-specific understanding, which is particularly valuable when dealing with a heterogeneous body of literature. To ensure a rigorous evaluation of the included studies, we employed the revised Cochrane Collaboration's risk of bias tool (RoB 2). This assessment is critical in the absence of GRADE and offers a robust method to gauge the reliability of the findings. Given the constraints of the dataset, including the limited number of studies per intervention, significant heterogeneity, and in-adequate statistical reporting, conducting a GRADE analysis would have been difficult and might not have yielded meaningful insights. The narrative synthesis combined with a risk of bias assessment was a more appropriate and effective approach for this review.

5. Results

5.1. Results of Searching and Selection Processes

As detailed in Graph 1., 1752 articles were identified from database searches. After a preliminary screening of titles and abstracts, 1533 articles were excluded as they comprised in vitro studies; animal studies; reviews; analysis of the herbs and its constituents; production, processing, and preparation of the herbs; and not meeting the inclusion criteria. 219 full-text articles were assessed for eligibility. After the full-text screening of articles, 13 studies were identified as eligible for inclusion in this systematic review. Several articles related to specific herbs did not meet the inclusion criteria set for this systematic review. Additionally, for some herbs, there were no randomized controlled trials (RCTs) available. Consequently, these studies were excluded from the final analysis to maintain the integrity and rigor of the review process, leaving no leaving no studies that referred to these specific herbs.

Figure 1. PRISMA flow chart for the study selection



5.2. Characteristics of Included Studies

Of the 13 trials identified in this review, the effects of several herbal treatment were investigated on insomnia disorder (4 studies), generalized anxiety disorder (9 study), and no studies found that examined generalized anxiety disorder symptoms and insomnia symptoms where the outcome is objective. There were 5 randomized, double-blind, placebo-controlled studies, 6 randomized double-blind controlled trials, 2 double-blind, randomized, parallel-group, placebo-controlled. The detailed characteristics of the studies included in this review were listed in (Table 1.)

Table 1. Characteristics of included studies

Author (Year)	Country	Participants			Study Design	Intervention		Methods of Assessing	Main outcome	Secondary outcome	Results
		Diagnosis	Sample Size	Age/ Mean Age		Duration	Type/ Dosage				
(Lee et al., 2020)	Korea	Insomnia disorder according to the DSM-V	IG: n= 55 Analyzed = 45 Placebo: n= 55 Analyzed = 39 Total = 110	18–59 years 40.47±11.68	Randomized, double-blind, placebo-controlled trial	2 weeks	IG: Passiflora incarnata extract 60 mg Capsule Placebo: soybean oil	PSG Sleep Diary	PSG - TST	Sleep Diary ISI PSQI CES-D Safety Tolerability	**TST** was significantly increased in the Passionflower group compared with placebo. **SE** showed a trend of improvement in the passionflower group compared with the placebo group. **ISI and PSQI** did not show any significant difference between the Passionflower group and the placebo group. **CES-D, BAI, and GARS** showed no significant difference compared with the placebo group. No serious adverse events (AE)
(Akhondzadeh et al., 2001)	Iran	GAD according to the DSM-IV (HAM-A) ≥ 14	IG: n= 18 Analyzed = 16 Placebo: n= 18 Analyzed = 16 Total = 36	19–47 years	Randomized, double-blind, controlled trial	4 weeks	IG: Passiflora extract 45 drops/day plus placebo tablet IG 2: Oxazepam 30 mg/day plus Passiflora drop	HAM-A	Reduction in HAM-A score	Impairment of job performance	**HAM-A score:** No significant difference in efficacy was observed between the two treatments. **Impairment of job performance** improved in passionflower group.
(Amsterdam et al., 2009)	USA	GAD according to the DSM-IV; SCID HAM-A ≥ 9	IG: n= 28 IG-2: n= 29 Total = 57	25-67 years	Randomized, double-blind, placebo-controlled study	8 weeks	IG: Chamomile capsule 220mg - 1100mg daily capsule Placebo: lactose monohydrate NF 1 to 5 capsules daily	HAM-A BAI PGWB CGI/S	Reduction in HAM-A scores	BAI PGWB CGI/S Proportion of patients achieving a ≥50% reduction in baseline HAM-A score.	**Mean total HAM-A score:** Significantly greater reduction during chamomile versus placebo therapy. **No statistically significant differences observed between treatment groups in any secondary outcome measure (BAI, PGWB, CGI)** **≥50% reduction in baseline HAM-A score**: A higher proportion of patients in the chamomile group achieved compared to the placebo group.
(Herrera-Arellano, A. et al., 2007)	Mexico	GAD according to	IG: n= 72 Analyzed = 55	18-65 years	Randomized, double-blind controlled	4 weeks	Intervention Group: 310 mg of dried	HAM-A	HAM-A	CGI PGE Tolerability	Both Treatments significantly lowered **HAM-A, CGI, and PGE.** **Safety** in both was 100%

		the DSM-IV HAM-A ≥ 19	IG-2: n= 80 Analyzed = 59 Total = 152		clinical study		aqueous G. glauca extract twice a day Control: 1 mg lorazepam			Safety	Lorapezam treatment showed more cases of **excessive sedation** than G. glauca treatment.
(Herrera-Arellano, Armando et al., 2012)	Mexico	GAD according to the DSM-IV HAM-A ≥ 20 HAM-D ≤ 16	IG: n= 94 Analyzed = 51 IG-2: n= 97 Analyzed = 53 Total = 191	IG: 40.10±11.24 years Placebo: 39.98±10.42 years	Randomized, double-blind, placebo-controlled study	15 weeks	IG: 2–4 capsule daily doses (0.350–0.700 mg of G-B) IG-2: lorazepam 0.5 mg	HAM-A HAM-D	≥ 50% Reduction in HAM-A Score	Safety Tolerability	**HAM-A score:** Galphimine-B showed greater anxiolytic effectiveness than that obtained with lorazepam, with high percentages of therapeutic **tolerability and safety.**
(dos Reis Lucena et al., 2021)	Brazil	Insomnia according to the DSM-V At least one year of amenorrhea	IG: n= 17 Analyzed = 17 Control group: n= 18 Analyzed = 18 Total: 33	48-65 years	Randomized, double-blind clinical study	36 days	IG: 0.12 mL of Lavandula angustifolia essential oil Placebo: 2 mL of sunflower oil	HADS ISI PSQI Polysomnography	Sleep Quality - PSQI	Polysomnography Severity of insomnia, anxiety and depression symptoms, and postmenopausal symptoms.	No significant differences between groups after intervention in **sleep quality.** Improvement in **WASO** with a large effect size. The aroma group showed a significant decrease in **SOL**, depression, hot flashes, postmenopausal symptoms and increased sleep efficiency compared to baseline. **Improved total HADS score in the depression and anxiety domains**
(Woelk & Schläfke, 2010)	Germany	GAD according to the DSM-IV HAM-A ≥18, and Item 1 ‘‘anxious mood’’ ≥ 2 and Item 2 ‘‘tension’’ ≥ 2	IG: n= 40 Analyzed = 36 Control group: n= 37 Analyzed = 33 Total: 77	18 to 65 years	Randomized, double-blind clinical study	6 weeks	IG: 80 mg Silexan (lavender oil) + placebo capsule IG-2: 0.5 mg Lorazepam + placebo capsule	HAM-A	Change in HAM-A scores	SAS PSWQ-PW SF-36 CGI	**Mean HAM-A-total score:** decreased clearly and to a similar extent in both groups **SAS** decreased in both groups **PSWQ-PW:** improved in Silexan Group **Both SF-36 sub scores:** increased in the two treatment groups during the active treatment period (Mental and Physical) **Therapeutic Efficacy (CGI):** had moderate to very good efficacy ratings compared to Lorazepam. **Sleep Diary Outcomes:** Latency to Fall Asleep: Improved more in the Lorazepam group. Waking Up Duration: Improved more in the Silexan group. Total Sleep Time: Prolonged in both groups, with a slightly more extended duration in the Silexan group.

(Langade et al., 2021)	India	INSOMNIA according to the DSM-IV	Healthy subjects: IG: n= 20 Analyzed = 18 Placebo: n= 20 Analyzed = 18 Total: 40 Insomnia subjects: IG: n= 20 Analyzed = 20 Placebo: n= 20 Analyzed = 17 Total: 40	18 and 50 years	Randomized, parallel-group, stratified design, placebo-controlled study	8 weeks	IG: 300 mg Ashwagandha root extract capsule (KSM-66) Placebo: Starch	Sleep actigraphy SOL TST WASO SE PSQI HAM-A	Sleep parameter actigraphy SOL	TST WASO SE PSQI HAM-A Mental alertness on rising Total Time in Bed	In both healthy and insomnia subjects, there was a significant improvement in the sleep parameters in the Ashwagandha root extract supplemented group. The improvement was found to be **more significant in insomnia subjects** than healthy subjects. There is a gradual improvement in the sleep quality with Ashwagandha treated group whereas the placebo group does not show improvement. **SOL, WASO:** In both Arm-A of healthy subjects and Arm-B of insomnia patients, there was a decrease. **TST, TTB, SE:** Increase in both groups. **The HAM-A outcomes** for the treatment group in the Insomnia division were found statistically significant. No adverse events were reported.
(Langade et al., 2019)	India	INSOMNIA according to the DSM-IV	IG: n= 40 Analyzed = 39 Placebo: n= 20 Analyzed = 19 Total: 60	18 and 60 years	Randomized, double-blind, placebo-controlled study	10 weeks	IG: 300 mg of ASH root extract (KSM-66®), twice daily, total daily dose of 600 mg/day Placebo: 300mg of starch, twice daily	Sleep actigraphy SOL TST SE WASO PSQI HAM-A	Sleep parameter actigraphy SOL	TST SE WASO total time in bed mental alertness on rising	**SOL and WASO scores:** Significant decrease in in the experimental group relative to the control group. **TST, TIB, and SE:** Significant increase was recorded in the experimental group in comparison to the control group. **PSQI scores:** Significant decrease in the experimental group when compared to the control group at week 5 and 10. **HAM-A score:** Significant decrease in the for the experimental group when compared with the control group. More number of patients with Ashwagandha were alert as compared to placebo. No adverse events were reported.
(Andreatini et al., 2002)	Brazil	GAD according to the DSM III-R-SCID-R	IG-1 - Valepotriates: n= 12 IG-2 - Diazepam: n= 12 Placebo: n= 12 Total: 36	IG-1 - Valepotriates: 44.6±12.8 IG-2 - Diazepam: 36.9±5.7 Placebo: 41.7±6.6	Randomized, double-blind, placebo-controlled, cross-over study	4 weeks	IG- 1: Valepotriates 50mg - 3 times/day IG-2: Diazepam 2.5mg - 3 times/day	HAM-A STAI	Reduction of HAM-A scores	STAI Evaluation of somatic and psychic factors within the HAM-A scores	**Between-group Analysis**: No significant difference was observed among the three groups at baseline and after intervention in HAM-A and STAI trait. **Within-group Analysis:** The placebo group showed a significant reduction in the total and somatic scores of HAM-A. The diazepam group showed a significant reduction in the STAI-trait and in the total,

							Placebo: Lactose - 3 times/day				somatic and psychic scores of HAM-A. STAI-state scores did not show a significant difference. The valepotriate group presented a significant reduction in the total, somatic and psychic scores of HAM-A. but STAI-trait and state did not show any significant differences. No adverse events were reported.
(Boerner et al., 2003)	Germany	GAD according to ICD-10 (F41.1) HAM-A >19 HAMD < 12	IG1 -KAVA n= 43 Analyzed = 38 IG2- Buspiron: n= 43 Analyzed = 39 IG3- Opipramol: n= 43 Analyzed = 42 Total: 129	25 to 65 years	Randomized, reference-controlled, double-blind, multi-centre clinical trial	8 weeks	IG1 -KAVA 400 mg Kava LI 150 daily IG2- Buspi-ron: 5 mg Buspirone Daily IG3- Opipramol: 50mg Opipramol daily	HAM-A BOEAS SAS CGI Bf-S SF-B AL	Reduction of HAM-A scores	HAMA subscales for "psychic anxiety" and "somatic anxiety." BOEAS SAS CGI Bf-S SF-B AL Patients. Remission rates	**HAM-A scores:** No significant differences were observed among the three treatment groups (Kava, Buspirone, Opipramol) regarding all efficacy measures. No significant differences between treatments could be observed regarding all primary and secondary efficacy variables. **50% reduction of HAMA score:** About 75% of patients were classified as responders in each treatment group, about 60% achieved full remission. **BOEAS, SAS, CGI, Bf-S, SF-B, and AL:** showed similar improvements across all treatment groups.
(Sarris et al., 2013)	Australia	GAD according to DSM-IV MADRS <17	IG -KAVA n= 27 Placebo: n= 30 Total: 57	18 to 65 years	Randomized, Placebo-controlled, double-blind clinical trial	8 weeks	IG: 120/240 mg of kavalactones per day depending on response. Placebo: calcium hydrogen phosphate, microcrystalli ne cellulose, sodium starch glycollate, and magnesium stearate.	HAM-A BAI	HAM-A BAI	HAM-A BAI	**HAM-A scores:** a significant reduction was observed in both groups for time with a significant group x time interaction in favor of kava over placebo occurring. **BAI:** Both groups experienced a significant reduction of anxiety across time **Tolerability:** Kava was well tolerated, and aside from more headaches reported in the kava group, no other significant differences between groups occurred for any other adverse effects, nor for liver function tests.
(Sarris et al., 2020)	Australia	GAD according to	IG -KAVA n= 86 Analyzed = 86	18 to 70 years	Randomized, Placebo-controlled,	16 weeks	IG -KAVA: 240 mg of kavalactones	HAM-A	HAM-A	BAI	**HAM-A score:** Non-significant difference in anxiety reduction between the Kava and placebo groups.

	DSM-5- MINI HAM-A ≥ 18	Placebo: n= 85 Analyzed = 85 Total: 171	double-blind clinical trial	per day Placebo: inert plant-based fiber	PSWQ MADRS WHOQOL K-10 ASEX ISI SAFTEE	**PSWQ:** Non-significant treatment effect (group × time interaction)

5.3. Risk of bias Assessment Outcomes

The quality of the included randomized control trials was assessed using the Cochrane Library risk of bias tool 2. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other sources of bias were the domains assessed for each study included. Each domain was evaluated and categorized into one of the three groups: "low risk," "some concerns," or "high risk" as applicable.

Figure 2. Summary of risk of bias assessment

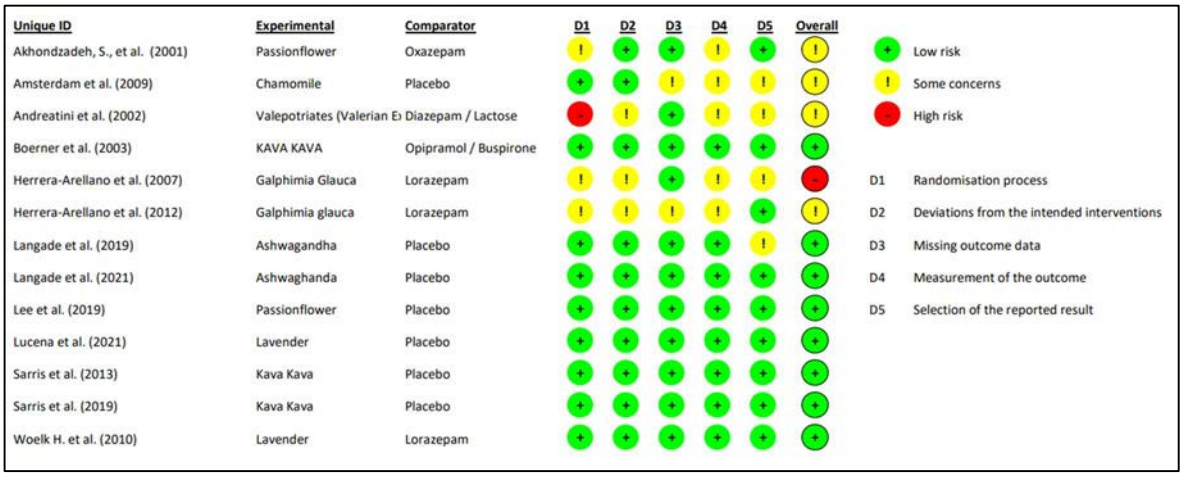
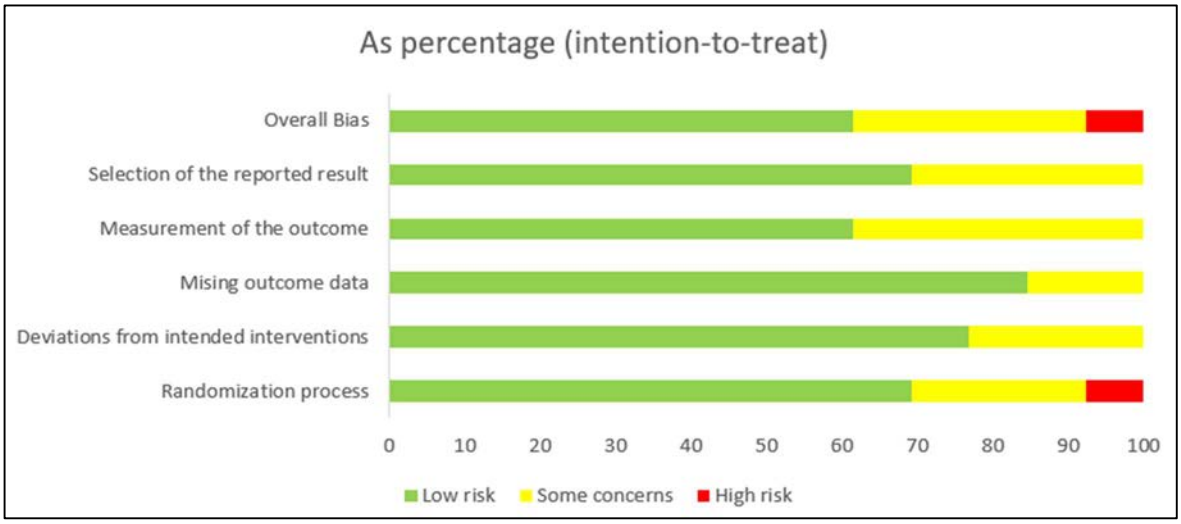


Figure 3. Risk of bias graph



5.4. Narrative Data Synthesis Results

5.4.1. Effects of Passionflower (Passiflora Incarnata) on Insomnia and Anxiety

A clinical trial was conducted to investigate the effects of Passionflower (Passiflora incarnata) on polysomnographic sleep parameters in individuals clinically diagnosed with Insomnia (Lee et al., 2020). This double-blind randomized placebo-controlled study included a total of 110 participants, in which 84 participants, with 45 individuals in the Passionflower group taking 60mg per day were analyzed. The primary outcome measure, total sleep time (TST), showed a significant improvement in the Passionflower group compared to the placebo group ($P = 0.049$). Additionally, sleep efficiency and wake after sleep onset (WASO) were significantly enhanced in the Passionflower group compared to baseline ($P = 0.008$, $P = 0.025$), however, these improvements did not reach statistical significance when compared to the placebo group. Furthermore, self-reported sleep parameters, as measured by sleep diaries and scales such as the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI), did not demonstrate significant differences between the Passionflower and placebo. This study assessed subjectively the level of stress and anxiety in participants using BAI and CES-D, however, the data reported was not significant to prove efficacy compared to placebo ($P= 0.395$, $P= 0.273$). The study also highlighted the importance of considering subjective satisfaction in clinical insomnia research and emphasized the necessity for further investigations with larger populations and extended treatment durations to fully elucidate the clinical efficacy of Passionflower in treating insomnia.

Another randomized, double-blind, controlled trial examined the effects of Passionflower (Passiflora Incarnata) in adults comparing Passionflower extract with oxazepam for the treatment of generalized anxiety disorder (Akhondzadeh et al., 2001). Participants in group 1 received daily fixed dose of Passiflora extract 45 drops (Pasipay™ drop, each 100 ml of this drop contains: 11-15mg total flavonoids) plus placebo tablet, whereas those in group 2 received oxazepam 30 mg plus Passiflora drop daily for a period of 4 weeks. Post-hoc comparisons revealed a significant reduction in HAM-A scores from baseline in both groups by the end of the trial ($P < 0.001$), with the oxazepam group showing a significant reduction from day 4 and the Passiflora group from day 7. While exact mean difference is not explicitly stated, differences at specific time points (e.g., day 4) showed the oxazepam group had significantly lower HAM-A scores than the Passiflora group ($P = 0.008$). However, after day 4, the differences were no longer significant, leading to the finding that

Passiflora extract and oxazepam are both effective in the treatment of GAD. Despite the statistical findings, the clinical relevance should be considered, especially regarding job performance, where Passiflora had a substantially lower incidence of impairment compared to oxazepam, oxazepam was associated with significantly more impairment of job performance (P = 0.049). In addition, there is no significant difference between the two groups in terms of total side effects (P = 0.831). These detailed results provide insights into the timeline of treatment response and the comparative effectiveness of Passionflower extract and oxazepam on GAD symptoms, highlighting the potential benefits of Passionflower extract in managing anxiety disorders. While the current evidence suggests that Passiflora incarnata extract is effective in reducing anxiety symptoms, the limitations in statistical reporting should be considered. The moderate quality of evidence underscores the need for further research with improved methodological and reporting standards to validate these findings and provide clearer guidance for clinical practice.

5.4.2. Effects of German Chamomile (Matricaria Recutita) on Insomnia and Anxiety

There were no published articles were identified that specifically investigated the effects of German Chamomile (Matricaria recutita) on DSM-diagnosed insomnia using polysomnography as an objective measure. While numerous studies have explored chamomile's potential benefits for anxiety and related conditions, the specific focus on insomnia, particularly through rigorous objective sleep assessments, remains limited. Further research endeavors are warranted to comprehensively address this gap in the scientific understanding of chamomile's impact on insomnia.

Chamomile was investigated in a randomized, double-blind, and placebo-controlled trial with outpatients diagnosed with mild to moderate Generalized Anxiety Disorder (GAD) (Amsterdam et al., 2009), had 220mg -1100mg daily capsule Chamomile in the form of 1 capsule daily for first week, 2 capsules daily for second week, and patients with a ≤ 50% reduction in total HAM-A score (versus baseline) were given 3 capsules daily during week 3, then reaching 4 capsules daily during week 4 of treatment (Amsterdam et al., 2009). Patients who remain to have a score of less than or equal to 50% reduction in baseline HAM-A, were increased to 5 capsules daily during study weeks 5 till week 8 of treatment. Results showed that the chamomile group showed a significantly greater reduction in mean total Hamilton Anxiety Rating (HAM-A) scores compared to the placebo group (p=0.047), which suggest that chamomile could be a valuable complementary and alternative

medicine option for managing anxiety. However additional findings showed a nonsignificant reduction in Beck Anxiety Inventory (BAI) scores in the chamomile group compared to the placebo group (p=0.411), which applies to The Psychological General Well-Being (PGWB) index score and Clinical Global Impressions Severity (CGI/S) score, which both showed greater improvements in the chamomile group compared to the placebo group (p=0.170 and p=0.187, respectively), which is statistically nonsignificant. Notably, a higher proportion of patients in the chamomile group achieved a ≥50% reduction in baseline HAM-A scores compared to the placebo group (57.13% vs. 37.93%; p=0.146), further indicating chamomile's potential benefits for managing anxiety. Future studies should include a larger sample size and extend the duration of the study to provide more insights into the long-term effects and sustainability of chamomile's benefits on anxiety.

5.4.3. Effects of Galphimia Glauca (Galphimia Glauca) on Insomnia and Anxiety

A randomized, double-blind clinical trial investigating the efficacy and tolerability of a standardized herbal product derived from Galphimia glauca (GgHP) in comparison to lorazepam for Generalized Anxiety Disorder (GAD) (Herrera-Arellano, A. et al., 2007), included a total of 114 participants, with 55 in the experimental group receiving capsules containing 310 mg of dried aqueous G. glauca extract twice a day for four weeks and analyzed compared to 80 participants in the control group receiving identical capsules with 1 mg lorazepam. The main outcome variable was therapeutic effectiveness, measured by the Hamilton Anxiety Rating Scale (HAM-A) scores, with a score of less than 18 indicating effectiveness. The secondary outcome is tolerability, which is the absence of excessive sedation, and safety which is the absence of pathological alteration in biochemical tests of renal and hepatic function (AST, ALT, ALP, urea, creatine)) assessments. GgHP reduced HAM-A scores from 29 to 9 points (65.62%), the CGI scores from 9 to 4, and PGE scores from 9 to 4. A 43.2% reduction in HAM-A score, reaching 90% at the end of third week reveals the anxiolytic effect of GgHp treatment which is like the reduction seen with lorazepam. Statistical analysis revealed no significant differences between the two treatment groups in terms of efficacy ($p \leq 0.0001$). The study also reported a higher incidence of excessive sedation in the lorazepam group compared to Galphimia glauca group, while safety was reported 100% for both treatments. These findings suggest that the Galphimia glauca may be a promising treatment for GAD, with comparable efficacy to lorazepam but potentially better tolerability. However, in this study, discrepancies in the reported statistics, particularly between the results section and the

corresponding tables were identified, which raises some concerns regarding the certainty of evidence.

Another study followed, investigating the therapeutic effectiveness of Galphimia glauca in treating patients with generalized anxiety disorder (GAD) (Herrera-Arellano, Armando et al., 2012), in a double-blind, randomized, controlled clinical trial compared the effects of G. glauca herbal medicinal product (Gg-HMP) with lorazepam, a common anxiolytic medication. The research included 191 patients, with 51 analyzed in the experimental group receiving Gg-HMP. The study assessed the patients' anxiety levels using the Hamilton Anxiety Rating Scale (HAM-A) throughout the treatment period. The results indicated that both treatments led to a significant reduction in anxiety symptoms, with the experimental group showing a mean HAM-A score of 29.11 at baseline and 9.84 at the end of the study. The repeated-measures ANOVA revealed a statistically significant difference in the therapeutic effectiveness between the two groups ($p = 0.0003$), with Gg-HMP demonstrating high percentages of therapeutic tolerability and safety compared to lorazepam, showing less sedative effect.

Other studies have reported similar findings, indicating that Galphimia glauca has an anxiolytic effect comparable to standard anxiolytic medications, with fewer side effects. However, while these initial findings are promising, more large-scale, long-term studies with rigorous methodologies are necessary to con-firm its efficacy and safety conclusively.

5.4.4. Effects of Lavender (Lavandula Angustifolia) on Insomnia and Anxiety

Lavandula angustifolia essential oil inhalation was studied on post-menopausal women with clinically diagnosed insomnia, with a total of 35 participants who completed the trial (17 in the intervention group) (dos Reis Lucena et al., 2021). The intervention involved inhaling Lavandula angustifolia essential oil for 36 days, diluted in sunflower oil at a concentration of 0.12 ml of Lavandula angustifolia in 2 ml sunflower oil. Participants were instructed to use one bottle per day at bedtime by emptying the contents onto a cotton ball beside their pillow, the results of the polysomnography assessments revealed significant improvements in various parameters. The study found no significant differences between groups in sleep quality following the intervention ($P = 0.22$; effect size = 0.69). However, polysomnography (PSG) data indicated a trend toward improvement in WASO, with a large effect size ($P = 0.07$; effect size = 0.81). While participants in the Aroma group (AG) exhibited a significant reduction in depression levels ($P = 0.025$), SOL ($P = 0.001$), hot flashes ($P < 0.001$), and postmenopausal symptoms ($P < 0.001$). Additionally, PSG data

revealed increased sleep efficiency (P = 0.002) compared to baseline. Post-intervention questionnaire results showed that all volunteers experienced significant improvements in insomnia severity (P < 0.001), total PSQI score (P < 0.001), and its domains: sleep quality, sleep onset latency, sleep duration, sleep efficiency, and daytime sleepiness (P < 0.05). Moreover, there were significant enhancements in total HADS score (P = 0.004), including both depression and anxiety domains (P < 0.05), and in total MRS score (P < 0.001) and all its domains (P < 0.05). Despite that there was not statistically significant data for sleep quality, however participants reported having overall improvement in sleep patterns, which may help women dealing with postmenopausal insomnia, taking into consideration that subjective reporting is a crucial part of assessing insomnia. Further studies with a larger scale of participants should be implemented taking into consideration the patient self-reported symptoms.

In another randomized controlled trial comparing Silexan, a lavender oil preparation, to Lorazepam for clinically diagnosed generalized anxiety disorder (GAD) (Woelk & Schläfke, 2010), a total of 69 participants aged 18 to 65 years completed the trial. Patients with a primary diagnosis of generalized anxiety disorder were included if they had a HAM-A score of at least 18 and "Item 1 ''anxious mood'' ≥ 2 and Item 2 ''tension'' ≥ 2" (Woelk & Schläfke, 2010). As per protocol evaluation, HAM-A total score decreased by 11.4±6.4 points in the silexan group (baseline score: 25±4 points) and by 11.3±6.4 points in the lorazepam group (baseline score: 25±4 points). Both treatments demonstrated significant reductions in anxiety symptoms over a 6-week period, the HAM-A scores decreased. Sub scores for somatic and psychic anxiety also decreased similarly in both groups. Secondary outcome measures, including the Self-rating Anxiety Scale, Penn State Worry Questionnaire, SF-36 Health survey, and Clinical Global Impressions of severity of disorder, showed comparable positive effects for both Silexan and Lorazepam. Safety evaluations indicated no serious adverse events during the study, with gastrointestinal disorders being the most common adverse events in the Silexan group and fatigue in the Lorazepam group. The study's findings show that giving adults with GAD a silexan 80 mg capsule formulation is equally as effective as giving them a 0.5 mg dose of lorazepam.

5.4.5. Effects of Ashwagandha (Withania Somnifera) on Insomnia and Anxiety

A recent study in 2019, was conducted to investigate the effects of Ashwagandha root extract on clinically diagnosed insomnia according to the DSM-IV in a randomized, double-blind, placebo-controlled trial involving 60 adult participants randomized in 2

groups to receive either Ashwagandha root extract (KSM-66 capsule) or a placebo for 10 weeks (Langade et al., 2019). The intervention group received a 300 mg of Ashwagandha root extract (KSM-66®), twice daily, total daily dose of 600 mg/day. The results of the sleep actigraphy at 10th week after the completion of the intervention, showed a significant decrease in SOL and WASO scores in the intervention group compared to control group. On the other hand, the study showed that there was a significant increase recorded in TST, TIB, and SE in the intervention group compared to the control group ($P < 0.001$). As for the anxiety outcomes, HAM-A scores significantly decrease in the experimental group compared to the control group. The HAM-A scores at baseline recorded 23.58 (3.15) and 23.42 (3.00) for the intervention and control groups, respectively. The HAM-A scores were recorded again in week 10, showing results of 18.48 (3.47) and 21.52 (3.22) for intervention and control group respectively. This 10-week trial demonstrated impact of the significant improvement in the sleep parameters SOL, SE, PSQI and anxiety parameters HAM-A. The obtained differences compared to the placebo group were found statistically significant, suggesting a strongly considerable effect of Ashwagandha in improving the sleep and reducing the anxiety of the patients. These findings suggest that Ashwagandha root extract may be a promising natural remedy for insomnia.

There was a following study in 2021, investigating the effects of ashwagandha root extract on sleep quality were investigated in a randomized controlled trial involving 80 participants (Langade et al., 2021). The study included 40 healthy subjects and 40 patients diagnosed with insomnia, with each group randomly assigned to either the ashwagandha group or the placebo group. The intervention involved the administration of ashwagandha root extract 300mg for a duration of 8 weeks. The results of the study revealed significant improvements in sleep parameters as measured by polysomnography, in both healthy subjects and insomnia patients, where SOL and WASO decreased accordingly. An increase in total sleep time, total time in bed and SE were shown over the 8-week study duration in both Ashwagandha and placebo group ($p < 0.0001$). Anxiety was measured by Hamilton Anxiety scale-A HAM-A at the study first, fourth, and eighth week, for both the groups and in healthy and insomniac patients simultaneously among the healthy subjects, the decrease in HAM-A scoring was not found to be much significant when compared to the decrease in the insomnia group. At the end of the trial, the Ashwagandha group recorded a score of 15.92 ± 1.00 and the placebo group 21.09 ± 1.08, showing a statistically significant reduction in the Ashwagandha group when compared to the placebo group in insomnia patient group. The HAM-A outcomes for the treatment group in the Insomnia

group showed statistically significant results ($p < 0.0001$). The outcomes suggest that Ashwagandha root extract has a remarkable effect in improving sleep and relegating anxiety among both healthy and subjects diagnosed with insomnia.

5.4.6. Effects of Valerian (Valeriana officinalis) on Insomnia and Anxiety

A total of 36 participants with a diagnosis of generalized anxiety disorder (GAD) according to the DSM III-R was evaluated with the structured clinical interview for DSM III-R -SCID-R were recruited to participate in a randomized, placebo-controlled pilot study to investigate the effect of Valepotriates (Valerian Extract) on anxiety (Andreatini et al., 2002). The participants met the inclusion criteria of having generalized anxiety disorder and undergoing a 2-week washout period prior to randomization. The intervention involved three treatment groups: placebo (lactose), diazepam (2.5 mg), and valepotriates (50 mg), administered for four weeks three times/day. The lowest dose given in the diazepam and valepotriate groups was one capsule of the active agent and two capsules of placebo; the intermediate dose was two capsules of active drug and one of placebo; and the higher dose was of three capsules containing the active drug, the dose was increases according to the patient's therapeutic response after conducting an evaluation interview following 1 week of treatment, by a psychiatrist it necessary. The number of capsules was reduced if the patient showed or reported any serious or unpleasant side effect. Evaluating their effects on anxiety symptoms using standardized scales such as the Hamilton Anxiety Scale (HAM-A) and the State-Trait Anxiety Inventory (STAI). The results revealed a significant reduction in anxiety symptoms in all three groups, and within group analysis showed a significant reduction in STAI-trait and in the total, somatic and psychic scores of HAM-A ($T = 4.00$, 0.00, 0.00 and 0.00, respectively) in the diazepam group, and the valepotriate group presented a significant reduction in the total, somatic and psychic scores of HAM-A ($T = 5.50$, 3.50 and 5.00, respectively) but STAI-trait and state did not show any significant differences ($T = 25.00$ and 25.50, respectively). The placebo group showed a significant reduction in the total and somatic scores of HAM-A ($T = 1.50$ and 0.00, respectively). The STAI-trait and state and the HAM-A psychic factor did not present any statistical differences ($T = 6.50$, $T = 5.00$ and $T = 5.50$, respectively). No moderate or serious adverse events were reported, indicating good tolerability of the interventions. These findings suggest potential anxiolytic effects of both diazepam and valepotriates in generalized anxiety disorder, emphasizing the need for further research to confirm these

preliminary results. Limitations of the study include the small sample size and methodological constraints that warrant caution in interpreting the findings.

5.4.7. Effects of KAVA (Piper Methysticum) on Insomnia and Anxiety

In a randomized, double-blind, parallel-group clinical trial, 129 patients meeting specific inclusion criteria as a clinically diagnosis of Generalized Anxiety Disorder (GAD) with a minimum total score of 19 on the Hamilton Anxiety Scale (HAMA), and a maximum total score of 12 on the 17-item, Hamilton Depression Scale (HAMD) was included in the intervention involved three treatment groups receiving different medications: Kava Kava extract LI 150 (400 mg daily), Buspirone (5 mg Daily), and Opipramol (50mg daily) (Boerner et al., 2003). The change in HAM-A total scores was the primary outcome measure, recorded from baseline to week 8 of the trial. A reduction in mean HAMA total scores from about 23 at baseline to 8 at week 8, showing no significant differences between treatments. A remarkable improvement of the HAMA total score could be seen to the same degree for Kava LI 150 (–6.8; 27.9%), Buspirone (–7.1; 29.7%), and Opipramol (–6.7; 27.9%), respectively in week 2. Sleep was impaired severely in all treatment groups as reflected by baseline scores recorded by SF-B (2.5). SF-B factor SQ (sleep quality) scores increased from 2.65 ± 0.68 to 3.60 ± 0.84 (Kava), 2.53 ± 0.67 to 3.68 ± 0.80 (Buspirone) and 2.66 ± 0.74 to 3.79 ± 0.82 (Opipramol). Adverse events were recorded and analyzed for each treatment group, with specific events and their frequencies reported, and from all abnormal laboratory values ranges at week 8, only a gamma-GT increased in an Opipramol patient and was rated to be of clinical relevance to be reported as an adverse event. The results showed a significant decrease in HAMA total scores from baseline to week 8 across all treatment groups, with no significant differences between treatments. The study's clinical significance lies in demonstrating the efficacy of Kava Kava extract LI 150 comparable to traditional medications like Buspirone and Opipramol in treating GAD. Limitations of the study may include sample size, funding sources of the supplements and medication, and the missing placebo control which may question the internal validity of the study.

A double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy of kava in treating Generalized Anxiety Disorder (GAD) (Sarris et al., 2013). A total of 57 participants met the inclusion criteria of having a clinical diagnosis of GAD, out of which 27 were assigned for the intervention group. Participants were randomized to receive either kava or placebo for a duration of 6 weeks, followed by a 1-week single-

blinded placebo observation period. The kava group received medically prescribed standardized kava extract containing 60mg of kavalactones per capsule for a total daily dose of 120 mg of kavalactones (one 3-g capsule twice per day) for the first 3-week controlled phase, being changed to 240 mg of kavalactones in patients with nonresponse to treatment for the second 3-week controlled phase (two 3-g tablets twice per day). The primary outcome measure was the reduction in anxiety assessed using HAM-A scores. A significant reduction in HAMA scores was observed in both groups for time ($P < 0.0001$), with a significant group x time interaction in favor of kava over placebo ($F1,57 = 4.16$; $P = 0.046$) occurring with a moderate effect size ($d = 0.63$) in favor of kava. Kava significantly reduced participant's anxiety from (mean [SD]) 21.63 (4.2) to 14.03 (7.01) (-7.6 points) compared with 19.50 (4.2) to 15.26 (6.2) (-4.2 points) for placebo from baseline to the end of the trial. No major adverse reactions were reported during the study. The study concluded that medically prescribed standardized kava is a moderately effective short-term treatment for GAD, with future research needed to confirm these results and explore long-term efficacy and safety effects. Limitations of the study included a sample size and the need for further research to confirm the findings.

Another study of a total of 171 participants with generalized anxiety disorder (GAD) were recruited meeting DSM-5 diagnostic criteria for GAD and presenting with moderate levels of anxiety (HAMA ≥ 18) to study the effect of the administration of Kava at a specific dosage over a 16-week period, with participants randomly assigned to either the Kava group or the placebo group with an aqueous extract of dried Kava root administered twice per day in tablet form (standardized to 120 mg of kavalactones twice/day) (Sarris et al., 2020). The primary outcome measure was the change in anxiety symptoms assessed by the Hamilton Anxiety Rating Scale (HAMA) at each time point. Analyses of primary and secondary outcomes were undertaken utilizing linear mixed-effects models (LMMs), the primary LMM revealed no significant effect of treatment on the HAMA (group × time interaction) $p=0.25$, indicating a minimal effect size in favor of placebo in reducing anxiety. Two serious adverse events were recorded in the trial, both in the placebo group. Each serious adverse event was deemed unrelated to study treatment by the study medical investigators. The study provides valuable insights into the use of Kava for GAD treatment, highlighting both its efficacy and safety profile. However, limitations such as the sample size and potential confounding variables should be considered when interpreting the results.

6. Discussion

This review aimed to assess the efficacy and safety of herbal treatments for insomnia and generalized anxiety disorder symptoms through a comprehensive search, which ultimately identified thirteen eligible randomized controlled trials. The analysis of the effects of various herbal treatments on insomnia and anxiety presents a mixed yet promising picture. Passionflower (Passiflora incarnata) has demonstrated potential in improving total sleep time (TST) and other polysomnographic parameters in individuals with insomnia (Lee et al., 2020). However, despite these improvements, subjective measures such as the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI) did not show significant differences between the Passionflower and placebo groups. This underscores the complexity of treating insomnia, where objective sleep improvements may not always align with subjective experiences, highlighting the need for further research with larger sample sizes and extended treatment durations to validate these findings. For anxiety, the comparison of Passionflower extract with oxazepam revealed that while both treatments significantly reduced HAM-A scores, the timeline of efficacy differed, with oxazepam showing a quicker response (Akhondzadeh et al., 2001). Importantly, Passionflower was associated with fewer impairments in job performance, suggesting its potential as a safer alternative in certain contexts. This finding aligns with the need to consider both efficacy and tolerability in clinical practice, particularly for treatments aimed at managing anxiety disorders. German Chamomile (Matricaria recutita) showed significant reductions in HAM-A scores in patients with generalized anxiety disorder (GAD) (Amsterdam et al., 2009), although other measures such as the Beck Anxiety Inventory (BAI) did not show significant changes. This discrepancy between different assessment tools suggests that while chamomile may have some anxiolytic effects, its impact may vary depending on the specific symptoms and scales used. Future studies should aim to clarify these effects with larger sample sizes and longer durations to better understand chamomile's role in anxiety management. Galphimia glauca demonstrated comparable efficacy to lorazepam in reducing anxiety symptoms (Herrera-Arellano, A. et al., 2007; Herrera-Arellano, Armando et al., 2012), with fewer side effects, particularly excessive sedation. These findings suggest that Galphimia glauca could be a viable alternative to traditional anxiolytics,

though discrepancies in statistical reporting highlight the need for more rigorous studies to confirm these results and ensure the reliability of the evidence.

Lavender (Lavandula angustifolia) showed promising results in improving various sleep parameters and reducing postmenopausal symptoms, including depression and hot flashes (dos Reis Lucena et al., 2021). Although the study did not find significant differences in sleep quality between groups, the improvements in other subjective and objective measures suggest potential benefits of lavender in managing insomnia and associated symptoms in postmenopausal women. Further studies with larger participant numbers are warranted to confirm these effects. Ashwagandha (Withania somnifera) was found to significantly improve sleep and reduce anxiety in both healthy subjects and those with insomnia (Langade et al., 2019; Langade et al., 2021), and these consistent findings across different populations and study designs highlight Ashwagandha's potential as a natural remedy for insomnia and anxiety, with significant improvements in sleep onset latency (SOL), wake after sleep onset (WASO), and total sleep time (TST). Valerian (Valeriana officinalis) showed anxiolytic effects comparable to diazepam (Andreatini et al., 2002), with significant reductions in anxiety symptoms measured by HAM-A and STAI. The absence of serious adverse events and good tolerability of Valerian suggests it could be a safe alternative for managing generalized anxiety disorder. However, the small sample size and methodological constraints call for cautious interpretation and further research to confirm these preliminary findings. Lastly, Kava (Piper methysticum) demonstrated significant reductions in anxiety symptoms in multiple studies (Boerner et al., 2003; Sarris et al., 2013; Sarris et al., 2020). The efficacy of Kava was found to be comparable to traditional medications like Buspirone and Opipramol, with no significant differences in treatment effects. These results support Kava's potential as an effective treatment for GAD, although the lack of a placebo control in some studies and other methodological limitations necessitate further research to fully establish its clinical utility and safety profile.

During the systematic review process, a comprehensive search of the PubMed database, the search included terms related to various herbs such as Rhodiola (Rhodiola rosea), Tulsi Holy Basil (Ocimum tenuiflorum), Schisandra (Schisandra chinensis), Siberian Ginseng (Eleutherococcus senticosus), Skullcap (Scutellaria lateriflora), Ginkgo (Ginkgo biloba), Bacopa (Bacopa monnieri), Lemon Balm (Melissa officinalis), Gotu Kola (Centella asiatica), Rosemary (Rosmarinus officinalis), Blue Vervain (Verbena hastata), Motherwort (Leonurus cardiaca), Hops (Humulus lupulus), Kanna (Sceletium tortuosum), Saffron

(Crocus sativus), Curcumin (Curcuma longa), St. John's Wort (Hypericum perforatum), Californian Poppy (Eschscholzia californica), Magnolia Bark (Magnolia officinalis), Lotus (Nelumbo nucifera), Drumstick Tree (Moringa oleifera), Yuan Zhi (Polygala tenuifolia), and Bitter Orange (Citrus aurantium). Despite this extensive search, randomized controlled trials meeting the inclusion criteria were not identified for many of these herbs, underscoring a significant gap in the literature and highlighting the need for future research to explore their potential therapeutic effects on anxiety and insomnia.

7. Strengths & Weaknesses of this work

The strength of this systematic review lies in its objective measurement of insomnia and anxiety, providing robust and quantifiable data. However, this methodological quality also introduces certain limitations. A significant concern is that subjective satisfaction, which is crucial in the clinical management of insomnia, may not be fully captured. Participants' experiences in a sleep laboratory can differ substantially from their usual sleep environments, potentially influencing the outcomes. Additionally, while several systematic reviews have shown improvements in sleep quality or anxiety levels with herbal treatments, these findings predominantly stem from studies on non-clinical populations. Thus, the applicability of these results to clinical settings remains uncertain, underscoring the need for further research involving clinically diagnosed individuals. Furthermore, the ethical implications of administering a placebo in clinical settings warrant careful consideration. The use of placebos can pose ethical challenges, particularly in populations with significant anxiety or insomnia, where withholding effective treatment may not be justifiable. Another limitation includes the potential variability in the quality and composition of herbal preparations, which can affect the consistency and reliability of the findings. Future studies should aim to address these limitations by incorporating larger, more diverse clinical populations, ensuring closer alignment with real-world conditions, and maintaining high standards of ethical conduct.

8. Conclusions

In conclusion, while the current evidence supports the efficacy of Passionflower, Lavender, and Ashwagandha in treating both insomnia and anxiety, limitations such as small sample sizes, short study durations, and methodological variations underline the need for further research with rigorous designs and larger populations to provide clearer guidance for clinical practice. Current evidence indicates that certain herbal medicines may be effective in reducing generalized anxiety disorder symptoms and improve sleep quality in patients dealing with insomnia. However, there is insufficient conclusive data to demonstrate that these herbal treatments have a superior benefit-to-risk ratio compared to existing pharmaceuticals. The variability in previous trials necessitates future research to utilize standardized forms of these herbal products in large-scale trials with rigorous methodologies to accurately assess their comparative effectiveness. Additionally, studies are needed to explore more the mechanisms of action of herbs to aid in establishing reliable dosage guidelines and verifying the effectiveness of herbal supplements. In addition, the review also highlights significant gaps in the research, particularly for clinical trials that measure objective outcome, instead of self-reporting outcomes which are prone to reporting biases. sleep measures. Future research should aim to address these limitations, with larger, well-designed clinical trials to validate the efficacy and safety of these herbal treatments for insomnia and anxiety.

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Appendices

Appendix 1: Bioethics Approval

Appendix 2: Consent Form

Appendix [last number]: Copyright Statement

Affirmation

The undersigned Razan Abou Assaf postgraduate student of the Postgraduate Program "LIFESTYLE MEDICINE" of the University of Thessaly

I declare responsibly that I accept the following terms concerning:

(a) the copyright of my Master's Thesis entitled "THE EFFECT OF HERBAL SUPPLEMENTS ON THE SEVERITY OF ANXIETY AND INSOMNIA SYMPTOMS IN ADULTS WITH GENERALIZED ANXIETY DISORDER OR INSOMNIA: A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS"

(b) the management of the research data I will collect in the course of its elaboration:

1. The copyright of the resulting volume of the master's thesis will belong to me. I will follow the instructions for writing, printing and depositing copies of the dissertation in the relevant repositories (in printed and/or electronic form).
2. The management of the dissertation data belongs jointly to me and the Director of Studies/Main Supervisor.
3. Any scientific publication or announcement (posted or oral), or reference derived from the material/data of this work will be made with authors myself, the main supervisor and/or other researchers (such as a member of the three-member advisory committee), depending on their contribution to the research or the writing of the research paper(s).
4. The order of names in scientific publications or scientific announcements will be decided jointly by me and the main supervisor (DOS) of the project before it begins. This decision will be certified in writing between myself and the main supervisor.

Finally, I declare that I am aware of the rules on plagiarism and intellectual property and that I will strictly follow them throughout my studies, I will attend to the educational obligations arising from this MSc, as well as will attend the publication procedures that will arise after the completion of my studies.

17th of June 2024

Razan Abou Assaf