Natural Remedies: "Cider Vinegar" & #TrendingRemedies

CLINICAL REFERENCE FOR PHYSICIANS

Evidence, mechanisms, dosing signals and interaction risks for the botanicals and nutraceuticals patients are most likely to be taking.

DISCLOSURES

Disclosure of Financial Relationships

The presenter has no financial relationships with any commercial interest related to the content of this activity. No relevant conflicts of interest to disclose.

ADDITIONAL STATEMENTS

No commercial support was received for this presentation, and no commercial entity had input into its content.

This activity discusses uses of dietary supplements and botanical products that are not approved by the FDA. Such off-label and unapproved uses are identified where they arise.

Content is offered for educational purposes and does not replace individual clinical judgement.

LEARNING OBJECTIVES

Objectives

01 Differentiate remedy categories

Differentiate complementary, alternative, and adjunctive natural remedies and supplements used by patients with psychiatric conditions, including the strength of evidence supporting their use.

02 Evaluate benefits, risks, and gaps

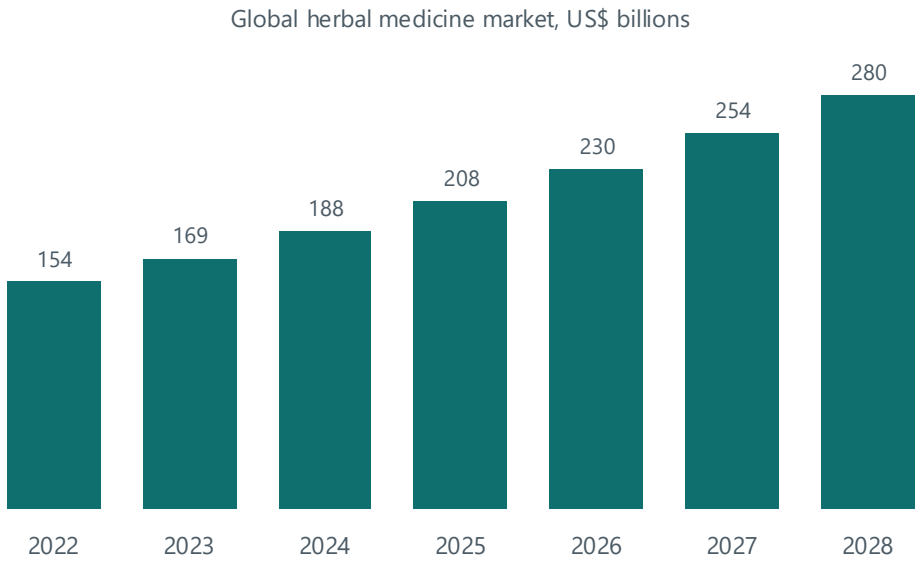
Evaluate the known benefits, risks, drug interactions, and evidence gaps associated with commonly used herbal products, supplements, and emerging compounds promoted through social media and other non-medical sources.

03 Apply screening and counseling

Incorporate structured screening and counseling strategies into clinical practice to identify patient use of natural remedies and supplements, assess safety concerns, and guide evidence-based treatment discussions.

MARKET AND SPENDING TRENDS

A Fast-Growing Parallel Market



$153.5B to $279.8B

Projected global herbal medicine market from 2022 to 2028 — a 10.6% compound annual growth rate.

$11.3B, up 17.3%

US spending on herbal supplements in 2020, a record single-year rise; nearly a quarter of the increase was for mental health reasons.

Largest market

The United States leads global herbal medicine consumption, followed by Europe, Australia and Canada.

BCC Research. Global Herbal Medicine Market. Report PHM278A, Nov 2023 ($169.1B in 2023 to $279.8B by 2028, CAGR 10.6%) — as cited in Reque PM et al. Adv Gut Microbiome Res. 2025; Smith T, Majid F, Eckl V, Morton Reynolds C. Herbal Supplement Sales in US Increase by Record-Breaking 17.3% in 2020. HerbalGram. 2021;131:52-65 (Nutrition Business Journal data, $11.261B) — as cited in Lewis BB. Psychiatric Times. 2022;39(10). Other years interpolated at the reported 10.6% CAGR.

CONTEXT FOR PRESCRIBERS

Why Herbal Use Is a Clinical Issue

Prevalence, complexity, and standardization

- Americans spent $11.3 billion on herbal supplements in 2020 — a record 17.3% year-over-year increase.
- Among consumers who increased supplement intake during the pandemic, nearly a quarter cited mental health reasons including stress and anxiety.
- Top-selling herbs with mental health applications: CBD, ashwagandha, turmeric, ginkgo, St. John's wort, valerian, maca and rhodiola — spending does not track the strength of the evidence.
- **Herbs are whole plants**, **not single molecules**: benefit may arise from synergistic, polyvalent interactions, which complicates standardized research and cross-product comparison, but we don't have the science available today to distinguish this for many in humans.

Smith T et al. HerbalEGram. 2021;131:52-65; Council for Responsible Nutrition COVID-19 Consumer Survey, 2020; Sarris J et al. Eur Neuropsychopharmacol. 2011;21(12):841-60; Lewis BB. Psychiatric Times. 2022;39(10).

PRACTICAL APPROACH

How to Use This Material in Practice

Depth over breadth, and always ask

- Learn two or three agents in depth rather than a little about many — enough to counsel confidently on evidence, dosing, and interactions.
- Alternatively, learn the ones your own patients already take; your local prescribing population defines which agents actually matter.
- Ask directly about herbs and supplements at every medication reconciliation — patients rarely volunteer them, and many do not consider them drugs.
- Document what they take, the product and dose, and revisit it as you would any other therapy.

Practice points for the clinician; see preceding slides for the underlying evidence and citations.

INTRODUCTION

Prescription Drugs vs. Herbals

Where each option currently stands

- *Scale of need: WHO estimates 970 million people live with a mental disorder, including 280 million with depression and 301 million with anxiety; depression-related costs exceed US $200 billion.*
- Conventional antidepressants take weeks to months to act, and roughly 30% of patients achieve an acceptable response, 40% a mixed response and 30% an insufficient one.
- No genuinely new class of synthetic antidepressant or anxiolytic has reached the market in the past decade, sustaining patient interest in plant-derived options.
- Herbal preparations are generally better tolerated, with fewer and milder adverse effects, though effect sizes are smaller and product quality varies widely.
- Several are formally recognized by regulators: the EMA lists St. John's wort, lemon balm and valerian, and Brazil's ANVISA lists passionflower, valerian, black cohosh and kava.

World Health Organization. Mental Health fact sheet (970 million with a mental disorder, 2019) and Global Strategic Direction for Mental Health (280 million depression, 301 million anxiety) — as cited in Reque PM et al. Adv Gut Microbiome Res. 2025. doi:10.1155/agm3/3675425, which is also the source for the response-rate, drug-development and regulatory-status statements.

READING THE EVIDENCE

Why Supplement Trials Disagree

Before comparing two studies of the same herb, check whether they studied the same thing at all.

Problem	What varies	Why it changes the result	What to check
Extract type	Root versus aerial parts, water versus ethanol extraction	Different extracts of one plant carry different active compounds	Named, characterised extract
Standardisation	Percentage of the marker compound, or none declared (Dosage)	A stated milligram dose says nothing without a consistently regulated process accuracy	Marker compound and percentage
Bioavailability	Absorption enhancers, formulation, food effects	Curcumin and resveratrol trials often failed on absorption, not mechanism	Formulation and co-administration
Study size and duration	Most herbal RCTs enroll tens of patients for 8–12 weeks	This is the norm here, not the exception — so effects look larger and rare harms stay invisible	Sample size and follow-up length
Outcome chosen	Surrogate markers versus symptoms that matter	Blood flow or antioxidant status is not the same as feeling or functioning better	Whether the endpoint is patient-relevant
Publication and funding	Manufacturer-sponsored and small positive studies	Negative supplement trials are published less often, inflating pooled estimates	Funding statement and registration
Product on the shelf	Content and purity differ from the trial product	A positive trial does not validate whatever the patient bought	Third-party testing on the actual brand

Applies across every table in this deck; the same caveats are raised in Kargozar 2017 and Mecocci 2014.

READING THE LABEL

What Standardisation Guarantees

The vocabulary behind "marker compound and percentage" - and what each term does and does not promise

Term	What it means	What it does not mean	What to check
Standardisation	Extract manufactured to a declared percentage of a chosen constituent	It guarantees content consistency, not that the product works	Marker named and percentage stated
Marker compound	Active marker drives the effect; analytical marker is only a proxy for correct extraction	Most botanical markers are analytical, so matching percentages are not equivalent products	Which of the two the label actually means
Assay	Quantifying the marker, usually by HPLC or HPTLC fingerprinting	A number printed on a label is not evidence an assay was run	Method named on the analysis report
Identity, purity, potency	Right species; free of adulterants, heavy metals and microbes; declared dose present	Clean and correctly identified is not the same as effective	All three reported, not potency alone
Certificate of Analysis	The manufacturer's batch-level test report, produced under cGMP	In the US it is self-attested, not verified before sale	Batch number matching the bottle in hand
Third-party certification	Independent verification: USP Verified, NSF/ANSI 173, ConsumerLab, BSCG for athletes	It certifies what is in the capsule, still not clinical benefit	Seal present on the brand actually bought
Pharmaceutical equivalence	The shelf product matching the material used in the trial	Rarely demonstrated for botanicals, however similar the label looks	Whether the brand studied is the brand sold

The one-line version: standardisation tells you the marker compound and its percentage; it does not tell you the product works, and it only means anything if a third party verified the assay.

MECHANISM

The Gut–Brain Axis

How plant compounds may act through the microbiota

- Gut and brain communicate bidirectionally through the vagus nerve, the autonomic and enteric nervous systems, and the hypothalamic–pituitary–adrenal axis.
- A healthy adult microbiota is dominated by Bacillota (30–52%), Bacteroidota (9–42%) and Actinobacteria (1–13%); dysbiosis increases intestinal permeability and circulating LPS, driving inflammation linked to anxiety and depression.
- Gut bacteria synthesize GABA, serotonin, dopamine, norepinephrine and acetylcholine, and produce short-chain fatty acids, butyrate, propionate and acetate that support the gut barrier and neuroimmune signaling.
- 90–95% of dietary polyphenols escape small-bowel absorption and reach the colon, where microbial metabolism generates the bioactive compounds behind many herbal effects.
- This underpins the emerging categories of psychobiotics, phytopsychobiotics and duplibiotics as adjuncts in mood and anxiety disorders.

Reque PM et al. Adv Gut Microbiome Res. 2025. doi:10.1155/agm3/3675425, reviewing Cryan JF, Dinan TG. Nat Rev Neurosci. 2012;13(10):701-712 (gut–brain axis); Rinninella E et al. Microorganisms. 2019;7(1):14 (healthy microbiota composition); Silva YP et al. Front Endocrinol. 2020;11:25 (short-chain fatty acids).

DEBUNKING THE WELLNESS SHELF

Trends Without the Evidence

Apple cider vinegar, spirulina and wheatgrass — what the data actually supports

- Apple cider vinegar: the weight-loss claim rests on one 12-week RCT (n=155) where 15-30 mL/day gave 1-2 kg more loss than placebo - trivial and regained on stopping (Kondo 2009); a review found the wider claims unsupported (Launholt 2020).
- It's one measurable effect, modest blunting of post-meal glucose (Johnston 2004), is smaller than any first-line agent. Harms are documented: enamel erosion, oesophageal injury, hypokalaemia on chronic high intake (Lhotta 1998).
- Spirulina: meta-analyses show small LDL and blood-pressure reductions on surrogate endpoints only, with no outcome data behind them. Its advertised B12 is an inactive analogue that can mask deficiency (Watanabe 2007), and unregulated products carry microcystin contamination.
- Wheatgrass: essentially no rigorous human data - the only positive trial is 23 patients with ulcerative colitis (Ben-Arye 2002).
- The shared pattern: one small trial, a surrogate endpoint, no replication, and a claim far larger than the finding.

Kondo T et al. Biosci Biotechnol Biochem. 2009;73(8):1837-1843; Launholt TL et al. Eur J Nutr. 2020;59(6):2273-2289; Johnston CS et al. Diabetes Care. 2004;27(1):281-282; Lhotta K et al. Nephron. 1998;80(2):242-243; Watanabe F. Exp Biol Med. 2007;232:1266-1274; Ben-Arye E et al. Scand J Gastroenterol. 2002;37(4):444-449.

Ranked by Strength of Evidence

Every agent in this deck, strongest data first. The slides that follow are ordered in these tiers.

Tier	What it means	Agents
1. Good, replicated evidence	Multiple positive RCTs and meta-analyses, or a positive guideline recommendation. Reasonable to recommend or endorse within a defined indication.	Omega-3 Fatty Acids · Saffron · St. John's Wort · S-Adenosylmethionine (SAMe) · L-Methylfolate · N-Acetylcysteine (NAC) · NAC for OCD-Spectrum Disorders · Broad-Spectrum Micronutrients · Ginkgo Biloba · Horse Chestnut Seed · Melatonin · Lavender
2. Promising but limited evidence	Positive signal from small or few trials, short follow-up, or surrogate endpoints. Reasonable to tolerate or trial as an adjunct; not a substitute for first-line care.	Curcumin · Chamomile · Saffron for Sexual Dysfunction · Rhodiola Rosea · Ashwagandha · Vitamin D · Zinc · Magnesium · Probiotics · Pycnogenol · L-Arginine and Citrulline · Panax Ginseng · Milk Thistle · Passionflower · Green Tea and L-Theanine · Lemon Balm · Galphimia Glauca
3. Insufficient or conflicting	Trials conflict, the largest and best-controlled studies are null, or human data is too sparse to judge. Neither endorse nor alarm — document use and monitor.	Valerian · Saw Palmetto · Black Cohosh · Echinacea · Inositol · Creatine · Vitamin C · Garlic · Dehydroepiandrosterone (DHEA) · Natural Remedies for ED · Cannabis and CBD · Lion's Mane · Other Medicinal Mushrooms · Supplements in Autism · Herbal Remedies in Autism · Autism: What to Discourage · Chasteberry for PMS and PMDD · Other Herbs in PMS and PMDD
4. Evidence against, or risk outweighs benefit	Negative trials, an explicit guideline recommendation against use, or a safety signal that outweighs any measured benefit. Actively counsel patients away from these.	Kava · Yohimbine · Tryptophan and 5-HTP · Acetyl-L-Carnitine · Evening Primrose Oil · Trends Without the Evidence

Tiers follow the graded evidence summarized later in this deck. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

STRONGEST DATA — EVIDENCE TIER 1

Tier 1 — Good, replicated evidence

Multiple positive RCTs and meta-analyses, or a positive guideline recommendation. Reasonable to recommend or endorse within a defined indication.

12 AGENTS IN THIS TIER

Omega-3 Fatty Acids · Saffron · St. John's Wort · S-Adenosylmethionine (SAMe) · L-Methylfolate · N-Acetylcysteine (NAC) · NAC for OCD-Spectrum Disorders · Broad-Spectrum Micronutrients · Ginkgo Biloba · Horse Chestnut Seed · Melatonin · Lavender

MILD-TO-MODERATE DEPRESSION

St. John's Wort

Hypericum perforatum

- Meta-analysis of 27 trials (3,808 patients) showed response and remission rates comparable to SSRIs, with fewer adverse effects.
- A Cochrane meta-analysis of 29 trials (5,489 patients) found superiority to placebo and rough equivalence to antidepressants.
- A potent inducer of CYP3A4 and P-glycoprotein: lowers oral contraceptive, methadone, cyclosporine, indinavir and digoxin levels — transplant rejection has been reported. Serotonin syndrome risk with SSRIs.
- Trial doses 300–1800 mg/day, standardized to 0.3% hypericin and 2–5% hyperforin. Titrate from 300 mg and reassess at 6 weeks.
- Adverse effects in 0.1–5.7% of users, comparable to placebo — mostly reversible dermatological and GI. Rarely triggers mania or psychosis.
- WFSBP/CANMAT taskforce grade: Recommended (+++) as monotherapy in mild-to-moderate MDD — the highest grade awarded to any phytoceutical — at 500–1800 mg/day standardized extract. Avoid in severe depression, bipolar disorder, pregnancy and with anticoagulants or anticonvulsants.

Ng QX et al. J Affect Disord. 2017; Linde K et al. Cochrane Database Syst Rev. 2008; Apaydin EA et al. Syst Rev. 2016; Reque PM et al. Adv Gut Microbiome Res. 2025; Lewis BB. Psychiatric Times. 2022;39(10); Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

STRONGEST OVERALL EVIDENCE

Omega-3 Fatty Acids

EPA / DHA

- Meta-review of 33 meta-analyses identified PUFAs, particularly EPA, as the best supported adjunctive nutraceutical for depression.
- Dose-response meta-analysis of 67 trials: greatest benefit near 1.5 g/day in patients with existing depression; doses ≥2 g/day were not more effective.
- EPA-predominant formulations (≥60% EPA) at 1–2 g/day show the most consistent antidepressant effect.
- No benefit for prevention, VITAL-DEP (n=18,353) found a slight increase in depression risk in non-depressed older adults.
- WFSBP/CANMAT grade: Recommended (+++) as adjunct in MDD (k=25, n=1,373) at 1–2 g/day of EPA or an EPA-predominant blend; separately Weakly Recommended (+) as adjunctive therapy in pediatric ADHD (k=10, n=699).

Firth J et al. World Psychiatry. 2019; Norouzi asl R et al. Br J Nutr. 2024; Kelaiditis CF et al. PLEFA. 2023; Okereke OI et al. JAMA. 2021; Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

TREATMENT-RESISTANT DEPRESSION

S-Adenosylmethionine (SAMe)

- Network meta-analysis: SAMe plus an antidepressant produced a large effect size (SMD 0.99); monotherapy outperformed antidepressants alone (SMD 0.52).
- Systematic review in the American Journal of Psychiatry supports adjunctive SAMe for major depressive disorder.
- Contraindicated in bipolar disorder across all ages because of manic switching, a particular concern in undiagnosed adolescents.
- Most trial data are in adults 25 to 65; possible neuroprotective role in Alzheimer's disease, but no pediatric data exist.
- WFSBP/CANMAT grade: Provisionally Recommended (++) for MDD, monotherapy or adjunctive, at 800–1600 mg/day (k=8, n=934; Papakostas 2010 Am J Psychiatry 167:942-948; Sarris 2018 Am J Psychiatry 175:493-495).

Cheng YC et al. Psychol Med. 2025; Sarris J et al. Am J Psychiatry. 2016; Sharma A et al. J Clin Psychiatry. 2017; Mischoulon D. Popular Herbal and Natural Remedies Used in Psychiatry. Focus (Am Psychiatr Publ). 2018;16(1):2-11. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

SSRI-RESISTANT DEPRESSION

L-Methylfolate

5-MTHF

- High-dose L-methylfolate (15 mg/day) is effective as adjunctive therapy in major depressive disorder; adjunctive folate showed SMD 0.64 in network meta-analysis.
- Best responders have elevated CRP or IL-6, obesity (BMI ≥30), or MTHFR polymorphisms, especially when two or more factors coexist.
- Post hoc analyses of two RCTs: patients with inflammation or obesity had mean HAM-D reduction of −2.74 vs. +0.99 in the overall sample.
- Preferred over folic acid for bioavailability. A retrospective study of 412 patients ≤18 years found no efficacy signal in youth.
- WFSBP/CANMAT grade: Provisionally Recommended (++) as adjunct in MDD at 15 mg/day methylfolate or 15–30 mg/day folinic acid (k=7, n=1,003; Papakostas 2012 Am J Psychiatry 169:1267-1274).

Jain R et al. CNS Spectr. 2020; Macaluso M. Front Psychiatry. 2022; Fava M, Mischoulon D. J Clin Psychiatry. 2010; Bopp EA et al. J Affect Disord. 2022; Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

SCHIZOPHRENIA AND OCD SPECTRUM

N-Acetylcysteine (NAC)

- Network meta-analysis suggests NAC may be the most effective nutritional supplement for improving PANSS scores in schizophrenia.
- Most consistent benefit is for negative and cognitive symptoms; evidence in bipolar disorder and MDD is promising but conflicting.
- May also benefit severe autism, OCD, trichotillomania and substance use disorders; benefits can take months to appear.
- Well-established safety profile in adults and children (FDA-approved since 1963); GI symptoms most common. Can potentiate nitrate vasodilators.
- WFSBP/CANMAT grades: Provisionally Recommended (++) as adjunct in schizophrenia at 2 g/day (k=7, n=458; Berk 2008 Biol Psychiatry 64:361-368), Weakly Recommended (+) in OCD-spectrum disorders, and Not Currently Recommended (±) in bipolar depression.

Xu X et al. Psychiatry Res. 2022; Zheng W et al. Acta Psychiatr Scand. 2018; Bradlow RCJ et al. CNS Drugs. 2022; Deepmala et al. Neurosci Biobehav Rev. 2015. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

BODY-FOCUSED REPETITIVE BEHAVIOURS

NAC for OCD-Spectrum Disorders

Trichotillomania, excoriation, OCD and tics — where the trials actually land

- Trichotillomania (adults): the strongest signal. 12-week RCT, n=50, NAC 1200–2400 mg/day, 56% responders vs 16% on placebo, with benefit emerging around week 9 (Grant 2009, Arch Gen Psychiatry 66:756-763).
- Excoriation/skin-picking disorder: 12-week RCT, n=66, NAC 1200–3000 mg/day, 47% much or very much improved vs 19% on placebo (Grant 2016, JAMA Psychiatry 73:490-496).
- Pediatric trichotillomania: negative. 12-week RCT in 39 children showed no separation from placebo (Bloch 2013, J Am Acad Child Adolesc Psychiatry 52:231-240), an adult result that does not transfer to children.
- Tourette syndrome and chronic tics: negative. 12-week RCT, n=31 children and adolescents, no reduction in tic severity (Bloch 2016, J Child Adolesc Psychopharmacol 26:327-334).
- OCD as an SRI adjunct: genuinely split. Positive augmentation trials (Afshar 2012, J Clin Psychopharmacol 32:797-803; Paydary 2016, J Clin Pharm Ther 41:214-219) are offset by negative ones (Costa 2017, J Clin Psychiatry 78:e766-e773; Sarris 2015, CNS Drugs 29:801-809). WFSBP/CANMAT grade: Weakly Recommended (+).
- Practical framing: reasonable as an adjunct in adult hair-pulling and skin-picking where habit-reversal therapy has stalled, at 1200–2400 mg/day for 12 weeks. Not a substitute for behavioral therapy or an SRI and not supported in children or in tics – (used often and seemingly helpful anecdotally).

Primary trials cited beside each result above. Deepmala et al. Neurosci Biobehav Rev. 2015; Sarris J et al. World J Biol Psychiatry. 2022.

COGNITION AND CLAUDICATION

Ginkgo Biloba

Ginkgo biloba leaf extract (EGb 761)

- Standardized leaf extract contains flavonol glycosides and terpene lactones; proposed actions include improved microcirculation and free-radical scavenging.
- Modest benefit reported in dementia and in intermittent claudication (increased pain-free walking distance); results across trials are inconsistent.
- Bleeding is the principal safety concern: spontaneous hyphema, subdural hematoma and intracerebral hemorrhage have been reported, several in patients on antiplatelet agents.
- Discontinue well before elective surgery and review carefully in patients on warfarin, aspirin or NSAIDs.
- WFSBP/CANMAT taskforce guidelines note weak support for ginkgo as an adjunct for negative symptoms in schizophrenia; it remains among the highest-selling herbs in the US.
- WFSBP/CANMAT grade: Weakly Recommended (+) as adjunct for negative and total symptoms in schizophrenia at 240–360 mg/day EGb 761 (k=8, n=1,033); preclinical work indicates part of its central effect is microbiota-mediated.

Zhou J, Fan Q, Cai X, et al. Chin J Nat Med. 2023;21(10):745-758. doi:10.1016/S1875-5364(23)60496-0 — as cited in Reque PM et al. Adv Gut Microbiome Res. 2025; De Smet PA. N Engl J Med. 2002;347(25):2046-56; Lewis BB. Psychiatric Times. 2022;39(10); Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

CHRONIC VENOUS INSUFFICIENCY

Horse Chestnut Seed

Aesculus hippocastanum (aescin)

- Standardized seed extract containing aescin is used for chronic venous insufficiency — leg edema, heaviness, pruritus and pain.
- Randomized trials show reduction in lower-leg volume broadly comparable to compression stockings.
- Well tolerated in standardized form; gastrointestinal upset, dizziness and pruritus are the usual complaints.
- Raw, unprocessed horse chestnut is toxic, only properly standardized, aescin-quantified preparations should be used.

De Smet PA. Herbal Remedies. N Engl J Med. 2002;347(25):2046-56.

MILD-TO-MODERATE DEPRESSION

Saffron

Crocus sativus stigma

- Meta-analysis of 5 high-quality RCTs showed a large effect size over placebo for depressive symptoms and an effect equal to comparator antidepressants.
- A 12-week double-blind RCT (n=60) of 50 mg/day was positive for both anxiety and depressive symptoms.
- Constituents crocin and safranal appear to inhibit reuptake of dopamine, norepinephrine and serotonin, with additional anti-inflammatory activity.
- Usable as monotherapy or adjunct in mild-to-moderate depression; favor a higher-dose supplement and twice-daily dosing.
- Caveat: trials are small, short, and predominantly Iranian, with little Western replication to date.
- WFSBP/CANMAT grade: Provisionally Recommended (++) for MDD, monotherapy or adjunctive, at 30 mg/day of standardized stigma extract (k=9, n=531; Akhondzadeh 2005 Phytother Res 19:148-151). In chronic restraint-stress models crocin also reshapes gut microbiota.

Xiao Q, Shu R, Wu C, et al. Crocin-I alleviates depression-like behaviors via modulating the microbiota-gut-brain axis. J Affect Disord. 2020;276:476-486. doi:10.1016/j.jad.2020.07.041 — as cited in Reque PM et al. 2025; Hausenblas HA et al. J Integr Med. 2013;11(6):377-83; Mazidi M et al. J Complement Integr Med. 2016;13(2):195-9; Lewis BB. Psychiatric Times. 2022;39(10); Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11.

ANXIETY AND MIXED ANXIETY-DEPRESSION

Lavender

Lavandula angustifolia

- 2021 meta-analysis of 17 articles found significant reduction in depressive symptoms; most studies used aromatherapy and five used oral lavender.
- Silexan (lavender essential oil) 80 mg vs. placebo in 318 patients with mixed anxiety-depressive disorder over 70 days improved depression scores and quality of life.
- Eructation, belching with a lavender taste, was the principal adverse effect; tolerability is otherwise good.
- Select soft-gel preparations delivering 80–160 mg of lavender essential oil per day.
- Evidence for monotherapy is weak; best positioned as an adjunct in major depressive disorder and generalized anxiety disorder. Evidence-based dose 80–160 mg/day of oil, with robust safety.
- WFSBP/CANMAT grade: Provisionally Recommended (++) for generalized anxiety disorder as Silexan 80–160 mg/day (k=5, n=1,173) — the best-graded phytoceutical for GAD in the guideline.

Reque PM et al. Adv Gut Microbiome Res. 2025; Firoozeei TS et al. Complement Ther Med. 2021;59:102679; Kasper S et al. Eur Neuropsychopharmacol. 2016;26(2):331-40; Lewis BB. Psychiatric Times. 2022;39(10). Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

Melatonin

Pineal hormone supplement

- Best evidence is for circadian rhythm problems, delayed sleep phase, shift work and jet lag, rather than for primary insomnia maintenance.
- Low doses (0.5–3 mg) taken several hours before the target bedtime work chronobiotically; higher doses are common but not clearly better.
- Frequently used in psychiatric populations, including for sleep disruption in mood disorders and in children with neurodevelopmental conditions.
- Generally well tolerated: headache, vivid dreams, daytime grogginess. Over-the-counter product content is poorly standardized in the US.
- Ask about it explicitly. Patients often do not report melatonin as a medication.

Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One. 2013;8(5):e63773. doi:10.1371/journal.pone.0063773 — as cited in Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. doi:10.1176/appi.focus.20170041.

pediatric ADHD — BEST-GRADED

Broad-Spectrum Micronutrients - aka multivitamin-multimineral supplement (MVM)

13 vitamins plus 15 minerals in a single formula

- The one broad-spectrum micronutrient approach the WFSBP/CANMAT taskforce grades as Weakly Recommended (+) and notably as monotherapy, not as an add-on (k=2, n=173).
- Trial dosing is high by supplement standards: 8-12 capsules per day of a combined vitamin and mineral formula, taken in divided doses with food.
- Rucklidge 2014 (Br J Psychiatry 204:306-315) randomized adults with ADHD and found improvement in inattention and hyperactivity over 8 weeks.
- Rucklidge 2018 (J Child Psychol Psychiatry 59(3):232-246) extended the signal to children, with the strongest effect on emotional dysregulation and aggression rather than core inattention.
- Johnstone 2020 (Nutrients 12(11):3394) confirmed feasibility and tolerability in a pediatric RCT; adverse effects were largely gastrointestinal and transient.
- Practical caveats: pill burden drives non-adherence, formulations are proprietary and not interchangeable, and cost is rarely covered. Set expectations before starting a trial.

Rucklidge JJ, Frampton CM, Gorman B, Boggis A. Br J Psychiatry. 2014;204:306-315; Rucklidge JJ, Eggleston MJF, Johnstone JM, et al. J Child Psychol Psychiatry. 2018;59(3):232-246; Johnstone JM et al. Nutrients. 2020;12(11):3394 — all as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

SUPPORTIVE BUT THIN — EVIDENCE TIER 2

Tier 2 — Promising but limited evidence

Positive signal from small or few trials, short follow-up, or surrogate endpoints. Reasonable to tolerate or trial as an adjunct; not a substitute for first-line care.

17 AGENTS IN THIS TIER

Curcumin · Chamomile · Saffron for Sexual Dysfunction · Rhodiola Rosea · Ashwagandha · Vitamin D · Zinc · Magnesium · Probiotics · Pycnogenol · L-Arginine and Citrulline · Panax Ginseng · Milk Thistle · Passionflower · Green Tea and L-Theanine · Lemon Balm · Galphimia Glauca

DEFICIENCY-LINKED MOOD SYMPTOMS

Magnesium

- Meta-analysis of 7 RCTs found significant improvement in depression scores (SMD −0.92).
- Open-label crossover trial of 248 mg/day elemental magnesium improved PHQ-9 and GAD-7 scores within two weeks.
- RCT in hypomagnesemic patients: 500 mg/day magnesium oxide for 8 weeks improved depression scores, with 88.5% normalizing magnesium levels.
- Benefit was independent of baseline magnesium, age, sex, severity, or concurrent antidepressant use. No pediatric or geriatric RCTs; overuse risks toxicity.
- Counterpoint, the WFSBP/CANMAT taskforce grades magnesium. Not Recommended (−) for MDD (k=2, n=149), judging the controlled evidence insufficient despite these positive meta-analytic signals. Reserve for documented deficiency.

Moabedi M et al. Front Psychiatry. 2024; Tarleton EK et al. PLoS One. 2017; Rajizadeh A et al. Nutrition. 2017. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

TREAT DEFICIENCY, NOT PREVENTION

Vitamin D

Cholecalciferol

- Effect is more pronounced in patients with existing depressive symptoms (SMD −0.57) than in the general population (SMD −0.32).
- Meta-analysis of 18 RCTs: depressed adults responded well (SMD −0.70) while children and adolescents showed essentially no benefit (SMD 0.10).
- VITAL-DEP (n=18,353) found no prevention benefit in any subgroup, including participants with low baseline vitamin D.
- Also used in men's sexual health to correct deficiency, a risk factor for endothelial dysfunction and ED; a level ≥30 ng/mL may be optimal.
- WFSBP/CANMAT grade: Weakly Recommended (+) as adjunct in MDD at 1,500–7,000 IU/day (k=4, n=948); monitor 25-OH vitamin D and avoid unsupervised high-dose use.

Ghaemi S et al. Psychol Med. 2024; Srifuengfung M et al. Nutrition. 2023; Okereke OI et al. JAMA. 2020; VA/DoD MDD Guideline, 2022. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

ADJUNCTIVE ANTIDEPRESSANT EFFECT

Zinc

- Network meta-analysis of nutraceuticals for depression: adjunctive zinc plus an antidepressant showed a large effect size (SMD 1.59).
- A meta-analysis of antioxidant supplementation also found significant benefit for zinc in depression and anxiety (SMD 0.59).
- Used to support testosterone production, which may enhance erectile function, particularly when the cause of ED is unclear.
- Best positioned as an adjunct rather than a replacement for standard therapy; evidence base is limited by dosing heterogeneity.
- WFSBP/CANMAT grade: Weakly Recommended (+) as adjunct in MDD at 25 mg/day elemental zinc (k=3, n=138; Ranjbar 2013 Nutr Neurosci 16:12-18). Take with food; higher chronic doses risk copper depletion.

Cheng YC et al. Psychol Med. 2025; Wang H et al. J Affect Disord. 2023; Conway, cited in natural ED treatment review. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

MONOTHERAPY AND ADJUNCT

Curcumin

Curcuma longa (turmeric root)

- Network meta-analysis found efficacy for depression both as monotherapy and as adjunctive therapy.
- Effect size as an add-on to antidepressants was large (SMD 1.03).
- Derived from the rhizome of turmeric; bioavailability is a recognized limitation of standard preparations.
- Evidence is constrained by study heterogeneity, variable dosing, and small sample sizes, treat as adjunctive, not first-line.
- Meta-analysis of 10 studies (530 participants) found a large effect for depressive symptoms and benefit for anxiety across 5 studies; a 6-week RCT of 1000 mg/day added to escitalopram lowered IL-1β, TNF-α and salivary cortisol while raising BDNF.
- Consider particularly when hs-CRP exceeds 1 mg/L. Choose formulations containing black pepper (piperine) extract, which markedly increases curcumin absorption. Evidence-based dose range 500–1000 mg/day (level A, robust safety).
- Counsel on hepatotoxicity: curcumin is now among the most frequently implicated supplements in drug-induced liver injury, especially in high-dose piperine-enhanced products (Likhitsup 2024).

Cheng YC et al. Psychol Med. 2025; Fusar-Poli L et al. Crit Rev Food Sci Nutr. 2020; Ng QX et al. J Am Med Dir Assoc. 2017; Yu JJ et al. J Clin Psychopharmacol. 2015; Lewis BB. Psychiatric Times. 2022;39(10); Reque PM et al. Adv Gut Microbiome Res. 2025.

THIRD-LINE ADJUNCT FOR MDD

Probiotics

Lactobacillus / Bifidobacterium

- Meta-analyses in clinical populations show significant reduction in depression (SMD −0.96) and moderate reduction in anxiety (SMD −0.59).
- JAMA Psychiatry RCT: adjunctive probiotics improved depressive and anxiety symptoms in patients with MDD already taking SSRIs.
- Multi-strain formulations at 1-10 billion CFU for 8-10 weeks show the most consistent effects.
- CANMAT 2026 guidelines cautiously recommend probiotics as a third-line adjunctive treatment for MDD. Pediatric data are sparse.
- Recommended for major depression at 1-10 billion units/day; benefit is attributed to restoring microbial diversity, short-chain fatty acid production and gut-barrier integrity along the gut–brain axis.
- WFSBP/CANMAT grade: Weakly Recommended (+) as adjunct in MDD (k=5, n=185), with the taskforce noting strain, dose and duration heterogeneity as the main barrier to a stronger grade.

Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, et al. Nutrition. 2016;32(3):315-320. doi:10.1016/j.nut.2015.09.003 — as cited in Reque PM et al. Adv Gut Microbiome Res. 2025; Asad A et al. Nutr Rev. 2025; Nikolova VL et al. JAMA Psychiatry. 2023; Bahji A et al. Can J Psychiatry. 2026; Kaur S et al. Psychoneuroendocrinology. 2025. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

ERECTILE DYSFUNCTION

L-Arginine and Citrulline

- Among the most commonly used natural remedies for ED; widens blood vessels and enhances penile blood flow.
- Both amino acids increase nitric oxide release, improving vasodilation and blood flow.
- Can be used alone, alongside PDE5 inhibitors, or combined with citrulline or propionyl-L-carnitine.
- Adverse reactions are uncommon and usually mild — headache, gastrointestinal upset and itching.

Natural ED treatment review (Dr. Conway), citing refs 14–16 of the source document.

COMBINED WITH L-ARGININE

Pycnogenol

Pinus pinaster bark extract

- A polyphenol-rich extract of French maritime pine bark used to potentiate the effect of L-arginine in erectile dysfunction.
- Shown to improve erectile function, shorten time to erection, and increase erection duration.
- Typically used in combination protocols rather than as a standalone agent.
- Herbal ED treatments generally lack the immediate effect of PDE5 inhibitors but may confer longer-term benefit without on-demand dosing.

Natural ED treatment review, citing refs 14–16 of the source document.

COMBINATION HERBAL ED PROTOCOLS

Panax Ginseng

- Listed among herbal ED remedies alongside Tribulus terrestris, Lepidium meyenii (maca), Ginkgo biloba and Epimedium (horny goat weed).
- These agents are typically used in combination because each has a distinct mechanism of action in supporting ED symptoms.
- Herbal treatments do not replicate the immediate erectile-enhancing effect of PDE5 inhibitors.
- They may provide more sustained benefit, potentially removing the need for medication timed to a sexual encounter.
- NEJM review: ginseng may lower blood glucose and has been associated with reduced warfarin effect; ginkgo, also used in these protocols, carries a bleeding risk with antiplatelet agents.

Natural ED treatment review (Dr. Conway), refs 15–17 of the source document; De Smet PA. Herbal Remedies. N Engl J Med. 2002;347(25):2046-56.

ANXIOLYTIC AND SEDATIVE

Galphimia Glauca

Rain of gold / thryallis

- An evergreen Malpighiaceae shrub native to Mexico, Guatemala and Panama, growing 1.8-03 m at altitudes of 920-2,600 m.
- Long used in traditional Mexican medicine for “nervios” (anxiety disorders) and for hay fever, asthma and allergic conditions.
- Contains triterpenes called galphimines; galphimine B drives the anxiolytic effect by reducing excitatory signaling in ventral tegmental dopaminergic neurons.
- Possibly safe short-term orally: tiredness, nausea, headache, somnolence and slowed breathing reported. Interacts with sedatives; avoid in pregnancy and lactation.
- Psychiatric herbal-medicine reviews classify galphimia as having modest evidence for anxiety disorders, promising but not yet a first-line recommendation.
- Evidence-based dosing for anxiety is 350-700 mg/day of standardized extract; safety is rated fair rather than robust, so supervise use and limit duration.

WebMD and RxList ingredient monographs; Lewis BB. Psychiatric Times. 2022;39(10); Reque PM et al. Adv Gut Microbiome Res. 2025 (Sarris level-A dosing table). Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

Ashwagandha

Withania somnifera

- An adaptogenic root that appears in the source document as a component of multi-ingredient over-the-counter sleep and stress support products.
- Increasingly encountered in combination “5-in-1” formulations rather than as a single agent, which complicates attribution of both effect and harm.
- Ask specifically about combination products. Patients frequently do not classify them as medications during history-taking.
- Reconcile the full ingredient list, since combination formulas can carry sedative and hepatic risk not evident from the marketed indication.
- Rated as having moderate evidence for anxiety disorders in psychiatric herbal-medicine reviews, and it is among the top US consumer categories by spending, so expect to encounter it.
- WFSBP/CANMAT grade: Weakly Recommended (+) for anxiety and stress at 300–600 mg/day of root extract standardized to 5% withanolides, with robust safety at those doses. It is also one of six botanicals tracked as a cause of liver injury (Likhitsup 2024).

Lewis BB. Psychiatric Times. 2022;39(10); Reque PM et al. Adv Gut Microbiome Res. 2025. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

HEPATIC DISEASE

Milk Thistle

Silybum marianum (silymarin)

- Silymarin, a flavonolignan complex from the seeds, is used for alcoholic and viral liver disease and as an antidote adjunct in Amanita poisoning.
- Proposed mechanisms include antioxidant activity, membrane stabilization of hepatocytes and stimulation of protein synthesis.
- Trial evidence for chronic liver disease is weak and heterogeneous; mortality benefit is unproven.
- Notably well tolerated — mild laxative effect is the most frequent complaint — which explains its persistence in patient self-care.

De Smet PA. Herbal Remedies. N Engl J Med. 2002;347(25):2046-56.

ANTIDEPRESSANT-INDUCED SEXUAL DYSFUNCTION

Saffron for Sexual Dysfunction

The one nutraceutical here with positive RCT data in SSRI-related sexual side effects

- Women: 4-week double-blind RCT in 38 women with fluoxetine-induced sexual dysfunction — saffron 30 mg/day significantly improved total Female Sexual Function Index score (Kashani 2013).
- The gains were concentrated in arousal and lubrication; orgasm, satisfaction and pain domains did not separate from placebo, so set expectations accordingly.
- Men: a parallel 4-week RCT (n=36) showed improved erectile function on the IIEF at the same 30 mg/day dose (Modabbernia 2012).
- Important limit: saffron failed in erectile dysfunction that was not drug-induced (Safarinejad 2011) — the signal looks specific to SSRI-related dysfunction, not to sexual dysfunction generally.
- Practical use: 30 mg/day divided, alongside the antidepressant for a 4-week trial — an alternative to dose reduction, drug holidays or switching in a patient otherwise responding well.
- Cautions: trials are small, short and mostly Iranian with no Western replication. Avoid in pregnancy and use care with anticoagulants.

Kashani L, Raisi F, Saroukhani S, et al. Hum Psychopharmacol. 2013;28(1):54-60; Modabbernia A et al. Psychopharmacology (Berl). 2012;223(4):381-388; Safarinejad MR et al. Phytother Res. 2011;25(4):508-516; Maleki-Saghooni N et al. Avicenna J Phytomed. 2018;8(3):198-209.

FATIGUE, STRESS AND LOW MOOD

Rhodiola Rosea

Golden root — arctic adaptogen

- An adaptogen traditionally used in Scandinavia and Russia for fatigue and stress resilience; active constituents include rosavins and salidroside.
- Reviewed in the psychiatric literature as a plausible option for mild depression and stress-related fatigue, with monoamine and HPA-axis modulation proposed as mechanisms.
- Trials are generally small and of short duration; effect sizes are modest and product standardization varies widely between manufacturers.
- Usually well tolerated; agitation, insomnia and jitteriness can occur, so avoid late-day dosing and use caution in bipolar disorder.
- Among the top-selling herbs with mental health applications in the US, so ask about it during medication reconciliation.
- WFSBP/CANMAT grade: Not Currently Recommended (±) for MDD — Darbinyan 2007 was positive but Mao 2015 (Phytomedicine 22(3):394-399) found rhodiola inferior to sertraline. Evidence-based dose 340–680 mg/day, robust safety.

Darbinyan V, Aslanyan G, Amroyan E, et al. Clinical trial of Rhodiola rosea L. extract SHR-5 in mild to moderate depression. Nord J Psychiatry. 2007;61(5):343-348. doi:10.1080/08039480701643290 — as cited in Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11; Mao JJ, Xie SX, Zee J, et al. Rhodiola rosea versus sertraline for major depressive disorder. Phytomedicine. 2015;22(3):394-399 — as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

GENERALIZED ANXIETY

Chamomile

Matricaria recutita

- Standardized chamomile extract has shown reduction in anxiety symptoms in controlled trials of generalized anxiety disorder, with a possible antidepressant signal.
- Apigenin and related flavonoids bind benzodiazepine receptor sites, offering a plausible anxiolytic mechanism without benzodiazepine dependence.
- Notably well tolerated — among the safer agents in the psychiatric herbal toolbox — and inexpensive and widely available as tea or capsules.
- Allergic reactions can occur in patients sensitized to Asteraceae species such as ragweed; theoretical additive effect with anticoagulants.
- Reasonable to support as an adjunct for mild anxiety in patients who prefer a non-pharmaceutical first step. Evidence-based dose 220–1500 mg/day, safety rated robust.
- WFSBP/CANMAT grade: Not Currently Recommended (±) for GAD — the positive Amsterdam 2009 trial was not replicated by Mao 2016 (Phytomedicine 23(14):1735-1742), which found no relapse-prevention benefit. Safe to tolerate, but set expectations.

Amsterdam JD, Li Y, Soeller I, et al. A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (chamomile) extract for generalized anxiety disorder. J Clin Psychopharmacol. 2009;29(4):378-382. doi:10.1097/JCP.0b013e3181ac935c — as cited in Mischoulon D. Focus. 2018;16(1):2-11; Mao JJ, Xie SX, Keefe JR, et al. Long-term chamomile therapy for generalized anxiety disorder. Phytomedicine. 2016;23(14):1735-1742 — as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

ANXIETY AND SLEEP ONSET

Passionflower

Passiflora incarnata

- Traditionally used as a mild anxiolytic and sleep aid; small trials suggest benefit for generalized anxiety and preoperative anxiety.
- Proposed mechanism is GABAergic modulation, consistent with its sedative profile.
- Frequently appears as one component of multi-herb sleep and calming formulations rather than as a single agent.
- Sedation, dizziness and confusion have been reported; additive with alcohol, benzodiazepines and other CNS depressants.
- WFSBP/CANMAT grade: Not Currently Recommended (±) for anxiety disorders — too few adequately powered trials to grade either way; reasonable as an adjunct, not a substitute for treatment of a primary anxiety disorder.

Akhondzadeh S, Naghavi HR, Vazirian M, et al. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther. 2001;26(5):363-367 — as cited in Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. doi:10.1176/appi.focus.20170041. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

ANXIETY AND MOOD

Lemon Balm

Melissa officinalis

- Rosmarinic acid and related phenolics inhibit GABA transaminase, raising synaptic GABA, and show monoamine oxidase-A inhibition in preclinical work.
- Approved by the European Medicines Agency as a traditional herbal medicine for mild stress and to aid sleep.
- A randomized controlled trial in patients with type 2 diabetes and depression reported significant improvement in depressive symptoms versus placebo.
- Modulates gut microbiota composition and reduces inflammatory signaling in animal models of chronic stress.
- Generally well tolerated; mild sedation is the main effect to counsel on, and additive sedation is possible with benzodiazepines or alcohol.

Safari M, Asadi A, Aryaeian N, et al. The effects of Melissa officinalis on depression and anxiety in type 2 diabetes patients with depression: a randomized double-blinded placebo-controlled clinical trial. BMC Complement Med Ther. 2023;23(1):140. doi:10.1186/s12906-023-03978-x — as cited in Reque PM et al. Adv Gut Microbiome Res. 2025; European Medicines Agency, HMPC monograph on Melissae folium.

STRESS AND HPA REGULATION

Green Tea and L-Theanine

Camellia sinensis

- Catechins, chiefly EGCG, are extensively metabolized by colonic bacteria and in turn reshape gut microbiota composition toward a less inflammatory profile.
- Inhibits hypothalamic–pituitary–adrenal axis activity, lowering cortisol responses to acute stress in controlled studies.
- L-theanine, a unique amino acid in tea leaves, regulates dopamine and serotonin transmission and increases alpha-wave activity associated with relaxed alertness.
- Typical study doses are 200–400 mg/day of L-theanine; benefits reported for perceived stress, sleep quality and anxiety in small trials.
- Caffeine content of whole-leaf preparations may offset anxiolytic effects — prefer decaffeinated extracts or isolated theanine in anxious patients. Concentrated green tea extract, unlike brewed tea, is a leading cause of supplement-related liver injury and acute liver failure — do not endorse high-dose extracts (Likhitsup 2024, Seeff 2015).

Unno K, Iguchi K, Tanida N, et al. Ingestion of theanine, an amino acid in tea, suppresses psychosocial stress in mice. Exp Physiol. 2013;98(1):290-303. doi:10.1113/expphysiol.2012.065532 — as cited in Reque PM et al. Adv Gut Microbiome Res. 2025. doi:10.1155/agm3/3675425.

DATA DOES NOT SETTLE IT — EVIDENCE TIER 3

Tier 3 — Insufficient or conflicting

Trials conflict, the largest and best-controlled studies are null, or human data is too sparse to judge. Neither endorse nor alarm — document use and monitor.

18 AGENTS IN THIS TIER

Valerian · Saw Palmetto · Black Cohosh · Echinacea · Inositol · Creatine · Vitamin C · Garlic · Dehydroepiandrosterone (DHEA) · Natural Remedies for ED · Cannabis and CBD · Lion's Mane · Other Medicinal Mushrooms · Supplements in Autism · Herbal Remedies in Autism · Autism: What to Discourage · Chasteberry for PMS and PMDD · Other Herbs in PMS and PMDD

WHEN THE CAUSE IS UNCLEAR

Natural Remedies for ED

Overview and safety profile

- Lifestyle change remains central to managing ED; certain dietary supplements, including antioxidants, have additionally been shown to improve sexual health.
- Zinc, vitamin D, and the amino acids L-arginine and citrulline may be particularly beneficial when the underlying cause of ED is unclear.
- Agents are often combined, since each has a different mechanism of action in supporting ED symptoms.
- Many natural remedies safely increase penile blood flow without serious adverse effects; reactions are uncommon and usually mild — headache, gastrointestinal upset and itching.

Natural ED treatment review (Dr. Conway), citing refs 14–17 of the source document.

MIXED EVIDENCE

Dehydroepiandrosterone (DHEA)

- Low endogenous DHEA levels are associated with erectile dysfunction.
- Some research suggests supplementation may improve sexual performance, but results across studies are mixed.
- Larger human studies on supplemental DHEA and erectile function are needed before routine recommendation.
- As a hormonal precursor, it warrants more caution than most nutraceuticals in this list.

Natural ED treatment review, citing ref 18 of the source document.

BENIGN PROSTATIC HYPERPLASIA

Saw Palmetto

Serenoa repens berry extract

- Lipophilic berry extract used for lower urinary tract symptoms of BPH; proposed 5-alpha-reductase and anti-inflammatory activity.
- Pooled trials reported improvement in urinary flow and symptom scores comparable to finasteride, with fewer sexual adverse effects.
- Generally well tolerated; mild gastrointestinal upset is the most common complaint.
- Does not lower PSA reliably in the way finasteride does — but confirm the diagnosis and exclude prostate cancer before endorsing self-treatment.

De Smet PA. Herbal Remedies. N Engl J Med. 2002;347(25):2046-56.

UPPER RESPIRATORY INFECTION

Echinacea

Echinacea purpurea / angustifolia

- Marketed as an immunostimulant for prevention and treatment of the common cold; preparations differ widely by species and plant part.
- Controlled trials are mixed — any effect on symptom duration is modest and inconsistent across products.
- Allergic reactions, including anaphylaxis, have occurred, particularly in patients sensitized to other Asteraceae (ragweed, chrysanthemum).
- Theoretical caution in autoimmune disease and immunosuppression; long-term continuous use is not supported. Pooled RCTs show only positive trends of questionable clinical relevance for the common cold, with no significant difference from placebo (Izzo 2016, De Smet 2002).

De Smet PA. Herbal Remedies. N Engl J Med. 2002;347(25):2046-56.

INSOMNIA

Valerian

Valeriana officinalis root

- Root extract used as a mild hypnotic; effects on sleep latency and quality are small and not consistently reproduced.
- Benefit, when present, may require several weeks of continuous use rather than acting on a single dose.
- Additive sedation with alcohol, benzodiazepines and other CNS depressants; morning grogginess is reported.
- Case reports describe a withdrawal-like syndrome after abrupt cessation of high chronic doses.
- Its effects are polyvalent: free GABA, benzodiazepine receptor-binding flavonoids, terpenes that inhibit GABA breakdown and relax smooth muscle, and lignans that inhibit serotonin binding — anxiolysis, muscle relaxation and sleep promotion in one plant.
- Valerian iridoids reaching the colon increase gut microbial richness and diversity, a proposed contributor to its anxiolytic and sleep effects.

Chauveau A, Treyer A, Geirnaert A, et al. Intestinal permeability and gut microbiota interactions of pharmacologically active compounds in valerian and St. John's wort. Biomed Pharmacother. 2023;162:114652. doi:10.1016/j.biopha.2023.114652 — as cited in Reque PM et al. 2025; Lewis BB. Psychiatric Times. 2022;39(10); Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11.

MENOPAUSAL SYMPTOMS

Black Cohosh

Actaea (Cimicifuga) racemosa

- Rhizome extract widely used for hot flashes and other vasomotor menopausal symptoms.
- Short-term trials suggest symptom relief; the mechanism is not estrogenic in the classical sense and long-term data are lacking.
- Idiosyncratic hepatotoxicity has been reported — counsel patients to stop and seek review for jaundice, dark urine or right upper quadrant pain.
- Use beyond six months is not well studied; caution in hormone-sensitive malignancy and in hepatic impairment. Black cohosh is one of the six botanicals under hepatotoxicity surveillance; check liver enzymes if symptoms arise (Likhitsup 2024).

De Smet PA. Herbal Remedies. N Engl J Med. 2002;347(25):2046-56.

MENOPAUSAL SYMPTOMS

Herbs Studied in Menopause - Part 1

Vasomotor and hormonally active herbs, with the mechanism and effect each trial reported - evidence quality is generally low

Herb	Proposed mechanism	Reported effect	Data	Cautions
Sage (Salvia officinalis)	GABA/benzodiazepine receptor binding; anti-perspirant and estrogenic effects	Hot flashes and sweats; memory and sedation	CT	Excess use: warmth, dizziness, tachycardia, seizures
Black cohosh (Actaea racemosa)	Terpene glycosides; suppresses LH without lasting estrogen-receptor effect	Night sweats, flashes, insomnia, irritability, palpitations	CT	GI upset and nausea; rare hepatotoxicity
Red clover (Trifolium pratense)	Isoflavone phytoestrogens; antioxidant and anti-angiogenic	flash frequency and severity; bone density support	CT	Avoid alongside hormonal therapy
Soy (Glycine max)	Daidzein and genistein isoflavones	Fewer flashes in some trials; others no different from placebo	CT	GI upset, longer cycles, contact dermatitis
Fenugreek (Trigonella foenum-graecum)	Steroidal saponins; inhibits excess testosterone activity	Vasomotor symptoms; lipid lowering	CT, SR	Repeated topical use may irritate skin
Vitex (Vitex agnus-castus)	Hypothalamic-pituitary axis; progesterone-receptor expression and prolactin	Hot flashes and early menopausal symptoms	RCT	Nausea, headache, dizziness, dry mouth
Licorice (Glycyrrhiza glabra)	Terpenes, saponins and isoflavonoids with estrogenic activity	Hot flashes; quality of life alongside exercise	CT	Prolonged use: hypertension, hypokalaemia, pseudohyperaldosteronism
Anise (Pimpinella anisum)	Estrogenic; caffeic acid derivatives	flash frequency and severity	CT	No harm reported at therapeutic doses
Alfalfa (Medicago sativa)	Estrogenic activity	Hot flashes and neurovegetative symptoms	CT	Hypokalaemia; sprout-borne infection risk

Mechanisms, effects and study types as tabulated in Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833 - a review of clinical trials published 1994-2016. CT = clinical trial, SR = systematic review. Most trials were small, short and heterogeneous in formulation.

Herbs Studied in Menopause - Part 2

Sleep, mood, cognition and urogenital symptoms - same review, same evidence caveats

Herb	Proposed mechanism	Reported effect	Data	Cautions
Lemon balm (Melissa officinalis)	Aroma and caffeic acid derivatives acting on the nervous system	Sleep disturbance, nervousness, GI symptoms	CT	No harm reported at therapeutic doses
Valerian (Valeriana officinalis)	Raises synaptic GABA by blocking reuptake	Hot flashes; sedation and sleep onset	CT x2	Daytime sedation; additive with other sedatives
Passionflower (Passiflora incarnata)	GABA-A receptor activation; phytoprogesterone flavonoids	Hot flashes, anxiety and insomnia	CT	No harm reported at therapeutic doses
St John's wort (Hypericum perforatum)	Benzodiazepine-receptor activity and monoaminergic effects	flashes, mood, libido, vaginal dryness, urinary symptoms	RCT	CYP3A4 and P-gp induction - fails contraception and other regimens; photosensitivity
Fennel (Foeniculum vulgare)	Anti-androgenic and anti-inflammatory (palmitic acid, beta-sitosterol)	Vaginal atrophy with vaginal cream; menopausal symptoms	RCT	No harm reported at therapeutic doses
Evening primrose (Oenothera biennis)	Gamolenic acid; prostaglandin and antioxidant effects	Vasomotor symptoms - benefit modest and inconsistent	RCT	GI upset; may lower seizure threshold
Ginkgo biloba	Antioxidant and vasodilator activity	Attention and memory after menopause - benefits limited	CT	Bleeding risk; interacts with anticoagulants
Panax ginseng	Estrogen-like and anti-inflammatory effects	Mood, fatigue and sleep - not flash frequency	RCT	Insomnia, headache, hypoglycaemia, GI upset
Black cumin (Nigella sativa)	Reduces visceral fat; regulates glucose and lipids	Metabolic syndrome after menopause, not vasomotor symptoms	CT	Limited long-term safety data

Same source as Part 1: Kargozar R, Azizi H, Salari R. Electron Physician. 2017;9(11):5826-5833, drawing on Chenoy 1994 (evening primrose), Abdali 2010 (hypericum), Yaralizadeh 2016 (fennel) and Mirabi 2013 (valerian). None of these herbs has guideline-level support for vasomotor symptoms.

MENOPAUSAL SYMPTOMS — VASOMOTOR

Sage

Salvia officinalis — leaf extract

- Kitchen herb whose leaf contains rosmarinic and carnosic acids, flavonoids and a thujone-containing volatile oil.
- Mechanism is mixed: GABA and benzodiazepine receptor binding, a direct anti-perspirant action, and weak estrogenic activity — which is why it is studied for sweats more than flashes alone.
- Trials are open-label or small, reporting reduced flash and sweat intensity over 4–8 weeks with secondary signals for memory. No adequately powered placebo-controlled trial supports it.
- Excess or prolonged use of thujone-containing preparations causes warmth, dizziness, tachycardia and, at extreme doses, seizures. Avoid in epilepsy and pregnancy.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

MENOPAUSAL SYMPTOMS — VASOMOTOR

Red Clover

Trifolium pratense — isoflavone extract

- The most concentrated dietary source of the isoflavones biochanin A and formononetin, metabolized to genistein and daidzein — phytoestrogens with selective affinity for estrogen receptor beta.
- Extracts also show antioxidant and anti-angiogenic activity, with small trials reporting effects on bone density and arterial compliance.
- Trials report fewer and less severe hot flashes, but effects are modest and inconsistent, and pooled analyses are limited by heterogeneous isoflavone content.
- The estrogenic mechanism is the caution: avoid alongside hormone therapy or tamoxifen, and not a first move after hormone-sensitive cancer.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

MENOPAUSAL SYMPTOMS — VASOMOTOR

Soy Isoflavones

Glycine max / Glycine soja — daidzein and genistein

- The most consumed phytoestrogen worldwide. Daidzein and genistein are partial estrogen-receptor agonists with higher affinity for ER-beta, giving a tissue-selective rather than systemic effect.
- Response is partly patient-dependent: only some people carry the gut bacteria that convert daidzein to equol, the more active metabolite — one reason trials disagree.
- Some trials show fewer, milder flashes; others match placebo. Onset takes weeks, and the effect is smaller than hormone therapy in every comparison.
- Generally, well tolerated. Dietary soy is not a concern after breast cancer, but concentrated isoflavone supplements are a different exposure — discuss with oncology first.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

Fenugreek

Trigonella foenum-graecum — seed extract

- Seeds rich in steroidal saponins (diosgenin, protodioscin), 4-hydroxyisoleucine and soluble fibre; the saponin fraction is the presumed active.
- Proposed mechanism is modulation of the androgen–estrogen balance, inhibiting excess testosterone activity; the same saponins underlie its lipid and glycaemic effects.
- Controlled trials and a systematic review report reduced vasomotor symptoms and better quality-of-life scores over 6–12 weeks, plus modest lipid reduction. Trials are small, industry-linked and use proprietary extracts.
- GI upset and a maple-syrup body odour are common. Additive with antidiabetic drugs; avoid in pregnancy given uterotonic traditional use.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

MENOPAUSAL SYMPTOMS — SAFETY-LIMITED

Licorice

Glycyrrhiza glabra — root extract

- Root containing glycyrrhizin, saponins and the isoflavonoids glabridin and glabrene, which have measurable estrogenic activity.
- Small trials report reduced flash frequency and duration alongside exercise. Evidence quality is low and durations short.
- The limiting factor is safety, not efficacy. Glycyrrhizin inhibits 11-beta-hydroxysteroid dehydrogenase type 2, letting cortisol act at the mineralocorticoid receptor: prolonged use causes pseudohyperaldosteronism with hypertension, hypokalaemia and edema.
- Avoid in hypertension, heart failure, renal or hepatic disease, and with diuretics, digoxin or corticosteroids.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

MENOPAUSAL SYMPTOMS — UROGENITAL

Fennel

Foeniculum vulgare — seed oil and vaginal cream

- An Apiaceae seed whose volatile oil is dominated by anethole, with beta-sitosterol contributing anti-androgenic and anti-inflammatory activity; anethole behaves as a weak phytoestrogen.
- It is the one herb here with a genuinely local application: randomised trials of 5% vaginal fennel cream report improved vaginal maturation index, pH and dryness scores over 8 weeks, without measurable systemic estrogen change.
- Oral preparations studied for general symptom scores show smaller, less consistent effects than the vaginal route.
- Well tolerated. A reasonable adjunct where a patient declines low-dose vaginal estrogen, which remains first-line for genitourinary syndrome of menopause.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

MENOPAUSAL SYMPTOMS — METABOLIC, NOT VASOMOTOR

Black Cumin

Nigella sativa — seed and thymoquinone

- Seeds whose principal active is thymoquinone, with antioxidant, anti-inflammatory and insulin-sensitizing effects shown mostly in animal and small human studies.
- In postmenopausal women the studied endpoint is metabolic, not vasomotor: reduced visceral fat, improved fasting glucose and better lipids — relevant to the cardiometabolic shift after menopause, but not a treatment for hot flashes.
- It appears in the PMS and PMDD literature with the same caveat of small, heterogeneous trials.
- Short-term tolerability is good; long-term data are limited. May potentiate antihypertensive, antidiabetic and anticoagulant therapy. Frame it as a metabolic adjunct at best.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

MENOPAUSAL SYMPTOMS — THINNEST EVIDENCE

Anise and Alfalfa

Pimpinella anisum and Medicago sativa

- Both appear in the menopause review on its thinnest evidence — single small trials, no replication, no guideline standing. They are here because patients ask about them.
- Anise: anethole gives weak estrogenic activity. One placebo-controlled trial of 330 mg three times daily reported reduced flash frequency and severity; no harm at therapeutic doses.
- Alfalfa: coumestrol and formononetin are the phytoestrogens, with trials reporting improved flashes and neurovegetative symptoms. L-canavanine has been linked to lupus-like reactions and SLE reactivation.
- Neither belongs in a first conversation; discourage alfalfa in autoimmune disease.

Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.

PRACTICAL BOTTOM LINE

What to Actually Recommend

No botanical has guideline-level support for vasomotor symptoms. This is where each option belongs in a real conversation.

Clinical situation	First-line, evidence-based option	Where herbs fit	What to say
Hot flashes, night sweats	Hormone therapy where not contraindicated; fezolinetant, SSRIs/SNRIs, gabapentin, CBT as nonhormone options (The Menopause Society, 2023)	Isoflavone-rich soy or red clover may give a modest reduction in frequency; effects are small and inconsistent	Reasonable to try if hormones are declined, but not a substitute
Hot flashes: patient asks about black cohosh	Same as above: hormone therapy or a nonhormone agent	Cochrane found no consistent benefit over placebo; rare but real hepatotoxicity signal	Do not initiate as first choice; stop if liver symptoms appear
Vaginal dryness, atrophy	Low-dose vaginal estrogen; nonhormonal moisturisers and lubricants	Vaginal fennel cream improved maturation and dryness scores in a small RCT	Acceptable adjunct where local estrogen is refused
Low mood, irritability	Screen for depression and treat it on its own merits	St John's wort improved flashes and quality of life; strong drug interaction profile	Check every concurrent medication before starting
Sleep disturbance	CBT for insomnia; treat the vasomotor driver	Valerian and sage appear in small trials with weak methodology	Low risk, low expectation
Hormone-sensitive cancer history	Nonhormone pharmacotherapy, decided with oncology	Phytoestrogens are the wrong first move; the estrogenic mechanism is the point of caution	Raise this before the patient self-prescribes
Anyone already self-treating	Take a full supplement history	Products are unstandardised; dose and extract type vary widely between trials and shelves	Ask what, how much, and for how long

Synthesised from Kargozar 2017, The Menopause Society (formerly NAMS) 2023 nonhormone therapy position statement, and the Cochrane reviews cited on the preceding menopause slides.

PREGNANCY AND BIRTH

Botanicals Used to Prepare for Labor

Widely self-prescribed and rarely disclosed; the safety picture matters more than the efficacy picture.

Botanical	Claimed use	What the trials show	What to say
Red raspberry leaf	Uterine tonic; shorter, easier labor. Usually, 1-3 cups tea or 2.4 g/day tablets from 32 weeks	RCT of 192 nulliparous women: no effect on first stage; second stage shorter by about 10 minutes; fewer forceps deliveries (19.3% vs 30.4%); no adverse effects	The safest of this group; expect little
Evening primrose oil	Cervical ripening, shorter labor	Oral use from week 37 did not shorten gestation or labor and was linked to prolonged rupture of membranes, oxytocin augmentation, arrest of descent and vacuum extraction	Do not recommend orally for this purpose
Blue cohosh	Labor induction	No efficacy data; case reports of neonatal myocardial infarction, congestive heart failure, multiorgan failure and perinatal stroke	Advise strongly against
Black cohosh	Induce menses and labor	Systematic review found no evidence of efficacy in labor; unverifiable dosing in over-the-counter products; German Commission E does not recommend it in pregnancy	Avoid in pregnancy
Feverfew	Migraine prophylaxis, menstrual complaints	Traditional abortifacient and emmenagogue use; no pregnancy safety data	Contraindicated in pregnancy
Motherwort, skullcap	Relaxation, uterine stimulation, pain relief in labor	Animal data only; no human efficacy or safety data	Insufficient evidence to recommend
Disclosure is the real issue	Around a third of women in antenatal surveys use a herbal supplement	Most are recommended by friends, relatives or midwives and are not reported to the clinician	Ask directly at the booking visit

Simpson M et al. J Midwifery Womens Health. 2001;46(2):51-59; Parsons M et al. Aust Coll Midwives Inc J. 1999;12(3):20-25; Dove D, Johnson P. J Nurse Midwifery. 1999;44(3):320-324; and the reviews cited on the source pages.

What to Avoid in Pregnancy

Every agent in this deck that carries a pregnancy concern, gathered in one place.

Agent	Concern	Basis	Advice
Blue cohosh	Neonatal cardiac and neurological harm	Case reports of myocardial infarction, heart failure, multiorgan failure and perinatal stroke; oxytocic glycosides in unverified doses	Avoid outright
Black cohosh	Uterine stimulation, no efficacy shown	German Commission E advises against use in pregnancy; hepatotoxicity signal separate from this	Avoid
Feverfew	Traditional abortifacient and emmenagogue	Long-standing traditional use to bring on menstruation; no human pregnancy safety data	Contraindicated
St John's wort	Interactions and limited safety data	Potent CYP and P-glycoprotein induction affecting concurrent medication; pregnancy data are thin	Avoid unless specialist-supervised
Evening primrose oil	Worse intrapartum outcomes	Oral use from week 37 linked to prolonged rupture of membranes, oxytocin augmentation, arrest of descent and vacuum extraction	Do not use to ripen the cervix
Kava	Hepatotoxicity	Rare but severe liver injury; already not recommended outside pregnancy	Avoid
Generally acceptable	Raspberry leaf, ginger, folate and other prenatal vitamins	Raspberry leaf showed no adverse maternal or neonatal effects in a randomised trial; ginger is well studied for nausea	Reasonable, with realistic expectations

Compiled from the reviews and trials cited on the individual agent slides in this deck; consult a clinician before starting or stopping anything in pregnancy.

Garlic

Allium sativum

- Allicin-derived compounds produce a small, often transient reduction in total cholesterol; effect attenuates beyond about six months.
- Modest antihypertensive and antiplatelet activity has been described.
- Inhibits platelet aggregation — bleeding, including spontaneous spinal epidural haematoma, has been reported, with additive risk on warfarin or aspirin.
- Also induces drug-metabolizing pathways: garlic supplements markedly reduce saquinavir plasma levels. Stop before elective surgery.

De Smet PA. Herbal Remedies. N Engl J Med. 2002;347(25):2046-56.

HIGH SPENDING, THIN EVIDENCE

Cannabis and CBD

Cannabis sativa — THC and cannabidiol

- Lancet Psychiatry review of 83 studies (40 RCTs, 3,067 participants) found a lack of evidence that cannabinoids improve depression, anxiety, ADHD, tics, PTSD or psychosis.
- The single positive signal was very-low-quality evidence that THC, with or without CBD, may ease anxiety in people with other medical conditions.
- A 2021 review of 8 very small studies likewise found insufficient evidence to recommend CBD or THC for mood, anxiety or PTSD.
- If a patient uses it: favour CBD-dominant products (about 20:1 CBD:THC), capsules or soft gels for dose consistency, typically 5–45 mg, titrating 15 mg at 30-minute intervals.
- Counsel that hemp seed oil contains no CBD and advise dispensary or high-quality brands. Warn about chronic THC use.

Black N et al. Lancet Psychiatry. 2019;6(12):995-1010; Stanciu CN et al. Psychiatr Serv. 2021;72(4):429-36; Lewis BB. Psychiatric Times. 2022;39(10).

MIGRAINE — TRADITIONAL USE, MIXED TRIALS

Feverfew

Tanacetum parthenium — the "medieval aspirin"

- Feverfew is an Asteraceae perennial used since antiquity for fever, headache and menstrual complaints. Its activity is attributed to sesquiterpene lactones, chiefly parthenolide, alongside flavonoids and a camphor-rich volatile oil.
- Proposed mechanisms are plural rather than single: inhibition of prostaglandin synthesis and of 5-lipoxygenase and cyclo-oxygenase in leukocytes, blockade of serotonin release from platelets, and reduced vascular smooth muscle spasm. Parthenolide also binds and inhibits IkB kinase, which underlies the anti-inflammatory and anticancer signals seen in cell lines.
- Clinically it is used for migraine prophylaxis, with trial results that remain inconsistent; the Cochrane review found the evidence insufficient to establish benefit. Preparations vary widely, and parthenolide content falls with drying above 60°C and with storage, so two products are rarely equivalent. Fresh-leaf chewing can cause mouth ulceration and contact dermatitis; avoid in pregnancy given its traditional abortifacient use.

Pourianezhad F, Tahmasebi S, Abdusi V, Nikfar S, Mirhoseini M. Review on feverfew, a valuable medicinal plant. J HerbMed Pharmacol. 2016;5(2):45-49; Pareek A et al. Pharmacogn Rev. 2011;5(9):103-110; Pittler MH, Ernst E. Cochrane Database Syst Rev. 2004;(1):CD002286.

Inositol

Myo-inositol

- A carbohydrate second-messenger precursor in the phosphatidylinositol signalling pathway, downstream of serotonergic receptors.
- Small trials have suggested benefit in panic disorder and obsessive-compulsive disorder at high doses, typically in the range of 12–18 g/day.
- Evidence in depression and bipolar depression is weaker and has not been consistently replicated.
- Main limitation is the large powder dose required; gastrointestinal upset, gas and loose stools are the usual complaints.
- WFSBP/CANMAT grade: Not Recommended (−) for MDD and bipolar depression (k=5, n=139) — the taskforce found the controlled evidence does not support routine use at any dose.

Levine J, Barak Y, Gonzalves M, et al. Double-blind, controlled trial of inositol treatment of depression. Am J Psychiatry. 1995;152(5):792-794. doi:10.1176/ajp.152.5.792 — as cited in Mischoulon D. Focus. 2018;16(1):2-11; grade from Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

ADJUNCT IN DEPRESSION — UNPROVEN

Vitamin C

Ascorbic acid

- WFSBP/CANMAT grade: Not Currently Recommended (±) as an adjunct in major depressive disorder — the evidence base is two small trials totalling 70 participants.
- Trial dosing was approximately 1 g/day, given alongside standard antidepressant therapy.
- Amr 2013 (Nutr J 12:31) reported benefit when vitamin C was added to fluoxetine in pediatric depression, but the sample was very small.
- Sahraian 2015 (Trials 16:94) studied adjunctive vitamin C in acute mania and did not establish a clear treatment effect.
- Safety is excellent at these doses; the limiting factor is efficacy evidence, not risk. High chronic intake can precipitate oxalate stones in susceptible patients.
- Reasonable to tolerate if a patient is already taking it, but do not position it as an antidepressant strategy.

Amr M, El-Mogy A, Shams T, Vieira K, Lakhan SE. Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder. Nutr J. 2013;12:31; Sahraian A, Ghanizadeh A, Kazemeini F. Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior. Trials. 2015;16:94 — as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

BIOENERGETIC ADJUNCT

Creatine

Creatine monohydrate

- Trial dose is 5 g/day of creatine monohydrate, always as an add-on; the rationale is impaired frontal-lobe phosphocreatine metabolism in depression.
- Lyoo 2012 added creatine to escitalopram in women with MDD - faster and greater improvement, d = 1.13 at 8 weeks. Sherpa 2025 (Eur Neuropsychopharmacol 90:28-35) added 5 g/day to CBT in 100 adults: PHQ-9 fell 5.1 points further than placebo.
- Against that: null as pharmacotherapy augmentation in adults, null in female adolescents, and null in bipolar depression (Nemets 2013), where two participants switched into hypomania or mania.
- Pooled to 2025: 11 RCTs, 1,093 patients, SMD -0.34 (95% CI -0.68 to 0.00) - about 2.2 HDRS points, below the 3-point minimum important difference, GRADE very low (Br J Nutr 2025).
- A 2025 systematic review found only 5 RCTs and 238 patients across all mental disorders - that is the entire psychiatric evidence base, and none of it tests creatine as monotherapy.
- Safety is the strong point: side effects in 13.7% of creatine arms versus 13.2% of placebo arms across 685 trials. Creatine raises serum creatinine and so lowers estimated GFR without changing measured kidney function - avoid in CKD, expect weight gain from water retention.

Lyoo IK, Yoon S, Kim TS, et al. Am J Psychiatry. 2012;169(9):937-945; Nemets B, Levine J. Int Clin Psychopharmacol. 2013;28(3):127-133; Sherpa NN, De Giorgi R, Ostinelli EG, et al. Eur Neuropsychopharmacol. 2025;90:28-35. doi:10.1016/j.euroneuro.2024.10.004; Creatine supplementation for treating symptoms of depression: a systematic review and meta-analysis. Br J Nutr. 2025; Fares BJ, Zhou C, Fabiano N, et al. The effect of creatine monohydrate on mental disorders: a systematic review of RCTs. Can J Psychiaty. 2026. doi:10.1177/07067437251408171; Kreider RB, Gonzalez DE, Hines K, et al. J Int Soc Sports Nutr. 2025;22(sup1):2488937.

GLUTAMATE MODULATOR

N-Acetylcysteine (NAC)

Glutathione precursor - strongest in body-focused repetitive behaviours

- A cysteine prodrug that restores glutathione and normalises glutamate tone in cortico-striatal circuits; psychiatric trials use 1,200-3,000 mg/day, divided, for 8-24 weeks.
- Strongest in body-focused repetitive behaviours: Grant 2009 in trichotillomania, 56% much or very much improved versus 16% on placebo; Grant 2016 in 66 adults with excoriation disorder, NE-YBOCS 18.9 to 11.5. It does not extend to children - Bloch 2013 in 39 children was negative, 25% versus 21%.
- Depression: 12 studies, 904 patients, SMD -0.24 (95% CI -0.44 to -0.05) - small. The two largest bipolar trials (Berk 2019, Ellegaard 2019) were negative.
- OCD: 6 RCTs, 195 patients, a Y-BOCS signal at 5-8 weeks only. Schizophrenia is weaker - Neill 2022, 84 clozapine-resistant patients on 2 g/day, found nothing on negative symptoms, cognition or quality of life.
- Addiction is contested: a 2024 meta-analysis of 11 RCTs found craving reduced (SMD -0.61); a 2025 meta-analysis of 9 trials found no separation from placebo (SMD 0.19).
- Well tolerated - nausea, diarrhoea, cramping; adverse events match placebo; caution in asthma, where bronchospasm has been reported.

Grant JE, Odlaug BL, Kim SW. Arch Gen Psychiatry. 2009;66(7):756-763; Grant JE, Chamberlain SR, Redden SA, et al. JAMA Psychiatry. 2016;73(5):490-496; Bloch MH, Panza KE, Grant JE, et al. J Am Acad Child Adolesc Psychiatry. 2013;52(3):231-240; Peng TR, et al. Efficacy of N-acetylcysteine for patients with depression: an updated systematic review and meta-analysis. Gen Hosp Psychiatry. 2024; Eghdami S, Eissazade N, Heidari Mokarar M, et al. Front Psychiatry. 2024;15:1421150; Neill E, Rossell SL, Yolland C, et al. Schizophr Bull. 2022;48(6):1263-1272; Cuocina M, Aiello G, Cutrufelli P, et al. Front Pharmacol. 2024;15:1462612; Winterlind EL, Malone SG, Setzer MR, et al. Addict Biol. 2025. doi:10.1111/adb.70001.

PREMENSTRUAL DISORDERS

Chasteberry for PMS and PMDD

Vitex agnus castus — the most-studied herb for premenstrual disorders

- ACOG names Vitex the herbal remedy most studied for premenstrual disorders but concludes the evidence is insufficient to make a formal recommendation — aligning with other expert guidelines that further study is needed (ACOG 2023).
- Proposed mechanism is dopamine receptor stimulation, with downstream modulation of prolactin and progesterone.
- A 2017 meta-analysis of 17 RCTs found a large pooled effect vs placebo (Hedges g −1.21; 95% CI −1.53 to −0.88), but with I^2 of 91% and high risk of bias — likely overestimated (Verkaik 2017).
- A 2019 meta-analysis of 3 RCTs found women taking Vitex more than twice as likely to improve (RR 2.57; 95% CI 1.52–4.35), with doses above 15 mg most effective (RR 3.96; 95% CI 1.79–8.78).
- Two PMS/PMDD reviews call it safe and well tolerated. Against fluoxetine, results were mixed — one trial equivalent, one favouring fluoxetine (Cerqueira 2017).
- SSRIs remain first-line for PMDD. For a patient preferring a complementary approach, a standardized Vitex extract above 15 mg/day is the most defensible herbal choice.

ACOG Clin Pract Guideline No. 7. Obstet Gynecol. 2023;142(6):1516-1533; Verkaik S et al. Am J Obstet Gynecol. 2017; Cerqueira RO et al. Arch Womens Ment Health. 2017.

PREMENSTRUAL DISORDERS

Other Herbs in PMS and PMDD

St. John's wort, chamomile and the standardization problem

- St. John's wort is limited and mixed. A double-blind placebo-controlled crossover trial (n=36, 900 mg/day) beat placebo for physical and behavioural symptoms but not for mood or pain (Canning 2010).
- A larger placebo-controlled trial (n=125, 600 mg/day) found only a nonsignificant trend toward benefit, possibly reflecting underpowering (Hicks 2004).
- The safety caveat is decisive here: St. John's wort is a potent CYP3A4 inducer. It reduces oral contraceptive efficacy — directly relevant in this population — and antiepileptic levels, and risks serotonin syndrome with SSRIs. Avoid in pregnancy and breastfeeding.
- Chamomile has anti-inflammatory and anxiolytic properties via apigenin modulating dopamine and serotonin, but a 2019 systematic review of 8 RCTs could not draw conclusions given heterogeneous forms and doses.
- Curcumin and Nigella sativa have mechanistic and small-study support through anti-inflammatory and antioxidant pathways but lack robust trial evidence (Sultana 2022).
- The recurring limitation across every herbal option here is product standardization — formulations and doses differ so widely between trials that pooled results are hard to act on.

Canning S, Waterman M, Orsi N, et al. CNS Drugs. 2010; Hicks SM et al. J Altern Complement Med. 2004; Sultana A, Rahman K, Heyat MBB, et al. Oxid Med Cell Longev. 2022; Sarris J. Phytother Res. 2018; Biggs WS et al. Am Fam Physician. 2025.

AUTISM SPECTRUM DISORDER

Supplements in Autism

Where the evidence is least weak — and what it actually covers

- The honest baseline: no supplement or herb reliably improves the core social-communication or repetitive symptoms of ASD. Everything below is adjunctive to behavioural, speech and educational therapy (Lai 2020).
- Melatonin is the best-supported agent — it shortens sleep onset and improves daytime behaviour with minimal adverse effects and is endorsed in primary care guidance (Westby 2025).
- Folinic acid: a double-blind RCT improved verbal communication in children with language impairment, strongest in those positive for folate receptor-α autoantibodies. Replication still needed.
- Sulforaphane from broccoli sprout extract reduced irritability and hyperactivity via antioxidant effects, but the trials are small.
- Vitamin D had the largest effect among dietary interventions in one umbrella review (SMD −0.45); heterogeneity limits it. Probiotics may help GI symptoms only (Shi 2026).
- Omega-3 is low strength of evidence. L-carnitine, methyl-B12, CoQ10, NAC and carnosine have small positive trials but remain insufficient.

Sathe N et al. Pediatrics. 2017; Westby A, Coburn-Pierce M. Am Fam Physician. 2025; Lai MC et al. Lancet Neurol. 2020; Shi J et al. Res Dev Disabil. 2026; Serafim SDS et al. Nutr Rev. 2025.

AUTISM SPECTRUM DISORDER

Herbal Remedies in Autism

Mechanistically appealing, almost entirely preclinical

- Nearly all herbal data in ASD come from animal models or very small studies, with no standardized formulations and no validated dosing (Aldekhail 2025, Kardani 2019).
- Bacopa monnieri, curcumin, ginkgo biloba, Centella asiatica and ashwagandha are proposed to act through antioxidant, neuroprotective and neurotransmitter-modulating pathways — the evidence is largely preclinical.
- Luteolin, a flavonoid found in green tea, has small clinical signals via anti-neuroinflammatory mechanisms. Saffron is preclinical to early clinical for ASD and its comorbidities (Wei 2026).
- Passionflower and valerian are proposed for anxiety and hyperactivity through GABAergic effects; the evidence is weak.
- Cannabinoids show modest signals for sleep and social engagement in some studies, but a network meta-analysis found lower acceptability — higher dropout — than most other interventions (Ma 2026).
- Counsel families on herb–drug interactions and on the absence of standardized, quality-controlled herbal products in this market. Interest is reasonable; the products are not yet reliable.

Aldekhail NM, Khojah H, Alsaadoun NH, et al. Altern Ther Health Med. 2025; Kardani A et al. Curr Pharm Des. 2019; Wei M et al. J Ethnopharmacol. 2026; Ma C, Wang Y, Ding Z, et al. Child Psychiatry Hum Dev. 2026.

AUTISM SPECTRUM DISORDER

Autism: What to Discourage

Interventions with no benefit, and some with real harm

- No benefit in randomized trials: magnesium with vitamin B6 beyond correcting a deficiency, gluten-free/casein-free diets, digestive enzymes, secretin, auditory integration training (Sathe 2017).
- Chelation and hyperbaric oxygen risk serious adverse events with no supporting evidence - discourage actively rather than merely tolerating them (Lai 2020).
- Vitamins and minerals help only where they correct a documented deficiency - screen for and treat genuine iron, vitamin D and B12 deficiency rather than supplementing empirically (Doherty 2024, Westby 2025).
- If blood work is refused: empiric repletion is defensible only where deficiency is likely, the dose is safe and response is monitored. The Endocrine Society's 2024 guideline supports empiric vitamin D without measuring 25(OH)D in children and adults 75 and over; thiamine is given empirically where deficiency is suspected.
- What that costs you: folate corrects the anemia of B12 deficiency while neuropathy progresses; prolonged iron overloads undiagnosed hemochromatosis; a treated count hides celiac disease, blood loss or malignancy. Offer topical anesthetic, one combined draw or capillary sampling first, then document and set a review date.
- Where supplements do help, benefit is small and tied to comorbidities - sleep, GI symptoms, anxiety, irritability - not to autism itself. For the visit: melatonin for sleep, folinic acid selectively, correct real deficiencies, keep core therapies in place.

Sathe N et al. Pediatrics. 2017; Lai MC, Anagnostou E, Wiznitzer M, et al. Lancet Neurol. 2020; Doherty M, Foley KR, Schloss J. J Autism Dev Disord. 2024; Westby A, Coburn-Pierce M. Am Fam Physician. 2025.

COGNITION — SMALL, MIXED TRIALS

Lion's Mane

Hericium erinaceus — the most-studied mushroom for cognition

- The most-cited positive trial is small: 30 adults aged 50–80 with mild cognitive impairment took 3 g/day of dried fruiting-body powder for 16 weeks and improved on cognitive scales — but scores fell back after stopping (Mori 2009).
- A 49-week pilot RCT in mild Alzheimer's used a different preparation — erinacine A-enriched mycelium, ~1.05 g/day at 5 mg/g — and improved MMSE and IADL versus placebo (Li 2020).
- Neither result is reliably replicated. In a 2024 review of 34 studies, observational data linked mushroom intake to better cognition, but the 10 controlled trials were mixed (Cha 2024).
- Mechanism is plausible but preclinical: hericenones and erinacines stimulate nerve growth factor synthesis, with antioxidant and BDNF/CREB effects.
- Formulation is poorly controlled — fruiting body and mycelium carry different actives, content varies widely, and no consensus dose exists.
- Well tolerated and cheap, though anaphylaxis has been reported. Not enough evidence to recommend for any specific disorder, including ALS.

Mori K et al. Phytother Res. 2009;23(3):367-372; Li IC et al. Front Aging Neurosci. 2020;12:155; Cha S et al. Neurosci Biobehav Rev. 2024; Muhanna M et al. ALSUntangled #73. 2024; Friedman M. J Agric Food Chem. 2015;63(32):7108-7123.

PRECLINICAL EVIDENCE ONLY

Other Medicinal Mushrooms

Reishi, cordyceps and relatives — mechanism without clinical outcomes

- Reishi (Ganoderma lucidum) is antidepressant-like in preclinical models, attributed to gut-microbiota modulation and immunomodulation. Human data address cancer-related quality of life, not depression endpoints (Du 2026, Gong 2025).
- An ex vivo human gut model showed lion's mane and reishi metabolites raised BDNF, CDNF and MANF and activated CREB/BDNF signalling — a pilot mechanistic finding, not a clinical outcome (Košzła 2025).
- Cordyceps militaris, Poria cocos, Fomitopsis officinalis and Pleurotus djamor show antidepressant- or anxiolytic-like effects in animal models only (Emil 2025).
- Psilocybin-containing mushrooms are a separate class — studied as fast-acting antidepressants and distinct from culinary or nootropic mushrooms. Do not let patients conflate the two.
- Counselling: these are food-grade and generally well tolerated, but the marketing consistently outruns the evidence.
- Treat a mushroom supplement as low-risk and unproven rather than as treatment, and check reishi's antiplatelet effect against anticoagulation.

Du XY et al. J Nutr. 2026; Gong P et al. Mol Nutr Food Res. 2025; Košzła O et al. J Ethnopharmacol. 2025; Lazur J et al. Antioxidants. 2023;12(3):623.

Supplements in Alzheimer Disease

Seven agents patients ask about - what the controlled trials showed, and what to say in clinic

Agent	What the trials show	Strength of evidence	Bottom line
Ginkgo biloba (EGb 761)	GEM trial, n=3069, 120 mg twice daily did not prevent dementia over a median 6 years; Cochrane finds results inconsistent, with 240 mg/day giving modest gains in some dementia trials	Large RCT negative for prevention	Not for prevention; unreliable effect in established dementia
Vitamin E	TEAM-AD, n=613, 2000 IU/day alpha-tocopherol slowed functional decline in mild-to-moderate disease; no benefit in mild cognitive impairment	One positive RCT, high dose	Discussable in mild-to-moderate disease; not for MCI or prevention
Omega-3 (DHA/EPA)	18-month RCT of 2 g/day DHA in mild-to-moderate disease showed no slowing of cognitive or functional decline	RCT negative	No role once the diagnosis is established
B vitamins (folate, B6, B12)	VITACOG lowered homocysteine and slowed brain atrophy in MCI with raised homocysteine; unselected populations show no cognitive benefit	Benefit confined to a biomarker subgroup	Test and correct deficiency; not a routine add-on
Huperzine A	A cholinesterase-inhibiting alkaloid; trials report cognitive gains but are small, single-region and methodologically weak	Weak and unreplicated	Advise against - drug-like cholinergic effects without drug-level oversight
Saffron (Crocus sativus)	Small randomized trials found 30 mg/day comparable to donepezil and better than placebo over 16-22 weeks in mild-to-moderate disease	Small trials, one region	Promising, not confirmed; no substitute for a cholinesterase inhibitor
Curcumin	Poor oral bioavailability limits brain exposure; controlled trials in Alzheimer disease have not shown cognitive benefit	RCTs negative	No benefit shown; watch for the hepatotoxicity signal

DeKosky ST, et al. JAMA. 2008;300(19):2253-2262 (GEM); Dysken MW, et al. JAMA. 2014;311(1):33-44 (TEAM-AD); Quinn JF, et al. JAMA. 2010;304(17):1903-1911; Smith AD, et al. PLoS One. 2010;5(9):e12244 (VITACOG); Akhondzadeh S, et al. Psychopharmacology. 2010;207(4):637-643. Lion's mane and coconut oil have no controlled dementia data - see the mushroom slides.

Nutraceuticals in Cognitive Impairment

Doses and trial quality as reported by Mecocci and colleagues.

Compound	Source	Dose studied	Reported effect	Trial quality
Flavanols	Cocoa, green tea, grape	520–990 mg cocoa flavanols; 300 mg EGCG	Better executive function and cerebral blood flow	Small, short
Flavonols	Ginkgo biloba (EGb761)	80–720 mg/day	Inconsistent; no dementia prevention in large trials	Large but negative
Isoflavones	Soy protein	25.6 g/day soy protein	Mixed; some verbal memory gain, no global benefit	Moderate
Anthocyanidins	Blueberry, grape juice	6–9 mL/kg/day juice, 12 weeks	Better learning and recall in mild impairment	Very small
Resveratrol	Grape, red wine	250–500 mg/day	More cerebral blood flow; cognitive benefit unproven	Preliminary
Curcumin	Turmeric (Curcumin C3)	2–4 g/day	No cognitive or biomarker change; poor bioavailability	Negative RCTs
Carotenoids	Beta-carotene, astaxanthin	50 mg beta-carotene alternate days	Benefit only after 18 years of exposure	Long-term only
Crocin and B vitamins	Saffron; folate, B6, B12	30 mg/day saffron	Saffron matched donepezil; B vitamins slowed atrophy	Promising

Mecocci P, et al. Nutraceuticals in cognitive impairment and Alzheimer's disease. Front Pharmacol. 2014;5:147, and the trials tabulated there.

PRACTICAL BOTTOM LINE

Cognition: What to Actually Recommend

No nutraceutical prevents or treats dementia. This is where each option belongs in a real conversation.

Situation	First-line, evidence-based option	Where nutraceuticals fit	What to say
Healthy adult worried about memory	BP, hearing, sleep, exercise, education, social contact	A polyphenol-rich diet is defensible; capsules are not	Diet pattern beats any single supplement
Mild cognitive impairment	Vascular risk management and monitoring	Cocoa flavanols and berry anthocyanidins: small gains, very small trials	Encouraging but not established
Established Alzheimer's disease	Cholinesterase inhibitors or memantine per stage	Saffron 30 mg/day matched donepezil in small trials	Adjunct at most, never a replacement
Raised homocysteine	Investigate and correct B12 or folate deficiency	B vitamins slowed gray matter atrophy in this subgroup	Targeted, not universal
Patient asking about ginkgo	As above	Prevention trials negative; bleeding risk with anticoagulants	Do not recommend for prevention
Patient asking about curcumin	As above	Trials in Alzheimer's were null; bioavailability is the limit	Promising mechanism, no clinical benefit yet
Anyone already self-treating	Take a full supplement history	Check anticoagulant, antiplatelet and antidiabetic interactions	Ask what, how much, how long

Synthesised from Mecocci 2014 and the dementia trials cited on the preceding slides.

ADVISE AGAINST — EVIDENCE TIER 4

Tier 4 — Evidence against, or risk outweighs benefit

Negative trials, an explicit guideline recommendation against use, or a safety signal that outweighs any measured benefit. Actively counsel patients away from these.

6 AGENTS IN THIS TIER

Kava · Yohimbine · Tryptophan and 5-HTP · Acetyl-L-Carnitine · Evening Primrose Oil · Trends Without the Evidence

USE ONLY UNDER SUPERVISION

Yohimbine

Pausinystalia johimbe bark

- An alkaloid derived from the bark of the yohimbe tree, used to facilitate blood flow to the penis.
- Carries a high risk of side effects relative to other natural ED remedies.
- Should be used only under medical supervision — the source review is explicit on this point.
- Counsel patients that over-the-counter availability does not imply a benign safety profile.

Natural ED treatment review, citing ref 6 of the source document.

ANXIETY — HEPATOTOXICITY RISK

Kava

Piper methysticum rhizome

- Kavalactone-standardized extracts reduce anxiety symptoms more than placebo in short-term controlled trials.
- Severe hepatotoxicity — including hepatitis, cirrhosis and fulminant liver failure requiring transplantation — prompted regulatory action in several countries.
- Potentiates CNS depressants; chronic heavy use causes a scaly dermopathy (kava dermopathy) and ataxia.
- Avoid in hepatic disease and with alcohol or sedatives; check liver enzymes if a patient insists on continuing.
- Clinical reviews attribute much of the hepatotoxicity to supplements made from the wrong plant part or cultivar and processed incorrectly — sourcing and preparation matter as much as dose.
- Important counterpoint — the WFSBP/CANMAT taskforce grades kava Not Recommended (−) for generalized anxiety disorder after the definitive 16-week RCT (Sarris, Byrne et al. Aust N Z J Psychiatry. 2020;54(3):288-297) was null; combined with the hepatic signal, the guideline advises against routine use despite older positive trials.

Reque PM et al. Adv Gut Microbiome Res. 2025; Teschke R. Ann Hepatol. 2010;9(3):251-65; Sarris J, Byrne GJ, Bousman CA, et al. Kava for generalised anxiety disorder: a 16-week double-blind randomised controlled trial. Aust N Z J Psychiatry. 2020;54(3):288-297. doi:10.1177/0004867419891246 — as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

SEROTONIN SYNDROME CAUTION

Tryptophan and 5-HTP

Serotonin precursors

- WFSBP/CANMAT grade: Not Currently Recommended (±) for depression — three small trials totalling 94 participants leave the question open rather than answered.
- Guideline dosing where used: up to 1 g/day of L-tryptophan, or 50–200 mg/day of 5-hydroxytryptophan.
- Shaw 2002 (Aust N Z J Psychiatry 36(4):488-491) reviewed tryptophan and 5-HTP for depression and found the trial evidence too sparse and heterogeneous to support routine use.
- Levitan 2000 (J Psychiatry Neurosci 25(4):337-346) tested tryptophan augmentation of fluoxetine, reporting a possible early effect that did not persist.
- The dominant safety issue is additive serotonergic load — avoid with SSRIs, SNRIs, MAOIs, triptans, tramadol and linezolid, and counsel patients explicitly.
- Historical eosinophilia-myalgia syndrome outbreaks were traced to a contaminated batch, which is why product sourcing matters here more than most.

Shaw K, Turner J, Del Mar C. Tryptophan and 5-hydroxytryptophan for depression. Aust N Z J Psychiatry. 2002;36(4):488-491; Levitan RD, Shen JH, Jindal R, Driver HS, Kennedy SH, Shapiro CM. J Psychiatry Neurosci. 2000;25(4):337-346 — as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

ADVISED AGAINST IN PEDIATRIC ADHD

Acetyl-L-Carnitine

ALCAR

- WFSBP/CANMAT grade: Not Recommended (−) for pediatric ADHD — an active recommendation against use, not merely absence of evidence (k=2, n=152).
- Trial dosing was 1–3 g/day, scaled to body weight in the pediatric studies.
- Arnold 2007 (J Child Adolesc Psychopharmacol 17(6):791-802) conducted a multi-site placebo-controlled trial in children with ADHD and found no overall benefit.
- Abbasi 2011 (Child Psychiatry Hum Dev 42(3):367-375) tested ALCAR as an adjunct to methylphenidate and likewise failed to show added benefit.
- Distinguish this from adult depression, where the separate acetyl-L-carnitine literature is more favourable — the negative grade is specific to pediatric ADHD.
- Generally well tolerated; agitation, a fishy body odour and gastrointestinal upset are the reported effects.

Arnold LE, Amato A, Bozzolo H, et al. Acetyl-L-carnitine in attention-deficit/hyperactivity disorder: a multi-site, placebo-controlled pilot trial. J Child Adolesc Psychopharmacol. 2007;17(6):791-802; Abbasi SH, Heidari S, Mohammadi MR, Tabrizi M, Ghaleiha A, Akhondzadeh S. Child Psychiatry Hum Dev. 2011;42(3):367-375 — as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

ADVISED AGAINST IN PEDIATRIC ADHD

Evening Primrose Oil

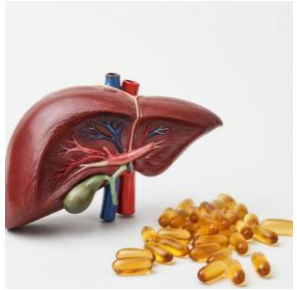
Oenothera biennis — omega-6 and omega-9 oils

- WFSBP/CANMAT grade: Not Recommended (−) for pediatric ADHD, based on two trials totalling 49 participants.
- Trial dosing was 2–3 g/day of evening primrose oil, valued for its gamma-linolenic acid content.
- Aman 1987 (J Abnorm Child Psychol 15(1):75-90) found no significant benefit of evening primrose oil on hyperactivity ratings in children.
- Arnold 1989 (Biol Psychiatry 25(2):222-228) compared it with d-amphetamine and placebo, and it did not separate from placebo.
- Note the contrast with omega-3 fatty acids, which the same guideline weakly supports in pediatric ADHD — the fatty acid class is not interchangeable.
- Bleeding risk with anticoagulants and a theoretical lowering of seizure threshold are the safety points worth raising.

Aman MG, Mitchell EA, Turbott SH. The effects of essential fatty acid supplementation by Efamol in hyperactive children. J Abnorm Child Psychol. 1987;15(1):75-90; Arnold LE, Kleykamp D, Votolato NA, et al. Biol Psychiatry. 1989;25(2):222-228 — as cited in Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041.

HERB-INDUCED LIVER INJURY

Hepatotoxicity of Supplements



The wellness shelf is now a leading cause of drug-induced liver injury

- Herbal and dietary supplements accounted for roughly 20% of drug-induced liver injury cases in 2013–2014, up from 7% in 2004–2005 — close to a tripling in a decade (Likhitsup 2024).
- An estimated 15.6 million US adults take at least one of six potentially hepatotoxic botanicals: turmeric/curcumin, green tea extract, ashwagandha, Garcinia cambogia, red yeast rice and black cohosh (Likhitsup 2024).
- Turmeric/curcumin and green tea extract are the most frequently implicated, with high-dose and bioavailability-enhanced formulations over-represented; some cases progress to acute liver failure and transplant (Seeff 2015, Stickel 2015).
- Kava and kratom remain the classic and the emerging causes respectively; both have produced fulminant hepatic failure.
- Injury is usually idiosyncratic and hepatocellular, appearing weeks to months in. It is not dose-predictable, so a normal label dose does not exclude the diagnosis (Stickel 2015).
- Practical step: ask about supplements by name in any unexplained transaminitis, stop all of them, and check for anabolic or weight-loss products, which are frequently adulterated (Bent 2008).

Likhitsup A, Chen VL, Fontana RJ. JAMA Netw Open. 2024; Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Gastroenterology. 2015; Stickel F, Shouval D. Arch Toxicol. 2015; Bent S. J Gen Intern Med. 2008.

HIGH USE, ABSENT BENEFIT

What the Trials Do Not Support

The fastest-growing supplement categories, measured against their evidence

- Supplement use in US adults rose from 51% to 60% between 1999 and 2023, and only about 1 in 4 users take them under professional guidance (Lam 2026).
- Heart health: in the SPORT trial, fish oil, cinnamon, garlic, turmeric, plant sterols and red yeast rice did not lower LDL-C versus placebo, while low-dose rosuvastatin cut it by roughly 38% (2026 ACC/AHA dyslipidemia guideline).
- It recommends against non-prescription fish oil: no clinical benefit in hypertriglyceridemia or ASCVD, with possible increases in LDL-C and atrial fibrillation risk.
- Immune and adaptogen products are the fastest-growing category but the thinnest: echinacea shows trends of questionable clinical relevance for colds, and ginseng trials support no specific indication (Izzo 2016, Ernst 2002).
- Weight-loss supplements do not treat obesity and are often adulterated with banned sympathomimetics; ephedra was withdrawn in 2004 after strokes, MIs and deaths (Tachjian 2010).
- In healthy adults, routine multivitamin use does not reduce cardiovascular disease or cancer risk, and collagen lacks outcome data (USPSTF 2022). Probiotics are the one category here where the trials genuinely conflict - the next slide sets out why.

Lam CS et al. JAMA Netw Open. 2026; Blumenthal RS et al. 2026 ACC/AHA Dyslipidemia Guideline. 2026; Izzo AA et al. Phytother Res. 2016; Tachjian A et al. J Am Coll Cardiol. 2010; Mangione CM et al. US Preventive Services Task Force Recommendation Statement. JAMA. 2022;327(23):2326-2333.

WHERE THE TRIALS CONFLICT

Probiotics for Mood

A genuine controversy: positive meta-analyses, null individual trials - and why both can be true

- The case for: pooled analyses consistently find a small benefit. Nikolova 2021 found probiotics effective as an adjunct to antidepressants but not stand-alone; later syntheses report modest reductions in depression and anxiety scores, largest in patients already on an SSRI.
- The case against: the individual trials are far less convincing. Romijn 2017 (L. helveticus and B. longum, 79 adults with low mood) found no separation from placebo on any outcome; Chahwan 2019 found a small effect on depressive symptoms only, not anxiety.
- Nikolova's 2023 JAMA Psychiatry adjunct trial tested feasibility rather than efficacy: acceptable and well tolerated, with estimates favouring probiotics but confidence intervals too wide to call a treatment effect.
- Why the pictures differ: different strains, doses and durations; 4 to 12 weeks in small samples; symptom scales rather than remission; pooling across strains that are not interchangeable; and null supplement trials go unpublished, so pooled estimates drift upward.
- Fair to say: best evidence is adjunctive, at roughly 1-10 billion CFU for 8-10 weeks in adults. No strain-level recommendation, no outcome data, no stand-alone role, nothing in children or older adults.
- Safety reassures: adverse events comparable to placebo in healthy adults. Caution in immunosuppression, central lines and critical illness.

Nikolova VL et al. J Clin Med. 2021;10(4):647; Nikolova VL, Cleare AJ, Young AH, Stone JM. JAMA Psychiatry. 2023;80(8):842-847; Romijn AR, Rucklidge JJ, Kuijer RG, Frampton C. Aust N Z J Psychiatry. 2017;51(8):810-821; Chahwan B et al. J Affect Disord. 2019;253:317-326.

Benefits and Dangers

Herbal and supplement use — what to weigh before endorsing, tolerating, or discontinuing a patient's regimen

BENEFITS

- Meaningful adjunctive effect for depression — omega-3, SAMe, methylfolate and St. John's wort all outperform placebo as add-ons.
- Often better tolerated than pharmacotherapy: St. John's wort matched SSRI efficacy with fewer adverse effects and lower dropout.
- Corrects genuine deficiency states — magnesium, zinc and vitamin D — where benefit is most reliable.
- Supports engagement with patients already self-treating, opening the door to honest medication reconciliation.

DANGERS

- Drug interactions are the dominant hazard — St. John's wort induces CYP3A4 and interacts with up to half of all medications.
- Serotonin syndrome, contraceptive failure, mania and psychotic relapse have all been reported.
- Supplements used instead of FDA-approved therapy may delay standard of care; none rival first-line treatment for moderate-to-severe illness.
- Study heterogeneity, variable dosing and small samples limit generalizability; product potency is not standardized.

De Smet PA. N Engl J Med. 2002 (Herbal Remedies); VA/DoD MDD Guideline, 2022; Firth J et al. World Psychiatry. 2019; Simon GE et al. JAMA. 2024; Mazhar H et al. J Child Adolesc Psychopharmacol. 2020; Lowance M et al. Curr Opin Pediatr. 2025.

QUICK REFERENCE

Dosing at a Glance

Doses and safety ratings as reported in the cited evidence reviews — confirm product standardization before recommending

Agent	Primary indication	Evidence-based daily dose	Evidence	Safety
St. John's wort	Mild-to-moderate depression	600–1800 mg extract (0.3% hypericin)	A	Interactions
Saffron	Mild-to-moderate depression	30 mg standardized stigma extract	A	Robust
Curcumin	Depression, monotherapy or adjunct	500–1000 mg with piperine	A	Robust
Omega-3 (EPA)	Depression adjunct	1–2 g, ≥60% EPA	A	Robust
SAMe	Treatment-resistant depression	800–1600 mg	B	Avoid in bipolar
L-methylfolate	SSRI-resistant depression	15 mg	B	Robust
Rhodiola rosea	Fatigue, stress, low mood	340–680 mg extract	A / ±	Robust
Lavender (Silexan)	Anxiety, mixed anxiety-depression	80–160 mg essential oil	A	Robust
Chamomile	Generalized anxiety	220–1500 mg extract	A / ±	Robust
Ashwagandha	Stress, anxiety, sleep	300–600 mg (5% withanolides)	A	Robust
Galphimia glauca	Anxiety	350–700 mg extract	A	Fair
Kava	Anxiety	60–250 mg kavalactones	–	Avoid — hepatic
Passionflower / valerian	Anxiety, sleep onset	Per product standardization	B	Sedation
Probiotics	Depression adjunct (third-line)	1–10 billion units, multi-strain	B	Robust
Melatonin	Circadian and sleep-onset problems	0.5–3 mg, timed to dusk	B	Robust
Broad-spectrum micronutrients	Pediatric ADHD monotherapy	8–12 capsules/day	+	GI upset

Dose and safety ratings from Sarris J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. Phytother Res. 2018;32(7):1147-1162, reproduced in Reque PM et al. Adv Gut Microbiome Res. 2025. doi:10.1155/agm3/3675425; Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. Evidence grade A = supported by controlled trials; symbols after a slash are the WFSBP/CANMAT taskforce grade where it differs — see the following slide.

Recommendation Grades

Consensus grades by agent and disorder — +++ recommended, ++ provisionally recommended, + weakly recommended, ± not currently recommended, − not recommended

Agent	Disorder and role	Guideline dose	Trials	Grade
St. John's wort	MDD — monotherapy	500–1800 mg/day extract	k=27	+++
Omega-3 (EPA)	MDD — adjunctive	1–2 g/day EPA	k=25, n=1373	+++
SAMe	MDD — mono or adjunctive	800–1600 mg/day	k=8, n=934	++
Methylfolate / folinic acid	MDD — adjunctive	15 mg / 15–30 mg/day	k=7, n=1003	++
Saffron	MDD — mono or adjunctive	30 mg/day extract	k=9, n=531	++
Curcumin	MDD — mono or adjunctive	500–1000 mg/day	k=9, n=531	++
N-acetylcysteine	Schizophrenia — adjunctive	2 g/day	k=7, n=458	++
Lavender (Silexan)	Generalized anxiety disorder	80–160 mg/day oil	k=5, n=1173	++
Vitamin D	MDD — adjunctive	1500–7000 IU/day	k=4, n=948	+
Zinc	MDD — adjunctive	25 mg/day elemental	k=3, n=138	+
Probiotics	MDD — adjunctive	1–10 billion CFU/day	k=5, n=185	+
Ginkgo biloba	Schizophrenia — adjunctive	240–360 mg/day EGb 761	k=8, n=1033	+
Broad-spectrum micronutrients	Pediatric ADHD — monotherapy	8–12 capsules/day	k=2, n=173	+
Vitamin C	MDD — adjunctive	1 g/day	k=2, n=70	±
Tryptophan / 5-HTP	Depression	≤1 g / 50–200 mg/day	k=3, n=94	±
Creatine	Depression — adjunctive	5 g/day monohydrate	k=2, n=64	±
Chamomile	Generalized anxiety disorder	220–1500 mg/day	k=2	±
Rhodiola rosea	MDD	340–680 mg/day extract	k=2	±
Magnesium	MDD	Various	k=2, n=149	−
Inositol	MDD and bipolar depression	12–18 g/day	k=5, n=139	−
Kava	Generalized anxiety disorder	60–250 mg/day kavalactones	k=3	−
Acetyl-L-carnitine	Pediatric ADHD	1–3 g/day	k=2, n=152	−
Evening primrose oil	Pediatric ADHD	2–3 g/day	k=2, n=49	−

Grades, doses and trial counts from Sarris J, Ravindran A, Yatham LN, Marx W, Rucklidge JJ, McIntyre RS, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: the World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) taskforce. World J Biol Psychiatry. 2022;23(6):424-455. doi:10.1080/15622975.2021.2013041. k = number of controlled trials; n = pooled participants where reported.

CONFLICTING EVIDENCE

Where the Guidelines Disagree

Seven agents where the WFSBP/CANMAT taskforce grades the evidence differently from the meta-analyses and reviews that preceded it — and how to handle each in clinic

Agent	Earlier reviews and meta-analyses said	WFSBP/CANMAT taskforce says	What to do
Kava	Level A for anxiety at 60–250 mg/day kavalactones (Sarris 2018 dosing table)	Not Recommended (−) for GAD after the 16-week RCT was null	Do not initiate; hepatic risk settles it
Magnesium	SMD −0.92 across 7 RCTs; open-label benefit within 2 weeks (Moabedi 2024; Tarleton 2017)	Not Recommended (−) for MDD; k=2, n=149 judged insufficient	Reserve for documented deficiency
Inositol	Benefit in panic and OCD at 12–18 g/day in small trials (Levine 1995)	Not Recommended (−) for MDD and bipolar depression	Do not position as a mood agent
Chamomile	Level A for GAD at 220–1500 mg/day (Amsterdam 2009)	Not Currently Recommended (±) — Mao 2016 found no relapse prevention	Safe to tolerate; set expectations
Rhodiola	Level A, robust safety at 340–680 mg/day (Darbinyan 2007)	Not Currently Recommended (±) — Mao 2015 found it inferior to sertraline	Reasonable trial, modest expectations
Probiotics	SMD −0.96 in clinical samples; CANMAT 2026 third-line adjunct (Asad 2025; Bahji 2026)	Weakly Recommended (+) only; strain and dose heterogeneity limit the grade	Adjunct, not a substitute
NAC	Possibly the most effective supplement for PANSS scores (Xu 2022 network meta-analysis)	Provisionally Recommended (++) in schizophrenia, but Not Currently Recommended (±) in bipolar depression	Indication-specific — do not generalize

Where a guideline and a meta-analysis conflict, the difference is usually a newer, larger and negative trial that the earlier review could not include. Sources: Sarris J et al. World J Biol Psychiatry. 2022;23(6):424-455; Sarris J, Byrne GJ, Bousman CA, et al. Aust N Z J Psychiatry. 2020;54(3):288-297; Mao JJ et al. Phytomedicine. 2015;22(3):394-399 and 2016;23(14):1735-1742; Moabedi M et al. Front Psychiatry. 2024; Asad A et al. Nutr Rev. 2025; Bahji A et al. Can J Psychiatry. 2026; Xu X et al. Psychiatry Res. 2022.

EVIDENCE BY AGE GROUP

Age Changes the Answer

Almost the entire nutraceutical evidence base sits in adults aged 18–60 — what holds there frequently does not hold in children or in older adults

Agent	Children and adolescents	Adults 18–60	Older adults ≥60
Omega-3 (EPA)	Very uncertain; sensitivity analysis gives SMD 0— no reliable effect (Cochrane, 5 RCTs, n=228)	Strongest evidence in the deck, as an adjunct at 1–2 g/day EPA	Mixed. No overall effect below 1.5 g/day; possible harm in prevention (VITAL-DEP HR 1.13, concentrated in women)
Vitamin D	Essentially no benefit (SMD 0.10)	Significant benefit where depression already exists (SMD −0.70)	No prevention benefit in any subgroup, including low baseline vitamin D
L-Methylfolate	No significant effect in 412 patients ≤ 18, regardless of MTHFR genotype or dose	Strong evidence at 15 mg/day, especially with inflammation or MTHFR polymorphism	May help where dementia coexists with folate deficiency — cognition and mood both improved
St. John's Wort	No RCTs for depression. Highest interaction risk of any agent here — CYP3A4, ADHD medication, contraceptives	Comparable to SSRIs for mild-to-moderate depression	Limited data; polypharmacy makes the interaction profile the dominant concern
Magnesium	No RCTs	Effective across the adult range regardless of age, sex or baseline severity	No RCTs above 60 years
SAMe	No data. Manic switching is a particular risk in undiagnosed bipolar adolescents	Strong evidence as monotherapy and adjunct	Possible cognitive benefit in Alzheimer's; no dedicated geriatric depression trials
Probiotics	Sparse data	Best evidence as an adjunct to SSRIs at 1–10 billion CFU for 8–10 weeks	Sparse data

No agent here is formally contraindicated in children, but absent efficacy data plus real interaction risk means the threshold to start should be higher, not lower, at both ends of the age range.

Sources: Campisi 2024 (Cochrane); Bai 2018, Bopp 2022, Srifuengfung 2023 (J Affect Disord / Nutrition); Okereke 2020, 2021 (JAMA); Hubner 2001 (Phytother Res); Tarleton 2017 (PLoS One); Sharma 2017 (J Clin Psychiatry); Kaur 2025 (Psychoneuroendocrinology); VA/DoD MDD Guideline 2022.

What Is Safe in Pregnancy

Pregnant and breastfeeding patients are excluded from almost every trial in this deck, so absence of reported harm is not evidence of safety — and botanicals are not screened for teratogenicity before sale

Agent	Pregnancy	Lactation	Bottom line
Omega-3 (EPA/DHA)	Reassuring safety; supports fetal neurodevelopment. Choose purified fish oil over fish liver oil (vitamin A)	Compatible; raises breast-milk DHA	Reasonable to continue, but two RCTs (DOMInO, MOMDHA) found no prevention of perinatal depression
Folate / L-methylfolate	Recommended regardless — 400–800 mcg/day preconception through first trimester for neural tube defect prevention	Compatible	The one supplement here with a positive obstetric indication
Vitamin D	Safe to 4,000 IU/day; deficiency is common in pregnancy	Compatible; maternal repletion raises infant levels	Test and replete rather than empirically megadose
Probiotics	No consistent signal of harm across pregnancy trials	Compatible	Low-risk, low-certainty
Chamomile	Not formally contraindicated, but avoid medicinal doses — uterine-stimulant activity, observational links to threatened miscarriage and preterm labour, and a reported case of fetal ductal constriction with heavy third-trimester intake	Limited data; occasional tea generally regarded as low risk	Occasional tea is fine; skip the supplements, and avoid entirely in the third trimester and near delivery (Asteraceae allergy, mild antiplatelet effect)
St. John's Wort	Avoid. Little human data; also lowers levels of many co-prescribed drugs	Avoid. Hyperforin passes into milk; infant colic and drowsiness reported	Highest interaction burden of any agent in the deck
Kava	Contraindicated — hepatotoxicity risk with no obstetric safety data	Contraindicated	Do not use
Black cohosh, chasteberry, ashwagandha	Avoid — hormonal activity, and traditional use as uterine stimulants or abortifacients	Avoid — no data	Common in menopause and stress products; screen for them
Ginkgo, garlic, high-dose vitamin E	Avoid near term — antiplatelet effect adds bleeding risk at delivery and with neuraxial anesthesia	Limited data	Stop at least 2 weeks before a planned delivery or surgery

Ask about supplement use at the first prenatal visit and again postpartum — most patients do not volunteer it. Makrides M et al. JAMA. 2010;304(15):1675-1683; Cuzzolin L et al. Pharmacoepidemiol Drug Saf. 2010;19(11):1151-1158; Lee A et al. J Clin Psychiatry. 2003;64(8):966-968; Dugoua JJ et al. Can J Clin Pharmacol. 2006;13(3):e257-e284; Teschke R et al. Ann Hepatol. 2010;9(3):251-265; ACOG, 2023.

PRACTICAL GUIDE

How to Counsel Patients

A six-step approach to supplement use in routine practice

1 Ask without judgment

Screen at every visit using concrete language — teas, powders, gummies, “natural” sleep aids, combination formulas. Most patients do not classify these as medications and will not volunteer them.

2 Reconcile the full label

Record the botanical name, the standardized marker compound, the dose and the manufacturer. Combination products carry ingredients the marketed indication never mentions.

3 Screen for interactions first

Prioritize St. John's wort, ginkgo, garlic, kava and yohimbine. Check anticoagulants, antiplatelets, oral contraceptives, immunosuppressants, antiretrovirals and serotonergic agents.

4 Match agent to severity

These are adjuncts. For moderate-to-severe or suicidal presentations, guideline pharmacotherapy and psychotherapy lead; do not let a supplement trial delay standard care.

5 Dose, standardize, and set a review date

Use the quick-reference dose range, choose a product with third-party verification, and reassess at 6–8 weeks with the same rating scale you would use for a prescription.

6 Document and de-prescribe deliberately

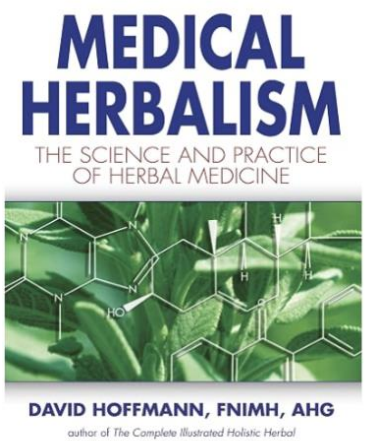
Record the trial in the medication list, taper sedating agents rather than stopping abruptly, and stop anything without benefit at review.

Synthesized from De Smet PA. N Engl J Med. 2002;347(25):2046-56; Lewis BB. Psychiatric Times. 2022;39(10); Mischoulon D. Focus (Am Psychiatr Publ). 2018;16(1):2-11. doi:10.1176/appi.focus.20170041; Reque PM et al. Adv Gut Microbiome Res. 2025. doi:10.1155/agm3/3675425.

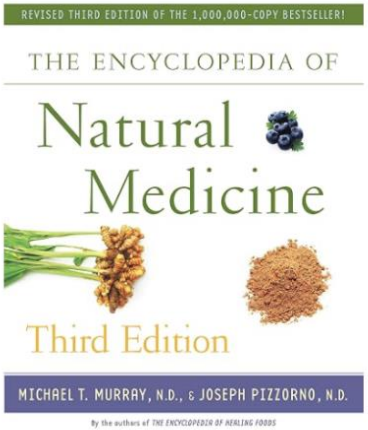
GOING DEEPER

Where to Read Next

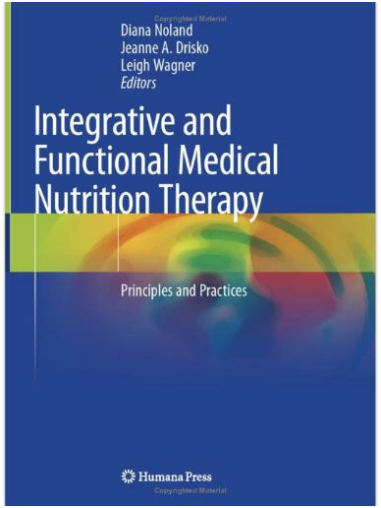
This deck is a summary of what is potentially relevant for Mental Health. These three cover the field properly, from clinical herbal practice to integrative nutrition.



Medical Herbalism
The Science and Practice of Herbal Medicine — David Hoffmann



The Encyclopedia of Natural Medicine
Third edition — Michael Murray and Joseph Pizzorno



Integrative and Functional Medical Nutrition Therapy
Principles and Practices — Noland, Drisko and Wagner

Cover images are shown for identification and reference only; inclusion here is not an endorsement of every claim these texts make.

EVIDENCE MAP — PART 1 OF 3

Data and Its Original Source

Every figure quoted in this deck, traced to the trial or meta-analysis it came from — omega-3, methylfolate, St. John's wort and vitamin D

Data point used in this deck	Original article	Type
Omega-3 dose-response: greatest benefit near 1.5 g/day; ≥ 2 g not better	Norouzi asl R, Zeraattalab-Motlagh S, Jayedi A, Shab-Bidar S. Br J Nutr. 2024	*Meta-analysis*
Long-chain omega-3 reduces anxiety and/or depression in adults	Kelaiditis CF, Gibson EL, Dyall SC. Prostaglandins Leukot Essent Fatty Acids. 2023	*Meta-analysis*
No prevention benefit; slight increase in incident depression (VITAL-DEP, n = 18,353)	Okereke OI, Vyas CM, Mischoulon D, et al. JAMA. 2021;326(23):2385-2394	*RCT*
Omega-3 in older adults: no overall effect, but > 1.5 g/day significant (d = −0.43)	Bai ZG, Bo A, Wu SJ, Gai QY, Chi I. J Affect Disord. 2018	*Meta-analysis*
Omega-3 in children and adolescents: very uncertain, no reliable effect	Campisi SC, Zasowski C, Bradley-Ridout G, et al. Cochrane Database Syst Rev. 2024	*Cochrane review*
L-methylfolate 15 mg/day for SSRI-resistant depression; clinical scenarios	Jain R, Manning S, Cutler AJ. CNS Spectr. 2020	*Review*
Methylfolate responders have raised inflammatory markers or high BMI	Macaluso M. Front Psychiatry. 2022	*Post hoc analysis*
Benefit in MTHFR C677T or A1298C carriers via homocysteine reduction	Mech AW, Farah A. J Clin Psychiatry. 2016	*RCT*
No efficacy signal for methylfolate in 412 patients aged ≤ 18	Bopp EA, Poweleit EA, Cox MO, et al. J Affect Disord. 2022	*Retrospective cohort*
Folate as adjunct to SSRI/SNRI in major depressive disorder	Altaf R, Gonzalez I, Rubino K, Nemec EC. Complement Ther Med. 2021	*Meta-analysis*
St. John's wort response and remission comparable to SSRIs (27 trials, 3,808 patients)	Ng QX, Venkatanarayanan N, Ho CY. J Affect Disord. 2017;210:211-221	*Meta-analysis*
Only pediatric St. John's wort data: 101 uncontrolled cases under 12 years	Hübner WD, Kirste T. Phytother Res. 2001;15(4):367-370	*Post-marketing surveillance*
Magnesium improves depression scores across 7 RCTs (SMD −0.92)	Moabedi M, Aliakbari M, Erfanian S, Milajerdi A. Front Psychiatry. 2024	*Meta-analysis*
248 mg/day elemental magnesium improved PHQ-9 within two weeks	Tarleton EK, Littenberg B, MacLean CD, Kennedy AG, Daley C. PLoS One. 2017	*RCT*
500 mg/day magnesium oxide in hypomagnesaemic depressed patients	Rajizadeh A, Mozaffari-Khosravi H, Yassini-Ardakani M, Dehghani A. Nutrition. 2017	*RCT*
Vitamin D dose-response: larger effect where depression already exists	Ghaemi S, Zeraattalab-Motlagh S, Jayedi A, Shab-Bidar S. Psychol Med. 2024	*Meta-analysis*

Compiled from the reference lists of the evidence dossier supplied for this deck. Several articles support more than one slide and are listed once against the claim they are quoted for; each remains cited in full on its own slide.

EVIDENCE MAP — PART 2 OF 3

Data and Its Original Source

Continued — magnesium, probiotics, the gut–brain evidence, and the NAC trials in OCD-spectrum and body-focused repetitive behaviours

Data point used in this deck	Original article	Type
Adults respond (SMD −0.70) while children and adolescents do not (SMD 0.10)	Srifuengfung M, Srifuengfung S, Pummangura C, et al. Nutrition. 2023	*Meta-analysis of 18 RCTs*
No vitamin D prevention benefit in any subgroup (VITAL-DEP)	Okereke OI, Reynolds CF, Mischoulon D, et al. JAMA. 2020;324(5):471-480	*RCT*
Prebiotics and probiotics reduce depression (SMD −0.96) and anxiety (SMD −0.59)	Asad A, Kirk M, Zhu S, Dong X, Gao M. Nutr Rev. 2025	*Meta-analysis*
Probiotics as third-line adjunctive treatment for MDD	Bahji A, Brietzke E, Cooke NCA, et al. Can J Psychiatry. 2026 (CANMAT task force)	*Guideline*
Gut microbiota consortium in the management of depression	Kaur S, Jangli A, Giridharan VV, Dandekar MP. Psychoneuroendocrinology. 2025	*Systematic review*
NAC across major mental disorders	Zheng W, Zhang QE, Cai DB, et al. Acta Psychiatr Scand. 2018	*Meta-analysis*
NAC 1200-2400 mg/day beat placebo in adult trichotillomania (56% vs 16%)	Grant JE, Odlaug BL, Kim SW. Arch Gen Psychiatry. 2009;66(7):756-763	*RCT*
NAC improved excoriation / skin-picking disorder (47% vs 19%)	Grant JE, Chamberlain SR, Redden SA, et al. JAMA Psychiatry. 2016;73(5):490-496	*RCT*
NAC failed in pediatric trichotillomania and in pediatric Tourette / chronic tics	Bloch MH et al. J Am Acad Child Adolesc Psychiatry. 2013;52(3):231-240 and J Child Adolesc Psychopharmacol. 2016;26(4):327-334	*RCTs*
NAC as an SRI adjunct in OCD - positive and negative trials in balance	Afshar H et al. J Clin Psychopharmacol. 2012;32(6):797-803; Costa DLC et al. J Clin Psychiatry. 2017;78(7):e766-e773	*RCTs*
Prenatal DHA did not prevent postpartum depression	Makrides M, Gibson RA, McPhee AJ, et al. JAMA. 2010;304(15):1675-1683 (DOMInO)	*RCT*
St. John's wort in breast milk associated with infant colic and drowsiness	Lee A, Minhas R, Matsuda N, et al. J Clin Psychiatry. 2003;64(8):966-968	*Cohort*
NAC most effective supplement for PANSS scores in schizophrenia	Xu X, Shao G, Zhang X, et al. Psychiatry Res. 2022	*Network meta-analysis*
Therapeutic potential of NAC in psychiatric disorders	Bradlow RCJ, Berk M, Kalivas PW, Back SE, Kanaan RA. CNS Drugs. 2022	*Review*
SAMe adjunctive to antidepressants in major depressive disorder	Sarris J, Murphy J, Mischoulon D, et al. Am J Psychiatry. 2016;173(6):575-587	*Meta-analysis*
SAMe for neuropsychiatric disorders, clinician-oriented	Sharma A, Gerbarg P, Bottiglieri T, et al. J Clin Psychiatry. 2017;78(6):e656-e667	*Systematic review*

Compiled from the reference lists of the evidence dossier supplied for this deck. Several articles support more than one slide and are listed once against the claim they are quoted for; each remains cited in full on its own slide.

EVIDENCE MAP — PART 3 OF 3

Data and Its Original Source

Continued — SAMe, perinatal safety data, comparative nutraceutical rankings, and the guidelines framing how all of it should be used

Data point used in this deck	Original artide	Type
Folates and SAMe for major depressive disorder	Papakostas GI, Cassiello CF, Iovieno N. Can J Psychiatry. 2012;57(7):406-413	*Review*
Nutraceutical comparative efficacy ranking (SAMe, zinc, curcumin effect sizes)	Cheng YC, Huang WL, Chen WY, et al. Psychol Med. 2025	*Network meta-analysis*
Nutrient supplements across mental disorders — omega-3 best supported	Firth J, Teasdale SB, Allott K, et al. World Psychiatry. 2019;18(3):308-324	*Meta-review*
Antioxidant supplementation for depression and anxiety, including zinc	Wang H, Jin M, Xie M, et al. J Affect Disord. 2023	*Meta-analysis*
Nutraceuticals for bipolar disorder	Ashton MM, Kavanagh BE, Marx W, et al. Can J Psychiatry. 2021	*Systematic review*
Magnesium plus vitamin B6 for mental health in stressed adults	Noah L, Dye L, Bois De Fer B, et al. Stress Health. 2021	*RCT post hoc*
Caution against supplements replacing FDA-approved treatment	VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. 2022	*Guideline*
Pharmacologic and nonpharmacologic treatment ranking for adult MDD	Gartlehner G, Dobrescu A, Chapman A, et al. Ann Intern Med. 2023 (ACP guideline)	*Network meta-analysis*
Contemporary management of depression in adults	Simon GE, Moise N, Mohr DC. JAMA. 2024;332(2):141-152	*Review*
Higher-dose EPA may still benefit late-life depression with raised inflammation	Dyall SC, Malau IA, Su KP. Curr Opin Clin Nutr Metab Care. 2025	*Review*
Saffron 30 mg/day improved arousal and lubrication in fluoxetine-related sexual dysfunction	Kashani L, Raisi F, Saroukhani S, et al. Hum Psychopharmacol. 2013;28(1):54-60	*RCT*
Saffron improved erectile function in SSRI-treated men, but not in non-drug-induced ED	Modabbernia A et al. Psychopharmacology. 2012;223(4):381-388; Safarinejad MR et al. Phytother Res. 2011;25(4):508-516	*RCTs*
Apple cider vinegar produced only 1-2 kg extra weight loss over 12 weeks	Kondo T, Kishi M, Fushimi T, et al. Biosci Biotechnol Biochem. 2009;73(8):1837-1843	*RCT*
Wider apple cider vinegar health daims unsupported	Launholt TL, Kristiansen CB, Hjorth P. Eur J Nutr. 2020;59(6):2273-2289	*Systematic review*
Spirulina B12 is a biologically inactive analogue	Watanabe F. Exp Biol Med. 2007;232(10):1266-1274	*Review*
Only positive wheatgrass trial - 23 patients with ulcerative colitis	Ben-Arye E, Goldin E, Wengrower D, et al. Scand J Gastroenterol. 2002;37(4):444-449	*RCT*

Compiled from the reference lists of the evidence dossier supplied for this deck. Several articles support more than one slide and are listed once against the claim they are quoted for; each remains cited in full on its own slide.

WHERE TO READ MORE

Source Articles

The sources behind this deck — key primary articles are listed in full on the next slide

Article	What it supports in this deck
Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for treating psychiatric disorders with nutraceuticals and phytoceuticals. World J Biol Psychiatry. 2022;23(6):424-455.	The recommendation-grade table, the guidelines-disagree slide, and the consensus grades and doses used throughout.
Reque PM, et al. Medicinal plants and herbal medicines for managing anxiety and depression via gut microbiota modulation. Adv Gut Microbiome Res. 2025.	Market and spending data, the gut–brain axis, lemon balm and green tea. Its dosing table comes from Sarris J. Phytother Res. 2018;32(7):1147-1162.
Mischoulon D. Popular herbal and natural remedies used in psychiatry. Focus (Am Psychiatr Publ). 2018;16(1):2-11.	Rhodiola, chamomile, passionflower, melatonin and inositol, plus context on St. John's wort, SAMe, omega-3, saffron, valerian, kava and ginkgo.
Lewis BB. Herbal medicine: what psychiatrists need to know. Psychiatric Times. 2022;39(10).	Saffron, lavender, cannabis and CBD, the US spending figures, and product-quality warnings.
De Smet PA. Herbal remedies. N Engl J Med. 2002;347(25):2046-2056.	Ginkgo, kava, saw palmetto, echinacea, valerian, black cohosh, milk thistle, garlic and horse chestnut, and the drug-interaction framing.
Cha S, Bell L, Shukitt-Hale B, Williams CM. A review of the effects of mushrooms on mood and neurocognitive health across the lifespan. Neurosci Biobehav Rev. 2024.	The two mushroom slides — 34 human studies, observational versus controlled.

Citation convention: each slide footnote names the original trial, meta-analysis or data source first, followed by “as cited in” the review that carried it — so a claim traces to the study it came from, not only to the review reporting it.

WHERE TO READ MORE — CONTINUED

Source Articles

Continued — the remaining source articles behind this deck

Article	What it supports in this deck
Aldekhail NM, Khojah H, Alsaadoun NH, et al. Herbal medicines in autism spectrum disorder: therapeutic potential, plant components, and dosage guidelines. Altern Ther Health Med. 2025.	The three autism slides — herbal mechanisms, dosing gaps and counselling points.
Sathe N, Andrews JC, McPheeters ML, Warren ZE. Nutritional and dietary interventions for autism spectrum disorder: a systematic review. Pediatrics. 2017.	The autism effect sizes, and the interventions with no benefit.
Committee on Clinical Practice Guidelines–Gynecology. Management of premenstrual disorders: ACOG Clinical Practice Guideline No. 7. Obstet Gynecol. 2023;142(6):1516-1533.	The two premenstrual disorder slides — the chasteberry position and the multimodal framing.
Compiled evidence dossier supplied for this deck — systematic reviews, meta-analyses, RCTs and guidelines on nutraceuticals in mental health.	49 primary articles behind every figure quoted here, listed on the three Evidence Map slides and cited in full on the next slide.
Lam CS, O'Connell K, Monroy-Iglesias MJ, et al. Emerging patterns in dietary supplement use among US adults, 1999-2023. JAMA Netw Open. 2026.	Supplement use trends and the categories driving growth
Blumenthal RS, Morris PB, Gaudino M, et al. 2026 ACC/AHA multisociety guideline on the management of dyslipidemia. Circulation / J Am Coll Cardiol. 2026.	Guideline position on cholesterol and heart-health supplements

Citation convention: each slide footnote names the original trial, meta-analysis or data source first, followed by “as cited in” the review that carried it — so a claim traces to the study it came from, not only to the review reporting it.

WHERE TO READ MORE — CONTINUED

Source Articles

Continued - the reviews and guidelines behind the menopause and Alzheimer disease slides

Article	What it supports in this deck
Kargozar R, Azizi H, Salari R. A review of effective herbal medicines in controlling menopausal symptoms. Electron Physician. 2017;9(11):5826-5833.	Both menopause tables - herbs, mechanisms, reported effects and study types.
The Menopause Society (formerly The North American Menopause Society). The 2023 nonhormone therapy position statement. Menopause. 2023;30(6):573-590.	The framing that botanicals are not recommended as first-line therapy for vasomotor symptoms.
Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012;(9):CD007244.	The absence of consistent benefit for black cohosh in menopause.
Ghazanfarpour M, Sadeghi R, Abdolahian S, Latifnejad Roudsari R. The efficacy of Iranian herbal medicines in alleviating hot flashes: a systematic review. Int J Reprod Biomed. 2016;14(3):155-166.	The pooled picture for fenugreek, licorice, anise and fennel.
Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2009;(1):CD003120.	The inconsistent cognitive results for ginkgo in dementia.
Farina N, Llewellyn D, Isaac MGEKN, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev. 2017;(4):CD002854.	The vitamin E evidence base and its limits in mild cognitive impairment.
Mecocci P, Tinarelli C, Schulz RJ, Polidori MC. Nutraceuticals in cognitive impairment and Alzheimer's disease. Front Pharmacol. 2014;5:147.	The dementia nutraceutical table - compounds, doses and trial quality.
The Menopause Society (formerly The North American Menopause Society). The 2023 nonhormone therapy position statement. Menopause. 2023;30(6):573-590.	The first-line options in the menopause recommendation table.
Pourianezhad F, Tahmasebi S, Abdusi V, Nikfar S, Mirhoseini M. Review on feverfew, a valuable medicinal plant. J HerbMed Pharmacol. 2016;5(2):45-49.	The feverfew slide - phytochemistry, mechanisms and traditional uses.
Pittler MH, Ernst E. Feverfew for preventing migraine. Cochrane Database Syst Rev. 2004;(1):CD002286.	The inconsistent migraine-prophylaxis evidence for feverfew.

Citation convention: each slide footnote names the original trial, meta-analysis or data source first, followed by “as cited in” the review that carried it — so a claim traces to the study it came from, not only to the review reporting it.

WHERE TO READ MORE — CONTINUED

Key Primary Sources

The trial-level and meta-analytic articles behind the figures quoted throughout this deck, cited in full - part 1 of 5

Article	What it supports in this deck
Norouziasl R, Zeraattalab-Motlagh S, Jayedi A, Shab-Bidar S. Omega-3 supplementation and depressive symptoms: dose-response meta-analysis. Br J Nutr. 2024.	Omega-3 dose-response — peak benefit near 1.5 g/day, no gain above 2 g/day.
Campisi SC, Zasowski C, Bradley-Ridout G, et al. Omega-3 for depression in children and adolescents. Cochrane Database Syst Rev. 2024.	The pediatric omega-3 result — very low certainty, no reliable effect.
Bai ZG, Bo A, Wu SJ, Gai QY, Chi I. Omega-3 and depressive symptoms in older adults: systematic review and meta-analysis. J Affect Disord. 2018.	Older-adult omega-3 — no overall effect, but significant above 1.5 g/day.
Mech AW, Farah A. Clinical response and homocysteine reduction with reduced B vitamins in MDD with MTHFR C677T or A1298C. J Clin Psychiatry. 2016.	The MTHFR genotype finding behind the L-methylfolate recommendation.
Altaf R, Gonzalez I, Rubino K, Nemec EC. Folate as adjunct to SSRI/SNRI in major depressive disorder: meta-analysis. Complement Ther Med. 2021.	Folate augmentation in treatment-resistant depression.
Hübner WD, Kirste T. St. John's wort in children under 12 with depressive symptoms. Phytother Res. 2001;15(4):367-370.	The only pediatric St. John's wort dataset — 101 uncontrolled cases.
Ashton MM, Kavanagh BE, Marx W, et al. Systematic review of nutraceuticals for bipolar disorder. Can J Psychiatry. 2021.	The bipolar-specific grades, including agents not recommended there.
Gartlehner G, Dobrescu A, Chapman A, et al. Treatments for adult major depressive disorder: network meta-analysis for the ACP. Ann Intern Med. 2023.	The ranking placing nutraceuticals against first-line treatments.
US Department of Veterans Affairs / Department of Defense. Clinical Practice Guideline for Major Depressive Disorder. 2022.	The caution against supplements substituting for approved treatment.

These are the most load-bearing of the primary articles behind the deck. The full set, mapped claim by claim, is on the three Evidence Map slides.

WHERE TO READ MORE — CONTINUED

Key Primary Sources

The trial-level and meta-analytic articles behind the figures quoted throughout this deck, cited in full - part 2 of 5

Article	What it supports in this deck
Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T. Improving effects of Hericium erinaceus on mild cognitive impairment: double-blind placebo-controlled trial. Phytother Res. 2009;23(3):367-372.	The 3 g/day lion's mane MCI result — and its reversal after stopping.
Li IC, Chang HH, Lin CH, et al. Prevention of early Alzheimer's disease by erinacine A-enriched Hericium erinaceus mycelia: pilot double-blind placebo-controlled study. Front Aging Neurosci. 2020;12:155.	The 49-week mycelium trial and the erinacine A dose specification.
Cha S, Bell L, Shukitt-Hale B, Williams CM. A review of the effects of mushrooms on mood and neurocognitive health across the lifespan. Neurosci Biobehav Rev. 2024.	The 34-study split between positive observational and mixed trial data.
Kożźła O, Kukula-Koch W, Jóźwiak K, et al. Biotransformation of Ganoderma lucidum and Hericium erinaceus for ex vivo gut–brain axis modulation. J Ethnopharmacol. 2025.	The CREB/BDNF gut–brain mechanism behind the reishi and lion's mane mood claims.
Lazur J, Hnatyk K, Kała K, Sułkowska-Ziaja K, Muszyńska B. Discovering the potential mechanisms of medicinal mushrooms' antidepressant activity: a review. Antioxidants. 2023;12(3):623.	The preclinical antidepressant mechanisms across cordyceps, poria and relatives.
Lai MC, Anagnostou E, Wiznitzer M, Allison C, Baron-Cohen S. Evidence-based support for autistic people across the lifespan. Lancet Neurol. 2020.	The folinic acid trial, and the harms of chelation and hyperbaric oxygen.
Westby A, Coburn-Pierce M. Autism spectrum disorder in primary care. Am Fam Physician. 2025.	The melatonin endorsement and the deficiency-screening approach.
Shi J, Cheng Y, Wei Y, Shi Y, Jiang Z. Effect of diet intervention on symptoms in autism spectrum disorder: an umbrella review. Res Dev Disabil. 2026.	The vitamin D effect size (SMD −0.45) and the probiotic GI signal.
Ma C, Wang Y, Ding Z, et al. Comparative efficacy and acceptability of non-pharmacological therapies and novel pharmacotherapies for autism: network meta-analysis. Child Psychiatry Hum Dev. 2026.	The cannabinoid acceptability and dropout finding in autism.

These are the most load-bearing of the primary articles behind the deck. The full set, mapped claim by claim, is on the three Evidence Map slides.

WHERE TO READ MORE — CONTINUED

Key Primary Sources

The trial-level and meta-analytic articles behind the figures quoted throughout this deck, cited in full - part 3 of 5

Article	What it supports in this deck
Doherty M, Foley KR, Schloss J. Complementary and alternative medicine for autism: a systematic review. J Autism Dev Disord. 2024.	The deficiency-correction-only conclusion for vitamins and minerals.
Verkaik S, Kamperman AM, van Westrhenen R, Schulte PFJ. The treatment of premenstrual syndrome with preparations of Vitex agnus castus: systematic review and meta-analysis. Am J Obstet Gynecol. 2017.	The pooled chasteberry effect size, and the heterogeneity and publication-bias caveats.
Cerqueira RO, Frey BN, Leclerc E, Brietzke E. Vitex agnus castus for premenstrual syndrome and premenstrual dysphoric disorder: a systematic review. Arch Womens Ment Health. 2017.	The PMDD-specific comparisons against fluoxetine.
van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus extracts for female reproductive disorders: a systematic review of clinical trials. Planta Med. 2013.	The tolerability and standardization findings for chasteberry extracts.
Canning S, Waterman M, Orsi N, et al. The efficacy of Hypericum perforatum for premenstrual syndrome: a randomized, double-blind, placebo-controlled trial. CNS Drugs. 2010.	The positive physical and behavioural symptom result at 900 mg/day.
Biggs WS, Romeu JM, Gaudard T. Premenstrual syndrome and premenstrual dysphoric disorder: common questions and answers. Am Fam Physician. 2025.	The SSRI-first-line framing and the dose-response chasteberry data.
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WHERE TO READ MORE — CONTINUED

Key Primary Sources

The trial-level and meta-analytic articles behind the figures quoted throughout this deck, cited in full - part 4 of 5

Article	What it supports in this deck
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Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology. 2015.	Mechanisms and patterns of herb-induced liver injury
Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol. 2015.	Idiosyncratic, non-dose-predictable injury pattern
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Wierzejska RE. Dietary supplements - for whom? Int J Environ Res Public Health. 2021.	Weight-loss supplements and vitamins in healthy adults
Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. J Am Coll Cardiol. 2010.	Ephedra, synephrine and cardiovascular herbal risk

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The trial-level and meta-analytic articles behind the figures quoted throughout this deck, cited in full - part 5 of 6

Article	What it supports in this deck
Chenoy R, Hussain S, Tayob Y, et al. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. BMJ. 1994;308(6927):501-503.	The evening primrose vasomotor result
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Ringman JM, Frautschy SA, Teng E, et al. Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. Alzheimers Res Ther. 2012;4(5):43.	The null curcumin result in Alzheimer's disease
Douaud G, Refsum H, de Jager CA, et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci USA. 2013;110(23):9523-9528.	The B-vitamin atrophy finding in raised homocysteine
Simpson M, Parsons M, Greenwood J, Wade K. Raspberry leaf in pregnancy: its safety and efficacy in labor. J Midwifery Womens Health. 2001;46(2):51-59.	The raspberry leaf second-stage and forceps findings
Dove D, Johnson P. Oral evening primrose oil: its effect on length of pregnancy and selected intrapartum outcomes in low-risk nulliparous women. J Nurse Midwifery. 1999;44(3):320-324.	The negative evening primrose oil labor result

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The trial-level and meta-analytic articles behind the figures quoted throughout this deck, cited in full - part 6 of 6

Article	What it supports in this deck
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Nahidi F, Zare E, Mojab F, Alavi-Majd H. Effects of licorice on relief and recurrence of menopausal hot flashes. Iran J Pharm Res. 2012;11(2):541-548.	The licorice hot flash relief and recurrence data
Ibrahim RM, Hamdan NS, Mahmud R, et al. A randomised controlled trial on hypolipidemic effects of Nigella sativa seeds powder in menopausal women. Adv Pharm Bull. 2014;4(1):29-33.	The black cumin lipid and metabolic findings
Nahidi F, Kariman N, Simbar M, Mojab F. The study of the effects of Pimpinella anisum on relief and recurrence of menopausal hot flashes. Iran J Pharm Res. 2012;11(4):1079-1085.	The anise placebo-controlled hot flash result
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