Routledge
Taylor & Francis Group

Journal of Mental Health

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijmh20

What over the counter (OTC) products have been evaluated for anxiety in adults aged 18–60? A scoping review

Rachael Frost, Sayem Uddin, Silvy Mathew, Verity Thomas, Adriana Salame, Sukvinder Kaur Bhamra, Juan Carlos Bazo-Alvarez, Cini Bhanu, Michael Heinrich & Kate Walters

To cite this article: Rachael Frost, Sayem Uddin, Silvy Mathew, Verity Thomas, Adriana Salame, Sukvinder Kaur Bhamra, Juan Carlos Bazo-Alvarez, Cini Bhanu, Michael Heinrich & Kate Walters (30 Sep 2024): What over the counter (OTC) products have been evaluated for anxiety in adults aged 18–60? A scoping review, Journal of Mental Health, DOI: 10.1080/09638237.2024.2408231

To link to this article: https://doi.org/10.1080/09638237.2024.2408231

JOURNAL OF MENTAL HEALTH
https://doi.org/10.1080/09638237.2024.2408231

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

What over the counter (OTC) products have been evaluated for anxiety in adults aged 18–60? A scoping review

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

[a]School of Public and Allied Health, Liverpool John Moores University, Liverpool, UK; [b]Department of Primary Care and Population Health, University College London, London, UK; [c]UCL Medical School, University College London, London, UK; [d]Division of Medicine, University College London, London, UK; [e]Medway School of Pharmacy, University of Kent, Kent, UK; [f]School of Pharmacy, University College London, London, UK; [g]China Medical University, Taichung, Taiwan

ABSTRACT

Background: Anxiety symptoms and disorders are common in the UK. Whilst waiting for, or alongside, treatments such as anxiolytics or psychological therapies, people often self-manage anxiety symptoms with products purchased over-the-counter (OTC), such as herbal medicines or dietary supplements. However, the evidence for these products is often presented across different reviews and is not easy for patients or healthcare professionals to compare and understand.

Aims: To determine the nature and size of the evidence base available for these products.

Methods: A scoping review. CENTRAL, MEDLINE, EMBASE, PsycInfo, and AMED (inception—Dec 2022) were searched for RCTs assessing OTC products in people aged 18–60 with symptoms or a diagnosis of anxiety.

Results: In total 69 papers assessing a range of products were found, which mostly focussed on kava, lavender, saffron, probiotics, Galphimia glauca and valerian. Studies used varying dosages. Compared to herbal medicine studies, there were much fewer dietary supplement studies and homeopathic remedy studies, despite some of use of these by the general public.

Conclusion: Future research needs to investigate commonly used but less evaluated products (e.g. chamomile, St John's Wort) and to evaluate products against or alongside conventional treatments to better reflect patient decision making.

ARTICLE HISTORY
Received 23 February 2024
Accepted 6 August 2024

KEYWORDS
Anxiety; herbal medicine; homeopathy; dietary supplements; over-the-counter

Introduction

An estimated 5.9% of UK adults have Generalised Anxiety Disorder (GAD) (Stansfeld et al., 2016), defined as excessive anxiety and worry occurring more days than not for over six months, which the individual finds difficult to control, with clinically significant distress or functional impairment. It must be associated with three or more of the following: restlessness, feeling easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance (American Psychiatric Association, 2022). In addition to affecting an individual's quality of life and functioning, anxiety is associated with poorer sleep, increased risk of depression and increased risk of coronary heart disease, cardiovascular mortality and stroke (Cox & Olatunji, 2020; Emdin et al., 2016; Saha et al., 2021). GAD is also associated with higher use of healthcare services and higher healthcare costs (Revicki et al., 2012). From a societal perspective, worse mental well-being can lead to more sick days and less productivity in the workforce (Santini et al., 2022).

Between 2013 and 2018 anxiety diagnoses and symptoms rose, particularly in younger age groups (Archer et al., 2022). National Institute for Health and Care Excellence (NICE) guidelines for GAD recommend a stepped care approach of active monitoring, low- and high-intensity psychological therapies and/or drug treatment (National Institute for Health & Care Excellence, 2020). Antidepressants are effective for anxiety compared to placebo (Chen et al., 2019), but side effects such as nausea, sleep disturbances, loss of libido, or headaches (Brahmbhatt et al., 2021) result in mixed acceptability (Parker & Banfield, 2022; Toledo-Chávarri et al., 2020). Psychological therapies are effective compared to waitlist controls (Chen et al., 2019), with greater acceptability than antidepressants (Hurtado et al., 2020; Parker & Banfield, 2022; Toledo-Chávarri et al., 2020), but frequently have long waiting times, discouraging engagement with treatment (Waumans et al., 2022). In the UK, only half of those with GAD receive mental health treatment, usually medication, with only 17% using psychological therapies (Stansfeld et al., 2016).

CONTACT Rachael Frost r.h.frost@ljmu.ac.uk School of Public and Allied Health, Liverpool John Moores University, Liverpool, UK.
Additional affiliation of Juan Carlos Bazo Alvarez: Escuela de Medicina, Universidad Cesar Vallejo, Trujillo, Peru.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/09638237.2024.2408231.

Repeated episodes of anxiety can mean people become involved in a long process to find effective and accessible treatments (Toledo-Chávarri et al., 2020). Anxiety is self-managed through a range of lifestyle coping mechanisms (Hurtado et al., 2020) in addition to formal healthcare, and is associated with greater complementary treatments usage (Hunt et al., 2010). NICE guidelines recommend discouraging the use of over the counter (OTC) preparations due to the lack of evidence to support their safe use (National Institute for Health & Care Excellence, 2020). Despite this, OTC products are clearly widely used. Estimates differ by country, but surveys suggest between 17% and 72.8% of participants have used herbal medicines for anxiety symptoms (Bystritsky et al., 2012; Dehghan et al., 2022; Garcia-Alvarez et al., 2014; McIntyre et al., 2016; Woodward et al., 2009), with between 14% and 27% survey respondents using complementary approaches or herbal products alongside conventional treatment (Bahceci et al., 2013; McIntyre et al., 2016). Usage rates are significantly higher in those with more severe mental disorders (McIntyre et al., 2016; Ravven et al., 2011).

Reasons for using herbal products for anxiety include perceptions they are gentler, safer and have fewer side effects than prescription medications, and positive experience of own and others' use (Garcia-Alvarez et al., 2014; McIntyre et al., 2015). The most consistently popular individual products in surveys are chamomile, lavender, valerian and St John's Wort, with some surveys also mentioning kava, ginseng, black cohosh, and chasteberry (Bystritsky et al., 2012; McIntyre et al., 2016; Ravven et al., 2011). Dietary supplement use for mental health has been examined less often, but it is suggested that vitamin and mineral use for mental health varies from 1.6% to 6.4% in US, Turkish and Iranian populations (Bahceci et al., 2013; Dehghan et al., 2022; Ravven et al., 2011). For OTC homeopathic preparations, one of the most common reasons for their use in the UK is psychological problems (Reid, 2002). An Australian simulated patient study found pharmacists recommended a range of products for distress, chiefly B-vitamin complex and Bach Rescue Remedy (Clayton et al., 2020).

People with anxiety report a lack of information as to treatment effectiveness (Toledo-Chávarri et al., 2020), seeking information through the internet or family and friends, with half not disclosing herbal medicine use to their general practitioner (McIntyre et al., 2016). Pharmacists' natural products knowledge has been shown to be limited in several studies (Waddington et al., 2015), with variable support provided to people for mental health problems (Morris et al., 2021). It is therefore important to clearly map the evidence for both patients and healthcare practitioners. Whilst many products have been reviewed (e.g. chamomile (Hieu et al., 2019), lemon balm (Ghazizadeh et al., 2021)), these are often in separate reviews, providing difficulties in comparing the volume and nature of the evidence across products. Inclusion criteria can also vary across reviews (e.g. including people with few symptoms at baseline, or acute anxiety), limiting their utility.

One previous network-meta-analysis has been carried out upon herbal products for anxiety (Zhang et al., 2022). Whilst this provided clear conclusions on the 12 herbal products included, it only focussed on studies in people with a GAD diagnosis and using Hamilton Anxiety Rating Scale (HAM-A) as an outcome. Those experiencing anxiety symptoms without a definitive diagnosis are also likely to take herbal products, whilst not all trials may use HAM-A as an outcome measure. It also did not account for dosages or include dietary supplements or medication. There remains a need to understand the size and nature of the evidence of all potential OTC products for anxiety symptoms and diagnoses, providing detail on preparations and taking an inclusive approach to outcome measures to comprehensively map the evidence base.

We therefore aimed to determine the size and scope of the evidence base regarding the effectiveness and safety of over-the-counter products for people with symptoms or a diagnosis of anxiety, through (1) mapping OTC products evaluated in trials for reducing anxiety symptoms in adults aged 18–60 and (2) summarising the characteristics of the evidence for each product. We summarise the results for adults only as those for older adults are synthesised separately, due to different issues with higher likelihood of comorbidities and concomitant medication.

Methods

We carried out a scoping review according to Joanna Briggs Institute (JBI) guidance (Peters et al., 2020) and PRISMA guidance for scoping reviews (Tricco et al., 2018). This was part of a larger review focussing on OTC products for depression, anxiety and insomnia that was prospectively registered on the Open Science Framework (https://osf.io/rkm57/), with results synthesised separately for each condition and for older/younger populations.

We searched, MEDLINE, EMBASE, PsycInfo, AMED, and CENTRAL (inception—Dec 2022). CENTRAL searches also included searches for ongoing trials and protocols. Using Boolean operators, we developed free text and MESH terms grouped into the following categories.

1. Over the counter products
2. Depression, anxiety and insomnia
3. RCT filters (where available)

Given the wide range of products, individual product names were not used. Broad and specific product terms were generated by the research team and piloted and refined in scoping searches in Medline and Embase (see Appendix 1 for the Medline search strategy). Search results were deduplicated and imported into Rayyan (Ouzzani et al., 2016) for title and abstract screening. Dual title and abstract screening was undertaken for 10% hits, and any discrepancies or unclear decisions were discussed in team meetings. Once agreement had been reached, remaining studies were screened by a single reviewer (RF, SM, SU, VT, and AS), with unclear studies reviewed by a second person. The same process was followed for full texts, with decisions documented in Excel. All were screened for inclusion in the overall review of all conditions; anxiety and anxiety with insomnia and/or depression studies are synthesised in this paper.

The eligibility criteria were:

- Adults (mean age or range within 18–60 years), in a community/outpatient setting with symptoms of anxiety (using a validated questionnaire) or an anxiety diagnosis.
- Oral over-the-counter medicines, herbal products, homeopathic products and dietary supplements, alone or as an adjunct treatment, used for at least one week.
- Measuring outcomes of anxiety symptoms using validated questionnaires or diagnosis using established diagnostic criteria and adverse events.
- Randomised controlled or crossover trials (RCTs), with any comparator.

We excluded studies on inpatients, people not meeting a minimum symptom threshold at baseline, other mental health conditions (aside from depression and insomnia) and studies where anxiety was part of a collection of other symptoms but did not have to meet a specified baseline level (e.g. menopause, substance abuse). Studies not reporting any age data or descriptors were assumed to be in adults ($n=1$) and included in the review. We excluded prescription medication, individualised treatments, non-pharmacological approaches (e.g. aromatherapy), studies of less than one week of treatment and individualised interventions. We excluded subgroup analyses of trials and conference abstracts (these were followed up to locate full texts where possible). We included studies from any time period, and any language (multilingual colleagues and Google Lens translated non-English texts).

Context is an important consideration within scoping reviews (Peters et al., 2020). The term OTC can include a wide range of products; with inconsistencies in what is available and the supporting regulatory frameworks in different countries (e.g. Kava is available in Australia but not the UK). We therefore included OTC products without practitioner input, irrespective of their status in the UK, after discussion with our clinical and PPI team members. This allowed the review to be as inclusive as possible, as a wider range of products can often be purchased online. We excluded Traditional Chinese Medicine combination products that typically require practitioner input and other obscure products unlikely to be widely used. Importantly, product definitions often vary in different countries and classification can therefore be challenging.

Data were extracted with a data extraction form devised with guidance from the JBI data extraction template. Data were extracted by one reviewer (SU), and checked by a second reviewer (RF), including study details, country and setting, sample size, condition definition and baseline scales, participant characteristics and inclusion criteria, product characteristics, comparators, and outcomes. RF additionally extracted adverse event data and data from non-English papers using Google Lens ($n=4$).

Data was summarised descriptively in tables and charts, according to product characteristics, sample characteristics and outcomes. We aimed to highlight products that were commonly researched and where there were gaps compared to common usage, promising products for further research and where there were gaps in patient populations.

Results

For the overall review we found 23,933 articles, 15,339 after deduplication. After title and abstract screening, 1346 full texts were screened for eligibility. Out of these 69 studies were eligible for inclusion in the adults with anxiety synthesis (Figure 1), representing 75 comparisons evaluating 43 different products (Figure 2).

Follow up of 50 protocols, trials register entries and conference abstracts located an additional eight relevant full texts (five published in 2023 after completion of searches), of which three were eligible for the anxiety synthesis (one depression only and four were excluded). Nine relevant ongoing studies were located from trials register entries and are summarised at the end of the results.

The 69 completed studies came from 15 different countries, including 13 Iran, 13 Germany, nine Australia, seven USA, five Brazil, four Mexico, four India, three Canada, three Netherlands, two France, two Italy, and one each from South Korea, Hungary, Japan and the UK. Sample size, participant characteristics, product details and comparators are summarised in Table 1. The year of publication indicates an increasing interest in products for anxiety over time. Sample sizes varied widely, and most studies were carried out in both men and women and focussed on anxiety alone ($n=53$) in people without comorbidities. The most common comparator was placebo ($n=49$), and most trials were double blind ($n=60$). Most studies (61/69) reported at least basic safety data on adverse events in the trial.

Herbal products

In total, 19 single herb (Table 2) and 13 multi-herb products (Table 3) were evaluated in 59 comparisons across 55 studies. Where two herbal extracts were compared without another comparator in a single study, the study is listed twice, once under each product.

Single herbal product studies

Kava (Piper methysticum L.)

Kava was tested in 13 studies, ten in people with anxiety, two in people with anxiety and insomnia and one in people with anxiety and menopause. Sample sizes ranged from 35 to 391 and studies lasted 1–25 weeks. Products varied somewhat. Doses were between 1×100 mg and 5×3.2 g tablets/day, although tablets were generally standardised to between 35 and 70 mg kavalactones where this was reported (Connor & Davidson, 2002; Gastpar & Klimm, 2003; Lehrl, 2004; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2020; Volz & Kieser, 1997), giving a more similar dosage of active constituents across products. One study standardised to 55% kavain (De Leo et al., 2001) and one to 30% kavapyrones (Boerner et al., 2003).

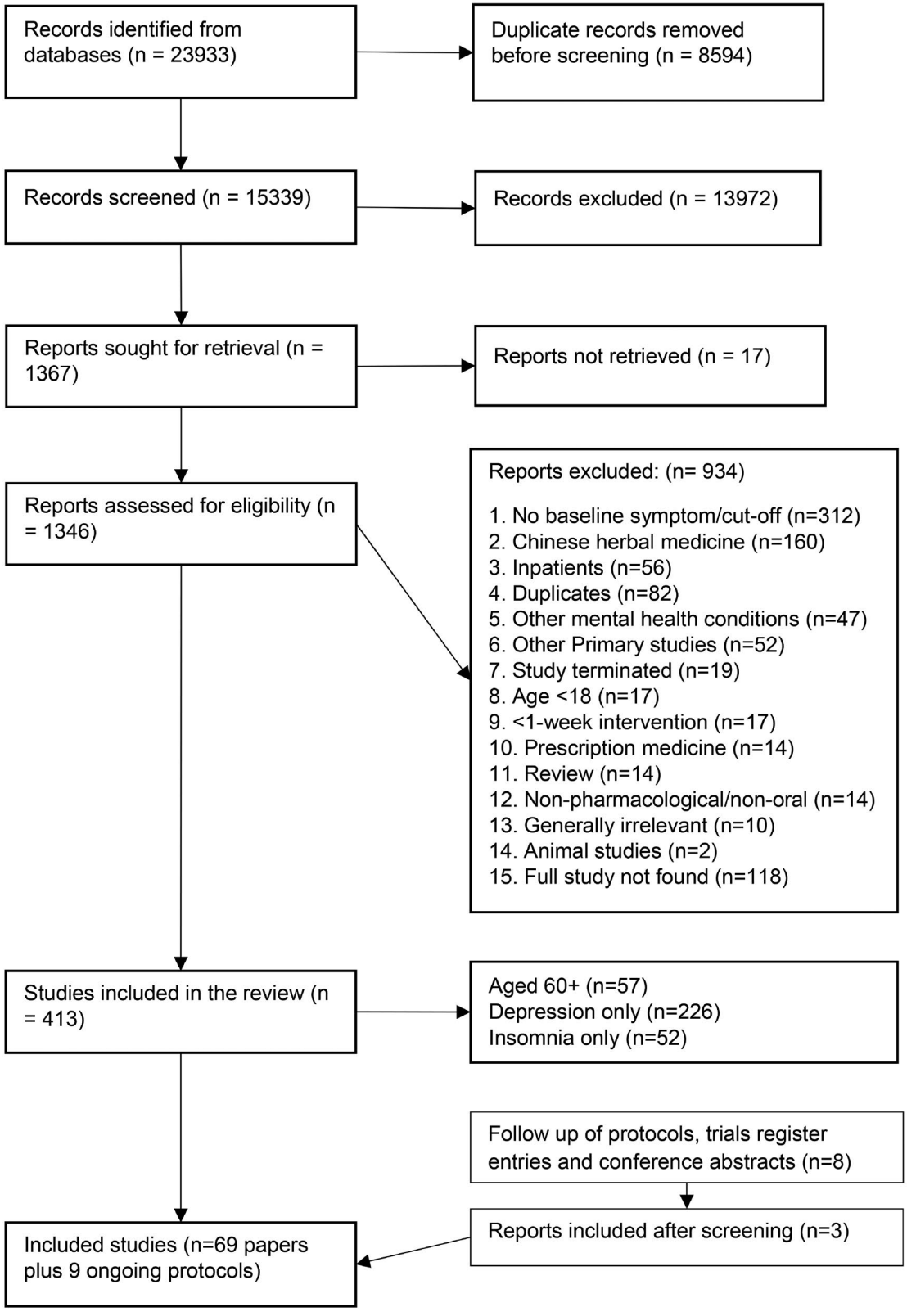

Figure 1. PRISMA Flow Diagram.

Seven of the 13 studies showed a significant difference to placebo (De Leo et al., 2001; Lehmann et al., 1996; Lehrl, 2004; Malsch & Kieser, 2001; Sarris et al., 2009; 2013; Volz & Kieser, 1997) (sample sizes 37–100), including one where Kava was an adjunct therapy to HRT for menopause (De Leo et al., 2001) ($n = 40$), and four studies found no significant difference (Connor & Davidson, 2002; Gastpar & Klimm, 2003; Jacobs et al., 2005; Sarris et al., 2020) (sample sizes 35–391). The two studies comparing kava to prescribed medication (oxazepam and bromazepam, $n = 145$ (Lerhl & Woelk, 2002), buspirone and opipramol, $n = 127$ (Boerner et al., 2003)) found similar decreases in anxiety in both

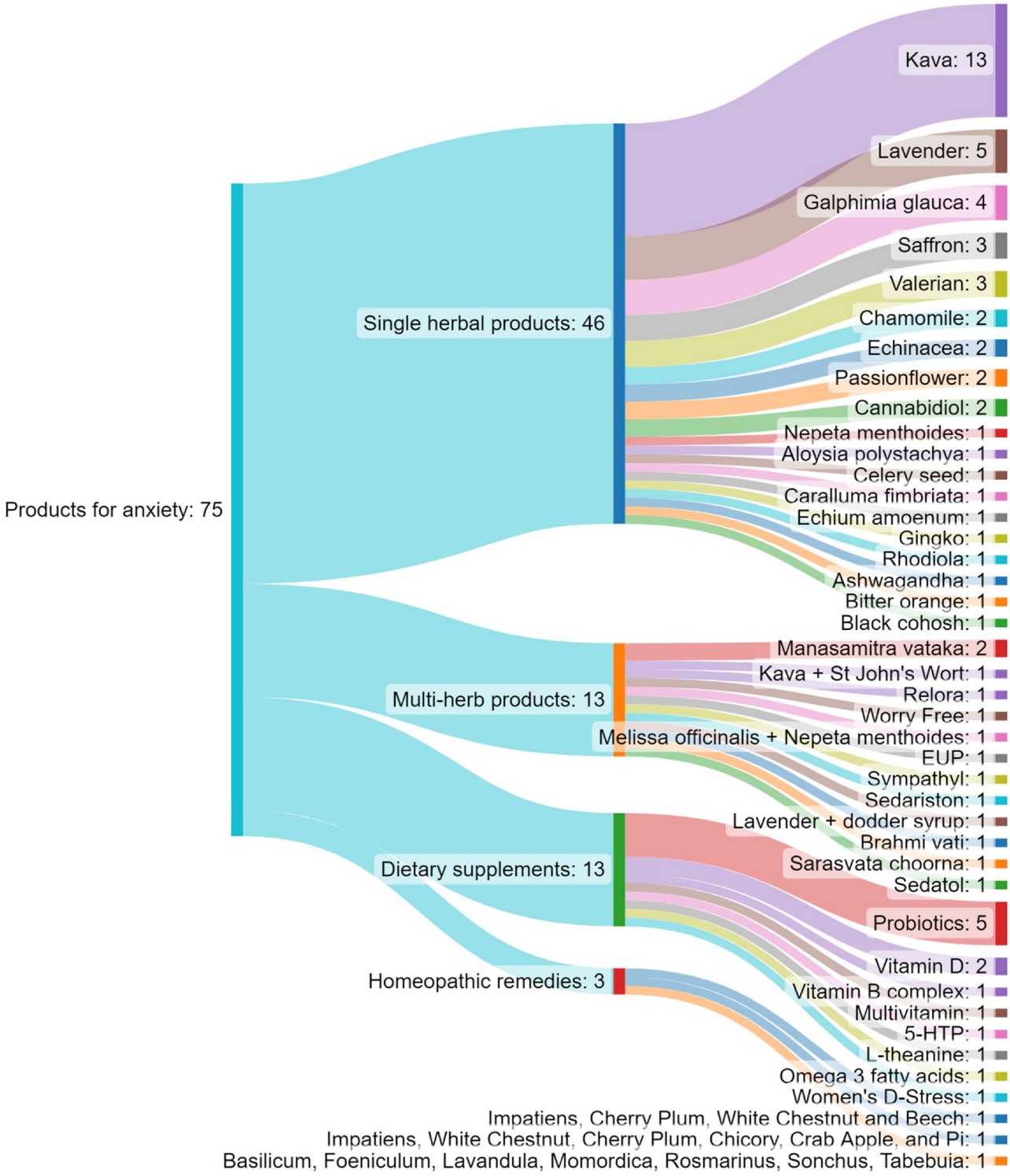

Figure 2. Plot of products evaluated in trials in this review.

groups, with no significant difference. One study ($n = 391$) also compared Kava to Valerian, with no differences in anxiety scores (Jacobs et al., 2005).

Twelve studies reported adverse events. Generally, there were no or few adverse events, with little difference between groups. Five reported no difference in liver function tests or other blood parameters between groups (Gastpar & Klimm, 2003; Malsch & Kieser, 2001; Sarris et al., 2009; Sarris et al., 2013; Volz & Kieser, 1997), but one reported slightly higher risk of liver function abnormalities from Kava (Sarris et al., 2020).

Lavender (Lavandula angustifolia Mill.)

The second most common herbal product evaluated was lavender, in five RCTs with sample sizes ranging from 77 to 523 (Farshbaf-Khalili et al., 2018; Kasper et al., 2010, 2014, 2015; Woelk & Schläfke, 2010). Four studies tested a lavender oil extract (proprietary name Silexan, usually one tablet 80 mg/day apart from one study with a second treatment arm of 160 mg/day) and one study evaluated capsules of 2 × 500 mg/day dried flower extract (Farshbaf-Khalili et al., 2018). Products were given for 6–10 weeks. Two were tested

Table 1. Descriptive summary of included studies.

		N reporting this	Mean (range) across trials
Sample size recruited		69	93 (10–539)
Sample size analysed		69	87 (10–523)
Gender (% female)		64	71% (18%–100%)
Age		58	40.0 (20.8–55.0) years
		N studies per category	
Year of publication	Before 2000		5
	2000–2009		22
	2010–2019		29
	2020 onwards		13
Target condition	Anxiety only		53
	Anxiety and depression		11
	Anxiety and insomnia		4
	Anxiety, depression and insomnia		3
Comorbid conditions	No comorbid conditions		59
	Menopause		3
	Overweight and obesity		2
	Type 2 diabetes		1
	Type 2 diabetes + vitamin D deficiency		1
	Irritable bowel syndrome		1
	Hypertension		1
	Pregnancy		1
Product type evaluated	Herbal products		55 (32 products)
	Dietary supplements		11 (8 products)
	Homeopathic remedies		3 (3 products)
	Single chemical medication		0
Evaluated as	Monotherapy		61
	Adjunct to antidepressant		7
	Adjunct to HRT		1
	Adjunct to CBT		1
Comparators	Placebo		49
	Active drug		11
	Active drug and placebo		3
	Other OTC		3
	Non-pharmacological approach and placebo		1
	Active drug and non-pharmacological approach		1
	No treatment		1
Blinding	Double blind		60
	Open label		3
	Triple blind		2
	Single blind		2
	Not reported		1
	Blinding for supplement but not high prebiotic diet (factorial trial)		1

in people with anxiety only (Kasper et al., 2014; Woelk & Schläfke, 2010), two in people with comorbid insomnia (Kasper et al., 2010, 2015), and one in menopausal women with anxiety (Farshbaf-Khalili et al., 2018). Study mean ages varied between 45.8 and 53.3 years.

Two studies compared lavender to an active drug, including 0.5 mg lorazepam (Woelk 2009) and 20 mg paroxetine (Kasper et al., 2014). Silexan was non-inferior to lorazepam ($n = 77$) (Woelk & Schläfke, 2010). In a four arm RCT ($n = 523$) comparing 80 mg Silexan, 160 mg Silexan, paroxetine and placebo, both Silexan dosages were significantly better than placebo at reducing anxiety, with the 160 mg dose significantly better than paroxetine (Kasper et al., 2014). Three other studies compared lavender and placebo and found significantly better anxiety scores (Farshbaf-Khalili et al., 2018; Kasper et al., 2010, 2015). One study with a bitter orange treatment arm ($n = 156$) found no difference compared to lavender (Farshbaf-Khalili et al., 2018). Similar numbers and types of adverse events were found across treatment arms in all studies.

Galphimia glauca Cav

The native Mexican *Galphimia glauca* (Mexico: calderona amarilla; USA: thryallis) was assessed in four trials, all in people with no comorbidities and sample sizes ranging from 34 to 135, with mean ages between 25 and 40 and mostly female samples. Products involved 1–2 capsules/day, standardised to 0.374 mg Galphimine B (Romero-Cerecero et al., 2018, 2019), 0.175 mg Galphimine B (Herrera-Arellano et al., 2012) and 0.348 mg Galphimine B (Herrera-Arellano et al., 2007). All studies compared *G. glauca* to an active drug, including alprazolam (Romero-Cerecero et al., 2019), sertraline (Romero-Cerecero et al., 2018) and lorazepam (Herrera-Arellano et al., 2007, 2012), and all studies found similar decreases in anxiety to the prescription drug, with no differences in effects. In three studies, adverse events were milder and less frequent in the *G. glauca* group (Herrera-Arellano et al., 2007, 2012; Romero-Cerecero et al., 2019), and one study found no differences (Romero-Cerecero et al., 2018).

Saffron (Crocus sativus L.)

Saffron was evaluated in three RCTs (Jafarnia et al., 2017; Mazidi et al., 2016; Milajerdi et al., 2018), with sample sizes between 40 and 60, mean ages ranging from 31 to 55 and mostly female participants. One was in people with anxiety alone (Jafarnia et al., 2017), one with comorbid depression (Mazidi et al., 2016) and one in comorbid depression and type 2 diabetes (Milajerdi et al., 2018). Doses varied: one study included 2 × 15 mg/day hydroalcoholic extract saffron for 8 weeks (Milajerdi et al., 2018), one used 2 × 50 mg/day capsules dried saffron stigma for 12 weeks (Mazidi et al., 2016), and one used a 500 mg capsules containing 450 mg saffron and 50 mg sertraline per day for 6 weeks (Jafarnia et al., 2017). All found significant reductions in anxiety compared to placebo (Mazidi et al., 2016; Milajerdi et al., 2018) or placebo plus sertraline (Jafarnia et al., 2017). Only one study reported adverse events, which found four patients reported side effects with saffron (Jafarnia et al., 2017).

Valerian (Valeriana officinalis L.)

Two studies assessed valerian and one valepotriates extract from valerian. Sample sizes ranged from 40 to 391 and mean ages from 33 to 41, with one study including people with both anxiety and insomnia (Jacobs et al., 2005). Valerian did not show promising effects for anxiety. One large three-arm RCT ($n = 391$) found no differences in anxiety between valerian and placebo or kava extract after 4 weeks, but a higher incidence of diarrhoea in the valerian group compared to placebo (Jacobs et al., 2005). Valerian showed similar effects to Sedatol capsules (a herbal mixture of passionflower, valerian, hawthorn, chamomile and piscidia) in a small study of people with anxiety (no significance testing) over 60 days in 40 participants, with no adverse effects (Rabezzana, 1995). Valepotriates extract was

Table 2. Trials of single herb products.

First author, year published country study type *n* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Kava (*n* = 14)					
De Leo et al., 2001 (De Leo et al., 2001) Italy 4 group RCT *N* = 40	100% f Aged 42–63 Physiological or surgical menopause	Kava 1 x 100 mg tablet/day(standardised to 55% kavain) + HRT (physiological menopause) or + ERT (surgical menopause) 6 months	Placebo + HRT (physiological menopause) Placebo + ERT (surgical menopause) 6 months	Greater reduction in HAM-A scores with adjunct Kava therapy	Not Reported
Sarris et al., 2020 (Sarris et al., 2020b) Australia *N* = 171	74% f 35 (12.6) yrs	2 × 2 tablets twice a day, (standardised to 60 mg kavalactones/tablet) 16 weeks	Placebo 16 weeks	No significant effect	2 SAEs in placebo group, no sig difs in total AEs (sig more poor memory and tremor in Kava group). Slightly higher risk of LFT abnormalities for Kava.
Sarris et al., 2013 (Sarris et al., 2013) Australia *N* = 58	65% f 30.1 (8.8) yrs	1 x 3 g tablets twice a day (titrated up to two tablets after 3 weeks if non-responsive), standardised to 60 mg kavalactones per tablets 6 weeks	Placebo	Significantly better HAM-A scores	No SAEs, more headaches in Kava group. No differences in LFTs between groups.
Boerner et al., 2003 (Boerner et al., 2003) Germany 3 arm RCT *N* = 127	84.3% f 20–29 yrs (13.4%) 30–39 yrs (27.6%) 40–49 yrs (33.9%) 50–59 yrs (16.5%) 60–71 yrs (8.6%)	1 x 400 mg tablet/day (standardised to 30% kavapyrones, LL150) 8 weeks + placebo tablet	1. 1 x 5 mg Buspirone hydrocholride twice per day + placebo 2. 1 x 50 mg Opipramol dihydrochloride twice per day + placebo	Similar decreases with no differences between treatments	No differences in AE types across groups, 1 SAE in Kava group (panic attack, hospitalised), 1 AE from abnormal lab values for Opipramol.
Volz 1996 (Volz & Kieser, 1997b) Germany *N* = 100	73% f 53.9 yrs	3 × 90–110 mg dried extract capsules per day (standardised to 70 mg kavalactones, WS1490) 25 weeks	Placebo	Significantly better HAM-A scores week 8 onwards	2 possibly related AEs for Kava and f2 for placebo. No clinically relevant changes in blood test results.
Sarris 2009a (Sarris et al., 2009) Australia Crossover trial *N* = 37	57% f 44.4 yrs	5 × 3.2 g tablets per day (standardised to 50 mg kavalactones) 1 week	Placebo	Significantly better reduction in HAM-A scores	No SAEs, 1 minor event leading to withdrawal (nausea), 4 minor AEs (3 Kava). No clinical signs of hepatotoxicity.
Gastpar 2003 (Gastpar & Klimm, 2003b) Germany *N* = 141	74% f 48.8 yrs	3 x 50 mg dry extract capsules per day (standardised to 35 mg kavalactones, WS 1490) 4 weeks	Placebo	No significant differences in ASI scores	6 withdrew due to AEs (unrelated to treatment), 3 AEs (2 placebo, 1 Kava). No abnormal values on LFTs or other blood tests.
Lehmann 1996 (Lehmann et al., 1996) Germany *N* = 58	74.1% f 42.9 yrs	3 x 100 mg capsules per day (WS 1490) 4 weeks	Placebo	Significantly better HAM-A scores	No undesirable events.
Malsch 2000 (Malsch & Kieser, 2001) Germany *N* = 40	37.5% f 40 yrs	2 x 50 mg capsules (standardised to 35 mg kavalactones) 3 times per day (gradual increase in week 1) + tapering off of benzodiazepine medication over two weeks	Placebo	Significantly better HAM-A scores	No SAEs. AEs in 5 kava and 10 placebo group patients, all attributed to benzodiazepine withdrawal. No clinically relevant laboratory test changes.
Connor 2002 (Connor & Davidson, 2002) USA *N* = 35	82% f 51.7 (11.6) yrs	1 x 70 mg capsules (70 mg kavalactones) twice a day for 1 week, 2 x 70 mg for 3 weeks	Placebo	No significant differences in HAM-A scores	No evidence of side effects.

(*Continued*)

Table 2. Continued.

First author, year published country study type *n* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Jacobs et al., 2005 (Jacobs et al., 2005) USA 3 arm RCT *N* = 391	79% f 41.4 yrs Insomnia	3 x 100 mg capsule per day + 2 placebo valerian capsules 4 weeks	1. Placebo (for Kava and Valerian) 2. Valerian softgel	No significant difference in STAI scores	Mild AEs, similar between groups.
Lehrl, 2004 (Lehrl, 2004) Germany *N* = 57	53.5% f 52.1 yrs Insomnia	2 x 100 mg dry extract capsules (standardised to 70 mg kavalactones) per day 4 weeks	Placebo	Significantly better HAM-A scores	1 AE (placebo)
Lerhl 2002 (Lerhl & Woelk, 2002) Germany 3 arm RCT *N* = 145	% f NR Age NR	300 mg/day WS1490 extract 6 weeks	1. Oxazepam (15 mg/day) 2. Bromazepam (9 mg/day)	Similar decreases with no differences between treatments	No undesirable effects or effects causally related to Kava reported.
Lavender *Lavandula angustifolia*					
Woelk 2009 (Woelk & Schläfke, 2010) Germany *N* = 77	77% f Age range 21–-65	1 x 80 mg Silexan lavender oil capsules per day + lorazepam placebo 6 weeks	1 × 0.5 mg lorazepam + Silexan placebo	Silexan non-inferior to lorazepam	No SAEs, 26 AEs Silexan, 19 lorazepam
Farshbaf-Khalili 2018 (Farshbaf-Khalili et al., 2018) Iran *N* = 156 3 arm RCT	100% f 53.32 yrs Menopause	2 x 500 mg capsules dried *Lavandula angustifolia* flower per day 8 weeks	1. Placebo 2. 2 x 500 mg bitter orange capsules	Significantly lower anxiety scores than placebo, no difference to bitter orange	Lavender: nausea (8.2%), palpitations (4.4%) and headache (4.1%) Bitter orange: nausea (4.2%), palpitations (4.2%) and headache (2.1%) Placebo: nausea (10.4%), palpitations (2.1%) and headache (6.3%)
Kasper et al., 2014 (Kasper et al., 2014b) Germany *N* = 523 4 arm RCT	73.7% f 45.8 yrs	1. 80 mg Silexan lavender oil capsules per day + paroxetine placebo 2. 160 mg Silexan capsules + paroxetine placebo10 weeks	1. 1 x 20 mg paroxetine + Silexan placebo 2. Placebo	Silexan 160 and 80 mg significantly better than placebo, 160 mg significantly better than paroxetine but not 80 mg.	5 SAEs (all unrelated), 48 AEs in 160 mg Silexan, 71 AEs in 80 mg Silexan, 89 AEs paroxetine, 73 AEs placebo.
Kasper 2015 (Kasper et al., 2015b) Germany *N* = 170	71.8% f 48.5 yrs Insomnia	1 x 80 mg Silexan lavender oil capsules per day 10 weeks	Placebo	Significantly lower anxiety scores than placebo	Silexan 34 AEs, placebo 36 AEs
Kasper et al., 2010 (Kasper et al., 2010) Germany *N* = 212	75% f 46.1 yrs Insomnia	1 x 80 mg Silexan lavender oil capsules per day 10 weeks	Placebo	Significantly lower anxiety scores than placebo	Silexan 55 AEs, placebo 68 AEs
Galphimia glauca					
Romero-Cerecero et al., 2019 (Romero-Cerecero et al., 2019) Mexico *N* = 135	NR Aged 30+ years	1 x *Galphimia glauca* capsule (standardised to 0.374 mg Galphimine B) per day 10 weeks	1 x 1 mg alprazolam per day	Similar decreases with no differences between treatments	Significantly fewer AEs in *G. glauca* group (68% vs 95%, $p < 0.001$)
Romero-Cerecero et al., 2018 (Romero-Cerecero et al., 2018) Mexico *N* = 34	79% f 25 yrs	2 x *Galphimia glauca* capsule (standardised to 0.374 mg Galphimine B) per day (1st week 1/day) 10 weeks	1 x 50 mg sertraline per day	Similar decreases with no differences between treatments	Similar tolerability, 1 patient in each group stopped treatment due to side effects
Herrera-Arellano et al., 2012 (Herrera-Arellano et al., 2012) Mexico *N* = 104	85% f 40 yrs	1–2 × 3.48 mg *Galphimia glauca* (standardised to 0.175 mg Galphimine B) capsule twice per day 12 weeks	1–2 × 0.5 mg lorazepam twice per day	Similar decreases with no differences between treatments	More frequent side effects in control
Herrera-Arellano et al., 2007 (Herrera-Arellano et al., 2007b) Mexico *N* = 114	77% f 37.8 yrs	2 x 310 mg Galphimia glauca capsule (standardised to 0.348 mg Galphimine B) per day 4 weeks	1 x 1 mg lorazepam twice per day	Similar decreases with no differences between treatments	Control produced more excessive sedation (21% vs 7%). No pathological alterations in laboratory tests in either group.

(*Continued*)

Table 2. Continued.

First author, year published country study type *n* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Saffron					
Jafarnia et al., 2017 (Jafarnia et al., 2017) Iran *N* = 40	65% f 31 yrs	1 x 500 mg capsule (450 mg saffron + 50 mg sertraline) per day 6 weeks	1 x capsule (placebo + 50 mg sertraline) per day	Significantly better reduction in anxiety scores	4 saffron patients reported side effects (not discontinued)
Milajerdi et al., 2018 (Milajerdi et al., 2018) Iran *N* = 52	77% f 55 yrs Depression, Type 2 diabetes mellitus (allowed to use up to 1.5 g metformin and or 10 mg glibenclamide)	2 x 15 mg capsules per day saffron hydroalcoholic extract 8 weeks	Placebo	Significantly better reduction in anxiety scores	Not reported
Mazidi et al., 2016 (Mazidi et al., 2016) Iran *N* = 60	70% f 43.2 yrs Depression	2 x 50 mg capsules per day dried saffron stigma 12 weeks	Placebo	Significantly better reduction in anxiety scores	Not reported
Valerian					
Jacobs et al., 2005 (Jacobs et al., 2005) USA 3 arm RCT *N* = 391	79% f 41.4 yrs Insomnia	2 x Valerian softgel capsule per day (standardised to 3.2 mg (1%) valerenic acids) + 1 placebo capsule for Kava 4 weeks	1) Placebo (for valerian and kava) 2) Kava extract	No significant difference in STAI scores	Mild AEs, similar between groups apart from higher incidence of diarrhoea in valerian vs placebo
Rabezzana, 1995 (Rabezzana, 1995) Italy *N* = 40	55% f 33.43 yrs	Valerian 50 mg/day 60 days	265 mg per day Sedatol capsules (Passionflower, valerian, hawthorn, chamomile and piscidia, mixed at a constant dosage (no further information))	Similar improvements in both groups (no significance testing)	No AEs
Andreatini 2001 (Andreatini et al., 2002) Brazil *N* = 36 Valepotriates	53% f 41.1 yrs	3 x 50 mg valepotriates capsules (80% dihydrovaltrate, 15% valtrate and 5% acevaltrate) 4 weeks	1. 2.5 mg diazepam three times per day 2. Placebo (3 lactose capsules per day)	No significant difference between any groups	No SAEs, 1 diazepam and 1 placebo patient withdrew due to AEs
Chamomile					
Mao et al., 2016 (Mao et al., 2016b) USA *N* = 93 Randomised after 12 weeks open-label chamomile therapy	70% f 47.3 yrs	3 x 500 mg chamomile capsule per day (standardised to 1.2% Api-7Glc and 0.2–0.6% tetracoumaroyl spermine (TCS)) 26 weeks	Placebo	No difference in time to or hazard of relapse but lower anxiety scores than placebo	No significant difference in AEs (17% vs 19%), all mild
Amsterdam et al., 2009 (Amsterdam et al., 2009) USA *N* = 57	60% f 45.7 yrs	1–5 x 220 mg capsules (standardised to 1.2% apigenin) per day (1 capsule/day first week, 2 second week, then adjusted based on response and side effects) 8 weeks	Placebo	Significantly better reduction in anxiety scores	1 per group discontinued treatment due to AEs, 11 chamomile AEs and 22 placebo (not significant)
Echinacea angustifolia					
Lopresti 2020 (Lopresti & Smith, 2021) Australia *N* = 106 3 arm RCT	59% f 41 yrs	2 x 20 mg Echinacea angustifolia EP107TM (alkamide content of 1–1.5%) twice daily 1 x 20 mg tablet + placebo tablet twice daily6 weeks	Placebo	No significant differences between groups	No SAEs, frequency of AEs similar across groups, 1 high dose and 1 low dose participant withdrew due to digestive complaints
Haller 2020 (Haller et al., 2020) Hungary *N* = 62	53% f 37.3 yrs	2 x 40 mg Echinacea angustifolia root tablets per day (Anxiofit-1, standardised to 1–1.5% alkamide content) 7 days	Placebo	Significantly better reductions in anxiety	4 patients reported 8 AEs, all in placebo group

(*Continued*)

Table 2. Continued.

First author, year published country study type *n* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Passionflower *(Passiflora incarnata)*					
Akhondzadeh et al., 2001 (Akhondzadeh et al., 2001) Iran *N* = 32	56% f Mean age NR	45 drops passionflower tincture (Passipay) per day + placebo pill 4 weeks.	30 mg oxazepam per day + placebo drops	Similar reductions across both groups, only significantly different at 4 day timepoint (favouring oxazepam)	No significant differences in total AEs
Nojoumi et al., 2016 (Nojoumi et al., 2016b) India *N* = 30	86% f 30.63 yrs	3 × 15 drops passionflower tincture per day (Pasipy) + 50 mg sertraline (first two weeks) and 100 mg sertraline (second two weeks) 4 weeks	Placebo (aqueous solution edible alcohol and colouring) + 50 mg sertraline (first two weeks) and 100 mg sertraline (second two weeks)	Significant improvement in anxiety symptoms vs placebo	No differences in major or significant AEs observed between groups
Cannabidiol (CBD)					
Masataka, 2019 (Masataka, 2019) Japan *N* = 37	30% f Mean age NR	1 x RSHO-X hemp oil (300 mg CBD per dose) per day 4 weeks	Placebo (olive oil)	Significant reduction compared to control	No systematic evaluation of AEs
Kwee et al., 2022 (Kwee et al., 2022) Netherlands *N* = 78	40% f 36.7 yrs	300 mg synthetic CBD ingested 2 hr before 8 x 90 min weekly CBT sessions 8 weeks	Placebo ingested before 8 x 90 min CBT sessions	No significant differences (placebo improved more numerically)	No SAEs, similar rates of AEs between groups
Other					
Firoozabadi et al., 2017 (Firoozabadi et al., 2017) Iran *N* = 70 Nepeta menthoides	75.8% f 36.31 yrs Depression	2 x 400 mg Nepeta menthoides per day (1 per day for first week) 4 weeks	2 x 50 mg Sertraline + 425 mg placebo capsule per day ((1 per day for first week)	Significant reductions compared to sertraline	1 AE N. menthoides group, 11 in sertraline
Carmona et al., 2019 (Carmona et al., 2019) Brazil *N* = 54 Aloysia polystachya	73.85% f 39.5 yrs	1 x 300 mg *Aloysia polystachya* (Griseb.) Moldenke capsules twice daily 8 weeks	Placebo	Significantly lower scores compared to placebo.	Similar mild AEs across groups.
Amsterdam et al., 2009 (Amsterdam et al., 2009) USA *N* = 24 Black Cohosh	100% f 53.75 yrs Menopause	2 x 32 mg Black cohosh (*Cimicifuga racemosa*) capsules per day (minimum 1, maximum 4 adjusted for greater effects or to reduce adverse effects) 12 weeks	Placebo	No significant difference between groups	1 discontinued Black cohosh treatment due to AEs, 14 possible, probable or definite AEs in Black cohosh and 8 in placebo, no difference in distribution
Kell 2019 (Kell et al., 2019) Australia *N* = 97 *Caralluma fimbriata*	71% f 44 yrs	500 mg Caralluma fimbriata capsules twice a day 8 weeks	Placebo	Significant reduction compared to control	Not reported
Rad 2022 (Shayani Rad et al., 2023) Iran *N* = 50 Crossover trial Celery seed	52% f 50.34 Hypertension	2 × 2 celery seed capsules per day (1.34 g total) 4 weeks	Placebo	Significant improvement compared to placebo	Mild AEs, no differences between groups
Sayyah et al., 2012 (Sayyah et al., 2012) Iran *N* = 37 Echium anoenum	48.64% f 25.5 yrs	3 x 250 mg capsules Echium anoenum per day plus fluoxetine (20 mg/day) 8 weeks	Placebo plus fluoxetine (20 mg/day)	Significant treatment x time interaction favouring *E. anoenum*	No difference in frequency of AEs between groups, most common side effect headache
Woelk 2007 Germany (Woelk et al., 2007) *N* = 104 Gingko biloba	62% f Mean age NR (range 18–70)	Gingko biloba extract (EGB 761, standardised to 22%–27% of flavone glycosides and 5%–7% terpene lactones) 3. 2 x 40 mg extract three times a day 4. 2 x 80 mg extract three times a day4 weeks	Placebo	Both groups significantly better than placebo	9 AEs (3 per group), no SAEs

(*Continued*)

Table 2. Continued.

First author, year published country study type *n* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Cropley 2015 (Cropley et al., 2015) UK *N* = 80 Rhodiola	39.5% f 21.9 yrs	2 x 200 mg Vitano capsules (Rosalin (WS® 1375), a proprietary dry extract from Rhodiola rosea roots) per day 14 days	No treatment	Significant reduction in anxiety compared to control	4 AEs in treatment group (forgetfulness, loss of appetite, food poisoning, pelvic infection)
Fuladi 2020 (Fuladi et al., 2021) Iran *N* = 40 Ashwagandha	45% f 40.20 yrs	2–3 x 1 g Withania somnifera capsules per day after 1 week of 1 capsule/ day + current SSRI treatment (no further details) 6 weeks	Placebo + current SSRI treatment	Significant reduction in anxiety scores compared to placebo	No difference in AEs, side effects rarely reported
Farshbaf-Khalili, 2018 (Farshbaf-Khalili et al., 2018) Iran *N* = 156 3 arm RCT Bitter orange	100% f 53.32 yrs Menopause	2 x 500 mg bitter orange (*Citrus aurantium*) capsules	1. Placebo 2. 2 x 500 mg capsules dried *Lavandula angustifolia* flower per day 8 weeks	Significantly lower anxiety scores than placebo, no difference to lavender.	Bitter orange: nausea (4.2%), palpitations (4.2%) and headache (2.1%) Lavender: nausea (8.2%), palpitations (4.4%) and headache (4.1%) Placebo: nausea (10.4%), palpitations (2.1%) and headache (6.3%)

ASI = anxiety status inventory, SAE = serious adverse event, AE = adverse event, RCT = randomised controlled trial, HRT = hormone replacement therapy (estradiol and progestogen), ERT = estradiol replacement therapy, HAM-A = Hamilton Anxiety Rating Scale, STAI = State-Trait Anxiety Inventory

not significantly different to diazepam or placebo after 4 weeks in another small RCT ($n = 36$), although had fewer withdrawals due to adverse events (Andreatini et al., 2002).

Other single herb studies

Chamomile, Echinacea, Passionflower, Cannabidiol and Manasamitra vataka all had two studies each.

For chamomile (*Matricaria recutita* L. and *Matricaria chamomilla* L.), two studies were carried out in people with anxiety in the USA, with positive effects. One mid-size trial showed effects compared to placebo for 1500 mg/day chamomile capsules for 26 weeks, with mild and similar side effects in both groups (Mao et al., 2016). The other trial was smaller ($n = 57$) and showed significantly better anxiety scores for between one and five 220 mg capsules per day (adjusted based on response and side effects) for eight weeks (Amsterdam et al., 2009). There were no significant differences in adverse events between groups.

Mixed effects upon anxiety were found for echinacea vs placebo (sample sizes 62 and 106), with similar frequency of adverse events (Haller et al., 2020; Lopresti & Smith, 2021). Both studies used *Echinacea angustifolia* DC. tablets (one root, one not specified), one at 2 × 40 mg/day (Haller et al., 2020) and one with two arms – 2 × 20 mg/day and 1 × 20 mg/day (Lopresti & Smith, 2021), with significant effects only in the higher dose study (Haller et al., 2020). Both standardised tablets to 1%–1.5% alkamide content. Similar adverse events were found between groups in one study (Lopresti & Smith, 2021) and only reported in the placebo group in the other (Haller et al., 2020).

Two small studies ($n = 30$ and 32) evaluated passionflower tincture (*Passiflora incarnata* L.) drops (45 drops/day) for 4 weeks (Akhondzadeh et al., 2001), one alongside 50–100 mg sertraline (Nojoumi et al., 2016). The latter study found significantly better anxiety scores than sertraline plus placebo (Nojoumi et al., 2016). The first compared passionflower to 30 mg oxazepam (Akhondzadeh et al., 2001) and found similar reductions in anxiety, that favoured oxazepam at one early timepoint. There were no differences in adverse events.

Mixed effects were found for cannabidiol (CBD) extracts from *Cannabis sativa* L., with a reduction in anxiety in 37 participants when 300 mg/day was provided for 4 weeks compared to placebo (Masataka, 2019). No additional impact was found when 300 mg CBD was ingested prior to weekly CBT sessions, compared to a placebo in 78 participants (Kwee et al., 2022). Adverse events were not reported in Masataka, 2019, but Kwee et al., 2022 showed similar events between CBD and placebo groups.

Ten single herb products were evaluated in individual studies, with small to moderate sample sizes (24 to 156). Promising products included *Nepeta menthoides* Boiss. & Buhse in people with comorbid depression (Firoozabadi et al., 2017), *Aloysia polystachya* (Griseb.) Moldenke (Carmona et al., 2019), *Caralluma fimbriata* Wall. (Kell et al., 2019), *Apium graveolens* L. (celery seed) in people with comorbid hypertension (Shayani Rad et al., 2023), *Echium amoenum* Fisch. & C.A. Mey. as an adjunct to fluoxetine (Sayyah et al., 2012), *Gingko biloba* (Woelk et al., 2007), *Rhodiola rosea* L. (Cropley et al., 2015), *Withania somnifera* (L.) Dunal (ashwagandha) as an adjunct to SSRI

Table 3. RCTs of multi-herb products for anxiety.

First author, year published country study type *N* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Tubaki et al., 2012 (Tubaki et al., 2012) India *N* = 65 3 arm RCT Manasamitra vataka	18% f 28.18 yrs	1 x 100 mg Manasamitra vataka (multiherb preparation, ingredients not reported) tablet twice a day 30 days	1. M. vataka + Shirodhara (oil dripping with Brahmi for 45 min for 7 days) 2. Clonazepam (0.25 mg in morning and 0.50 mg at night)	No differences between groups	Mild side effects in all groups
Khot 2021 (Khot et al., 2022) India *N* = 54 Manasamitra vataka	62.5% f 37.65 yrs	Manasamitra vataka (multi-herb product, ingredients not reported) capsules 500 mg three times per day 45 days	500 mg Brahmi vati (multi-herb product, ingredients not reported) capsules three times per day	No significant difference between groups	No AEs, normal liver function tests (LFTs), blood parameters and serum creatinine
Sarris 2009 (Sarris et al., 2009) Australia Pilot crossover trial *N* = 18 Kava + St John's Wort	75% f 42.9 (12.4) yrs Depression	1 × 2.66 g Kava and St John's Wort aqueous extract tablets (standardised to 50 mg kavalactones) 3 times/ day 4 weeks	Placebo	No significant differences on BAI	No SAEs, 2 AEs (1 per group). No changes in LFTs for Kava. 1 withdrawal due to possible reaction (heightened anxiety)
Ranjbar et al., 2018 (Ranjbar et al., 2018) Iran *N* = 45 Melissa and nepeta	Gender NR but more females 39.14 yrs Depression, insomnia	3 x 500 mg capsules (total 1000 mg of *Melissa officinalis* and 400 mg *Nepeta menthoides)* per day 4 weeks	Placebo	Significant improvement in anxiety compared to placebo	No SAEs, some AEs but groups not reported
Kalman 2007 (Kalman et al., 2008) USA *N* = 40 Relora	100% f 38.6 yrs Overweight	3 x 250 mg Relora capsules (*Magnolia officinalis* bark and *Phellodendron amurens* bark, standardised ≥1.5% honokiol and ≥0.1% berberine) 6 weeks	Placebo	Significantly reduced state anxiety vs placebo	No SAEs, 2 treatment and 1 placebo dropout due to AEs
Mills 2002 (Mills et al., 2002) USA *N* = 10 Worry Free	Not reported	2 x tablets twice a day (dose not reported) (Withania somnifera, Tinospora cordifolia, Herpestis monniera, Nardostachys jatamansi, Convolvolus pluricalis, Glycyrrhiza glabra, Pearl pisti, and Alpinia galangal) 6 months	Placebo	Significant reduction vs placebo	No AEs
Khot 2021 (Khot et al., 2022) India *N* = 54 Brahmi vati	62.5% f 37.65 yrs	500 mg Brahmi vati (multi-herb product, ingredients not reported) capsules three times per day 45 days	Manasmitra vataka (multi-herb product, ingredients not reported) capsules 500 mg three times per day	No significant difference between groups	No AEs, normal LFTs, blood parameters and serum creatinine
Bourin 1997 (Bourin et al., 1997) France *N* = 91 Euphytose (EUP)	Not reported	2 capsules EUP (dry extracts of Passiflora incarnata (40 mg), Valeriana officinalis (50 mg), Crataegus oxyacantha (10 mg), Ballota foetida (10 mg) and of powder of Paullinia cupana (15 mg) and of Cola nitida (15 mg)) three times a day 28 days	Placebo	Significant differences favouring EUP group	4 EUP AEs, 8 placebo AEs, no SAEs
Firoozeei et al., 2020 (Firoozeei et al., 2020) Iran *N* = 50 Lavender-dodder	80% f 37.35 yrs Depression	2 × 5 ml Lavender-dodder herbal syrup per day + 1 placebo tablet/day 6 weeks	Citalopram 20 mg per day + 5 ml placebo syrup twice a day	Greater reduction in anxiety symptoms in syrup group	No significant differences in side effects, most common side effect in both groups was drowsiness

(*Continued*)

Table 3. Continued.

First author, year published country study type *N* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Gupta 2014 (Gupta et al., 2014) India *N* = 102 Sarasvata choorna	54.4% f Not reported	1 g Sarasvata choorna (Kushta Root 1 part, Ashwagandha Root 1 part, Saindhava lavana 1 part, Ajamoda Fruit 1 part, Shweta jeeraka Fruit 1 part, Krishna jeeraka Fruit 1 part, Sunthi Rhizome 1 part, Maricha Fruit 1 part, Pippali Fruit 1 part, Patha Root 1 part, Shankhapushpi Whole plant 1 part, Vacha Rhizome 11 parts, Brahmi Whole plant Quantity sufficient for bhavana (tituration)) mixed with honey and ghee three times a day 60 days	Placebo (roasted wheat powder with honey and ghee)	No significant difference between groups	Not reported
Rabezzana, 1995 (Rabezzana, 1995) Italy *N* = 40 Sedatol	55% f 33.43 yrs	265 mg per day Sedatol capsules (Passionflower, valerian, hawthorn, chamomile and piscidia, mixed at a constant dosage (no further information)) 60 days	Valerian 50 mg/day	Similar improvements in both groups (no significance testing)	No AEs
Panijel, 1985 (Panijel, 1985) Germany *N* = 100 Sedariston	66% f 52.5 yrs	1 capsule (90–100 mg St John's Wort standardised to 0.05 mg hypericin, 50 mg Valerian) twice a day, increased to two if insufficient (*n* = 27) 2 weeks	1 x 2 mg Diazepam capsule twice a day, increased to two if needed (*n* = 35)	Better anxiety scores compared to control	AEs in 4% phytotherapy patients and 14% diazepam patients (including dizziness, increased daytime sleepiness and dejection)
Hanus 2004 (Hanus et al., 2004) France *N* = 264 Sympathyl	81% f 44.6 yrs	2 x Sympathyl tablets (75 mg Crataegus oxyacantha, 20 mg Eschscholtzia californica, 75 mg elemental magnesium) twice a day 3 months	Placebo	Significant decreases in anxiety at most timepoints	No differences in AEs between groups (22 study drug, 15 placebo, 28 possibly related)

treatment (Fuladi et al., 2021) and *Citrus x aurantium* L. (bitter orange) in menopausal women (Farshbaf-Khalili et al., 2018). Only *Cimicifuga racemosa* (L.) Nutt. (black cohosh) did not show an impact upon anxiety in 24 menopausal women (Amsterdam et al., 2009).

Multi-herb product studies

Eleven multi-herb products were evaluated in single studies and one in two studies (Table 2), with sample sizes from 10 to 264. Multi-herb products often combined those also tested alone.

Manasamitra vataka, an Ayurvedic preparation (ingredients not specified but a multi-herb mix) for 30 and 45 days was not significantly different to Brahmi vati (another multi-herb Ayurvedic preparation) in 54 participants (Khot et al., 2022), or clonazepam or Manasamitra vataka plus Shirodhara oil dripping in 65 participants (Tubaki et al., 2012). Studies found no or mild side effects (Khot et al., 2022; Tubaki et al., 2012).

Kava plus St John's Wort did not improve anxiety scores in a pilot crossover trial (*n* = 18) in people with comorbid depression (Sarris et al., 2009). *Melissa officinalis* L. plus *N. menthoides* (in people with comorbid depression and insomnia), Relora (*Magnolia officinalis* Rehder & E.H. Wilson and *Phellodendron amurense* Rupr.) in overweight people, Worry Free (a mix of ashwagandha, *Tinospora cordifolia* Miers., *Herpestis monniera, Nardostachys jatamansi, Convolvolus pluricalis, Glycyrrhiza glabra, Pearl pisti,* and *Alpinia galangal*), Euphytose (a mix of *Passiflora incarnata* (passionflower), *Valeriana officinalis* L. (valerian), *Crataegus oxycantha* (hawthorn), *Ballota foetida* (black horehound), *Paullinia cupana* (guarana) *and Cola nitida* (cola)) and Sympathyl (a mix of *Crataegus oxyacantha* L. (hawthorn), *Eschscholtzia californica* Bernh. (Californian poppy) and magnesium) reduced anxiety scores compared to placebo (Bourin et al., 1997; Hanus et al., 2004; Kalman et al., 2008; Mills et al., 2002; Ranjbar et al., 2018). Sedariston (*Hypericum perforatum* L. (St John's Wort) and *Valeriana officinalis* L. (valerian)) reduced anxiety compared to diazepam (Panijel,

1985), whilst lavender and dodder syrup (*Lavandula angustifolia* Mill. and *Cuscuta chinensis* Lam.) reduced anxiety compared to citalopram in people with comorbid depression (Firoozeei et al., 2020). Brahmi vati was not significantly different to Manasamritra vataka (Khot et al., 2022) and Sarasvata choorna was not significantly different to placebo (Gupta et al., 2014). Similar effects were found between Sedatol (a mix of passionflower, valerian, hawthorn, chamomile and piscidia) and valerian (Rabezzana, 1995). Most studies reported no or mild AEs.

Dietary supplements

Eleven trials of dietary supplements for anxiety evaluated 13 comparisons of eight different products (Table 4). Five RCTs evaluated probiotics, with sample sizes between 39 and 118. Probiotics were given for 6–8 weeks in four studies (Eskandarzadeh et al., 2021; Freijy et al., 2022; Lee et al., 2021; Pinto-Sanchez et al., 2017) and from 26 to 30 weeks of pregnancy until delivery in one pilot study (Browne et al., 2021). Two were in people with comorbid depression (Freijy et al., 2022; Lee et al., 2021), one in comorbid depression and irritable bowel syndrome (Pinto-Sanchez et al., 2017), one in pregnancy with comorbid anxiety or depression (Browne et al., 2021), and one in anxiety alone (Eskandarzadeh et al., 2021). Four used capsules and one used sachets (Pinto-Sanchez et al., 2017), and one was given as an adjunct to sertraline (Eskandarzadeh et al., 2021). One RCT tested a single probiotic strain (Pinto-Sanchez et al., 2017), whilst others tested a combination of 2–9 strains. All compared probiotics to placebo, and one also compared probiotics to a high prebiotic diet in a factorial RCT. Three studies found no difference (Browne et al., 2021; Freijy et al., 2022; Pinto-Sanchez et al., 2017), one a significant difference (Eskandarzadeh et al., 2021) and one a significant at only one timepoint (Lee et al., 2021). Adverse events showed little difference between groups.

Out of the six remaining studies, few showed any promising effects at reducing anxiety. Fortnightly vitamin D tablets in people with anxiety and comorbid type 2 diabetes and vitamin D deficiency showed a significant reduction in anxiety after 16 weeks compared to placebo (Fazelian et al., 2019), however a three arm trial comparing vitamin D to a vitamin B complex and a multivitamin formula found both formulas were significantly better than vitamin D in people with comorbid depression (Kaplan et al., 2015). The latter study showed no difference in adverse events (Kaplan et al., 2015) (not reported in Fazelian et al., 2019).

Further studies evaluated 5-hydroxytryptophan (5-HTP), L-theanine, omega 3 fatty acids and a multivitamin supplement. For 5-HTP, 25–150 mg/day over eight weeks showed no difference to placebo or clomipramine, with no side effects data reported (Kahn et al., 1987). L-theanine (550 mg/day alongside current antidepressant) showed no difference to placebo alongside current antidepressant in effectiveness or safety over eight weeks (Sarris et al., 2019), whilst omega 3 fatty acids (3 × 500 mg/day for 8 weeks) in women with psychological distress found no significant difference to placebo, but a higher rate of adverse events such as fish aftertaste and constipation (Lucas et al., 2009). One multivitamin and mineral supplement (also containing Ashwagandha root) also showed no effects in women with psychological distress compared to placebo, and did not report safety data (Oliver-Baxter et al., 2018).

Homeopathic products

Three RCTs tested three different homeopathic remedies (Table 4), with samples sizes ranging from 30 to 81 (Batistella et al., 2021; Fusco et al., 2021; Salles & Silva, 2012). All were combinations of four to seven flower essences given as 4 × 4 drops/day, with no adjunctive therapies, for between four weeks and two months. Two were in people with anxiety only (Batistella et al., 2021; Salles & Silva, 2012), and one in people with comorbid overweight or obesity (Fusco et al., 2021). All found positive effects upon anxiety scores compared to the placebo group, although one study reported intergroup comparisons for a 1–3 rating scale with intragroup comparisons only for the validated questionnaire (Batistella et al., 2021). None reported safety data.

Ongoing studies (protocols)

Nine trial protocols labelled as ongoing in the trials registry entry were included. Two were from the USA and one each was from Brazil, the Netherlands, Australia, Canada, India, South Korea, and the UK. Target sample sizes ranged from 30 to 300. Six are recruiting samples with anxiety alone; one is recruiting people with diffuse glioma and anxiety, one with chronic pain and anxiety and one with depression, stress and anxiety. The vast majority of studies ($n = 6$) are testing a cannabidiol preparation, ranging in doses from 50 to 800 mg/day for between 3 and 10 weeks. Five are comparing CBD to a placebo and one to clonazepam (0.5 mg/day). The remaining three studies are testing WLTH calm ease powder (an Ayurvedic herbal preparation with no further descriptors or content details) vs placebo, SB-109 (*Platycodon grandiflorum* and *Poncirus trifoliate*, 2 × 600 mg tablets once a day) vs placebo and a high-EPA multinutrient supplement (1125 mg EPA, 441 mg DHA, 330 mg magnesium and 7.5 mg α-tocopherol) vs placebo. A list of relevant registry entries is provided in Supplementary File 2.

Discussion

This scoping review found 69 RCTs and nine protocols of ongoing studies testing 43 OTC products in people with anxiety. Most products were herbal medicines. Studies were concentrated on a small number of species - mainly Kava, with three to five studies for lavender, *G. glauca,* saffron and valerian products. Otherwise, the vast majority of products were tested in individual studies. Ongoing protocols indicate an increased interest in evaluating CBD for anxiety but few other product trends. Fewer dietary supplement trials were found. Those included focussed mainly on probiotics, which showed limited effects. We found only three studies of homeopathic remedies, all of which were flower essences. No studies on OTC medicines containing a single active chemical were found.

Table 4. RCTs of dietary supplements for anxiety.

First author, year published country study type *N* analysed	Population % female Age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Pinto Sanchez 2017 (Pinto-Sanchez et al., 2017) Canada *N* = 44 Probiotics	54% f Age NR Depression and IBS	1 x sachet of Bifdobacterium longum NCC3001 (1.0E + 10 colony-forming units/1 g powder with maltodextrin) per day 6 weeks	Placebo	No difference to placebo	No SAEs
Eskandarzadeh et al., 2021 (Eskandarzadeh et al., 2021) Iran *N* = 39 Probiotics	81.25% f 33.92 yrs	1 x capsule Probiotics (Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis and Lactobacillus acidophilus with $18*10^9$ colony forming units) + sertraline 8 weeks	Placebo	Significant reduction in anxiety vs placebo	1 in each group excluded due to side effects (dizziness, pruritis), no other AEs
Lee et al., 2021 (Lee et al., 2021) South Korea *N* = 122 Probiotics	68% f 38.26 yrs Depression	2 x 500 mg NVP1704 (Lactobacillus reuteri NK33 and Bifidobacterium adolescentis NK98 freeze-dried with maltodextrin, 2.5 × 10 to power 9 CFU) capsules once per day 8 weeks	Placebo	Significant decrease in anxiety at third but not fourth visit	No difference in AEs between groups
Freijy et al., 2022 (Freijy et al., 2022) Australia *N* = 118 Factorial RCT Probiotics	91% f 35.38 yrs Depression (psychological distress)	1 x capsules twice a day (Bifidobacterium bifidum (Bb-06): 2 billion CFU; Bifidobacterium animalis subsp. lactis (HN019): 1 billion CFU; Bifidobacterium longum (R0175): 1 billion CFU; Lactobacillus acidophilus (La-14): 2 billion CFU; Lactobacillus helveticus (R0052): 2 billion CFU; Lactobacillus casei (Lc-11): 2 billion CFU; Lactobacillus plantarum (Lp-115): 1 billion CFU; Lactobacillus rhamnosus (HN001): 1 billion CFU) 8 weeks	1. high-prebiotic diet (7+ servings per day pre-biotic rich food (min 5 g/day) introduced gradually over 5 days, video advice and food hamper) + placebo 2. Probiotic + pre-biotic diet 3. Placebo + diet as usual.	No effect of probiotic or symbiotic treatments compared to placebo	Rare and similarly distributed between groups
Browne et al., 2021 (Browne et al., 2021) Netherlands *N* = 39 Pilot Probiotics	100% f 30.7 yrs Pregnancy 26–30 weeks, with depression or anxiety	Ecologic Barrier 1 x 2 g/day (Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58), 2.5 × 10^9 CFU/g Until delivery	Placebo	No difference in anxiety symptoms	No differences in SAEs and AEs (17 in probiotic, 12 in placebo). No SAEs related to study.
Kaplan 2015 (Kaplan et al., 2015) Canada *N* = 56 Various	97.3% 46 yrs Depression	1. Vitamin D tablets 1 x 1000 IU/day 2. Vitamin B complex 1/day (20 mg B6, 500 mcg B12, 50 mg thiamine, 20 mg riboflavin, 400 mcg folate, 50 mg delta-pantothenic acid, 300 mcg biotin, 300 mg niacin, 20 mg intrinsic factor) 3. Broad spectrum mineral/vitamin formula 4/day (384 mcg vitamin A, 8 mg B6, 200 mcg B12, 133.2 mg C, 320IU D, 53.6 mg E, folate 320 mcg, 4.8 mg delta-pantothenic acid, 240 mcg biotin, 20 mg niacin, 138.8 mcg Chromium, 1.6 mg copper, 45.2 mcg Iodine, 3.2 mg iron, 293.2 mg Ca, 133.2 mg Mg, 2.0 mg Manganese, 32 mcg Molybdenum, 186.8 mg phosphorus, 53.2 mg potassium, 45.2 mcg selenium, 10.8 mg zinc)		Anxiety significantly reduced in Vitamin B complex and Broad spectrum formula compared to Vitamin D	No differences in AEs across groups
Fazelian et al., 2019 (Fazelian et al., 2019) Iran *N* = 51 Vitamin D	100% f 47.41 yrs Type 2 diabetes and vitamin D deficiency	Vitamin D (50 000 IU cholecalciferol) fortnightly 16 weeks	Placebo	Anxiety significantly reduced compared to placebo	Not reported

(*Continued*)

Table 4. Continued.

First author, year published country study type *N* analysed	Population % female Age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Kahn et al., 1987 (Kahn et al., 1987) Netherlands *N* = 45 5-HTP	68.9% f 33 yrs	25 mg 5 HTP, gradually increased to a max of 150 mg over two weeks depending on tolerability and response 8 weeks	1. 25 mg Clomipramine gradually increased to a max 150 mg over 2 weeks depending on tolerability and response 2. Placebo	No significant difference to placebo or clomipramine (clomipramine better than placebo)	Not reported
Lucas et al., 2009 (Lucas et al., 2009) Canada *N* = 106 Omega-3 fatty acids	100% f 48.75 yrs Depression (psychological distress)	3 x 500 mg Ethyl-eicosapentaenoic acid Omega-3 fatty acids (350 mg EPA and 50 mg DHA) per day 8 weeks	Placebo	No significant difference to placebo	Higher rates of AEs in E-EPA group (40% vs 19.6%), mainly fish aftertaste and constipation
Sarris 2018 (Sarris et al., 2019) Australia *N* = 37 L-theanine	84.7% f 36.5 yrs	2 x 225 mg L-theanine capsules per day, plus current antidepressant (must have been on stable regimen for 4 weeks) 8 weeks	Placebo	No significant difference to placebo	No difference in AEs between groups
Oliver-Baxter 2017 (Oliver-Baxter et al., 2018) Australia *N* = 50 Women's D-Stress	100% f 40 yrs Depression (psychological distress)	Women's D-Stress (B1-12.5 mg, B2-12.5 mg, niacin-25 mg, B5-37.5, B6-25 B12 25 µg biotin 37.5 µg, folic acid 150 µg, vit C 75 mg, magnesium oxide 109 mg, zinc amnio acid chelate 30 mg, Ashwagandha 1.5 g dry root extract) 8 weeks	Placebo	No group x time interaction compared to placebo	Not reported

Table 5. Homeopathic products evaluated for anxiety.

First author, year published country study type *N* analysed	Population % female age (y) co-morbidities	Intervention(s)	Control	Effectiveness on anxiety outcomes	Adverse events
Salles 2011 (Salles & Silva, 2012) Brazil *N* = 30	97% f 37 yrs	4×4 drops flower essence (Impatiens, Cherry Plum, White Chestnut and Beech) per day 2 months	Placebo	Effective compared to placebo	Not reported
Fusco et al., 2021 (Fusco et al., 2021) Brazil *N* = 81	91.25% f 40.7 yrs Obesity or overweight	4×4 drops flower remedy (30 ml containing 30% hydro-brandy solution with 2 drops each of Impatiens, White Chestnut, Cherry Plum, Chicory, Crab Apple, and Pi) per day 4 weeks	Placebo	Effective compared to placebo	Not reported
Batistella 2023 (Batistella et al., 2021) Brazil *N* = 62	92% f 20.8 yrs	4×4 drops flower essence (Basilicum, Foeniculum, Lavandula, Momordica, Rosmarinus, Sonchus, Tabebuia plus mineral water and 20% preservative) per day 30 days	Placebo	Effective on one anxiety measure, other not reported between groups	Not reported

The number of studies evaluating products for anxiety is steadily increasing over time, a positive step given the increasing prevalence of anxiety symptoms and diagnoses. Most trials evaluated capsules or pills, the most common OTC preparation in European countries (Garcia-Alvarez et al., 2014). Few trials assessed teas, despite their common use in some countries (Nadaf et al., 2019), which may be due to teas overlapping in definition between food and medicinal products, or the difficulties associated with ensuring sufficient dosage or blinding with herbal tea products.

The studies available somewhat reflected common usage. The most consistently popular individual products reported in surveys of people with anxiety across various countries include: chamomile, lavender, valerian, lemon balm, and St John's Wort, with some surveys also mentioning kava, ginseng, black cohosh, *Echium amoenum*, passionflower and chasteberry (Bystritsky et al., 2012; Dehghan et al., 2022; Garcia-Alvarez et al., 2014; McIntyre et al., 2016; Nadaf et al., 2019; Ravven et al., 2011). Some of these are represented in this review (e.g. lavender and valerian), however others have relatively few studies for their usage (e.g. lemon balm and chamomile). Trials of CBD products for anxiety are increasing, which likely reflects increasing public interest. A recent survey suggested that 3% of people are likely to use CBD products for preventing or managing anxiety (Bhamra et al., 2021), whilst the market for CBD products in Europe is expected to be 3.47 billion euros in 2024 (Statista, 2022). The dosages evaluated varied considerably

for some herbal products and a consistent and methodical approach is needed to evaluate these in future, such as the trials featuring high- and low-dose arms as well as a comparator.

We did not aim to provide definitive statements on effectiveness as part of this review. However, a recent network meta-analysis evaluated herbal products for people with GAD, with 72% of included studies deemed at low risk of bias (Zhang et al., 2022). Within 29 studies, the most effective preparation was Silexan (Lavender oil), followed by Kava. *Withania somnifera* also showed good effects but only in small numbers of participants, whilst *G. glauca*, Kava, Manasamitra vataka, and Silexan were indistinguishable from conventional drugs. Results were less consistent for chamomile, passionflower, saffron and valerian. Tolerability for most products was similar to or better than placebo and standard drugs (Zhang et al., 2022). However, Zhang et al's (2022) review was more restrictive in terms of diagnosis and outcome measures used than our review. We included 55 studies of 32 herbal products vs the 29 studies of 12 herbal products identified and included in Zhang et al. (2022). Nevertheless, both reviews indicate that herbal products are more likely to be promising anxiety treatments than dietary supplements, which showed a lower volume of evidence and little promise at present in our review and are taken by fewer people according to surveys (Bahceci et al., 2013; Dehghan et al., 2022; Ravven et al., 2011). Supporting our findings, a 2018 meta-analysis of probiotics for anxiety symptoms found no effects (Liu et al., 2018). Homeopathic products may be worth further evaluation, as although safety data were not reported in our included studies the likelihood of interactions is low.

A mean age of 40 years across trials suggests a wide age range is being tested, although most studies had a higher number of women. Whilst this may reflect the higher prevalence of anxiety in women (Stansfeld et al., 2016) it may also show a need to recruit more male participants to OTC product trials. Only nine studies evaluated products in people with comorbidities, such as diabetes or hypertension, and all focussed on different products. As people with medical conditions and anxiety are twice as likely to use complementary therapies (Bystritsky et al., 2012), further research in people with other comorbidities beyond other mental health conditions is warranted.

This review took a comprehensive approach to searches and included non-English studies and ongoing trials. As we took a broad approach to searching and did not mention specific product names, it is possible a small number of individual product trials were missed, although we tried to overcome this through searching for trial protocols, which also allowed us to detect ongoing work. One limitation despite a large review team was a lack of resources for dual screening all titles, abstracts and full texts or to dual extract data. We overcame this by standardising our approach to inclusion, dual screening where there was doubt about the decision and a second reviewer checking data extraction with original papers. We included patient and public involvement members in all stages of the study, and they informed our review remit, choice of products and interpretation of findings.

This review demonstrates that a wide range of OTC herbal products have been tested for anxiety. Whilst many show promise alongside good safety data, results need to be replicated for many of the products, with larger sample sizes and dose-response evaluations. These should focus on the commonly used products to better inform self-management advice for patients. No studies where products were concurrently used with other medications showed increased incidence of side effects, leading to greater confidence in using L-theanine, ashwagandha, passionflower, probiotics, *Echium amoenum* and saffron alongside antidepressants. Only one study evaluated a product alongside CBT (CBD oil). More studies testing products alongside prescribed medication and psychological therapies are needed to assess for positive additive effects. Dietary supplements appear to be a less promising avenue for further research, whilst homeopathic products warrant further more rigorous exploration. Few OTC medications are likely to be relevant for anxiolytic effects, so the lack of studies found is not surprising. No studies assessed the economic impact of OTC products for anxiety; this remains a gap to determine whether using these products leads to greater, lesser or similar use of other healthcare services.

Conclusion

Trials into OTC products for anxiety have concentrated on a few key products, namely kava, but also lavender, probiotics, *G. glauca,* saffron and valerian. Whilst most herbal product trials reported positive results, many of these need to be replicated, particularly for commonly used products such as chamomile, lemon balm and St John's Wort, alone or in combination. Presumably, more definitive conclusions on the effects of CBD for anxiety will be drawn over the coming years as ongoing trials complete. Dietary supplements at present do not appear promising for anxiety. Homeopathic remedies require further investigation before conclusions can be drawn. More trials are needed at different doses to evaluate the use of products against or alongside conventional anxiety treatments, such as antidepressants and cognitive behavioural therapy, to better inform patient decision making.

Acknowledgements

The authors would like to thank Tanya Cohen and Christine Vial for their input as Patient and Public Involvement representatives into the design, methods and synthesis for this review.

Disclosure statement

The authors declare no conflict of interest.

Funding

This review was linked to a project funded by the National Institute National Institute for Health and Care Research (NIHR) School for Primary Care Research (project reference 635). The views expressed are those of the author(s) and not necessarily those of the NIHR or the

Department of Health and Social Care. JCBA is supported by the National Institute for Health and Care Research ARC North Thames. The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care.

References

Akhondzadeh, S., Naghavi, H. R., Vazirian, M., Shayeganpour, A., Rashidi, H., & Khani, M. (2001). Passionflower in the treatment of generalized anxiety: A pilot double-blind randomized controlled trial with oxazepam. *Journal of Clinical Pharmacy and Therapeutics*, *26*(5), 363–367. https://doi.org/10.1046/j.1365-2710.2001.00367.x

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association Publishing.

Amsterdam, J. D., Li, Y., Soeller, I., Rockwell, K., Mao, J. J., & Shults, J. (2009). A randomized, double-blind, placebo-controlled trial of oral matricaria recutita (chamomile) extract therapy for generalized anxiety disorder. *Journal of Clinical Psychopharmacology*, *29*(4), 378–382. https://doi.org/10.1097/JCP.0b013e3181ac935c

Andreatini, R., Sartori, V. A., Seabra, M. L. V., & Leite, J. R. (2002). Effect of valepotriates (valerian extract) in generalized anxiety disorder: A randomized placebo-controlled pilot study. *Phytotherapy Research: PTR*, *16*(7), 650–654. https://doi.org/10.1002/ptr.1027

Archer, C., Turner, K., Kessler, D., Mars, B., & Wiles, N. (2022). Trends in the recording of anxiety in UK primary care: A multi-method approach. *Social Psychiatry and Psychiatric Epidemiology*, *57*(2), 375–386. https://doi.org/10.1007/s00127-021-02131-8

Bahceci, B., Bagcioglu, E., Ozturk, A., Bulbul, F., Sahiner, I. V., Tuncer, B. E., Guzel, H. İ., & Hocaoglu, C. (2013). Complementary and alternative medicine use in patients with mental disorders in Turkey. *Complementary Therapies in Clinical Practice*, *19*(4), 221–226. https://doi.org/10.1016/j.ctcp.2013.06.005

Batistella, C. E., Camilo, I. R., Comparin, K. A., Aragão, F. A., & Frare, J. C. (2021). Efetividade da terapia floral para redução de sintomas de ansiedade em universitários: Ensaio clínico randomizado. *Research, Society and Development*, *10*(1), e44710111926. https://doi.org/10.33448/rsd-v10i1.11926

Bhamra, S. K., Desai, A., Imani-Berendjestanki, P., & Horgan, M. (2021). The emerging role of cannabidiol (CBD) products; a survey exploring the public's use and perceptions of CBD. *Phytotherapy Research: PTR*, *35*(10), 5734–5740. https://doi.org/10.1002/ptr.7232

Boerner, R. J., Sommer, H., Berger, W., Kuhn, U., Schmidt, U., & Mannel, M. (2003). Kava-Kava extract LI 150 is as effective as opipramol and buspirone in generalised anxiety disorder: An 8-week randomized, double-blind multi-centre clinical trial in 129 out-patients. *Phytomedicine: international Journal of Phytotherapy and Phytopharmacology*, *10*(Suppl 4), 38–49. https://doi.org/10.1078/1433-187X-00309

Bourin, M., Bougerol, T., Guitton, B., & Broutin, E. (1997). A combination of plant extracts in the treatment of outpatients with adjustment disorder with anxious mood: Controlled study versus placebo. *Fundamental & Clinical Pharmacology*, *11*(2), 127–132. https://doi.org/10.1111/j.1472-8206.1997.tb00179.x

Brahmbhatt, A., Richardson, L., & Prajapati, S. (2021). Identifying and managing anxiety disorders in primary care. *The Journal for Nurse Practitioners*, *17*(1), 18–25. https://doi.org/10.1016/j.nurpra.2020.10.019

Browne, P. D., Bolte, A. C., Besseling-van Der Vaart, I., Claassen, E., & De Weerth, C. (2021). Probiotics as a treatment for prenatal maternal anxiety and depression: A double-blind randomized pilot trial. *Scientific Reports*, *11*(1), 3051. https://doi.org/10.1038/s41598-021-81204-9

Bystritsky, A., Hovav, S., Sherbourne, C., Stein, M. B., Rose, R. D., Campbell-Sills, L., Golinelli, D., Sullivan, G., Craske, M. G., & Roy-Byrne, P. P. (2012). Use of complementary and alternative medicine in a large sample of anxiety patients. *Psychosomatics*, *53*(3), 266–272. https://doi.org/10.1016/j.psym.2011.11.009

Carmona, F., Coneglian, F. S., Batista, P. A., Aragon, D. C., Angelucci, M. A., Martinez, E. Z., & Pereira, A. M. S. (2019). Aloysia polystachya (Griseb.) Moldenke (Verbenaceae) powdered leaves are effective in treating anxiety symptoms: A phase-2, randomized, placebo-controlled clinical trial. *Journal of Ethnopharmacology*, *242*, 112060. https://doi.org/10.1016/j.jep.2019.112060

Chen, T.-R., Huang, H.-C., Hsu, J.-H., Ouyang, W.-C., & Lin, K.-C. (2019). Pharmacological and psychological interventions for generalized anxiety disorder in adults: A network meta-analysis. *Journal of Psychiatric Research*, *118*, 73–83. https://doi.org/10.1016/j.jpsychires.2019.08.014

Clayton, K., Luxford, Y., Colaci, J., Hasan, M., Miltiadou, R., Novikova, D., Vlahopoulos, D., & Stupans, I. (2020). Community pharmacists' recommendations for natural products for stress in Melbourne, Australia: A simulated patient study. *Pharmacy Practice*, *18*(1), 1660. https://doi.org/10.18549/PharmPract.2020.1.1660

Connor, K. M., & Davidson, J. R. T. (2002). A placebo-controlled study of Kava kava in generalized anxiety disorder. *International Clinical Psychopharmacology*, *17*(4), 185–188. https://doi.org/10.1097/00004850-200207000-00005

Cox, R. C., & Olatunji, B. O. (2020). Sleep in the anxiety-related disorders: A meta-analysis of subjective and objective research. *Sleep Medicine Reviews*, *51*, 101282. https://doi.org/10.1016/j.smrv.2020.101282

Cropley, M., Banks, A. P., & Boyle, J. (2015). The effects of *Rhodiola rosea* L. extract on anxiety, stress, cognition and other mood symptoms: *Rhodiola rosea*, mood and cognition. *Phytotherapy Research: PTR*, *29*(12), 1934–1939. https://doi.org/10.1002/ptr.5486

De Leo, V., La Marca, A., Morgante, G., Lanzetta, D., Florio, P., & Petraglia, F. (2001). Evaluation of combining kava extract with hormone replacement therapy in the treatment of postmenopausal anxiety. *Maturitas*, *39*(2), 185–188. https://doi.org/10.1016/S0378-5122(01)00197-9

Dehghan, M., Ghanbari, A., Ghaedi Heidari, F., Mangolian Shahrbabaki, P., & Zakeri, M. A. (2022). Use of complementary and alternative medicine in general population during COVID-19 outbreak: A survey in Iran. *Journal of Integrative Medicine*, *20*(1), 45–51. https://doi.org/10.1016/j.joim.2021.11.004

Emdin, C. A., Odutayo, A., Wong, C. X., Tran, J., Hsiao, A. J., & Hunn, B. H. M. (2016). Meta-analysis of anxiety as a risk factor for cardiovascular disease. *The American Journal of Cardiology*, *118*(4), 511–519. https://doi.org/10.1016/j.amjcard.2016.05.041

Eskandarzadeh, S., Effatpanah, M., Khosravi-Darani, K., Askari, R., Hosseini, A. F., Reisian, M., & Jazayeri, S. (2021). Efficacy of a multispecies probiotic as adjunctive therapy in generalized anxiety disorder: A double blind, randomized, placebo-controlled trial. *Nutritional Neuroscience*, *24*(2), 102–108. https://doi.org/10.1080/1028415X.2019.1598669

Farshbaf-Khalili, A., Kamalifard, M., & Namadian, M. (2018). Comparison of the effect of lavender and bitter orange on anxiety in postmenopausal women: A triple-blind, randomized, controlled clinical trial. *Complementary Therapies in Clinical Practice*, *31*, 132–138. https://doi.org/10.1016/j.ctcp.2018.02.004

Fazelian, S., Amani, R., Paknahad, Z., Kheiri, S., & Khajehali, L. (2019). Effect of Vitamin D supplement on mood status and inflammation in Vitamin D deficient Type 2 diabetic women with anxiety: A randomized clinical trial. *International Journal of Preventive Medicine*, *10*(1), 17. https://doi.org/10.4103/ijpvm.IJPVM_174_18

Firoozabadi, A., Kolouri, S., Zarshenas, M. M., Salehi, A., Mosavat, S. H., & Dastgheib, S. A. (2017). Efficacy of a freeze-dried aqueous extract of Nepeta menthoides Boiss & Buhse in the treatment of anxiety in patients with depression: A double-blind, randomized, controlled trial. *Journal of Herbal Medicine*, *10*, 17–23. https://doi.org/10.1016/j.hermed.2017.08.003

Firoozeei, T. S., Barekatain, M., Karimi, M., Zargaran, A., Akhondzadeh, S., & Rezaeizadeh, H. (2020). Lavender and dodder combined herbal syrup versus citalopram in major depressive disorder with anxious distress: A double-blind randomized trial. *Journal of Integrative Medicine*, *18*(5), 409–415. https://doi.org/10.1016/j.joim.2020.06.002

Freijy, T. M., Cribb, L., Oliver, G., Metri, N.-J., Opie, R. S., Jacka, F. N., Hawrelak, J. A., Rucklidge, J. J., Ng, C. H., & Sarris, J. (2022). Effects of a high-prebiotic diet versus probiotic supplements versus synbiotics on adult mental health: The "Gut Feelings" randomised controlled trial. *Frontiers in Neuroscience*, *16*, 1097278. https://doi.org/10.3389/fnins.2022.1097278

Fuladi, S., Emami, S. A., Mohammadpour, A. H., Karimani, A., Manteghi, A. A., & Sahebkar, A. (2021). Assessment of the efficacy of Withania somnifera root extract in patients with generalized anxiety disorder: A randomized double-blind placebo- controlled trial. *Current Reviews in Clinical and Experimental Pharmacology*, *16*(2), 191–196. https://doi.org/10.2174/1574884715666200413120413

Fusco, S. D. F. B., Pancieri, A. P., Amancio, S. C. P., Fusco, D. R., Padovani, C. R., Minicucci, M. F., Spiri, W. C., & Braga, E. M. (2021). Efficacy of flower therapy for anxiety in overweight or obese adults: A randomized placebo-controlled clinical trial. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *27*(5), 416–422. https://doi.org/10.1089/acm.2020.0305

Garcia-Alvarez, A., Egan, B., De Klein, S., Dima, L., Maggi, F. M., Isoniemi, M., Ribas-Barba, L., Raats, M. M., Meissner, E. M., Badea, M., Bruno, F., Salmenhaara, M., Milà-Villarroel, R., Knaze, V., Hodgkins, C., Marculescu, A., Uusitalo, L., Restani, P., & Serra-Majem, L. (2014). Usage of plant food supplements across six European countries: Findings from the PlantLIBRA consumer survey. *PLoS One*, *9*(3), e92265. https://doi.org/10.1371/journal.pone.0092265

Gastpar, M., & Klimm, H. D. (2003). Treatment of anxiety, tension and restlessness states with Kava special extract WS® 1490 in general practice: A randomized placebo-controlled double-blind multicenter trial. *Phytomedicine: international Journal of Phytotherapy and Phytopharmacology*, *10*(8), 631–639. https://doi.org/10.1078/0944-7113-00369

Ghazizadeh, J., Sadigh-Eteghad, S., Marx, W., Fakhari, A., Hamedeyazdan, S., Torbati, M., Taheri-Tarighi, S., Araj-khodaei, M., & Mirghafourvand, M. (2021). The effects of lemon balm (*Melissa officinalis* L.) on depression and anxiety in clinical trials: A systematic review and meta-analysis. *Phytotherapy Research: PTR*, *35*(12), 6690–6705. https://doi.org/10.1002/ptr.7252

Gupta, K., Mamidi, P., & Thakar, A. (2014). Randomised placebo controlled study on Sarasvata choorna in generalised anxiety disorder. *International Journal of Green Pharmacy*, *8*(4), 231. https://doi.org/10.4103/0973-8258.142677

Haller, J., Krecsak, L., & Zámbori, J. (2020). Double-blind placebo controlled trial of the anxiolytic effects of a standardized echinacea extract. *Phytotherapy Research: PTR*, *34*(3), 660–668. https://doi.org/10.1002/ptr.6558

Hanus, M., Lafon, J., & Mathieu, M. (2004). Double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of a fixed combination containing two plant extracts (Crataegus oxyacantha and Eschscholtzia californica) and magnesium in mild-to-moderate anxiety disorders. *Current Medical Research and Opinion*, *20*(1), 63–71. https://doi.org/10.1185/030079903125002603

Herrera-Arellano, A., Jiménez-Ferrer, E., Zamilpa, A., Morales-Valdéz, M., García-Valencia, C., & Tortoriello, J. (2007). Efficacy and tolerability of a standardized herbal product from *Galphimia glauca* on generalized anxiety disorder. A randomized, double-blind clinical trial controlled with lorazepam. *Planta Medica*, *73*(8), 713–717. https://doi.org/10.1055/s-2007-981539

Herrera-Arellano, A., Jiménez-Ferrer, J., Zamilpa, A., García-Alonso, G., Herrera-Alvarez, S., & Tortoriello, J. (2012). Therapeutic effectiveness of galphimia glauca vs. Lorazepam in generalized anxiety disorder. A controlled 15-week clinical trial. *Planta Medica*, *78*(14), 1529–1535. https://doi.org/10.1055/s-0032-1315110

Hieu, T. H., Dibas, M., Surya Dila, K. A., Sherif, N. A., Hashmi, M. U., Mahmoud, M., Trang, N. T. T., Abdullah, L., Nghia, T. L. B., Y, M. N., Hirayama, K., Huy, & N. T. (2019). Therapeutic efficacy and safety of chamomile for state anxiety, generalized anxiety disorder, insomnia, and sleep quality: A systematic review and meta-analysis of randomized trials and quasi-randomized trials. *Phytotherapy Research: PTR*, *33*(6), 1604–1615. https://doi.org/10.1002/ptr.6349

Hunt, K. J., Coelho, H. F., Wider, B., Perry, R., Hung, S. K., Terry, R., & Ernst, E. (2010). Complementary and alternative medicine use in England: Results from a national survey: CAM use in England: A national survey. *International Journal of Clinical Practice*, *64*(11), 1496–1502. https://doi.org/10.1111/j.1742-1241.2010.02484.x

Hurtado, M. M., Villena, A., Vega, A., Amor, G., Gómez, C., & Morales-Asencio, J. M. (2020). 'I have anxiety, but I have values and preferences' experiences of users with generalized anxiety disorder: A qualitative study. *International Journal of Mental Health Nursing*, *29*(3), 521–530. https://doi.org/10.1111/inm.12690

Jacobs, B. P., Bent, S., Tice, J. A., Blackwell, T., & Cummings, S. R. (2005). An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine*, *84*(4), 197–207. https://doi.org/10.1097/01.md.0000172299.72364.95

Jafarnia, N., Ghorbani, Z., Nokhostin, M., Manayi, A., Nourimajd, S., & Razeghi Jahromi, S. (2017). Effect of saffron (Crocus Satious L.) as an add-on therapy to sertraline in mild to moderate generalized anxiety disorder: A double blind randomized controlled Trial. *Archives of Neuroscience*, *4*(4), e14332. https://doi.org/10.5812/archneurosci.14332

Kahn, R., Westenberg, H., Verhoeven, W., Gispen-de Wied, C., & Kamerbeek, W. (1987). Effect of a serotonin precursor and uptake inhibitor in anxiety disorders: A double-blind comparison of 5-hydroxytryptophan, clomipramine and placebo. *International Clinical Psychopharmacology*, *2*(1), 33–45. https://doi.org/10.1097/00004850-198701000-00003

Kalman, D. S., Feldman, S., Feldman, R., Schwartz, H. I., Krieger, D. R., & Garrison, R. (2008). Effect of a proprietary Magnolia and Phellodendronextract on stress levels in healthy women: A pilot, double-blind, placebo-controlled clinical trial. *Nutrition Journal*, *7*(1), 11. https://doi.org/10.1186/1475-2891-7-11

Kaplan, B. J., Rucklidge, J. J., Romijn, A. R., & Dolph, M. (2015). A randomised trial of nutrient supplements to minimise psychological stress after a natural disaster. *Psychiatry Research*, *228*(3), 373–379. https://doi.org/10.1016/j.psychres.2015.05.080

Kasper, S., Anghelescu, I., & Dienel, A. (2015). Efficacy of orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep: A randomized, placebo-controlled trial. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *25*(11), 1960–1967. https://doi.org/10.1016/j.euroneuro.2015.07.024

Kasper, S., Gastpar, M., Müller, W. E., Volz, H.-P., Möller, H.-J., Dienel, A., & Schläfke, S. (2010). Silexan, an orally administered Lavandula oil preparation, is effective in the treatment of 'subsyndromal' anxiety disorder: A randomized, double-blind, placebo controlled trial. *International Clinical Psychopharmacology*, *25*(5), 277–287. https://doi.org/10.1097/YIC.0b013e32833b3242

Kasper, S., Gastpar, M., Müller, W. E., Volz, H.-P., Möller, H.-J., Schläfke, S., & Dienel, A. (2014). Lavender oil preparation Silexan is effective in generalized anxiety disorder: A randomized, double-blind comparison to placebo and paroxetine. *The International Journal of Neuropsychopharmacology*, *17*(6), 859–869. https://doi.org/10.1017/S1461145714000017

Kell, G., Rao, A., & Katsikitis, M. (2019). A randomised placebo controlled clinical trial on the efficacy of Caralluma fimbriata supplement for reducing anxiety and stress in healthy adults over eight weeks. *Journal of Affective Disorders*, *246*, 619–626. https://doi.org/10.1016/j.jad.2018.12.062

Khot, S. G., Tubaki, B. R., & Gonugade, V. B. (2022). Efficacy of Brahmi vati in generalised anxiety disorder: Randomized double blind comparative clinical trial. *Journal of Ayurveda and Integrative Medicine*, *13*(2), 100552. https://doi.org/10.1016/j.jaim.2022.100552

Kwee, C. M., Baas, J. M., Van Der Flier, F. E., Groenink, L., Duits, P., Eikelenboom, M., Van Der Veen, D. C., Moerbeek, M., Batelaan, N. M., Van Balkom, A. J., & Cath, D. C. (2022). Cannabidiol enhancement of exposure therapy in treatment refractory patients with social anxiety disorder and panic disorder with agoraphobia: A randomised controlled trial. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *59*, 58–67. https://doi.org/10.1016/j.euroneuro.2022.04.003

Lee, H. J., Hong, J. K., Kim, J.-K., Kim, D.-H., Jang, S. W., Han, S.-W., & Yoon, I.-Y. (2021). Effects of probiotic NVP-1704 on mental health and sleep in healthy adults: An 8-week randomized, double-blind, placebo-controlled trial. *Nutrients*, *13*(8), 2660. https://doi.org/10.3390/nu13082660

Lehmann, E., Kinzler, E., & Friedemann, J. (1996). Efficacy of a special Kava extract (Piper methysticum) in patients with states of anxiety, tension and excitedness of non-mental origin: A double-blind placebo-controlled study of four weeks treatment. *Phytomedicine:*

international Journal of Phytotherapy and Phytopharmacology, *3*(2), 113–119. https://doi.org/10.1016/S0944-7113(96)80024-9

Lehrl, S. (2004). Clinical efficacy of kava extract WS® 1490 in sleep disturbances associated with anxiety disorders results of a multicenter, randomized, placebo-controlled, double-blind clinical trial. *Journal of Affective Disorders*, *78*(2), 101–110. https://doi.org/10.1016/S0165-0327(02)00238-0

Lerhl, V., & Woelk, H. (2002). Angstsymptome nehmen kontinuierlich ab. *Fortschritte Der Medizin*, *23*, 47.

Liu, B., He, Y., Wang, M., Liu, J., Ju, Y., Zhang, Y., Liu, T., Li, L., & Li, Q. (2018). Efficacy of probiotics on anxiety-A meta-analysis of randomized controlled trials. *Depression and Anxiety*, *35*(10), 935–945. https://doi.org/10.1002/da.22811

Lopresti, A. L., & Smith, S. J. (2021). An investigation into the anxiety-relieving and mood-enhancing effects of Echinacea angustifolia (EP107™): A randomised, double-blind, placebo-controlled study. *Journal of Affective Disorders*, *293*, 229–237. https://doi.org/10.1016/j.jad.2021.06.054

Lucas, M., Asselin, G., Mérette, C., Poulin, M.-J., & Dodin, S. (2009). Ethyl-eicosapentaenoic acid for the treatment of psychological distress and depressive symptoms in middle-aged women: A double-blind, placebo-controlled, randomized clinical trial. *The American Journal of Clinical Nutrition*, *89*(2), 641–651. https://doi.org/10.3945/ajcn.2008.26749

Malsch, U., & Kieser, K. (2001). Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines. *Psychopharmacology*, *157*(3), 277–283. https://doi.org/10.1007/s002130100792

Mao, J. J., Xie, S. X., Keefe, J. R., Soeller, I., Li, Q. S., & Amsterdam, J. D. (2016). Long-term chamomile (Matricaria chamomilla L.) treatment for generalized anxiety disorder: A randomized clinical trial. *Phytomedicine: international Journal of Phytotherapy and Phytopharmacology*, *23*(14), 1735–1742. https://doi.org/10.1016/j.phymed.2016.10.012

Masataka, N. (2019). Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. *Frontiers in Psychology*, *10*, 2466. https://doi.org/10.3389/fpsyg.2019.02466

Mazidi, M., Shemshian, M., Mousavi, S. H., Norouzy, A., Kermani, T., Moghiman, T., Sadeghi, A., Mokhber, N., Ghayour-Mobarhan, M., & Ferns, G. A. A. (2016). A double-blind, randomized and placebo-controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression. *Journal of Complementary and Integrative Medicine*, *13*(2), 195–199. https://doi.org/10.1515/jcim-2015-0043

McIntyre, E., Saliba, A. J., & Moran, C. C. (2015). Herbal medicine use in adults who experience anxiety: A qualitative exploration. *International Journal of Qualitative Studies on Health and Well-Being*, *10*(1), 29275. https://doi.org/10.3402/qhw.v10.29275

McIntyre, E., Saliba, A. J., Wiener, K. K., & Sarris, J. (2016). Herbal medicine use behaviour in Australian adults who experience anxiety: A descriptive study. *BMC Complementary and Alternative Medicine*, *16*(1), 60. https://doi.org/10.1186/s12906-016-1022-3

Milajerdi, A., Jazayeri, S., Shirzadi, E., Hashemzadeh, N., Azizgol, A., Djazayery, A., Esmaillzadeh, A., & Akhondzadeh, S. (2018). The effects of alcoholic extract of saffron (Crocus satious L.) on mild to moderate comorbid depression-anxiety, sleep quality, and life satisfaction in type 2 diabetes mellitus: A double-blind, randomized and placebo-controlled clinical trial. *Complementary Therapies in Medicine*, *41*, 196–202. https://doi.org/10.1016/j.ctim.2018.09.023

Mills, P., Farag, N., Newton, R., & Parry, B. (2002). Effects of a traditional herbal supplement on anxiety in patients with generalized anxiety disorder. *Journal of Clinical Psychopharmacology*, *22*(4), 443–444. https://doi.org/10.1097/00004714-200208000-00024

Morris, C., Wong, M., & McKinlay, E. (2021). A qualitative study of community pharmacists' perceptions of their role in primary mental health care in New Zealand. *The International Journal of Pharmacy Practice*, *29*(5), 499–507. https://doi.org/10.1093/ijpp/riab039

Nadaf, M., Joharchi, M. R., & Amiri, M. S. (2019). Ethnomedicinal uses of plants for the treatment of nervous disorders at the herbal markets of Bojnord, North Khorasan Province, Iran. 9(2).

National Institute for Health and Care Excellence. (2020). *Generalised anxiety disorder and panic disorder in adults: Management (Clinical guideline [CG113])*. https://www.nice.org.uk/guidance/cg113/chapter/Recommendations

Nojoumi, M., Ghaeli, P., Salimi, S., Sharifi, A., & Raisi, F. (2016). *Effects of passion flower extract, as an add-on treatment to sertraline, on reaction time in patients with generalized anxiety disorder: A double-blind placebo-controlled study*.

Oliver-Baxter, J. M., Whitford, H. S., Turnbull, D. A., & Bond, M. J. (2018). Effects of vitamin supplementation on inflammatory markers and psychological wellbeing among distressed women: A randomized controlled trial. *Journal of Integrative Medicine*, *16*(5), 322–328. https://doi.org/10.1016/j.joim.2018.06.001

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—A web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1), 210. https://doi.org/10.1186/s13643-016-0384-4

Panijel, M. (1985). Die Behandlung mittelschwerer Angstzustaende: Randomisierte Doppelblindstudie zum klinischen Wirksamkeitvergleich eines Phytotherapeutikums mit Diazepam. *Therapiewoche*, *41*, 4659–4668.

Parker, E., & Banfield, M. (2022). Consumer perspectives on anxiety management in Australian general practice. *International Journal of Environmental Research and Public Health*, *19*(9), 5706. https://doi.org/10.3390/ijerph19095706

Peters, M., Godfrey, C., McInerney, P., Munn, Z., Tricco, A., & Khalil, H. (2020). Chapter 11: Scoping reviews. In *JBI Manual for Evidence Synthesis*. JBI. https://doi.org/10.46658/JBIMES-20-12

Pinto-Sanchez, M. I., Hall, G. B., Ghajar, K., Nardelli, A., Bolino, C., Lau, J. T., Martin, F.-P., Cominetti, O., Welsh, C., Rieder, A., Traynor, J., Gregory, C., De Palma, G., Pigrau, M., Ford, A. C., Macri, J., Berger, B., Bergonzelli, G., Surette, M. G., … Bercik, P. (2017). Probiotic Bifidobacterium longum NCC3001 reduces depression scores and alters brain activity: A pilot study in patients with irritable bowel syndrome. *Gastroenterology*, *153*(2), 448–459.e8. https://doi.org/10.1053/j.gastro.2017.05.003

Rabezzana, G. (1995). Trattamento dei disturbi d'ansia di grado lieve e medio con prodotti a base naturale: Valutazione dell'efficacia e tollerabilita del Sedatol. *Psichiatria*, *15*, 126–133.

Ranjbar, M., Firoozabadi, A., Salehi, A., Ghorbanifar, Z., Zarshenas, M. M., Sadeghniiat-Haghighi, K., & Rezaeizadeh, H. (2018). Effects of Herbal combination (Melissa officinalis L. and Nepeta menthoides Boiss. & Buhse) on insomnia severity, anxiety and depression in insomniacs: Randomized placebo controlled trial. *Integrative Medicine Research*, *7*(4), 328–332. https://doi.org/10.1016/j.imr.2018.08.001

Ravven, S. E., Zimmerman, M. B., Schultz, S. K., & Wallace, R. B. (2011). 12-month herbal medicine use for mental health from the National Comorbidity Survey Replication (NCS-R). *Annals of Clinical Psychiatry: official Journal of the American Academy of Clinical Psychiatrists*, *23*(2), 83–94.

Reid, S. (2002). A survey of the use of over-the-counter homeopathic medicines purchased in health stores in central Manchester. *Homeopathy: The Journal of the Faculty of Homeopathy*, *91*(4), 225–229. https://doi.org/10.1054/homp.2002.0053

Revicki, D. A., Travers, K., Wyrwich, K. W., Svedsäter, H., Locklear, J., Mattera, M. S., Sheehan, D. V., & Montgomery, S. (2012). Humanistic and economic burden of generalized anxiety disorder in North America and Europe. *Journal of Affective Disorders*, *140*(2), 103–112. https://doi.org/10.1016/j.jad.2011.11.014

Romero-Cerecero, O., Islas-Garduño, A. L., Zamilpa, A., Herrera-Arellano, A., Jiménez-Ferrer, E., & Tortoriello, J. (2019). Galphimine-B standardized extract versus alprazolam in patients with generalized anxiety disorder: A ten-week, double-blind, randomized clinical trial. *BioMed Research International*, *2019*, 1037036–1037039. https://doi.org/10.1155/2019/1037036

Romero-Cerecero, O., Islas-Garduño, A. L., Zamilpa, A., Pérez-García, M. D., & Tortoriello, J. (2018). Therapeutic effectiveness of *galphimia glauca* in young people with social anxiety disorder: A pilot study. *Evidence-Based Complementary and Alternative Medicine: eCAM*, *2018*(1), 1716939. https://doi.org/10.1155/2018/1716939

Saha, S., Lim, C. C. W., Cannon, D. L., Burton, L., Bremner, M., Cosgrove, P., Huo, Y., & McGrath, J. (2021). Co-morbidity between mood and anxiety disorders: A systematic review and meta-analysis.

Depression and Anxiety, *38*(3), 286–306. https://doi.org/10.1002/da.23113

Salles, L. F., & Silva, M. J. P. D. (2012). Efeito das essências florais em indivíduos ansiosos. *Acta Paulista de Enfermagem*, *25*(2), 238–242. https://doi.org/10.1590/S0103-21002012000200013

Santini, Z. I., Thygesen, L. C., Koyanagi, A., Stewart-Brown, S., Meilstrup, C., Nielsen, L., Olsen, K. R., Birkjær, M., McDaid, D., Koushede, V., & Ekholm, O. (2022). Economics of mental wellbeing: A prospective study estimating associated productivity costs due to sickness absence from the workplace in Denmark. *Mental Health & Prevention*, *28*, 200247. https://doi.org/10.1016/j.mhp.2022.200247

Sarris, J., Byrne, G. J., Bousman, C. A., Cribb, L., Savage, K. M., Holmes, O., Murphy, J., Macdonald, P., Short, A., Nazareth, S., Jennings, E., Thomas, S. R., Ogden, E., Chamoli, S., Scholey, A., & Stough, C. (2020). Kava for generalised anxiety disorder: A 16-week double-blind, randomised, placebo-controlled study. *The Australian and New Zealand Journal of Psychiatry*, *54*(3), 288–297. https://doi.org/10.1177/0004867419891246

Sarris, J., Byrne, G. J., Cribb, L., Oliver, G., Murphy, J., Macdonald, P., Nazareth, S., Karamacoska, D., Galea, S., Short, A., Ee, C., Birling, Y., Menon, R., & Ng, C. H. (2019). L-theanine in the adjunctive treatment of generalized anxiety disorder: A double-blind, randomised, placebo-controlled trial. *Journal of Psychiatric Research*, *110*, 31–37. https://doi.org/10.1016/j.jpsychires.2018.12.014

Sarris, J., Kavanagh, D. J., Byrne, G., Bone, K. M., Adams, J., & Deed, G. (2009). The Kava Anxiety Depression Spectrum Study (KADSS): A randomized, placebo-controlled crossover trial using an aqueous extract of Piper methysticum. *Psychopharmacology*, *205*(3), 399–407. https://doi.org/10.1007/s00213-009-1549-9

Sarris, J., Kavanagh, D. J., Deed, G., & Bone, K. M. (2009). St. John's wort and Kava in treating major depressive disorder with comorbid anxiety: A randomised double-blind placebo-controlled pilot trial. *Human Psychopharmacology*, *24*(1), 41–48. https://doi.org/10.1002/hup.994

Sarris, J., Stough, C., Bousman, C. A., Wahid, Z. T., Murray, G., Teschke, R., Savage, K. M., Dowell, A., Ng, C., & Schweitzer, I. (2013). Kava in the treatment of generalized anxiety disorder: A double-blind, randomized, placebo-controlled study. *Journal of Clinical Psychopharmacology*, *33*(5), 643–648. https://doi.org/10.1097/JCP.0b013e318291be67

Sayyah, M., Siahpoosh, A., Khalili, H., Malayeri, A., & Samaee, H. (2012). A double-blind, placebo-controlled study of the aqueous extract of echium amoenum for patients with general anxiety disorder.

Shayani Rad, M., Moohebati, M., & Mohajeri, S. A. (2023). Beneficial effects of celery seed extract (Apium graveolens), as a supplement, on anxiety and depression in hypertensive patients: A randomized clinical trial. *Inflammopharmacology*, *31*(1), 395–410. https://doi.org/10.1007/s10787-022-01083-y

Stansfeld, S., Clark, C., Bebbington, P., King, M., Jenkins, R., & Hinchliffe, S. (2016). *Adult psychiatric morbidity survey 2014 Chapter 2: Common mental disorders*. Health and Social Care Information Centre. https://digital.nhs.uk/data-and-information/publications/statistical/adult-psychiatric-morbidity-survey

Statista. (2022). *CBD sales forecast for Europe from 2022 to 2026*. https://www.statista.com/statistics/1306959/forecast-cbd-sales-europe/

Toledo-Chávarri, A., Ramos-García, V., Torres-Castaño, A., Trujillo-Martín, M. M., Peñate Castro, W., Del Cura-Castro, I., Serrano-Aguilar, P., & Perestelo-Pérez, L. (2020). Framing the process in the implementation of care for people with generalized anxiety disorder in primary care: A qualitative evidence synthesis. *BMC Family Practice*, *21*(1), 237. https://doi.org/10.1186/s12875-020-01307-6

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Annals of Internal Medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Tubaki, B. R., Chandrashekar, C. R., Sudhakar, D., Prabha, T. N. S., Lavekar, G. S., & Kutty, B. M. (2012). Clinical Efficacy of *Manasamitra Vataka* (an Ayurveda Medication) on generalized anxiety disorder with comorbid generalized social phobia: A randomized controlled study. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *18*(6), 612–621. https://doi.org/10.1089/acm.2010.0778

Volz, H.-P., & Kieser, M. (1997). Kava-kava extract WS 1490 versus placebo in anxiety disorders—A randomized placebo-controlled 25-week outpatient trial. *Pharmacopsychiatry*, *30*(1), 1–5. https://doi.org/10.1055/s-2007-979474

Waddington, F., Naunton, M., Kyle, G., Thomas, J., Cooper, G., & Waddington, A. (2015). A systematic review of community pharmacist therapeutic knowledge of dietary supplements. *International Journal of Clinical Pharmacy*, *37*(3), 439–446. https://doi.org/10.1007/s11096-015-0092-5

Waumans, R. C., Muntingh, A. D. T., Draisma, S., Huijbregts, K. M., Van Balkom, A. J. L. M., & Batelaan, N. M. (2022). Barriers and facilitators for treatment-seeking in adults with a depressive or anxiety disorder in a Western-European health care setting: A qualitative study. *BMC Psychiatry*, *22*(1), 165. https://doi.org/10.1186/s12888-022-03806-5

Woelk, H., & Schläfke, S. (2010). A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. *Phytomedicine: international Journal of Phytotherapy and Phytopharmacology*, *17*(2), 94–99. https://doi.org/10.1016/j.phymed.2009.10.006

Woelk, H., Arnoldt, K. H., Kieser, M., & Hoerr, R. (2007). Ginkgo biloba special extract EGb 761® in generalized anxiety disorder and adjustment disorder with anxious mood: A randomized, double-blind, placebo-controlled trial. *Journal of Psychiatric Research*, *41*(6), 472–480. https://doi.org/10.1016/j.jpsychires.2006.05.004

Woodward, A. T., Bullard, K. M., Taylor, R. J., Chatters, L. M., Baser, R. E., Perron, B. E., & Jackson, J. S. (2009). Complementary and alternative medicine for mental disorders among African Americans. *Black Caribbeans, and Whites*, *60*(10), 1342–1349.

Zhang, W., Yan, Y., Wu, Y., Yang, H., Zhu, P., Yan, F., Zhao, R., Tian, P., Wang, T., Fan, Q., & Su, Z. (2022). Medicinal herbs for the treatment of anxiety: A systematic review and network meta-analysis. *Pharmacological Research*, *179*, 106204. https://doi.org/10.1016/j.phrs.2022.106204