

# Nutraceuticals and phytochemicals for treating psychiatric disorders: a synopsis of the WFSBP and CANMAT 2022 clinician guidelines

*Nutracêuticos e fitoterápicos para o tratamento de transtornos mentais: uma síntese das recomendações da WFSBP e do CANMAT 2022*

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A growing abundance of clinical trial evidence assessing the efficacy and safety of plant-based 'phytochemicals' and nutrient-based 'nutraceuticals' has meant that their use has become increasingly common in the treatment of mental disorders. Between 2019 and 2021, The World Federation of Societies of Biological Psychiatry (WFSBP) and the Canadian Network for Mood and Anxiety Disorders (CANMAT) convened an international taskforce involving 31 clinicians and academics from 15 countries. These nutraceutical and phytochemical guidelines (1) were recently published, aiming to provide an evidence-informed approach to assist clinicians in making decisions regarding these agents for major psychiatric disorders.

Regarding methodology, initial taskforce discussions framed the focus of the guidelines. In summary, it was decided to centre on biological interventions due to the vast amount of literature available. It was also decided that the initial meta-reviews conducted by taskforce members (2,3) would form the basis of the guidelines (supplemented with a current additional literature search). The literature search, covering a list of over 50 nutraceuticals and phytochemicals, was initially provided to the taskforce for review. This was assessed and amended across May to September 2020. The evidence was assessed based on the priorly established WFSBP grading of evidence (4). Due to the breadth of data available, the evidence grading was amended to focus on Grade A evidence (two or more RCTs or a meta-analysis). Both the 'level of evidence' and the direction of this evidence were assessed to determine whether the intervention was given a grading of 'Recommended', 'Provisionally Recommended', 'Weakly Recommended', 'Not Currently Recommended', or 'Not Recommended'.

Findings revealed 20 phytochemicals and nutraceuticals that had been studied, indicating that their research and use is evolving a significant evidence base. The results showed that in the treatment of anxiety disorders, adjunctive or monotherapy lavender and ashwagandha were provisionally recommended, while adjunctive N-Acetylcysteine (NAC) and monotherapy galphimia were weakly recommended. Monotherapy use of kava in anxiety showed no efficacy in Generalized Anxiety Disorder, while adjunctive or monotherapy chamomile showed mixed data.

In the treatment of psychotic disorders, adjunctive and monotherapy omega-3 fatty acids showed no efficacy (in schizophrenia), and hence could not be recommended for this application. Adjunctive methylfolate and NAC were provisionally recommended for negative symptoms in schizophrenia, while adjunctive ginkgo or vitamin D were weakly recommended.

Monotherapy micronutrients and adjunctive or monotherapy vitamin D were weakly recommended in the treatment of ADHD, while adjunctive or monotherapy omega-9 fatty acids and ALC showed no efficacy. There were mixed data in the case of monotherapy or adjunctive ginkgo, omega-3 fatty acids, and zinc for ADHD.

In respect of the evidence revealed for mood disorder treatment, adjunctive methylfolate, probiotics, zinc, and monotherapy (or adjunctive) use of saffron and curcumin were provisionally recommended. Adjunctive omega-3 fatty acids and monotherapy St John's wort were

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recommended for use in mood disorders. Further, adjunctive or monotherapy use of lavender or vitamin D, monotherapy use of probiotics, and adjunctive use of SAME were all weakly recommended. Monotherapy SAME, omega-3, and adjunctive and monotherapy tryptophan, vitamin C, rhodiola, creatine, and adjunctive NAC, revealed mixed data, with a lack of confidence in the methodological quality of the evidence. Adjunctive or monotherapy magnesium, folic acid, and inositol revealed no efficacy, and thereby cannot be recommended for unipolar depression. Additionally, the use of NAC was not recommended, while omega-3 in bipolar depression had weak support.

The taskforce recognized that the underlying studies in varying meta-analyses did not adhere to the highest methodological standard. Several flaws were noted including, varied doses (with failure to standardize active constituents), small sample sizes, and in some cases insufficient communication of trial designs. Further, members of the taskforce advised caution when recommending phytoceuticals and nutraceuticals or as monotherapies for patients severe psychiatric disorders. For this reason, there was a recommendation that they be considered only when used in concert with conventional care. Despite this, it is recognized that many phytoceuticals and nutraceuticals may be safely used to augment conventional therapies, such as pharmaceutical medication or psychotherapy.

Many factors were raised as needing to be considered when prescribing these agents. These include differences in treatment history, clinical presentation, biomarker data, and regard to co-use with emerging technologies (5). With respect to brands, this can entail considerable ambiguity for both clinicians and consumers. For example, it is often challenging to determine the quality and standardization of a natural supplement. While it was outside the taskforce's remit advise on the use of particular brands, it was suggested that clinicians only recommend reputable manufacturers.

The WFSBP taskforce acknowledged that several of the nutraceuticals and phytoceuticals reviewed in the guidelines still needed to be investigated in more robust RCTs which have larger sample sizes. All of the agents were however attested to have a solid level of tolerability and safety, with their being low-risk with general over-the-counter use. Quality and constituent standardization of phytoceuticals was also raised by the taskforce as an element which currently limits confidence in respect to achieving batch-to-batch therapeutic consistency. Additionally, the taskforce communicated that such use of phytoceuticals or nutraceuticals be only recommended adjunctively within a standard medical care model (especially in cases of severe psychiatric disorders).

While select phytoceuticals or nutraceuticals are supported by positive findings from robust clinical trials, many however are only supported by modest evidence.

One important future research direction discussed, was that optimization of these agents (initially in pre-clinical studies) to potentially enhance additive or synergistic effects in combination with psychoactive pharmaceutical medications.

Based on the clinician input and the data reviewed, a range of these agents were given either a supportive or provisional recommendation across a range of various mental disorders. However, it is recognized that several had only a weak endorsement for potential use. Further, for a few of them it was not possible to reach a clear recommendation, while some other agents showed no obvious therapeutic mental health benefit. In conclusion, these guidelines should inform health professional and psychiatric practice globally. It is intended that clinicians may be able to prescribe/recommend (or not recommend) these agents with greater confidence.

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