EMERGING RESEARCH: Key Nutraceuticals for the Treatment of Some Common Psychiatric Disorders

Integrative Medicine Education & Research Group  May 11 2011

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The University of Melbourne
Department of Psychiatry;
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Swinburne University
Overview of Presentation

Focus on mood and anxiety disorders

- Common mechanisms of action
- Omega-3
- S-adenosyl methionine (SAMe)
- St John’s wort (*Hypericum perforatum*)
- Kava (*Piper methysticum*)
Some Publications in the Area

Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence

Journal of Psychiatric Research

Review

Adjuvant use of nutritional and herbal medicines with antidepressants, mood stabilizers and benzodiazepines

Jerome Sarris\textsuperscript{a, b, *}, David J. Kavanagh\textsuperscript{b}, Gerard Byrne\textsuperscript{a}

Major depressive disorder and nutritional medicine: a review of monotherapies and adjuvant treatments

* 2010 Vol. 44, pp32-41

Jerome Sarris, Niikee Schoendorfer, and David J Kavanagh

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 15, Number 8, 2009, pp. 1–10
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DOI: 10.1089/acm.2009.0066

Kava and St. John’s Wort: Current Evidence for Use in Mood and Anxiety Disorders

THE JOURNAL OF CLINICAL PSYCHIATRY

Mechanisms of Action in Mood/Anxiety Disorders

Modulation of monoamine activity
(reuptake, synthesis, receptor binding)
  e.g. St John’s wort, SAMe, 5-HT

GABA/Glutamatergic activity
  e.g. Kava, N-Acetyl cysteine

Anti-inflammatory effects or cytokine alteration
  e.g. Omega 3 fatty acids

Calcium/Sodium channel regulation
  e.g. Kava, Magnesium

Enhanced methylation
  ↑ one-carbon cycle
  e.g. SAMe, Folic acid

Neuroendocrine system modulation
  e.g. St John’s wort, Rhodiola, Ginseng

Enzyme and cell signaling modulation
  e.g. Omega 3 fatty acids

Anti-oxidant effects
  e.g. N-acetyl cysteine
Omega-3 fatty acids

**Thymoleptic effect:**
- Reuptake inhibition of serotonin & dopamine
- Modulation of secondary messengers
- Enhanced cell membrane fluidity
- Anti-inflammatory effects

**Mood stabilisation:**
- Modulation of cell-signalling pathways via effects such as T(2) marker reduction (increasing cell membrane fluidity)
- Select cytokine and arachidonic acid inhibition, and phosphoinositide (PI)-protein kinase C antagonism (down-regulation)

(Sarris, Mischoulon, Schweitzer 2011)
Forest plot examining the effect of the type of ω3 LC-PUFA supplementation employed on the reduction in depressive symptoms.

**Group** | **Study [reference]** | **Statistics for each study** | **Relative weight**
--- | --- | --- | ---
**Mainly** | Grenyer et al. 2007 [47] | Std diff: 0.170; Lower limit: -0.262; Upper limit: 0.601 | 26.16
**DHA** | Rees et al. 2008 [51] | Std diff: -0.352; Lower limit: -1.127; Upper limit: 0.423 | 13.36
| Rogers et al. 2008 [52] | Std diff: -0.022; Lower limit: -0.288; Upper limit: 0.243 | 35.69
| Silvers et al. 2005 [53] | Std diff: 0.611; Lower limit: 0.153; Upper limit: 1.069 | 24.79
| **Overall effect size** | | Std diff: 0.141; Lower limit: -0.195; Upper limit: 0.477 | 7.68

**EPA** | Behan et al. 1990 [44] | Std diff: -0.761; Lower limit: -1.287; Upper limit: -0.236 | 4.01
| da Silva et al. 2008 ω3 [42] | Std diff: -1.175; Lower limit: -2.359; Upper limit: 0.009 | 4.15
| da Silva et al. 2008 ω3 + AD [42] | Std diff: -1.621; Lower limit: -2.769; Upper limit: -0.472 | 7.95
| Fontani et al. 2005 [68] | Std diff: -0.226; Lower limit: -0.710; Upper limit: 0.258 | 7.72
| Freeman et al. 2008 [57] | Std diff: 0.507; Lower limit: -0.012; Upper limit: 1.026 | 6.40
| Hallahan et al. 2007 [41] | Std diff: -0.954; Lower limit: -1.677; Upper limit: -0.232 | 5.54
| Hirashima et al. 2004 [69] | Std diff: 0.151; Lower limit: -0.715; Upper limit: 1.016 | 8.73
| Lucas et al. 2009 [58] | Std diff: -0.083; Lower limit: -0.441; Upper limit: 0.275 | 4.79
| Nemets et al. 2006 [43] | Std diff: -1.353; Lower limit: -2.361; Upper limit: -0.345 | 6.15
| Stoll et al. 1999 [38] | Std diff: -1.016; Lower limit: -1.778; Upper limit: -0.254 | 4.65
| Su et al. 2008 [40] | Std diff: -0.877; Lower limit: -1.592; Upper limit: -0.162 | 9.18
| van de Rest et al. 2008 0.4g [59] | Std diff: 0.089; Lower limit: -0.184; Upper limit: 0.363 | 9.17
| van de Rest et al. 2008 1.8g [59] | Std diff: 0.021; Lower limit: -0.255; Upper limit: 0.297 | 7.43
| Warren et al. 1999 [55] | Std diff: 0.490; Lower limit: 0.073; Upper limit: 1.053 | 7.43
| **Overall effect size** | | Std diff: -0.446; Lower limit: -0.753; Upper limit: -0.138 | (Martins 2009)
Omega-3 in bipolar disorder: A meta-analysis

- Studies using augmentation omega-3 have been conducted
- Evidence indicates a positive effect which often is not significant due potentially to small sample sizes
- Meta-analytic pooling of the studies may be of benefit

- Methods: PubMed, CINAHL, Web of Science and Cochrane Library databases were searched during mid 2010 for:
  - Randomized, controlled studies, four weeks or longer
  - Omega-3 in combination with pharmacotherapies or treatment as usual to treat BD depression and mania

(Sarris, Mischoulon, Schweitzer 2011)
## Studies Included in Meta-analysis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study²</th>
<th>Dose</th>
<th>Design</th>
<th>Duration (wk)</th>
<th>Patients (n)</th>
<th>Age (mean)</th>
<th>Sample</th>
<th>Co-medication</th>
<th>Outcomes³</th>
<th>Results</th>
<th>Quality analysis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaxseed oil</td>
<td>Graciouš</td>
<td>Flaxseed oil capsules titrated to maximum of 6.6 g α-lNA vs. placebo</td>
<td>Ran DB PC</td>
<td>16</td>
<td>51</td>
<td>13</td>
<td>DSM-IV BD I/II</td>
<td>Stable psychotropic medication</td>
<td>CDRS-R YMRS</td>
<td>No significant differences between groups occurred. Less drop outs on flax oil than placebo</td>
<td>9</td>
</tr>
<tr>
<td>EPA</td>
<td>Frangou 2007 ³²</td>
<td>EPA 2g per day or liquid paraffin placebo capsules</td>
<td>Ran DB PC</td>
<td>12</td>
<td>14</td>
<td>42</td>
<td>DSM-IV BD I</td>
<td>Stable lithium</td>
<td>HAMD</td>
<td>No statistically significant differences were found between the groups on HAMD</td>
<td>7.5</td>
</tr>
<tr>
<td>EPA</td>
<td>Frangou 2006³⁰</td>
<td>EPA 1g or 2g per day vs. placebo capsules</td>
<td>Ran DB PC</td>
<td>12</td>
<td>75</td>
<td>47</td>
<td>DSM-IV BD I/II</td>
<td>Stable psychotropic medication &gt; 8 weeks</td>
<td>HAMD-17 YMRS</td>
<td>A significant reduction of 1g and 2g EPA versus placebo on HAMD, but not on YMRS</td>
<td>9.5</td>
</tr>
<tr>
<td>EPA</td>
<td>Keck 2006³¹</td>
<td>EPA 6g per day or placebo capsules</td>
<td>Ran B PC</td>
<td>16</td>
<td>121</td>
<td>44</td>
<td>DSM-IV BD I/II or BD NOS</td>
<td>A stable therapeutic dose of a mood stabilizer</td>
<td>IDS-C YMRS</td>
<td>No significant differences between EPA or placebo was found on any outcome</td>
<td>8</td>
</tr>
<tr>
<td>EPA/DHA</td>
<td>Chiu 2005³⁰</td>
<td>EPA 4.4g, DHA 2.4g per day or olive oil placebo capsules</td>
<td>Ran DB PC</td>
<td>4</td>
<td>15 (14)*</td>
<td>NA</td>
<td>DSM-IV BD I (acute mania)</td>
<td>Valproate (fixed dose 20mg/kg/day)</td>
<td>YMRS</td>
<td>Reductions in both groups on YMRS from baseline but no difference between groups</td>
<td>6</td>
</tr>
<tr>
<td>EPA/DHA</td>
<td>Stoll 1999 ²⁹</td>
<td>EPA 6.2g, DHA 3.4g per day vs. placebo capsules</td>
<td>Ran DB PC</td>
<td>16</td>
<td>44 (30)*</td>
<td>43</td>
<td>DSM-IV screening for mania and depression</td>
<td>Medication treatment as usual</td>
<td>HAMD YMRS</td>
<td>Omega 3 group significantly reduced HAMD scores over placebo, but not on YMRS</td>
<td>9.5</td>
</tr>
</tbody>
</table>
Omega-3 for Bipolar Depression

Meta-analysis of six studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gracious 2010</td>
<td>0.058</td>
<td>-0.491</td>
<td>0.637</td>
<td>0.636</td>
<td>19.87</td>
</tr>
<tr>
<td>Frangou 2007</td>
<td>0.451</td>
<td>-0.610</td>
<td>1.512</td>
<td>0.405</td>
<td>7.13</td>
</tr>
<tr>
<td>Frangou 2006 1g</td>
<td>0.612</td>
<td>-0.077</td>
<td>1.302</td>
<td>0.062</td>
<td>14.44</td>
</tr>
<tr>
<td>Frangou 2006 2g</td>
<td>0.452</td>
<td>-0.226</td>
<td>1.130</td>
<td>0.191</td>
<td>14.80</td>
</tr>
<tr>
<td>Keck 2006</td>
<td>0.042</td>
<td>-0.323</td>
<td>0.406</td>
<td>0.823</td>
<td>31.38</td>
</tr>
<tr>
<td>Stoll 1999</td>
<td>1.016</td>
<td>0.254</td>
<td>1.778</td>
<td>0.009</td>
<td>12.38</td>
</tr>
</tbody>
</table>

BD depression a significant effect in favor of omega-3 (p=0.029)

Moderate effect size
Hedges g=0.34
(weighted mean difference of effect sizes)

- Heterogeneity was found via regression analysis between sample size and effect size (p=0.05)
- Funnel plot analysis revealed no significant likelihood of publication bias ($I^2=33\%; p=0.190$)

(Sarris, Mischoulon, Schweitzer 2011)
Omega-3 for Bipolar Mania

Meta-analysis of 6 studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Std diff in means and 95%CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gracius 2010</td>
<td>0.123, -0.427, 0.672, 0.661</td>
<td>18.36</td>
<td></td>
</tr>
<tr>
<td>Frangou 2006 1g</td>
<td>0.425, -0.257, 1.107, 0.222</td>
<td>11.93</td>
<td></td>
</tr>
<tr>
<td>Frangou 2006 2g</td>
<td>0.103, -0.567, 0.774, 0.763</td>
<td>12.33</td>
<td></td>
</tr>
<tr>
<td>Keck 2006</td>
<td>0.184, -0.181, 0.549, 0.323</td>
<td>41.67</td>
<td></td>
</tr>
<tr>
<td>Chiu 2005</td>
<td>0.117, -0.931, 1.166, 0.827</td>
<td>5.04</td>
<td></td>
</tr>
<tr>
<td>Stell 1999</td>
<td>0.277, -0.444, 0.997, 0.452</td>
<td>10.68</td>
<td></td>
</tr>
</tbody>
</table>

- A non-significant trend in favor of omega-3 was found (p=0.099)
- Effect size of g=0.20
- Note: The largest study by Keck et al. 2006 non-sig (p=0.323)

(Sarris, Mischoulon, Schweitzer 2011)
Clinical Recommendations

**Take home messages**

- Several adjunctive studies – mainly positive
- Evidence is appearing to support EPA or higher EPA to DHA formulations over DHA alone
- Effective in bipolar depression but not mania
- May have an especially beneficial role in comorbid cardiovascular conditions or if diet is deficient
- Dose- 1g-1.5g of EPA or with additional DHA (equivalent to approximately 6-8 x 1g capsules per day)

**Food sources**

- **Fats and fatty acids**
  - Saturated fats: Animal fats, butter, lard
  - Unsaturated fats
    - Polyunsaturated fats
      - Omega 3 fatty acids: Eicosapentanoic acid: fish, shellfish; Docosahexanoic acid: fish, shellfish
      - Omega 6 fatty acids: Corn oil; Safflower oil; Sunflower oil
    - Monounsaturated fats
      - Omega 9 fatty acids: Olive oil; Avocados; Peanuts; Almonds
S-Adenosyl Methionine (SAMe)

- SAMe serves as a necessary methyl donor of methyl groups involved with the metabolism and synthesis of neurotransmitters.

- Folate deficiency is implicated in causing increased homocysteine levels, linked to poor response to antidepressants.

- Metabolism of homocysteine to S-adenosyl-methionine (SAMe) or back to methionine requires folate, B6 and B12.

- SAMe and folate are involved with the methylation pathways in the ‘one-carbon’ cycle, responsible for the metabolism and synthesis or various monoamines.

- Folate is also most notability involved with the synthesis of SAMe, an endogenous antidepressant formed from homocysteine.

(Williams et al. 2005)
S-Adenosyl Methionine/ Folate Cycle

(Mischoulon & Fava cited in Papakostas 2009)
S-Adenosyl Methionine (SAMe)

- Several human clinical trials using SAMe in MDD have been conducted.
- All have revealed beneficial antidepressant effects, and comparable effects to synthetic antidepressants.
- Increases alacrity of response of SSRIs.
- Parenteral or oral administration is effective.
- Good safety profile.

(Papakostas 2009)
A 6-week RCT using adjunctive oral SAMe (target dose: 800 mg twice daily: n=73) in MDD participants unresponsive to stable SSRIs.

George I. Papakostas, M.D.
David Mischoulon, M.D., Ph.D.
Irene Shyu, B.A.
Jonathan E. Alpert, M.D., Ph.D.
Maurizio Fava, M.D.
S-adenosyl methionine (SAMe)

**Clinical considerations**

- Most clinical studies involved parenteral or intramuscular injections of SAMe, rather than oral preparations.

- Considering pharmacokinetic variability between administration techniques, oral preparations may not provide the same alacrity of effect (still however effective).

- SAMe should be used with caution in patients with a history of (hypo)mania due to concerns over switching from unipolar depression to mania.

- SAMe is expensive and the cost may be prohibitive for some.

- 200mg bid titrated to 400-800mg bid (be aware of stimulation).
Adjunctive Use with Antidepressants

<table>
<thead>
<tr>
<th>Herbal/nutritional medicine</th>
<th>Clinical evidence</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3</td>
<td>Four studies have demonstrated positive results after 2 or more weeks of omega-3 (1–6.6 g/day) with SSRIs, TCAs, MAOIs (Jazayeri et al., 2008; Nemets et al., 2002; Peet and Horrobin, 2002)</td>
<td>High dosage may ↑ INR (caution with warfarin) High dosage may also alter triglyceride levels</td>
</tr>
<tr>
<td>S-Adenosyl-methionine (SAMe)</td>
<td>Intramuscular and oral augmentation of SAMe with antidepressants has demonstrated ↑ response and remission rates (Berlanga et al., 1992). May enhance response in antidepressant non-responders (Alpert et al., 2004)</td>
<td>May interact with serotonergic antidepressants; caution in bipolar patients to avoid switching to mania</td>
</tr>
</tbody>
</table>

(Sarris and Byrne 2009)
St John’s wort (*Hypericum perforatum*)

- *Hypericum perforatum* is a plant medicine with established efficacy in treating MDD (>40 clinical trials)

  - Modulation of monoamine transmission via Na+ channel
  - Nonselective inhibition of re-uptake of serotonin, dopamine, norepinephrine
  - Decreased degradation of neurochemicals
  - Increased binding/sensitivity/density to 5-HT<sub>1A,B</sub>
  - Dopaminergic activity (prefrontal cortex)
  - Inhibited neuronal release of glutamate
  - Neuroendocrine modulation
  - Anti-depressant and anxiolytic activity in animal models

**Precautions**

- Potential drug interactions
- Switching in Bipolar Disorder
- Serotonin Syndrome

(Butterweck 2003, Sarris and Kavanagh 2009)
St John’s wort (*Hypericum perforatum*) (Sarris & Kavanagh 2009)

<table>
<thead>
<tr>
<th>Study</th>
<th>n of trials</th>
<th>Participants</th>
<th>Mean response&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SJW</td>
<td>Comparison</td>
</tr>
<tr>
<td><strong>SJW versus placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linde et al. (2008)</td>
<td>9 larger</td>
<td>1129</td>
<td>915</td>
</tr>
<tr>
<td></td>
<td>9 smaller</td>
<td>506</td>
<td>514</td>
</tr>
<tr>
<td>Röder et al. (2004)</td>
<td>18</td>
<td>1086</td>
<td>1043</td>
</tr>
<tr>
<td>Werneke et al. (2004)</td>
<td>18</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Whiskey et al. (2001)</td>
<td>14</td>
<td>690</td>
<td>646</td>
</tr>
<tr>
<td><strong>SJW versus synthetic antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linde et al. (2008)</td>
<td>12 SSRIs</td>
<td>905</td>
<td>889</td>
</tr>
<tr>
<td></td>
<td>5 Tri/tetracyclic</td>
<td>508</td>
<td>508</td>
</tr>
<tr>
<td>Röder et al. (2004)</td>
<td>15</td>
<td>1117</td>
<td>1114</td>
</tr>
<tr>
<td>Whiskey et al. (2001)</td>
<td>9</td>
<td>694</td>
<td>700</td>
</tr>
</tbody>
</table>

<sup>a</sup>When not available, not reported.

<sup>b</sup>RR (95% CI).

<sup>c</sup>P > 0.05.
**SJW**: Example Study (Woelk 2000)

- Six-week RCT
- SJW extract (Remotiv: Ze 117) vs. imipramine
- Mild to moderate MDD
- \( n=324 \)
SJW: large long-term study (Kasper et al. 2008)

- Multicenter RCT: SJW extract WS® 5570 in preventing relapse during 6 months' continuation treatment and 12 months' long-term maintenance (N=426)

- Adult out-patients with a recurrent episode of moderate major depression

- After 6 weeks of single-blind treatment with 3 × 300 mg/day SJW patients with score ≤ 2 on item ‘Improvement’ of the CGI scale and a HAMD decrease ≥ 50% versus baseline were randomized to 3 × 300 mg/day SJW or placebo for 26 week

- Relapse rates during continuation treatment were 51/282 (18.1%) for SJW and 37/144 (25.7%) for placebo. Average time to relapse was 15 days less for SJW; p=0.034

- In long-term maintenance treatment a pronounced prophylactic effect of SJW was observed in patients with an early onset of depression as well as in those with a high degree of chronicity
St John’s wort  (*Hypericum perforatum*)

Hypericum Clinical Trial Study Group 2002

8-week 3-arm RCT (n=344)

SJW vs. sertraline vs. placebo
St. John’s wort and Kava in treating major depressive disorder with comorbid anxiety: a randomised double-blind placebo-controlled pilot trial

Jerome Sarris¹*, David J. Kavanagh², Gary Deed¹ and Kerry M. Bone³

HUMAN PSYCHOPHARMACOLOGY

- Ten week study
- Cross-over RCT
- Two wk placebo run-in
- SJW + Kava vs. placebo
- 37 participants with MDD + comorbid anxiety
- Most results not significant
SJW: Genomics (Jungke et al. 2010)

- Compared two doses of SJW versus fluoxetine and control on genes involved in depression
- Hypothalmic and hippocampal gene expression was tested in a chronic restraint stress animal model
- Genes involved in inflammation, oxidative stress, and cognition were modified by both SJW and fluoxetine
SJW: Genomics (Wong et al. 2004)

- Differential hypothalmic gene expression was tested in rats treated with imipramine and SJW
- Chronic SJW treatment regulated 68 genes, imipramine 60 genes, with 6 common genes effected
- Mitochondrial genes most effected involved energy metabolism
- Genes also involved in intra-cellular transport and neurotransmission

<table>
<thead>
<tr>
<th>Tx</th>
<th>Acc #</th>
<th>Gene name</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMI</td>
<td>AA799276</td>
<td>ATPase, Ca(^{2+}) transporting, cardiac muscle</td>
</tr>
<tr>
<td>IMI</td>
<td>M58758</td>
<td>ATPase, H(^{+}) transporting, lysosomal</td>
</tr>
<tr>
<td>SJW</td>
<td>AI177026</td>
<td>ATPase, Na(^{+})K(^{+}) transporting, alpha 2</td>
</tr>
<tr>
<td>SJW</td>
<td>M86621</td>
<td>Calcium channel, voltage-dependent, alpha2</td>
</tr>
<tr>
<td>SJW</td>
<td>H33656</td>
<td>EST, similar to K(^{+}) voltage-gated channel, beta 2</td>
</tr>
<tr>
<td>IMI</td>
<td>AF001423</td>
<td>N-methyl D-aspartate 2A receptor</td>
</tr>
<tr>
<td>SJW</td>
<td>AF071014</td>
<td>Alpha1D adrenergic receptor gene</td>
</tr>
<tr>
<td>SJW</td>
<td>AF030253</td>
<td>Vesicular inhibitory amino acid transporter</td>
</tr>
<tr>
<td>SJW</td>
<td>AA892520</td>
<td>EST, similar to vesicle amine transport protein 1</td>
</tr>
</tbody>
</table>
SJW and Antidepressants?

**Cautions**

- Don’t use high doses of SJW with higher doses of ADs
- Patient must give informed consent and their GP should be advised
- Consider drug interactions mediated by CYP 3A4, P-glycoprotein drug pump

**Co-administration**

- Use low hyperforin (e.g. Ze 117)
- Only used adjunctively when ADs are being slowly withdrawn and are at a lower dose e.g. 10mg paroxetine/fluoxetine
- SJW can then be titrated up gradually starting at a lower dose
Clinical Recommendations

- Quality issue: Use standardised products made via GMP
- Using lower ‘hyperforin’ SJW extracts to minimise induction of Pgp and CYP 3A detoxification pathways (e.g. Ze 117)
- Caution in Bipolar Disorder
- May have a role in being introduced in people withdrawing from antidepressants when at the lower end of titration
- SJW can be gradually titrated up
Kava (*Piper methysticum*)

- GABA channel modulation (lipid membrane structure and sodium channel function)
- Weak GABA binding (increased synergistic effect of [3H]muscimol binding to GABA-α receptors)
- β-adrenergic downregulation
- MAO-B inhibition
- Re-uptake inhibition of norepinephrine

![Image of kava plant]

![Image of kava drink]

*Kava: a comprehensive review of efficacy, safety, and psychopharmacology*  
Australian and New Zealand Journal of Psychiatry 2011; 45:27–35  
Jerome Sarris, Emma LaPorte, Isaac Schweitzer
Neurocognitive effects of kava (*Piper methysticum*): a systematic review

E. LaPorte\(^1\), J. Sarris\(^1,2\), C. Stough\(^1,3\) and A. Scholey\(^1,3\)

**Mechanism of action**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Study design</th>
<th>Key observations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modulation of calcium and sodium channels</td>
<td><em>In vitro</em></td>
<td>Interaction of kavain with voltage-dependent sodium and calcium channels. When applied before anoxia the sodium channel blockers tetrodotoxin and kavain preserved vesicular ATP content, prevented both the veratridine-induced increases of Na(^+) and Ca(^{2+})</td>
<td>Gleitz <em>et al.</em> 1996/95 [20, 68]</td>
</tr>
<tr>
<td>Voltage-dependent sodium channel inhibition</td>
<td><em>In vitro</em></td>
<td>Both kavain and methysticin inhibited voltage-dependent Na(^+) channels in acutely dissociated rat CA1 hippocampal neurons leading to a decrease of cellular excitability</td>
<td>Magura <em>et al.</em> 1997 [69]</td>
</tr>
<tr>
<td>Inhibition of voltage-dependent calcium channels</td>
<td><em>In vitro</em></td>
<td>Kavain interacted with the M3 receptor or the M3 associated G-protein receptor. The actions of kavain did not affect the prostaglandin pathways and nitric oxide mediated relaxation was not observed</td>
<td>Martin <em>et al.</em> 2000 [70]</td>
</tr>
<tr>
<td>Reduced neuronal re-uptake of dopamine</td>
<td><em>In vivo</em></td>
<td>High doses of kavain and desmethoxyyangonin increased dopamine levels in the nucleus accumbens of rats</td>
<td>Baum <em>et al.</em> 1998 [71]</td>
</tr>
<tr>
<td>Reduced neuronal re-uptake of noradrenaline</td>
<td><em>In vitro</em></td>
<td>Kavain and methysticin inhibited the uptake of noradrenaline in rat cerebral cortex and hippocampal synaptosomes</td>
<td>Seitz <em>et al.</em> 1997 [72]</td>
</tr>
<tr>
<td>Enhanced ligand binding to GABA-(\alpha) receptors</td>
<td><em>In vitro</em></td>
<td>Yangonin, kavain, dihydrokavain, methysticin, and dihydromethysticin enhanced the specific binding of [3H]-bicuculline methochloride (although did not inhibit the specific binding of [3H]-flunitrazepam)</td>
<td>Boonen <em>et al.</em> 1998 [28]</td>
</tr>
<tr>
<td>Enhanced regulation of GABAergic neurotransmission</td>
<td><em>In vitro</em></td>
<td>Kavalactones or dihydrokavain significantly reduced the rat brain stem nucleus tractus solitarius inhibitory effects induced by muscimol</td>
<td>Yuan <em>et al.</em> 2002 [73]</td>
</tr>
</tbody>
</table>
Kava: Meta-analysis (Pittler & Ernst 2003)

Analysis 1.1. Comparison | Kava versus placebo for anxiety, Outcome | Improvement (HAMA-score).

Review: Kava extract versus placebo for treating anxiety

Comparison: Kava versus placebo for anxiety

Outcome: Improvement (HAMA-score)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
<td>IV(Random,95% CI)</td>
</tr>
<tr>
<td>Connor 2002</td>
<td>17</td>
<td>5.7 (7.6)</td>
<td></td>
<td>15.5 %</td>
<td>-2.80 [-6.90, 1.30]</td>
</tr>
<tr>
<td>Geier 2004</td>
<td>25</td>
<td>12.7 (6.7)</td>
<td></td>
<td>15.8 %</td>
<td>0.40 [-3.48, 4.28]</td>
</tr>
<tr>
<td>Kindler 1991</td>
<td>29</td>
<td>12.3 (8.7)</td>
<td></td>
<td>15.1 %</td>
<td>8.70 [4.30, 13.10]</td>
</tr>
<tr>
<td>Lehrl 2004</td>
<td>34</td>
<td>10.6 (7.3)</td>
<td></td>
<td>14.6 %</td>
<td>1.40 [-3.37, 6.17]</td>
</tr>
<tr>
<td>Malsch 2001</td>
<td>20</td>
<td>3 (7.5)</td>
<td></td>
<td>15.9 %</td>
<td>2.40 [-1.46, 6.26]</td>
</tr>
<tr>
<td>Voelz 1997</td>
<td>52</td>
<td>21 (13)</td>
<td></td>
<td>13.8 %</td>
<td>4.80 [-0.57, 10.17]</td>
</tr>
<tr>
<td>Warncke 1991</td>
<td>20</td>
<td>25.61 (12.8)</td>
<td></td>
<td>9.3 %</td>
<td>17.96 [9.01, 26.91]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>197</strong></td>
<td><strong>183</strong></td>
<td><strong>3.85 [0.05, 7.66]</strong></td>
<td><strong>100.0 %</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 19.89 \); \( \chi^2 = 27.47, df = 6 \) \( P = 0.00012 \); \( I^2 = 78\% \)

Test for overall effect: \( Z = 1.98 \) \( P = 0.047 \)
The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of *Piper methysticum*

J. Sarris · D. J. Kavanagh · G. Byrne · K. M. Bone · J. Adams · G. Deed

- 3-week RCT (n=60)
- Cross-over study
- Kava vs. Placebo
- Tx Generalised Anxiety

**Anxiety Outcome**

![Graph showing Anxiety Outcome](image1)

*Fig. 2 Results on the Hamilton Anxiety Scale (HAMA)*

**Depression Outcome**

![Graph showing Depression Outcome](image2)

*Fig. 4 Results on the Montgomery–Asberg Depression Rating Scale (MADRS)*
Figure 2. Predictive effect of baseline depression to reduction of anxiety

$r = .17, p = 0.32$
Kava Safety

• Previous issues with liver toxicity

• Over 100 cases (liver failure/death)

• Still safe compared to paracetamol
  • 2 cases/100 million doses

• May be due to...
  • Poor quality kava
  • Incorrect plant parts
  • Co-use with alcohol/medication
  • Genetic 2D6 insufficiency
Kava hepatotoxicity solution: A six-point plan for new kava standardization
Rolf Teschke\textsuperscript{a,\,*}, Jerome Sarris\textsuperscript{b,c}, Vincent Lebot\textsuperscript{d}

Proposals for future strategies.

Recommendations
1. Vanuatu legislation regarding the preferred noble cultivar(s) such as Borogu
2. Additional legislation of peeled rhizome and roots to be used for water based kava extracts
3. Corresponding legislation also in other countries of the South Pacific Islands
4. Regulatory definition of noble cultivar such as Borogu and use of its peeled rhizomes and roots
5. Regulatory standardization of quantitative method for kavalactones in the extract
6. Limitation of kava use to water based extracts
7. Regulatory definition of daily dose and duration of use
8. Mandatory prescription guidance for kava drugs to minimize risks
9. Regulatory surveillance of cultivators, harvesters, farmers, and manufacturers
The KALM Project

- 8 week RCT (n=100)
- Participants with GAD
- Kava (120mg kavalactones) versus placebo (titrated to 240mg in non-response)
- Outcomes: anxiety scales, quality of life, sexual function, liver function
- Genetic polymorphisms: CYP 2D6, 5HT& dopamine & noradrenaline transporters, BDNF, GABA
Thanks!

www.INIMH.org

The International Network of Integrative Mental Health (INIMH)

An organization advancing a global vision for the integrated whole person approach to mental health via education, research, networking and advocacy
References

Butterweck V. Mechanism of action of St John’s wort in depression: what is known? CNS Drugs. 2003; 17:539-62


Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr. 2009; 28:525-42


