

Natural Medications for Psychiatric Disorders

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Organization	Support	Role
Nordic Naturals	Donated drug and placebo for clinical trial	Clinical investigator
heckel medizintechnik GmbH	Donated Whole Body Hyperthermia device for clinical trial	Clinical investigator
MGH Clinical Trials Network and Institute (CTNI)	Salary support through CTNI from multiple pharmaceutical companies and NIMH	Clinical Rater and Director of Training

Objectives

- To understand the evidence base for efficacy of natural/complementary therapies in psychiatry
- To identify the risks and benefits of various natural/complementary treatments in psychiatry
- To be able to educate patients on when/how to use these treatments safely and effectively

Pros and Cons of Natural Therapies

- In 2022, 37% of Americans used CAM practices and products (NCCIH, 2022)
 - About \$30.2 billion/year out-of-pocket cost
- Global market growth from \$209 billion in 2017 to \$373 billion in 2025
- Easy access, good tolerability
- Used by many who don't respond to standard therapies
- Limited research, few rigorous studies
- “Natural” does NOT mean “safe”
- Toxicity, adverse effects, interactions
- Different preparations/purity
- Insurance does not cover them

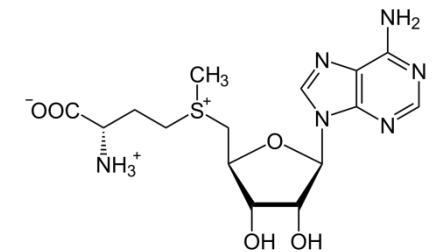


Natural Antidepressants

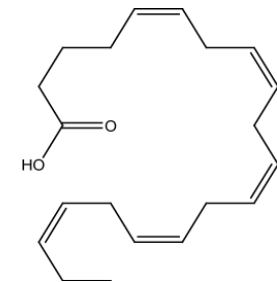
- **St John's Wort:** ~40 clinical trials; monotherapy effective; 900-1800 mg/day; watch out for photophobia and drug-drug interactions; don't combine with SSRIs (serotonin syndrome); little data on breastfeeding; applications in smoking cessation, OCD?
- **SAMe:** ~45 clinical trials; effective monotherapy and augmentation; 400-1600 mg/day (up to 3200 mg/day); no interactions; GI upset common; safe to combine; little data in pregnancy; tosylate and phytate forms more bioavailable
- **Omega-3:** >70 trials in depression as monotherapy and augmentation; a few trials in bipolar disorder; >20 meta-analyses; best for depression or depressed phase of bipolar; dosed at 1-2 g/day (EPA:DHA = 3:2 preferred); safe combined with other meds; recent evidence suggests 4 g/day may be effective in inflammatory depression; probably safe in pregnancy; limited evidence in ADHD



St John's
Wort



SAMe



EPA

Natural Anxiolytic-Hypnotics

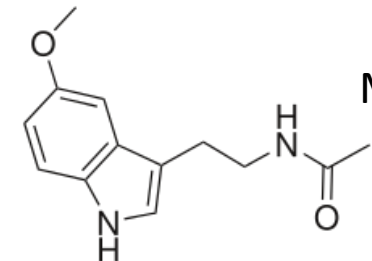
- **Kava:** >12 studies; effective for generalized anxiety; doses from 60-300 mg/day; recent negative 16-week study in N=171 with GAD, 120 mg bid (Sarris et al, 2020); cases of liver toxicity/death, but recent evidence suggests safety; use with caution and preferably for short periods
- **Valerian:** >60 studies in insomnia and anxiety; recent meta-analyses show inconsistent outcomes due to variability of preps; 450-600 mg at bedtime; little toxicity; apparently safe in pregnancy and in elderly but caution advised
- **Melatonin:** ~20 studies, 2 strong meta-analyses; effective for insomnia, particularly if circadian disturbance-based; dosed at 0.3-10.0 mg/day; start low and increase gradually; some concerns about toxicity in immunosuppressed individuals; prolonged-release form (2mg) effective in elderly; effective in children



Kava



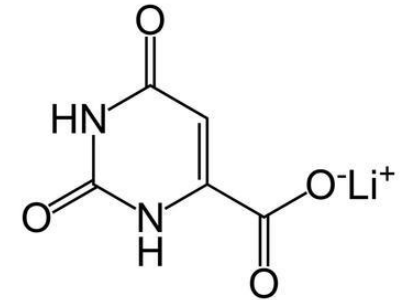
Valerian



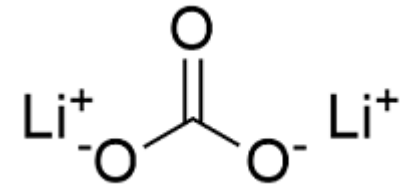
Melatonin

Possible Mood Stabilizer: Lithium Orotate ($\text{LiC}_5\text{H}_3\text{N}_2\text{O}_4$; LiOr)

- Li_2CO_3 supplanted by atypicals, but may be better long-term
- LiOr supported by Hans Nieper in 1970s
- Orotic acid: precursor/substrate of pyrimidine synthesis; mineral carrier
- May cross blood–brain barrier and enter cells easier than Li_2CO_3
 - May reduce dosage requirements and toxicity
- Interest dropped in late 1970s due to concerns about kidney toxicity
- Remains available as nutraceutical; popular alternative to Li_2CO_3



Lithium Orotate



Lithium Carbonate

Efficacy/Safety of LiOr

- No clinical trials for LiOr in bipolar disorder
- One study in alcohol use disorder
 - N=42, LiOr 150 mg daily for 6 months
 - 23 subjects remained relapse-free for 1-10 years
 - Minor adverse effects in only 8 patients
- Other studies not as encouraging
- Concerns about kidney toxicity, carcinogenic effects in rats

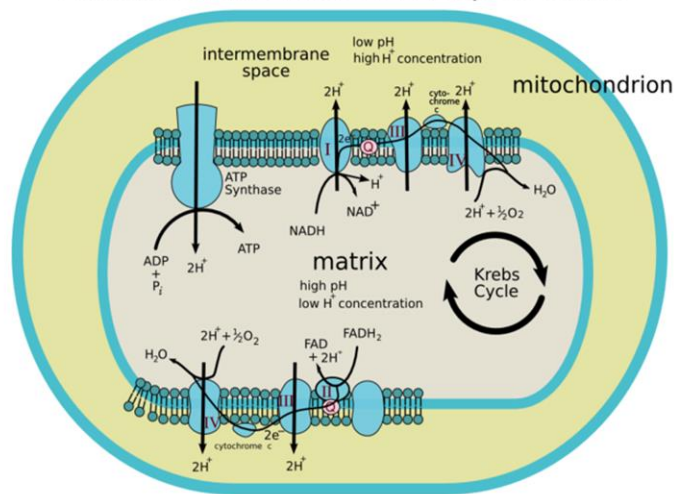
→ Not generally recommended due to limited data, no dosing guidelines

Pacholko and Bekar, Brain Beh 2021

Versatile Agents: N-Acetyl-Cysteine (NAC)

“Mitochondrial Modulator”

Mitochondrial Electron Transport Chain



Mitochondria Inner Structure

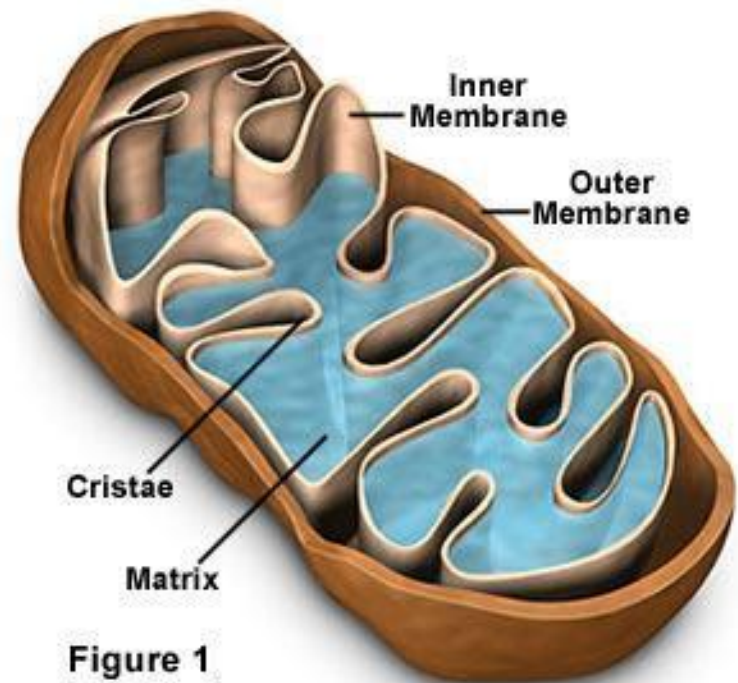
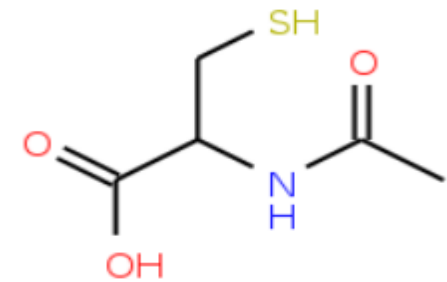


Figure 1



NAC

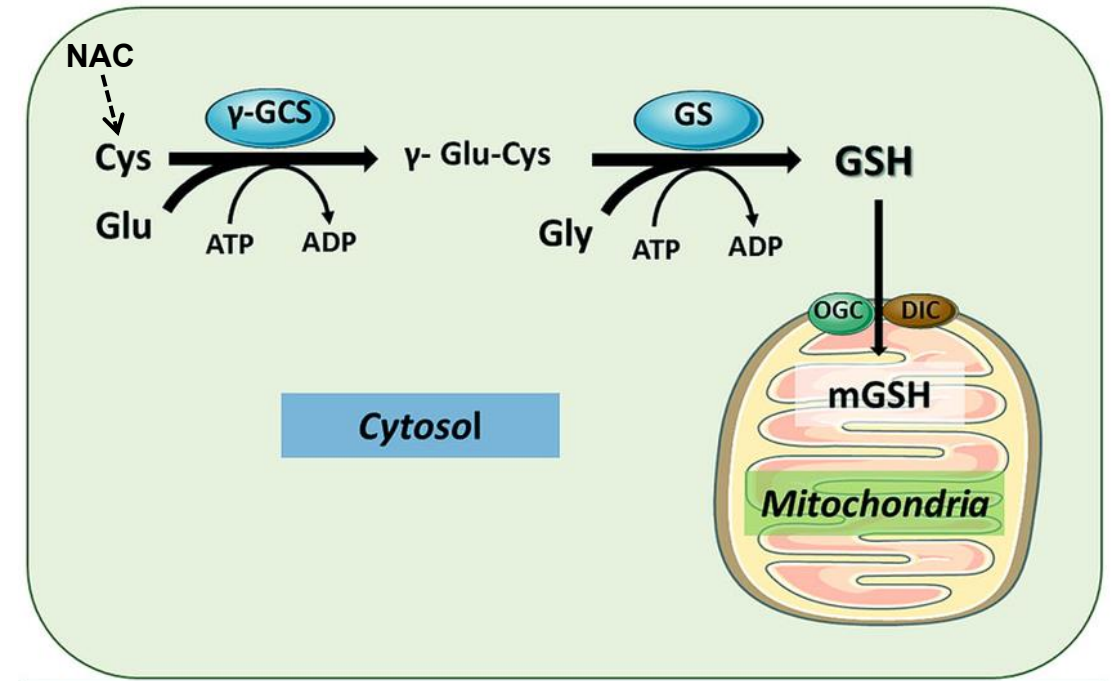
<http://people.eku.edu/ritchisong/301notes1.htm>

<http://science-quest.wikispaces.com/>

Bradlow et al, 2022

NAC: Mechanisms

- Increases glutathione (GSH) synthesis → reduces oxidative stress in mitochondrial electron transport chain
- Protects brain cells
- May have activity similar to lithium and valproate



Ribas et al, *Frontiers in Pharmacology* 2014; 5:151

NAC in Major Depressive Disorder

- 2 RCTs
- Berk et al (2014): N=269; 12 wks; 2000 mg/d
 - Significant improvement in various scales
- Porcu et al (2018): N=67; 12 wks; 1800 mg/d
 - Significant improvement in CGI

NAC in Bipolar Disorder

- 7 RCTs
- Usually BP I and BP II
- 12-24 wks; samples from N=17-181; 1000-3000 mg/d
- Results mixed
- Degree of inflammation may impact on efficacy
- One positive open study in pediatric bipolar disorder (Wozniak et al, 2022)

NAC: Other Applications

- Mixed evidence in OCD spectrum disorders at 800-3000 mg/d
 - OCD, trichotillomania, onychophagia, excoriation disorder
- Mostly positive evidence in schizophrenia at 600-3600 mg/d
- Mostly negative evidence in substance use disorders and gambling at 1200-3600 mg/d
- Some evidence of benefit in neurologic disorders at doses from 500-2400 mg/day
 - Autism Spectrum Disorder, Alzheimer's, Traumatic Brain Injury, Williams Syndrome

Versatile Agents: Rhodiola Rosea

- Found in mountains of Europe and Asia
- Used for centuries in traditional medicine of Asia, Scandinavia, Eastern Europe
- “Adaptogen” -- increases resistance to chemical, biological, and physical stressors
 - Stimulates nervous system
 - Enhances physical and mental performance
 - Prevents altitude sickness
 - Alleviates fatigue, stress, depression, sexual dysfunction



Rhodiola

Efficacy and Mechanisms

- Studied in Russia and Scandinavia for >40 years
 - Most reports not yet translated to English
- Multiple active ingredients
 - Adaptogenics (rosavins, tyrosol), antioxidants (flavonoids), monoamine modulation, MAO-A and B inhibition, opioid-like effects
- ≥ 4 controlled trials support efficacy in depression and anxiety as well as cognition
 - Doses from 100-680 mg/day

Recent RCT of Rhodiola for MDD

- Mild-to moderate MDD; N=100; 12 weeks
 - Group A: Sertraline ('high dose') + PBO
 - Group B: Sertraline and Rhodiola 600 mg/day
 - Group C: Sertraline + Rhodiola 300 mg/day
- All had statistically significant reduction in HAM-D, BDI, CGI
 - Improvement significantly greater for group B vs. groups C and A
- Higher doses of Rhodiola may be best

Gao et al. J Affect Disord 2020; 265:99-103.

Safety and Tolerability

- SFX mild, uncommon
 - Allergy, irritability, fatigue, unpleasant sensations
 - Especially at high doses
 - Insomnia/vivid dreams; take early in day
 - Best on empty stomach, before meals
- No interactions with other drugs
 - Combined with TCAs; reduces TCA side effects
- No data on pregnancy or bipolar cycling
 - Use with caution

For Dementia: Ginkgo Biloba

- Cognition enhancer; slows cognitive decline
- Approx. 30 studies in Alzheimer's, mostly supportive
- Contains flavonoids and terpene lactones
- Stabilizes neuronal membranes, scavenges free radicals
- Meta-analyses and systematic reviews suggest efficacy (Weinmann et al, 2010; Brondino et al, 2013; Hashiguchi et al, 2015; Liu et al, 2019)
- Cholinesterase inhibitors somewhat more effective but not as well tolerated; may be combined (Mazza et al, 2006; Yancheva et al, 2009; Cornelli, 2010; Nasab et al, 2012; Canevelli et al, 2014)
- No clear preventive effects (Andrade et al, 2009)



Ginkgo leaf

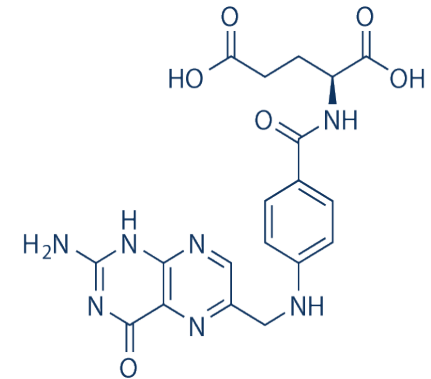
Clinical Recommendations

- Suggested dose = 120-240 mg/day
- Best started early; full assessment may require 1 year
- No data on longer-term impact
- May alleviate antidepressant-induced sexual dysfunction
- Side effects: mild GI upset, headache, irritability, dizziness, seizures in epileptic disorders
- Inhibits platelet activating factor (PAF); may cause bleeding in patients on anticoagulants or having surgery
 - No increased risk of bleeding, based on hemostatic outcomes in meta-analysis of 18 trials (Kellermann et al, 2011)
 - PAF inhibition may increase risk of bleeding in pregnancy

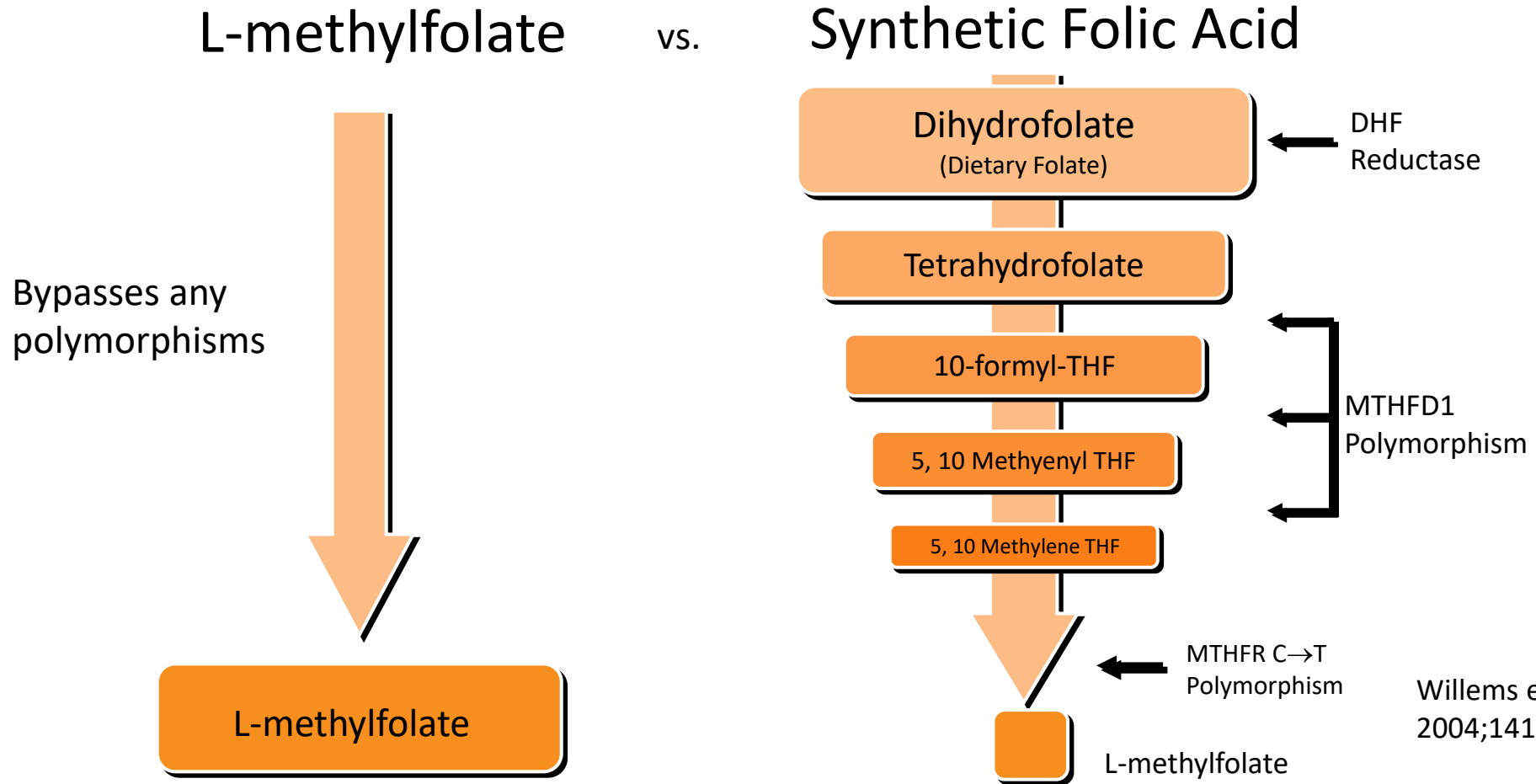
For Dementia (and Depression): Folic Acid

- Association between low folic acid and depression, dementia
- High dietary intake associated with lower risk of dementia
- Low folate associated with worse cognitive function, higher risk of cognitive decline
- Low folate associated with decreased chance of response to antidepressants
- May protect brain via decreased homocysteine

Folic Acid



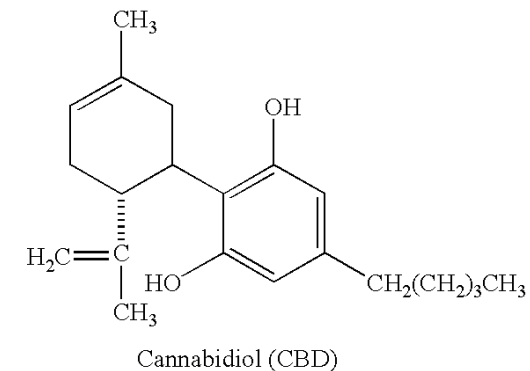
L-methylfolate/Deplin



Willems et al. Br J Pharmacol. 2004;141:825-30.

Cannabidiol (CBD)

- Cannabinoid constituent of cannabis
- Often supplied as oil containing only CBD (no THC), a full-plant CBD-dominant hemp extract oil, capsules, dried cannabis, or liquid solution
- Approved for MS pain (Canada, Sweden), childhood epilepsy disorders (USA)
 - Sold openly in most states
- Multiple mechanisms, including serotonergic
- Side effects
 - Sleepiness, decreased appetite, diarrhea, fatigue, malaise, weakness, insomnia; no intoxicating effects



Cannabis Products: Systematic Review

- Possible reduction of social anxiety
- Mixed (mainly positive) evidence for adjunctive use in schizophrenia
- Limited evidence in insomnia and PTSD
- No evidence of benefit for depression from high THC therapeutics or for CBD in mania
- Some potential efficacy for an oral cannabinoid/terpene combination in ADHD

Sarris et al. BMC Psychiatry 2020; 20:24. doi: 10.1186/s12888-019-2409-8.

CBD Recommendations

- Caution with high-THC formulations
 - esp. in youth, and anxiety or psychotic disorders
- Slow titration
- Regular assessment
- Caution in cardiovascular, respiratory disorders, pregnancy and breast-feeding
- Consider occupational safety as well

Sarris et al. BMC Psychiatry 2020; 20:24. doi: 10.1186/s12888-019-2409-8.

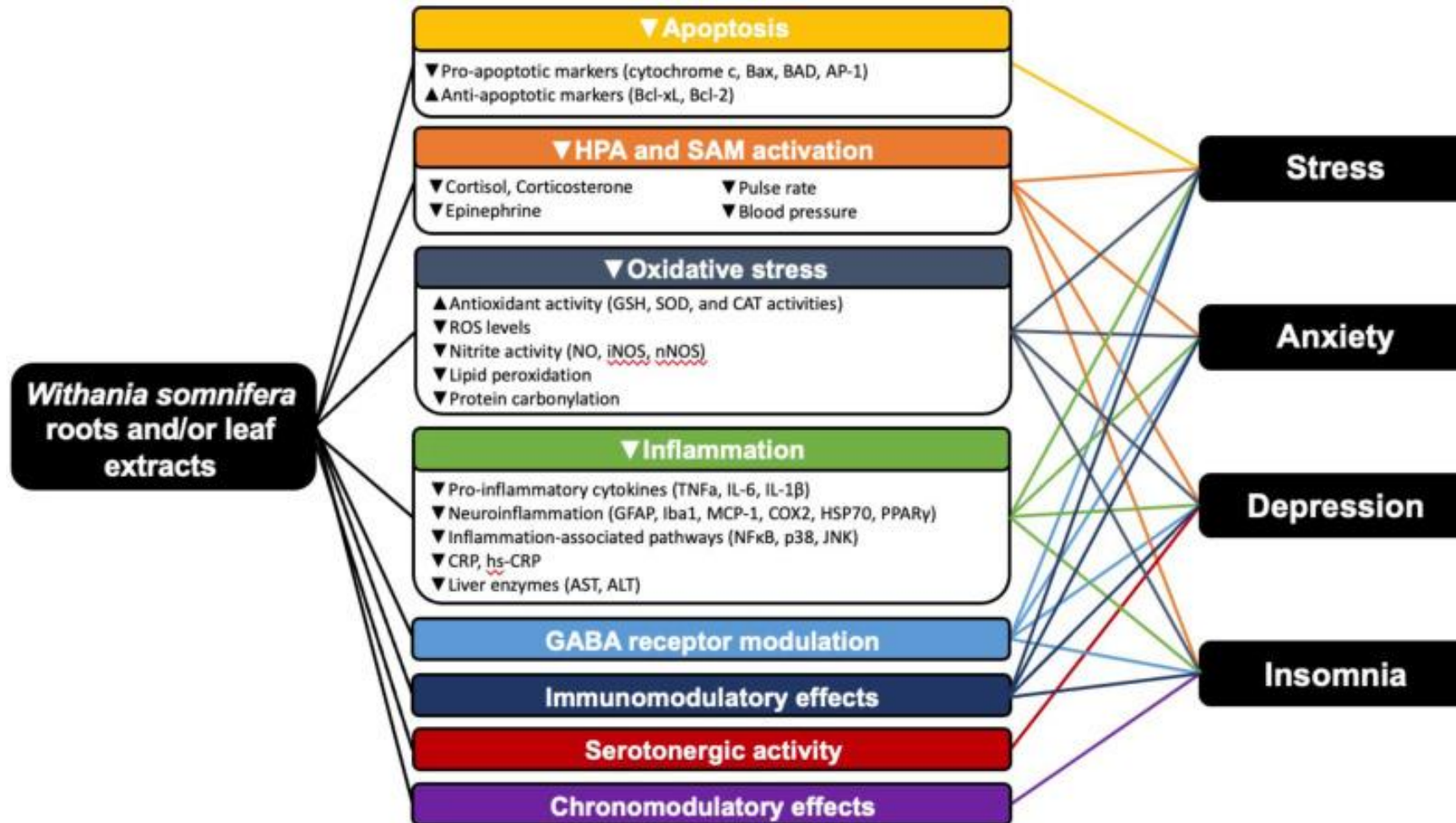
Ashwagandha (ASW)

- Extract of *Withania somnifera* (Indian winter cherry plant)
- Dozens of chemical components
 - benefits and risks associated of each is unknown
- Improves exercise capacity, sleep quality, cognitive functioning post TBI and/or in high risk of dementia
- May benefit anxiety, depression, OCD, schizophrenia, ADHD, SUD/withdrawal
- Side effects: diarrhea, nausea and vomiting, due to direct irritation to intestinal mucosa



D'Cruz & Andrade, 2022

Mechanisms of Action



Speers et al, 2021

Anxiety and Stress

- Review/meta-analysis of 12 papers (N=1002; ages 25-48)
- ASW supplementation significantly reduced anxiety and stress levels compared to PBO
- For stress: max 300-600 mg/d
- For anxiety: max 12,000 mg/d
- But overall quality of studies was less than optimal

Akhgarjand et al, 2022

Anxiety, Depression, and Insomnia

- 7 human trials reviewed (125-1000 mg/d)
 - also several animal studies
- Improved symptoms of depression and insomnia,
 - too few studies to determine with certainty
- Safety and tolerability good
- Significant variability in WS extracts prevents consensus on optimum preparation or dosage

Speers et al, 2021

Stress, Anxiety, Depression

- Dose-response meta-analysis of 22 RCTs
 - Significant improvements in stress, anxiety, and depression
 - Dose-response relationship for stress
- Doses range from 240–600 mg/day of standardized root extract over 8–12 weeks
- Consistent reductions in HAM-A, PSS, and GAD-7 scores versus placebo

Alsanie et al, 2026

Limitations

- Most trials are small (30–70 participants), short-duration (60–90 days), and predominantly conducted in India
- Significant heterogeneity in extract preparations and dosing
- No consensus on optimal regimen
- Studies primarily enrolled individuals with mild-to-moderate or subclinical symptoms, not patients with diagnosed psychiatric disorders on standard treatment
- High heterogeneity in meta-analyses raises concerns about consistency

Safety

- **Hepatotoxicity:** Case reports of liver injury, at least one case requiring liver transplant
- **Thyroid effects:** Increased T4 levels associated with thyrotoxicosis
 - Potentially dangerous in hyperthyroid patients or those on thyroid medication
- **Endocrine disruption:** Testosterone elevation, potential adrenal suppression
- Short-term safety appears reasonable
 - Large RCT (n=1002) of 600 mg/day for 8 weeks found no serious adverse events
 - Systematic review of 23 trials (n=2317) confirmed normal laboratory parameters at doses up to 600 mg/day for up to 180 days
- No long-term safety data
- Herb-drug interactions poorly characterized, particularly with psychotropics
- Lack of standardization, contaminants vary widely
- → Caution generally advised

Non-Pharmacologic Interventions: Light Therapy for Seasonal Depression

- Seasonal Affective Disorder (SAD), circadian disturbances (jet lag, shift work)
- Box containing 10,000 lux full spectrum or cool white fluorescent lights behind UV shield
- 30 min-2 hrs per day, 2X/d, for 2-4 weeks
- Many studies (small samples)
 - 53% remission rate
 - 43% of moderate-severe SAD attained remission
- Combination with antidepressants may be optimal





Safety

- Side effects
 - Headache
 - Eyestrain
 - Agitation/Irritation
 - Nausea
- Reducing side effects
 - Make sure light hits eyes *indirectly*
 - Reduce treatment time
 - Move farther from light box
 - Take breaks between sessions
 - Change time of day of use

- **Relative Contraindications**
 - Retinal disease
 - Medications or medical conditions (e.g., Lupus) that increase light sensitivity
 - Mania or hypomania can be triggered by light therapy in bipolar disorder



Non-Pharmacologic Interventions: Exercise for Depression

- Usually recommended as adjunctive treatment
 - Optimal form and dose still unclear
 - Meta-analysis of four types (**aerobic, resistance, mixed, mind-body**) and dose-response relationships
 - 46 RCTs (N=3164, 18+ yo with MDD)
 - Aerobic > Mind-Body > Mixed > Resistance > Control
 - U-shaped curve between dose and depressive symptoms
 - Vigorous exercise at least 45-60 minutes per week is about the minimum for effect
 - Optimal response between 2-3 hours of vigorous exercise per week
- Carefully select appropriate type and dose based on patient characteristics, needs, and concomitant interventions

Tian et al, 2024

Synthesis: CANMAT Recommendations

Table 3. Summary of Recommendations for Natural Health Products.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
St. John's wort	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Omega-3	Mild to moderate MDD	Second line	Level 1	Monotherapy or adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
SAM-e	Mild to moderate MDD	Second line	Level 1	Adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Acetyl-L-carnitine	Mild to moderate MDD	Third line	Level 2	Monotherapy
<i>Crocus sativus</i> (saffron)	Mild to moderate MDD	Third line	Level 2	Monotherapy or adjunctive
DHEA	Mild to moderate MDD	Third line	Level 2	Monotherapy
Folate	Mild to moderate MDD	Third line	Level 2	Adjunctive
<i>Lavandula</i> (lavender)	Mild to moderate MDD	Third line	Level 3	Adjunctive
Inositol	Mild to moderate MDD	Not recommended	Level 2	
Tryptophan	Mild to moderate MDD	Not recommended	Level 2	
<i>Rhodiola rosea</i> (roseroot)	Mild to moderate MDD	Not recommended	Insufficient evidence	

DHEA, dehydroepiandrosterone; MDD, major depressive disorder; SAM-e, S-adenosyl-L-methionine.

Ravindran et al, Can J Psychiatry 2016; 61: 576-587

CANMAT Recommendations (cont'd)

Table 2. Summary of Recommendations for Physical and Meditative Treatments.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
Exercise	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 1	Adjunctive
Light therapy	Seasonal (winter) MDD	First line	Level 1	Monotherapy
	Mild to moderate nonseasonal MDD	Second line	Level 2	Monotherapy and adjunctive
Yoga	Mild to moderate MDD	Second line	Level 2	Adjunctive
Acupuncture	Mild to moderate MDD	Third line	Level 2	Adjunctive
Sleep deprivation	Moderate to severe MDD	Third line	Level 2	Adjunctive

MDD, major depressive disorder.

Ravindran et al, Can J Psychiatry 2016; 61: 576-587

Conclusions: Who Should Use Natural/Complementary Therapies?

- Mildly ill people with a strong interest in natural remedies who don't mind the cost
- People who have tried most everything else and have not responded, or had many side effects
 - But they are often the most difficult to treat
- Be careful with
 - Pregnant or breastfeeding women
 - Patients on multiple medications
 - Beware drug-drug interactions!

Questions?

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