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Psychiatry and Addictions Case Conference
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Brain Boosters? Nutritional Supplements in the Treatment of Anxiety and Depression

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ECHO

SPEAKER DISCLOSURES

I have no disclosures

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

- Understand the level of oversight involved in supplement manufacturing
- Explore the benefits and limitations of counselling patients on supplement use
- Provide a framework for further evaluation of supplements in practice
- Identify common supplements and examine evidence for their use

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Nutritional Supplements

- ***Nutraceutical**:* Nutrient-based natural products which are produced via pharmaceutical GMP, standardised and optimised
- ***Phytoceutical**:* Plant-based natural products which are produced via pharmaceutical GMP, standardised and optimised[1]
- **Supplement**: to food supply or to therapeutic toolkit?[2]

Addressing the Dichotomy

Source

Source

Source

Oversight of Nutritional Supplements

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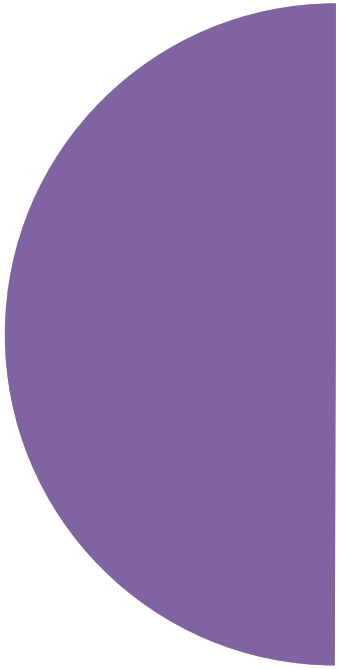
FDA's History with Dietary Supplements[2]

1906: Federal Food and Drugs Act was established

- Defined drugs as substances used to *cure, mitigate, or prevent disease* and had to abide by the *standards of strength, quality, and purity*
- Defined foods as *food, drink, confectionary, or condiment* — did not have to meet standards as drugs did

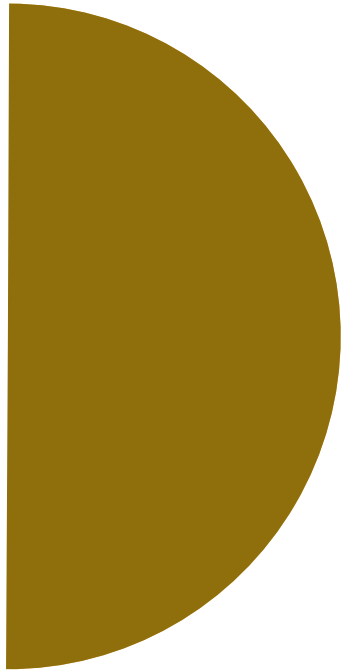
1922: interest in vitamins grew and the FDA began collecting info on their manufacture, the ingredients used, labelling, and advertising. The agency elected to regulate vitamins and minerals as special dietary foods under these regulations.[2]

> "... labeling of food products with claims implying that they possess curative, health-giving, healing qualities, when, as a matter of fact, they merely possess those wholesome, nutritive qualities which a food of that particular description should possess, is a misbranding within the meaning of the food and drugs act and subjects the product so labeled to the penalties imposed by that act. In like manner, extreme and unwarranted vitamin claims must be classed as illegal.52-54"



"FDA regulates both finished dietary supplement products and dietary ingredients. FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA)"[3]

US Food and Drug Administration



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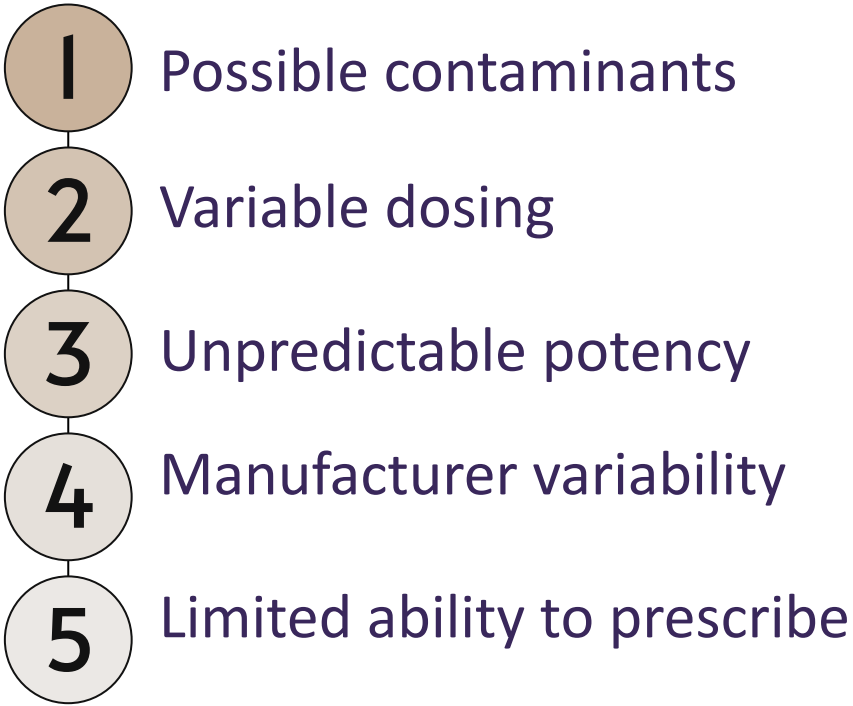
Medications[4]	Supplements
Therapeutic agents	Subset of food
Must demonstrate safety and efficacy through FDA-reviewed clinical trials *before* marketing	Products can be sold without proving safety or efficacy
Strict pharmaceutical GMP; consistent potency, purity, and quality required.	Dietary supplement GMP, which are less stringent; more variability in potency, purity, and consistency.
FDA reviews and approves formulation, labeling, dosing, and safety data.	FDA does not verify formulation or label accuracy prior to sale; third-party testing is optional.
Rigorous post-market surveillance; manufacturers must report adverse events, and FDA can intervene quickly.	FDA intervenes only **after** safety problems emerge; burden is on FDA to prove a product is unsafe.
FDA can recall or restrict a drug immediately if risks arise.	FDA must gather evidence of harm before taking action; recalls are slower and less frequent.

Where does this leave us?



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Why talk about supplements?

- Easily Accessible
- Counselling on safe use
- Medication interactions
- Aligning with patients
- Cultural considerations
- Leveraging buy-in

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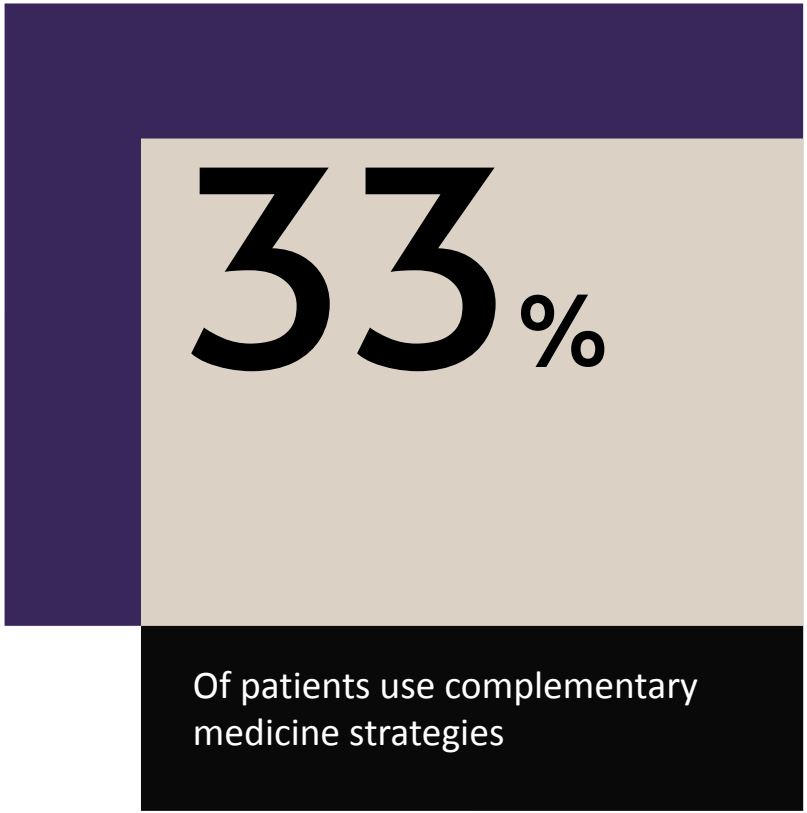
CAM Use is Common[16]



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Framework for Evaluating Supplements

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I.

Is it harmful?

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Is it Harmful?

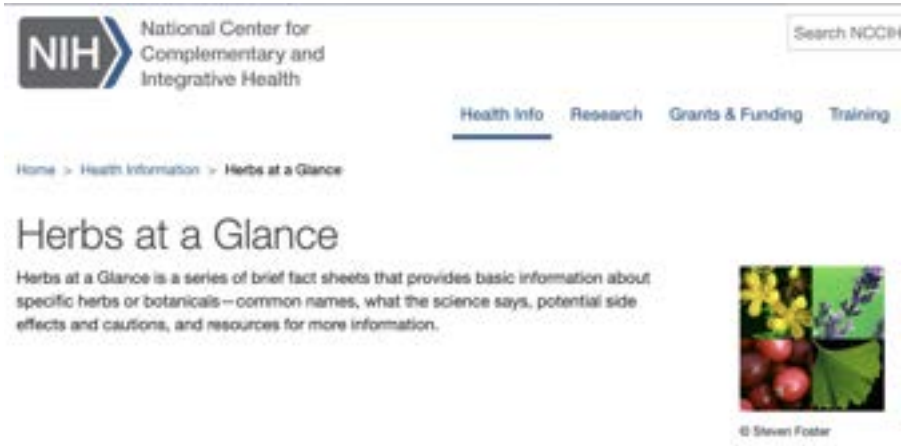
- Consider third party testing → NSF and USP[5]
- Review FDA Guidelines on Selecting Supplements[6]

Additional Resources

- Use drug interaction tools
  ⟶ Natmedpro or Lexicomp

Resources for Patients

- NIH Herbs at a Glance[7]
- MSK database[8]
- FDA Consumer Information on Dietary Supplements[9]



Common interactions and risks of natural supplements

	Main Use	Key Interaction	Notable Risk
Kava	Anxiety	Additive sedation with benzodiazepines, barbiturates, alcohol	CNS depression, confusion, hepatotoxicity
Ginkgo biloba	Memory, cognitive enhancement	↑ bleeding risk with anticoagulants/antiplatelets; may ↓ seizure threshold	Hemorrhage, seizures
Ginseng	Energy, immune function	Antagonizes warfarin, ↑ risk of mania with antidepressants	Hypertension, insomnia, irritability
St. John's Wort	Depression	Potent CYP3A4 inducer → ↓ levels of many drugs (OCPs, cyclosporine, warfarin, HIV meds, some antidepressants)	Serotonin syndrome if combined with SSRIs/SNRIs/MAOIs

Narrow-Spectrum Micronutrients[10]

- Vitamin A⟶ increased cardiovascular deaths and lung cancer
- Vitamin E ⟶colorectal cancer and prostate cancer
- Beta-carotene ⟶ stomach and lung cancer
- Larger doses of synthetic folic acid have been linked to very slight increase of some cancers[1]

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2.

Is it helpful?

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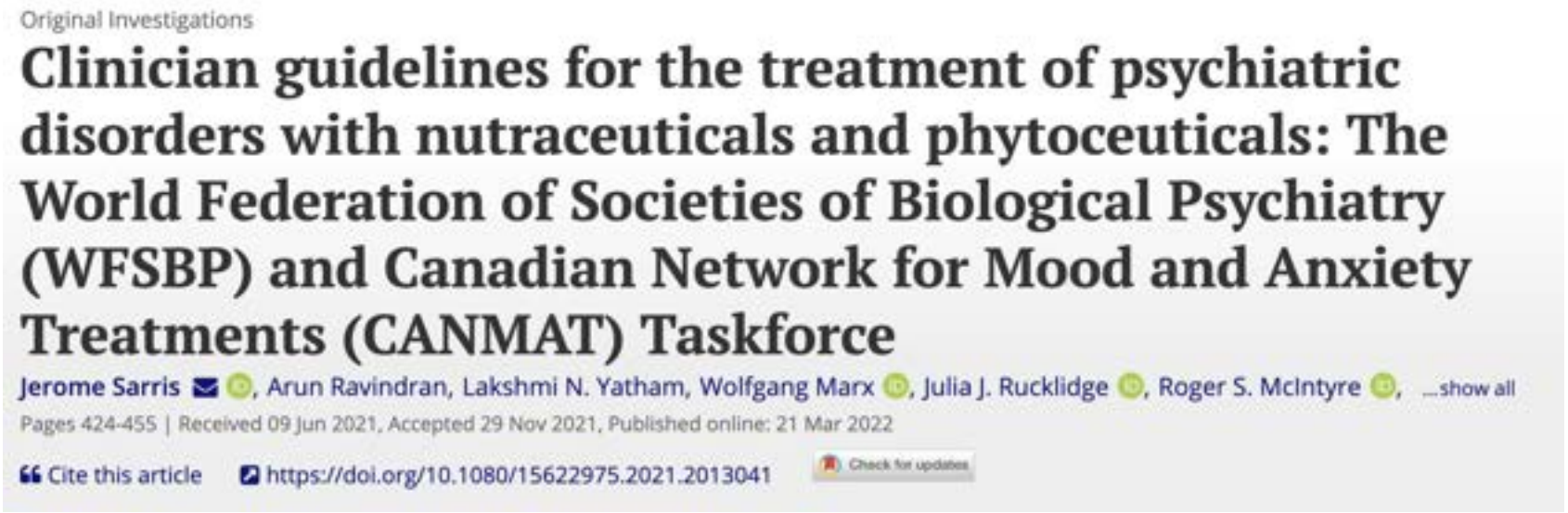
WFSBP and CANMAT Taskforce[1]



Original Investigations

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

Jerome Sarris, Arun Ravindran, Lakshmi N. Yatham, Wolfgang Marx, Julia J. Rucklidge, Roger S. McIntyre, ...show all

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About the Taskforce[1]

- 31 members from 15 countries including psychiatrists, psychologists, natural product psychopharmacologists, epidemiologists, integrative medicine practitioners, nutritionists, preclinical scientists, pharmacists, and statisticians
- Examined data from two meta-reviews of meta-analyses
- **Aims:**
  - provide definitive evidence-informed approach to assist in greater clinical clarity around the use of nutraceuticals and phytoceuticals across major psychiatric disorders
  - Safety and tolerability
  - Clinical advice around prescription considerations for specific clinical indications

Domains of Evaluation[1]

Level of Evidence

Availability of RCTs and meta-analysis data

Direction of Evidence

Whether data supports benefit of the specific intervention

Safety

Additional expert recommendation on safety, tolerability, cost, and practicability

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Recommendation *FOR* or AGAINST using the intervention	Grade	Level of Evidence (LoE)
Recommended	+++	'A' LoE with robust positive data meta-analyses or meta-reviews involving underpinning RCTs, with ROBUST, ACCEPTABLE, or FAIR safety/tolerability
Provisionally Recommended	++	'A' LoE with mainly positive data from either meta-analyses or meta-reviews or ≥2 RCTs of good or average quality, with ROBUST, ACCEPTABLE, or FAIR safety/tolerability
Weakly Recommended	+	'A' LoE mixture of (primarily) positive and negative data from either meta-analyses or meta-reviews or ≥2 RCTs of good or average underpinning quality, tending towards positive findings, with ROBUST, ACCEPTABLE, or FAIR safety/tolerability
Not Currently Recommended	+/–	'A' LoE mixture of positive and negative data from either meta-analyses or meta-reviews or ≥2 RCTs of good or average or weak underpinning quality, with ROBUST, ACCEPTABLE, or FAIR tolerability
Not Recommended	–	'A' LoE with robust negative data from meta-analyses or meta-reviews or ≥2 RCTs and/or POOR safety/tolerability

Recommendation framework reporting from WFSBP and CANMAT Taskforce[1]

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Omega 3

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Omega-3	MDD (Adj)(Mono)	A (Meta + 5 RCTs)	++++/–	1 g–2 g of EPA or mixed EPA/DHA	ROBUST Caution with blood-thinning medication; Potential GI upset	Potentially more effective adjunctively with antidepressants, and in raised inflammatory markers and/or obesity	MDD: (Mocking et al. 2016; Gabbay et al. 2018; Carney et al. 2019; Fristad et al. 2019; Chang et al. 2020; Jana et al. 2020)

Quality limitations, product may contain high levels of oxidation

Vitamin D

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Vitamin D	MDD (Adj/Mono)	A (Meta + 2 RCTs)	+	1500 IU–4000 IU	ROBUST Considered safe	Unlikely to be of benefit in those with sufficient skin exposure to sufficient non-winter sunlight and/or dietary intake	(Alghamdi et al. 2020; Cheng et al. 2020; Vellekkatt et al. 2020)

RCT suggested that vitamin 03 (1,500 IU daily) augmentation of fluoxetine enhanced outcome in 42 adults starting at week 4, with an ES of 0.5[11]

Probiotics

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Probiotics	MDD (Adj/Mono)	A (Meta)	++	1–10 billion colony forming units (varying strains)	ROBUST Considered safe	The most appropriate probiotics strains for depression have not been confirmed, certain and variations are potentially more beneficial depending on an individual's genetics and diet	(Sanada et al. 2020)

- The most appropriate probiotics strains for depression have not been confirmed, and it is likely that variations are more beneficial depending on an individual's genetics and diet and microbiome composition
- May be more beneficial for older patients due to microbiome dysbiosis[10]

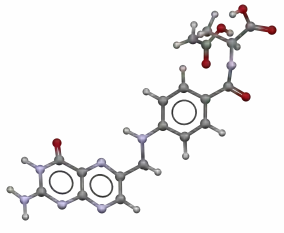
Zinc

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Zinc	MDD (Adj)	A (Meta)	++	~25 mg elemental	ACCEPTABLE Considered safe below 40mg per day, although nausea may occur on an empty stomach	May have a specialised use in cases of comorbid lowered immune response or raised inflammation, or high oxidative stress (especially if dietary deficient)	(Schefft et al. 2017)

- May have a specialised use in cases of comorbid lowered immunity, raised inflammation, or high oxidative stress (especially in dietary deficiency)
- Certain chelations are recommended due to being more absorbable e.g. amino acid chelates or picolinate

Folate



Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Folate-based compounds	MDD (Adj)	A (Meta)		Methylfolate (15 mg)	FAIR Fairly safe, however larger doses of synthetic folic acid have been linked to very slight increase of some cancers	Methylfolate potentially more effective due to the metabolic bypass of the T677C polymorphism	(Bedson et al. 2014; Roberts et al. 2018)
Folic acid		–					
MTHF/acid		++					

- May have additional benefits in those with inflammation and/or obesity, or for use in preconception care or pregnancy
- effect size (ES) of 0.35-0.4[10]

St John's Wort

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
St John's wort	Mono	A (Meta)	+++	600 mg–1800 mg (standardised to hypericin 0.2–0.3% AND/OR 5–6% hyperforin)	ACCEPTABLE Caution for use in Bipolar Disorder. May cause photosensitivity. Do not use with SSRIs or SNRIs due to potential of serotonin syndrome. Hyperforin-rich extracts may reduce serum levels of many drugs	Use of quality standardised extracts is vital to be confident of replicated effects shown in RCTs	(Apaydin et al. 2016)

- Per day standardised to a dose of approximately 0.2–0.3% hypericin and/or 5–6% hyperforin (once to three times per day depending on extract)
- One of the few agents with evidence for monotherapy

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Saffron

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Saffron	MDD (Adj/Mono)	A (Meta)	++	30 mg per day of stigma (standardised to safranal or crocin isomers)	ACCEPTABLE Considered safe, aside from potential minor adverse effects e.g. gastrointestinal symptoms, increased stimulation	Stigma/petal combinations may still provide antidepressant effects (and be much cheaper than stigma alone)	(Marx et al. 2019)

- Quality and standardisation of saffron extracts are essential
- Cost may be prohibitive

Curcumin

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Curcumin	MDD (Adj/Mono)	A (Meta)	++	500 mg–1000 mg (curcumin)	ACCEPTABLE Considered safe	Potential adjuvant benefit in comorbid inflammatory disorders. Bioavailable forms are advised e.g. liposomal	(Fusar-Poli et al. 2020)

- Potential adjuvant benefit in comorbid inflammatory disorders
- Formulations with evidence of sufficient bioavailability are advised (e.g. consider liposomal forms)

Lavender

Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Lavender	MDD (Adj/Mono)	A (3 RCTs)	++	80 mg–160 mg per day of a specialised oil (in capsule form) or 500 mg–1.5 g of dried flower (standardised to linalool)	ACCEPTABLE Considered safe	Use of standardised capsule formulations advised over tea preparations of unknown quality	(Akhondzadeh et al. 2003; Nikfarjam et al. 2013, 2017)
	GAD (Adj/Mono)	A (3 RCTs)	++	80 mg–160 mg per day of a specialised oil (in capsule form) or 500 mg–1.5 g of dried flower (standardised to linalool)	ACCEPTABLE Considered safe	Highly standardised essential oil based extracts potentially more effective than general dried raw material	(Kasper et al. 2014, 2015; Farshbaf-Khalili et al. 2018)

Preference for standard preparation over tea

Nutraceutical	Indications	Level of evidence	Grade* (+ or −)	Suggested dosage per day	Tolerability/ safety	Clinical advice	References
S-adenosyl methionine	MDD	A (5 RCTs)		800 mg–3200 mg	*ACCEPTABLE*	SAMe is an unstable compound and enteric coating and storage in blister packs under refrigeration may be advised	(Pancheri et al. 2002; George I. Papakostas et al. 2010; Mischoulon et al. 2014; Sarris et al. 2018; Sarris, Murphy, et al. 2020)
	(Mono)		+/−		A safe compound, however, caution is advised in bipolar disorder		
	(Adjunctive)		+				
Vitamin C	MDD (Adj)	A (2 RCTs)	+/−	-1 g	*ROBUST* Considered safe, however excess doses may cause gastrointestinal disturbance (e.g. diarrhea)	While evidence is not supportive, there may be a potential role in cases of Vit C deficiency or comorbid immune system deficiency	(Amr et al. 2013; Sahraian et al. 2015)
Tryptophan & 5-HTP	MDD (Adj/Mono)	A (Meta +1 RCT)	+/−	-1 g (tryptophan), 50 mg–200 mg (5-HTP)	*ACCEPTABLE* Caution is advised in co-use with antidepressants	Older research showing mixed efficacy. 5-HTP a preferred form as a precursor of serotonin. May be of benefit in the evening for comorbid insomnia	(Levitan et al. 2000; Shaw et al. 2002)
Creatine	MDD (Adj/Mono)	A (2 RCTs)	+/−	5 g	*FAIR* Caution in excess doses and in people with kidney issues	May have a role in people with MDD and comorbid fatigue	(Lyoo et al. 2012, Nemets and Levine 2013)
Inositol	MDD (Adj)	A (Meta)	−	-12 g	*ACCEPTABLE* Considered safe, however may cause gastrointestinal discomfort at high doses	Not effective for use in MDD	(Mukai et al. 2014)
Magnesium	MDD (Adj)	A (2 RCTs)	−	100–400 mg elemental	*ROBUST* Considered safe	While evidence is not supportive for use in MDD, there may still be an application in deficiency	(Mehdi, Atlas et al. 2017; Ryszewska-Pokraśniewicz et al. 2018)
N-acetyl cysteine	BD (Adj)	A (4 RCTs)	+/−	1g–3 g	*ACCEPTABLE* Considered safe	May have a specialised use across a range of comorbid psychiatric disorders, especially in cases of high oxidative stress	(Berk et al. 2008, 2012; Bauer et al. 2017; Ellegaard et al. 2019)

Additional compounds with weaker grade of evidence for depression

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Ashwaganda

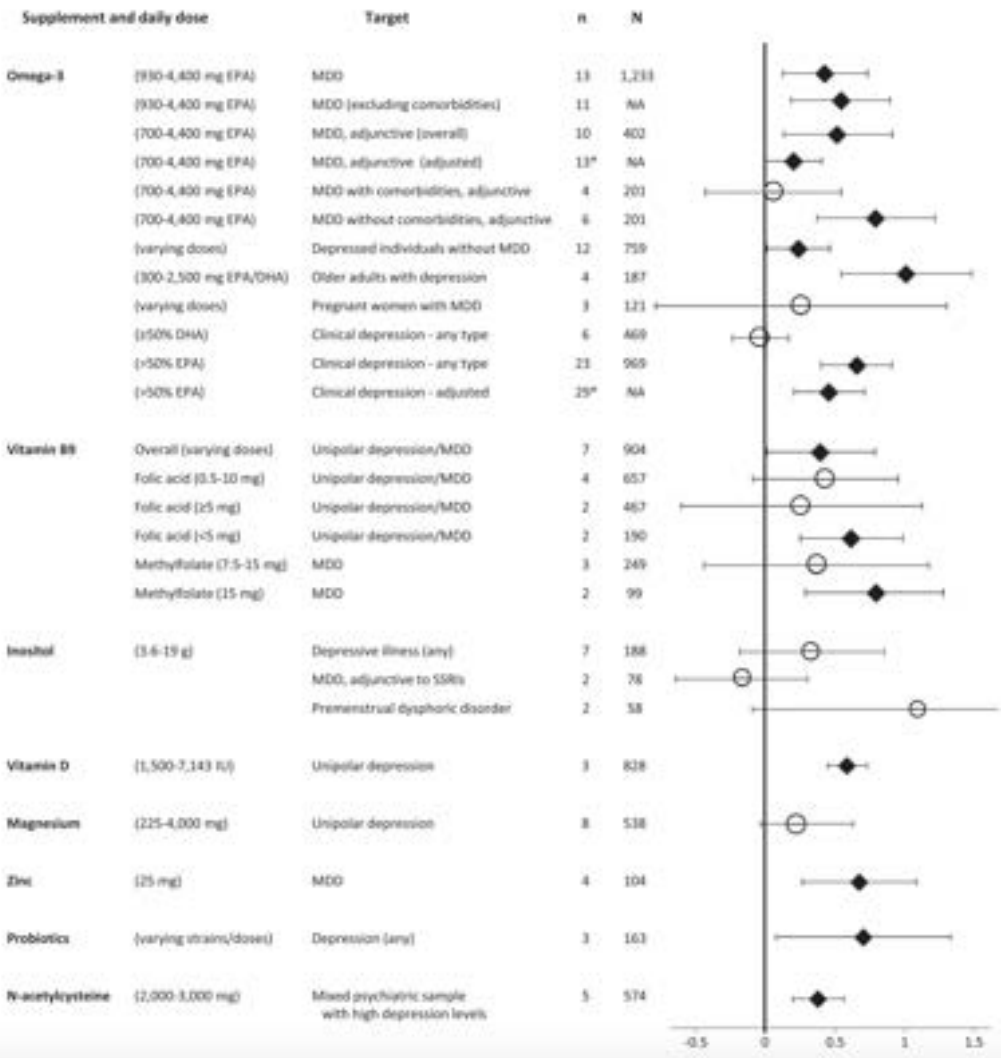
Source

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Ashwagandha	GAD (Adj/Mono)	A (3 RCTs)	++	300 mg–600 mg (standardised to 5% withanolides)	ACCEPTABLE Considered safe	May be of additional benefit in improving cognition in BD	(Andrade et al. 2000; Sud Khyati and Anup 2013; Fuladi et al. 2020)

May have procognitive effects and benefit to fatigue

	Indications	Level of evidence	Grade* (+ or –)	Suggested dosage per day	Tolerability/safety	Clinical advice	References
Kava	GAD (Mono)	A (Meta + 2 RCTs)	–	60mg-250mg of kavalactones	FAIRCaution for use in people with liver issues, and avoidance with alcohol and benzodiazepines	While not effective for GAD, potential use for acute or short-term management of general anxiety symptoms supportedImportant to recommend only the use of 'noble' varieties of the rootstock of the plant standardised to a sufficient level of kavalactones	(Barić et al. 2018; Kuchta et al. 2018; Sarris, Byrne, et al. 2020)
Galphimia	GAD (Mono)	A (2 RCTs)	+	350 mg–700 mg (standardised to galphimine-B)	FAIR Considered safe	Not commonly used outside South America, sourcing could be an issue	(Herrera-Arellano et al. 2007, 2012)
Chamomile	GAD (Adj/Mono)	A (2 RCTs)	+/–	220 mg–1500 mg (potentially standardised to chrysin or apigenin)	ROBUST Robust safety data	Standardised extracts preferable to teas of unknown quality	(Amsterdam et al. 2009; Mao et al. 2016)

Additional compounds with weaker grade of evidence for anxiety



Effects of nutraceuticals in depressive disorders[12]

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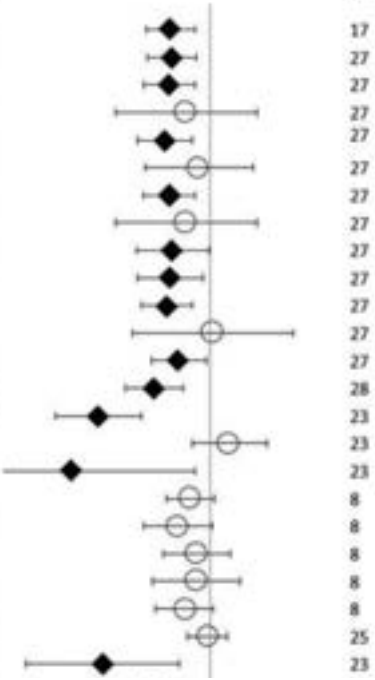
Phytoceutical	Condition	Dose	Outcome	n=	N=	A2
Curcumin	MDD	500-1000mg/day	Depressive symptoms	377	6	17
	MDD	"	"	342	6	27
	MDD - middle-age group	"	"	302	5	27
	MDD - old-age group	"	"	40	1	27
	MDD - duration 6 weeks or more	"	"	70	4	27
	MDD - duration <6 weeks	"	"	212	2	27
	MDD - dosage subgroup analysis	1g/day	"	302	5	27
	MDD - dosage subgroup analysis	500mg/day	"	40	1	27
	MDD - Curcumin plus piperine	500-1000mg/day	"	146	3	27
	MDD - Curcumin without enhancers	"	"	196	3	27
	MDD - no comorbidities	"	"	312	5	27
	MDD - comorbidity (obesity)	"	"	30	1	27
	MDD - RCT	"	"	231	5	27
St John's wort	MDD	150mg-1200mg	Depressive scales (HAMD)	2922	16	28
Saffron	Depression	28-30mg/day	Depressive symptoms	716	14	23
	Depression - saffron vs antipressant	"	"	210	5	23
	Depression - adjunctive saffron	"	"	144	4	23
Kava	Anxiety - Non-Psychotic Anxiety Disorders	150mg-300mg	Anxiety symptoms (HAMA)	345	6	8
	Anxiety - younger participants	200mg-300mg	"	166	5	8
	Anxiety - older participants only	150mg-300mg	"	178	6	8
	Anxiety - male participants only	"	"	101	5	8
	Anxiety - female participants only	"	"	236	6	8
	GAD and Anxiety Disorders	35mg-70mg	"	498	4	25
Saffron	Anxiety	28 - 450mg/day	"	375	6	23



Effects of phytoceuticals in psychiatric disorders[13]

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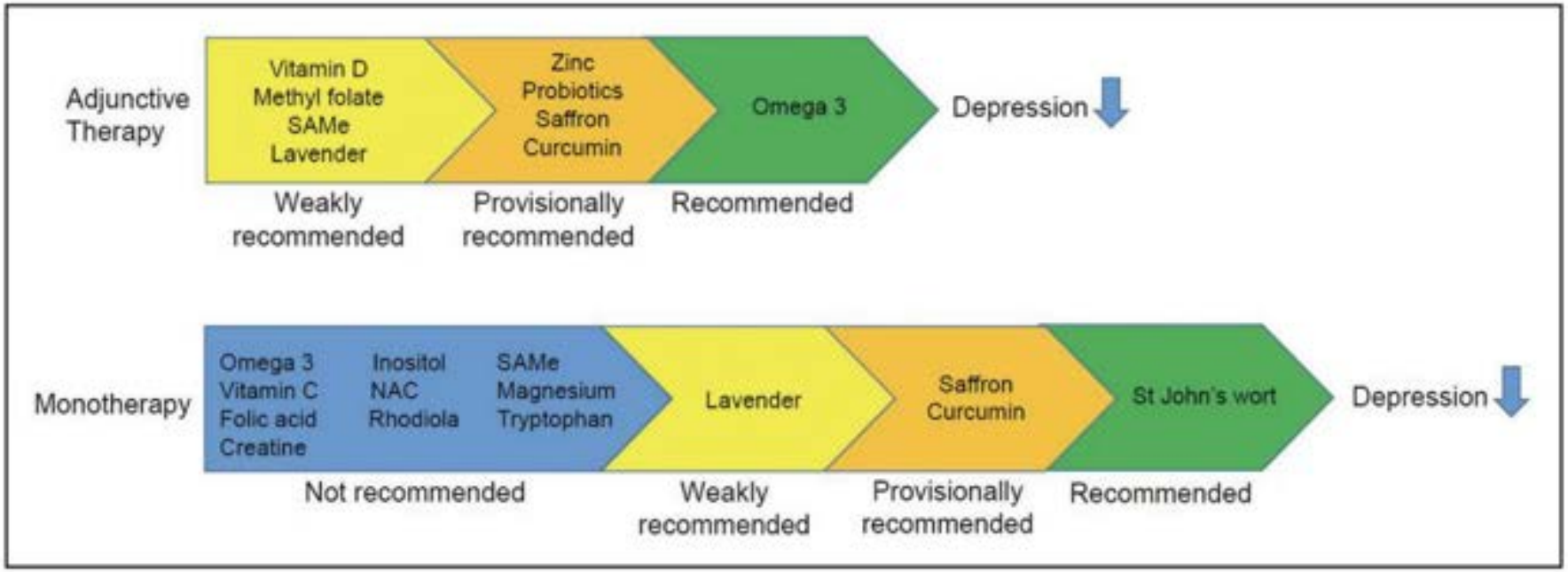
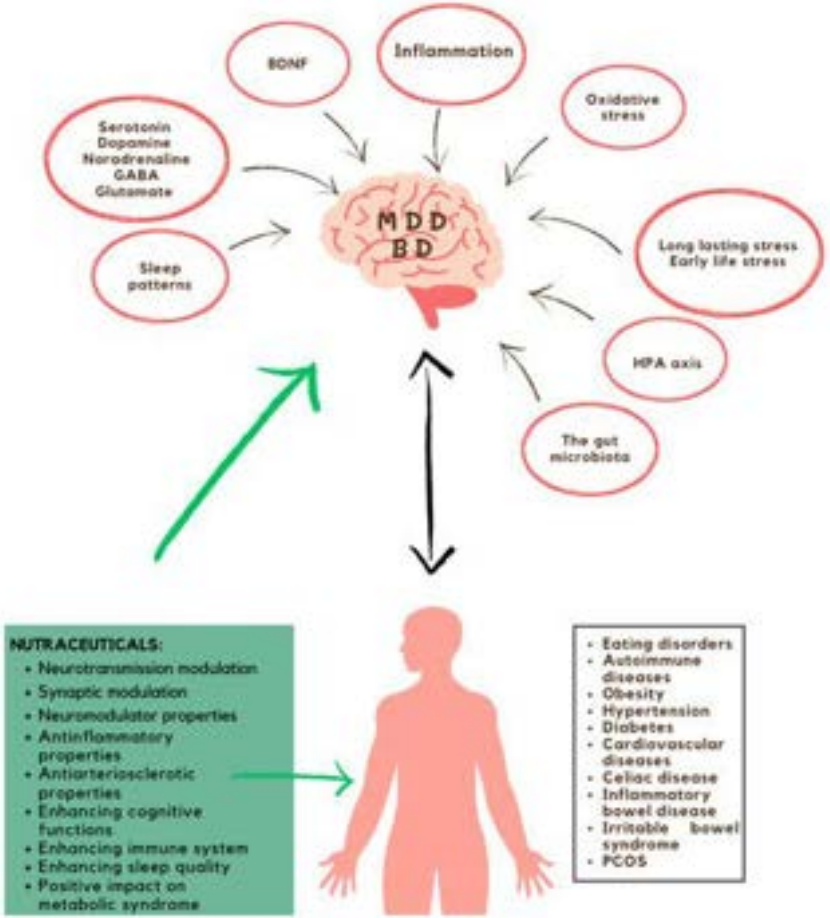


Additional evidence-based recommendations for the treatment of depression with nutraceuticals[14]



Summary of nutraceuticals' proposed impact on the mechanisms involved in the development of mood disorders.[15]

Supplement	Proposed MoA
Vitamin D	Participating in the neurotransmitters synthesis Enhancing the immune system Enhancing neurogenesis
Omega 3	Neurotransmission modulation Enhancing neurogenesis Enhancing immune system Preserving the integrity of the neuronal cell membrane
Probiotics	The production and control of neurotransmitters Enhancing cognitive functions Enhancing immune system Improving BDNF levels HPA axis modulation Reduction of pro-inflammatory bacteria Mitigating the adverse effect of antibiotic administration
Zinc	Neuroplasticity modulation Preserving the integrity of the neuronal cell membrane Enhancing memory and learning mechanisms Enhancing cognitive functions Increasing BDNF levels Participating in glutamatergic transmission Pro-inflammatory cytokine reduction
Magnesium	Reducing neuronal hyperexcitability Increasing the availability of GABA Counteracting the inflammation Anxiety modulation Microbiota–gut–brain axis modulation
Folate	Participating in neurotransmitters metabolism Engaging in the development of the nervous system Protection against neurotoxicity

Proposed mechanisms of action (MoA) of various nutraceuticals[15]

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Literature Limitations[10]

- small sample sizes
- poorly defined populations
- sampling and randomization problems
- blinding and design problems
- inadequate outcome measures
- weak statistical analysis
- clinically insignificant changes
- findings that cannot be replicated

Source

Counselling Patients

Source

- Understand the patient's priorities: efficacy vs tolerability
- Promote a combined approach of supplements + medications
- Highlight the limitations in testing and surveillance and quality of evidence
- Describe your personal framework for recommendations

References

Special thank you to Dr. Emily Kauwe, MD for her guidance and teaching on this topic

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