Q/Which nutritional therapies are safe and effective for depression?

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EVIDENCE-BASED ANSWER

A/ **St. John's wort** is effective for short-term relief of mild to moderate depression (strength of recommendation [SOR]: **A**; 1 systematic review). Its safety profile is superior to older antidepressants; data comparing it with newer antidepressants (such as selective serotonin reuptake inhibitors) are limited (SOR: **A**, 1 systematic review).

A small but statistically significant clinical benefit has been demonstrated for saffron, lavender, borage, dan zhi xiao yao (SOR: **B**, 1 systematic review and 3 randomized controlled trials), folate (SOR: **A**, 1 systematic review), and S-adenosylmethionine (SAMe) (SOR: **A**, 1 meta-analysis and 1 systematic review). Most trials of these preparations were short and small, limiting the ability to detect adverse effects.

Tryptophan (SOR: **A**, 1 systematic review) and 5-hydroxytryptophan (5-HTP) (SOR: **A**, 1 systematic review) have demonstrated superiority over placebo in alleviating symptoms of depression, but concerns exist about their safety.

N-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) and omega-3 fatty acids don't appear effective in treating major depressive disorder (SOR: **A**, 1 systematic review.)

St. John's wort is safer than older antidepressants, but hasn't been compared extensively with newer drugs, such as SSRIs.

Evidence summary

TABLE W1 (see page 100a) summarizes study results and recommendations for nutritional therapies for depression.[1-16]

St. John's wort works as well as standard antidepressants

A recent Cochrane review suggested that St. John's wort is more effective than placebo in patients with mild to moderate depression and as effective as standard antidepressants.[1]

Other supplements also have benefits

A systematic review of 4 small randomized controlled trials (RCTs) suggested that **saffron** (30 mg) is superior to placebo in treating short-term depression (6 weeks). Treatment and outcomes were equivalent to fluoxetine and imipramine.[2] A later RCT yielded results consistent with the systematic review.[3]

Combined **lavender tincture** (60 drops per day) and imipramine were more effective than imipramine alone in 1 small RCT.[4]

Borage, a traditional Persian medicine, was superior to placebo in reducing depressive symptoms in 1 small RCT.[2]

Dan zhi xiao yao, a traditional Chinese medicine, was as effective as the tricyclic antidepressant maprotiline in 1 small RCT.[2]

Three RCTs suggested that **folate** may be used to supplement conventional treatments for depression, but it isn't clear whether this would help patients with normal folate levels.[5]

A meta-analysis of 13 controlled clinical trials and a later systematic review of 11 articles including 2 RCTs concluded that **SAMe** is more effective than placebo and as efficacious as tricyclic antidepressants in treating major depression in adults. However, further trials are needed to answer questions about absorption, mechanism of action, and bioavailability.[6,7]

Tryptophan's benefit comes with risk

In a Cochrane review of 2 RCTs, tryptophan

and 5-HTP were superior to placebo in alleviating symptoms of depression. However, some published case reports have linked tryptophan use to potentially fatal eosinophilia-myalgia syndrome.[8]

No clear evidence for inositol or n-3 PUFAs

A Cochrane review of 4 small double-blind RCTs investigating inositol as a nutritional supplement in depression treatment failed to find clear evidence of therapeutic benefit.[9]

Three RCTs demonstrated significantly higher red blood cell membrane levels of n-3 PUFAs in nondepressed patients compared with depressed patients.[10] However, a systematic review of 12 RCTs failed to demonstrate any benefit of n-3 PUFA supplementation over placebo in treating depressed mood.[11] The authors concluded that larger trials are needed to demonstrate efficacy because of marked heterogeneity among the RCTs.

Safety issues. A recent Cochrane review found fewer adverse effects for St. John's wort than tricyclic antidepressants.[1] The most common adverse reactions were sensitivity to light, skin symptoms, gastrointestinal symptoms, and agitation. Data comparing St. John's wort with newer antidepressants are lacking.

St. John's wort does have pharmacokinetic interactions and should not be taken concurrently with other antidepressants, immunosuppressants, anti-HIV drugs, coumarin-type anticoagulants, or certain antineoplastic agents.[17]

Reviews of meta-analyses, case reports, population studies, RCTs, and other literature have reported virtually no adverse effects for PUFAs;[18] trials investigating saffron, lavender, borage, dan zhi xiao yao, folate, SAMe, and inositol also reported no safety concerns. However, the size and duration of these studies limit their ability to detect significant problems.[2,5,6,9] As previously noted, concerns exist regarding an association between tryptophan and eosinophilia-myalgia syndrome.[8]

A small but statistically significant clinical benefit has been found for saffron, lavender, borage, dan zhi xiao yao, folate, and SAMe.

Recommendations

The World Federation of Societies of Biological Psychiatry doesn't recommend St. John's wort for moderate to severe depression, but suggests it can be considered for treating mild to moderate depressive episodes provided the prescriber considers potential pharmacokinetic interactions with other medications and understands possible variations in purity and potency of extracts.[19] The Federation also states that St. John's wort is an alternative for patients reluctant to take traditional antidepressants. JFP

References

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TABLE W1

What the studies say about nutritional therapies for depression

Supplement	Study type	Number of subjects	Comparison group	Outcome measure	Results	Conclusion	SOR
Borage (*Echium amoenum*)	1 small RCT	35[2,16]	Placebo	HAM-D	Improved HAM-D scores significantly at week 4 (borage 18.3 ± 3.9 vs placebo 21.9 ± 3.9; t=2.51; P=.02); no significant difference at Week 6[2,16]	Superior to placebo in reducing symptoms of depression	B
Dan zhi xiao yao	1 small RCT	63[2]	Maprotiline	HAM-D, SDS, SAS, scale for traditional Chinese medicine syndrome and symptom differentiation	87% depression reduction (dan zhi xiao yao) vs 84% depression reduction (maprotiline)	As effective as maprotiline in treating depression	B
Folate	Cochrane review of 3 RCTs	247[5]	Studies 1 and 2: folate vs folate + other treatment (Study 1: low folate levels; Study 2: normal folate levels) Study 3: folate vs trazodone (normal folate levels)	HAM-D	Superior to placebo (NNT=5, defined as 50% reduction in HAM-D); comparable to trazodone (RR=0.97; 95% CI, 0.14-2.01)[7]	May have role as supplement to other treatments for depression Efficacy unclear in patients with normal folate levels	A
Inositol	Cochrane review of 4 RCTs	141[9]	Studies 1-3: placebo plus conventional antidepressants Study 4: placebo only	HAM-D, MADRS	Pooled estimate of effect of all 3 studies (SMD= –0.08; 95% CI, –0.45 to 0.30)	No clear evidence of therapeutic benefit	A
Lavender (*Lavandula angustifolia*)	1 small RCT	45[4]	Imipramine	HAM-D	Imipramine plus lavender showed significant effect compared with imipramine alone (F=26.87; DF=3.01; P<.0001)	Synergistic effect suggested when used with imipramine	B

BDI, Beck Depression Inventory; CI, confidence interval; DF, degrees of freedom; ES, effect size; F, F statistic; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MUFAs, monounsaturated fatty acids; n-3 PUFAs, n-3 long-chain polyunsaturated fatty acids; NNT, number needed to treat; OR, odds ratio; PUFAs, polyunsaturated fatty acids; RBC, red blood cell; RCT, randomized controlled trial; RR, relative risk; SAS, self-rating anxiety scale; SDS, self-rating depression scale; SFAs, saturated fatty acids; SMD, standard weighted mean difference; SOR, strength of recommendation; SSRI, selective serotonin reuptake inhibitor.

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TABLE W1

What the studies say about nutritional therapies for depression CONTINUED

Supplement	Study type	Number of subjects	Comparison group	Outcome measure	Results	Conclusion	SOR
n-3 long-chain poly-unsaturated fatty acids	Systematic review including 3 RCTs;[10] meta-analysis of 12 RCTs[11]	102[10] 1032[11]	Various comparison groups included	Serum SFAs, MUFAs, PUFAs; RBC membrane levels n-3 PUFAs[2] HAM-D, BDI[3]	Systematic review:[10] Study 1: n=30; ES=3.61 Study 2: n=24; ES=1.2 Study 3: n=48; ES=2.43 Meta-analysis:[11] Pooled ES=0.13; 95% CI, 0.01-0.25	Significantly higher RBC membrane levels of n-3 PUFAs in nondepressed vs depressed patients[10] No significant effect for supplementation[11] Larger trials with adequate power needed[2,3]	A
S-adenosyl-methionine (SAMe)	Meta-analysis of 13 RCTs,[6] systematic review including 2 RCTs[7]	399[6] 78[7]	Placebo and conventional antidepressants	HAM-D	NNT=2.5 for HAM-D decrease of ≥25%;[6] NNT=6.25 for HAM-D decrease of ≥50%[6]	May have role in treatment of major depression Further trials are needed to address unanswered questions about absorption, mechanism of action, and bioavailability[7]	A
Saffron (*Crocus sativus*)	Systematic review of 4 small RCTs, 1 later RCT	30[12] 40[13] 40[14] 40[15] 40[3]	Imipramine[12] Placebo[13,15] Fluoxetine[5,14]	HAM-D	Systematic review: Study 1: imipramine and saffron equally efficacious (F=2.91; P=.09)[12] Study 2: Improved HAM-D scores: −12.20 ± 4.67 (saffron) vs −5.10 ± 4.71 (placebo) (P<.0001)[13] Study 3: Improved HAM-D scores: saffron petal −12.00 ± 4.10; fluoxetine −13.50 ± 4.91; difference between 2 treatments not significant (P=.27)[14] Study 4: Improved HAM-D scores: −14.01 ± 5.53 (saffron petal) vs −5.05 ± 4.63 (placebo) (P<.0001)[15] Study 5:[5] NNT=10	Efficacy of extract and petal suggested to treat mild to moderate depression Large-scale trials are warranted	B

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TABLE W1

What the studies say about nutritional therapies for depression CONTINUED

Supplement	Study type	Number of subjects	Comparison group	Outcome measure	Results	Conclusion	SOR
St. John's wort (*Hypericum perforatum L.*)	Cochrane review of 29 RCTs	5489[1]	SSRIs, tri/tetracyclic antidepressants, placebo	Responder rate ratio	St. John's wort vs placebo: 9 larger trials: RR=1.28; 95% CI, 1.10-1.49[1] 9 smaller trials: RR=1.87; 95% CI, 1.22-2.87[1] St. John's wort vs SSRIs: 12 trials: RR=1.00; 95% CI, 0.90-1.11[1] St. John's wort vs tricyclics: 5 trials: RR=1.02; 95% CI, 0.90-1.15[1]	Effective for treating mild to moderate depression	A
Tryptophan and 5-hydroxy-tryptophan (5-HTP)	Cochrane review of 2 RCTs	64[8]	Placebo	HAM-D	NNT=2.78 vs placebo (OR=4.1; 95% CI, 1.28-13.15	Superior to placebo Insufficient evidence regarding safety	A