Kava
(*Piper methysticum*)

2022

Professor Jerome Sarris

Disclosures: Current Scientific Advisor to Fiji Kava (consultancy payments);
Previous funding for kava research from Integria Healthcare, MediHerb, and the NHMRC

Kava (*Piper methysticum*)

- A medicinal plant from the South Pacific
- The ground root used as a drink extract to reduce anxiety/tension & improve mood
- Supportive evidence found in studies using Kava for generalised anxiety
- Concerns however over liver problems with some previous extracts (mainly European companies using acetonic and ethanolic extraction of kavalactones potentially from cheaper non-root plant material e.g. stem peelings)

Kava (*Piper methysticum*)

- Inhibition of GABA voltage-dependent sodium/calcium channels
- Enhances ligand binding to GABA-α
- Increases GABA receptor numbers & regulates GABA transmission
- Noradrenaline re-uptake inhibition (pre-frontal cortex)
- Dopamine re-uptake inhibition (nucleus accumbens)
- Reversible MAO-B inhibition

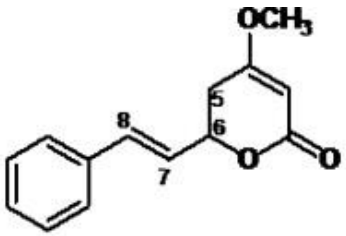
Kava: a comprehensive review of efficacy, safety, and psychopharmacology

Jerome Sarris, Emma LaPorte, Isaac Schweitzer

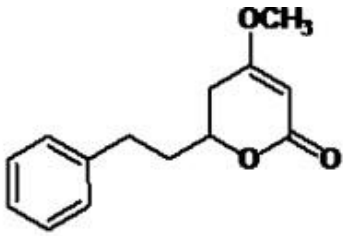
Australian and New Zealand Journal of Psychiatry 2011; 45:27–35

Kava Chemistry

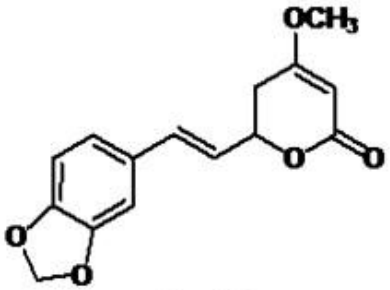
(*Lebot 2006*)



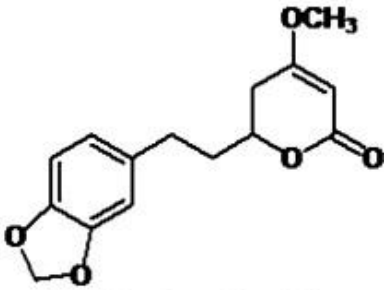
kavain



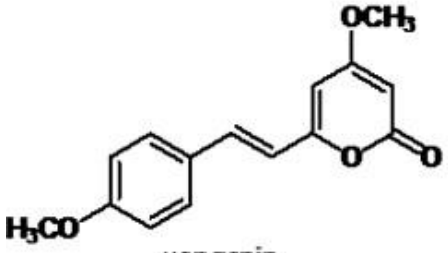
7,8-dihydrokavain



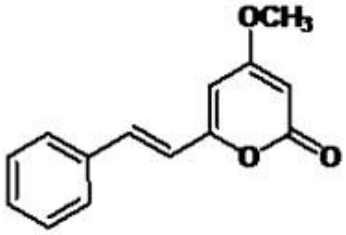
methysticin



7,8-dihydromethysticin



yangonin

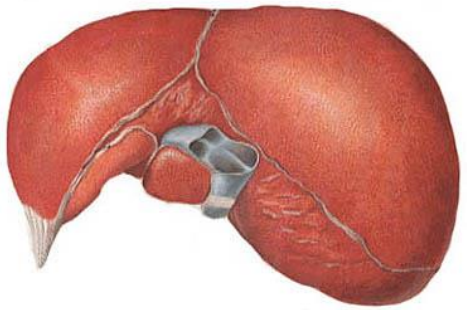


desmethoxyyangonin

Major Constituents

- Lipophilic resins called "kavalactones" or "kavapyrones"
- 18 in total with 6 major kavalactones
- Chemotypes labelled from 1-6 (Lebot system) e.g. 425631

Kava and the Liver



- **Previous global issues with liver toxicity**
- **Over 100 cases of 'reputed' liver toxicity (pharmaceutical & traditional extracts)**
- **Still comparably very safe (2 cases/100 million doses)**
- **No major concerns noted in the literature over the past 15 years to my knowledge**

May be due to...

- Poor quality kava processing/storage/manufacturing, or use of chemicals
- Incorrect plant parts
- Inappropriate cultivars
- Co-use with alcohol/medication
- Genetic differences/insufficiency

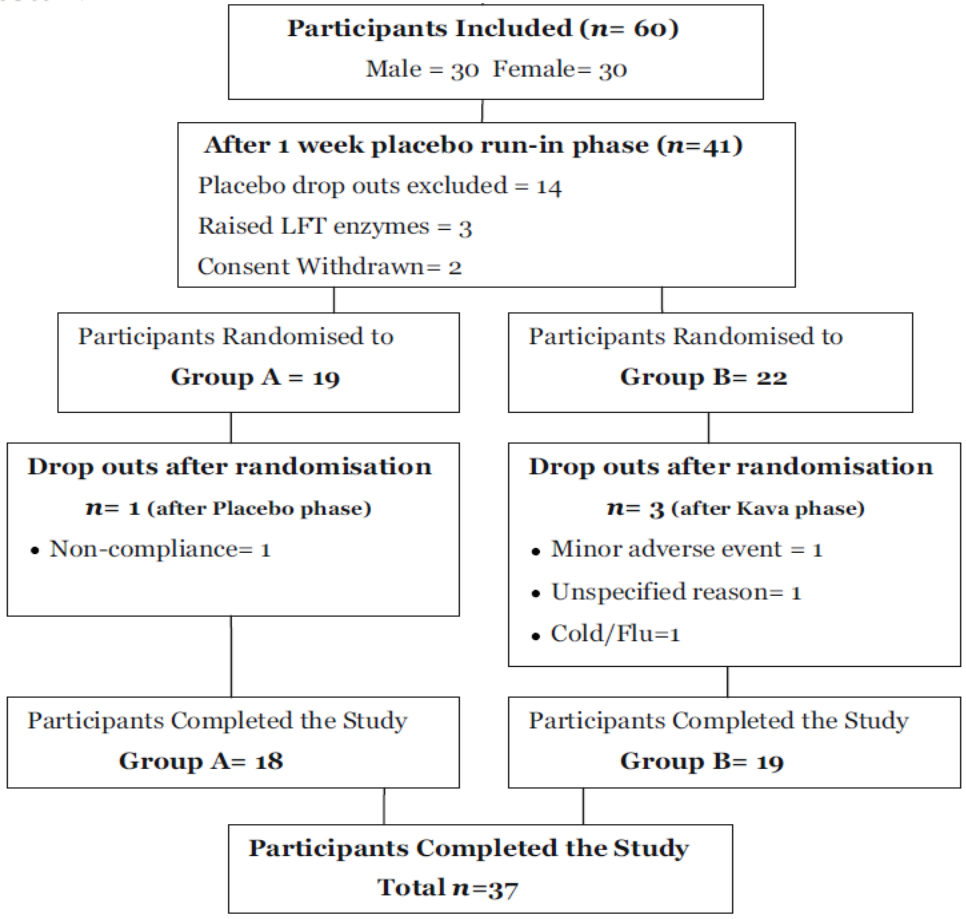
Psychopharmacology
DOI 10.1007/s00213-009-1549-9

ORIGINAL INVESTIGATION

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 (tablets) (250mg of kavalactones)
- Adults with generalised anxiety and different levels of depression



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Anxiety Outcome

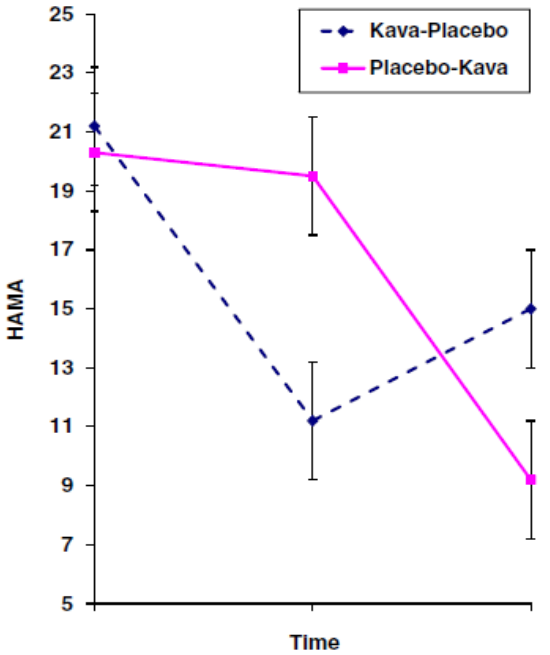


Fig. 2 Results on the Hamilton Anxiety Scale (*HAMA*)

Depression Outcome

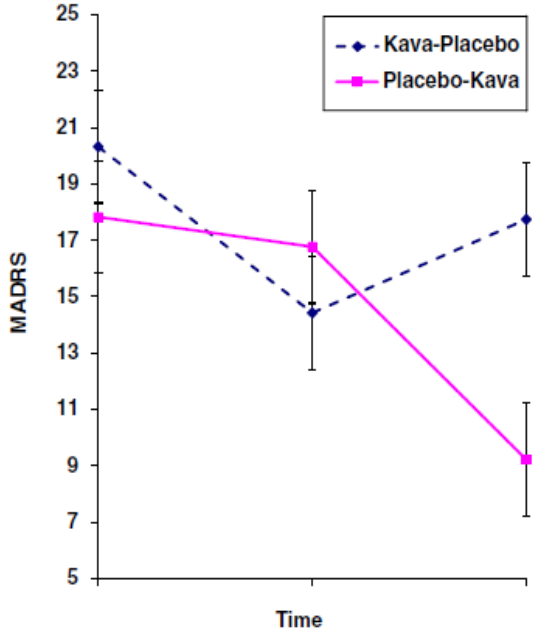


Fig. 4 Results on the Mongomery–Asberg Depression Rating Scale (*MADRS*)

The KALM Study

Re-introduction of Kava (*Piper methysticum*) to the EU: Is There a Way Forward?

Jerome Sarris[1,2], Rolf Teschke[3], Con Stough[2], Andrew Scholey[2], Isaac Schweitzer[1]

Planta Med 2011; 77: 107–110

- 8 week RCT (*n*=75)
- Participants with GAD and no depression
- Kava (120mg kavalactones) versus placebo (titrated to 240mg in non-response)
- Outcomes: anxiety scales, quality of life, sexual function, liver function
- Genetic polymorphisms:

GABA & noradrenalin transporters

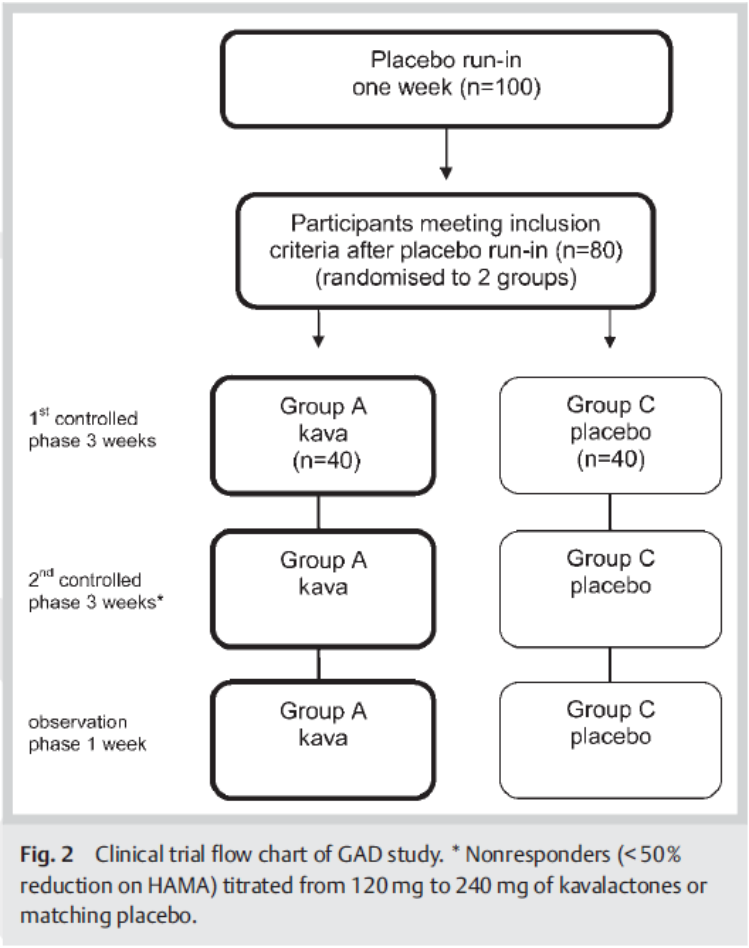


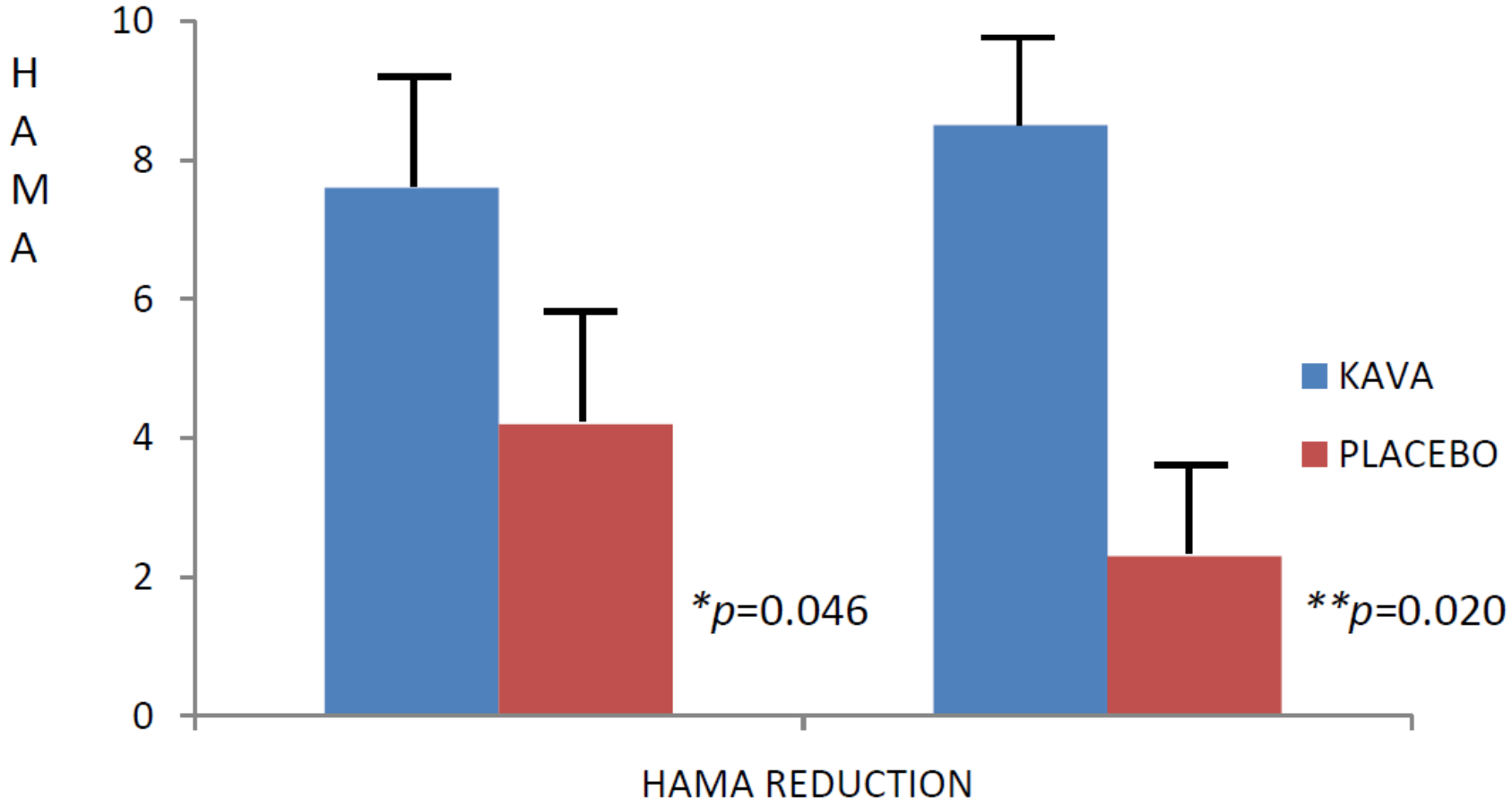
Fig. 2 Clinical trial flow chart of GAD study. * Nonresponders (< 50% reduction on HAMA) titrated from 120 mg to 240 mg of kavalactones or matching placebo.

Kava in the Treatment of Generalized Anxiety Disorder

A Double-Blind, Randomized, Placebo-Controlled Study

Jerome Sarris, PhD, MHSc,†‡ Con Stough, PhD,†‡ Chad A. Bousman, PhD, MPH,*† Zahra T. Wahid, BPsych (Hons),†‡ Greg Murray, MPsych, PhD,§ Rolf Teschke, MD,|| Karen M. Savage, BSc(Hons),†‡ Ashley Dowell, BSc,¶ Chee Ng, MD,* and Isaac Schweitzer, MD**

(*J Clin Psychopharmacol* 2013;33:



*Full sample with GAD + other comorbid anxiety disorders

** Pure GAD sample

Savage *et al. Trials* _####################_
DOI 10.1186/s13063-015-0986-5

TRIALS

STUDY PROTOCOL Open Access

Kava for the treatment of generalised anxiety disorder (K-GAD): study protocol for a randomised controlled trial

Karen M. Savage[1,2*], Con K. Stough[2], Gerard J. Byrne[3], Andrew Scholey[2], Chad Bousman[2,4,5,6], Jenifer Murphy[1], Patricia Macdonald[3], Chao Suo[7], Matthew Hughes[8], Stuart Thomas[9], Rolf Teschke[10], Chengguo Xing[11] and Jerome Sarris[1,2]

Abstract

Background: Generalised anxiety disorder (GAD) is a chronic and pervasive condition that generates high levels of psychological stress, and it is difficult to treat in the long term. Current pharmacotherapeutic options for GAD are in some cases only modestly effective, and may elicit undesirable side effects. Through targeted actions on the gamma-aminobutyric acid (GABA) pathway, the South Pacific medicinal plant kava (*Piper methysticum*) is a non-addictive, non-hypnotic anxiolytic with the potential to treat GAD. The evidence for the efficacy of kava for treating anxiety has been affirmed through clinical trials and meta-analyses. Recent research has also served to lessen safety concerns regarding the use of kava due to hepatotoxic risk, which is reflected in a recent German court overturning the previous kava ban in that country (which may in turn influence a reinstatement by the European Union). The aim of current research is to assess the efficacy of an 'aqueous noble cultivar rootstock extract' of kava in GAD in a larger longer term study. In addition, we plan to investigate the pharmacogenomic influence of GABA transporters on response, effects of kava on gene expression, and for the first time, the neurobiological correlates of treatment response via functional and metabolic imaging.

Methods/Design: This clinical trial is funded by the Australian National Health and Medical Research Council (APP1063383) and co-funded by MediHerb (Integria Healthcare (Australia) Pty. Ltd). The study is a phase III, multi-site, two-arm, 18-week, randomised, double-blind, placebo-controlled study using an aqueous extract of noble kava cultivar (standardised to 240 mg of kavalactones per day) versus matching placebo in 210 currently anxious participants with diagnosed GAD who are non-medicated. The study takes place at two sites: the Centre for Human Psychopharmacology (Swinburne University of Technology), Hawthorn, Melbourne, Australia; and the Academic Discipline of Psychiatry (The University of Queensland) based at the Royal Brisbane and Women's Hospital, Herston, Brisbane, Australia. Written informed consent will be obtained from each participant prior to commencement in the study. The primary outcome is the Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A). The secondary outcomes involve a range of scales that assess affective disorder symptoms and quality of life outcomes, in addition to the study of mediating biomarkers of response (assessed via genomics and neuroimaging).

(Continued on next page)

NHMRC Grant APP1063383

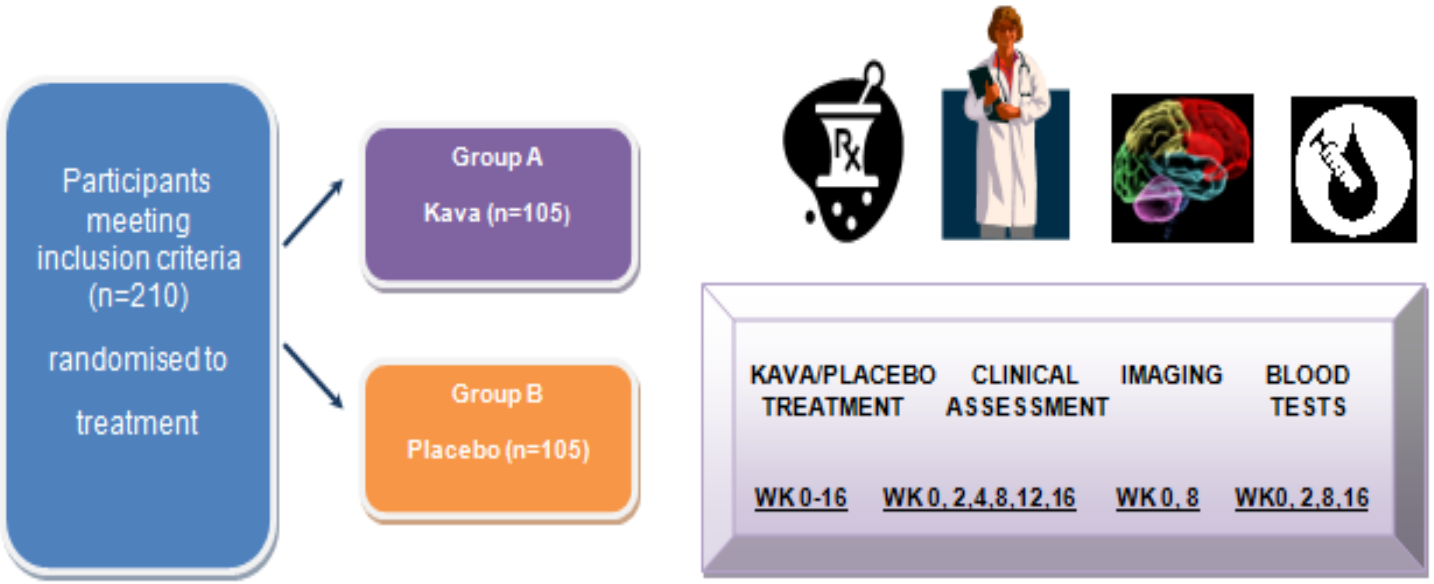
Co-sponsored by Integria Healthcare

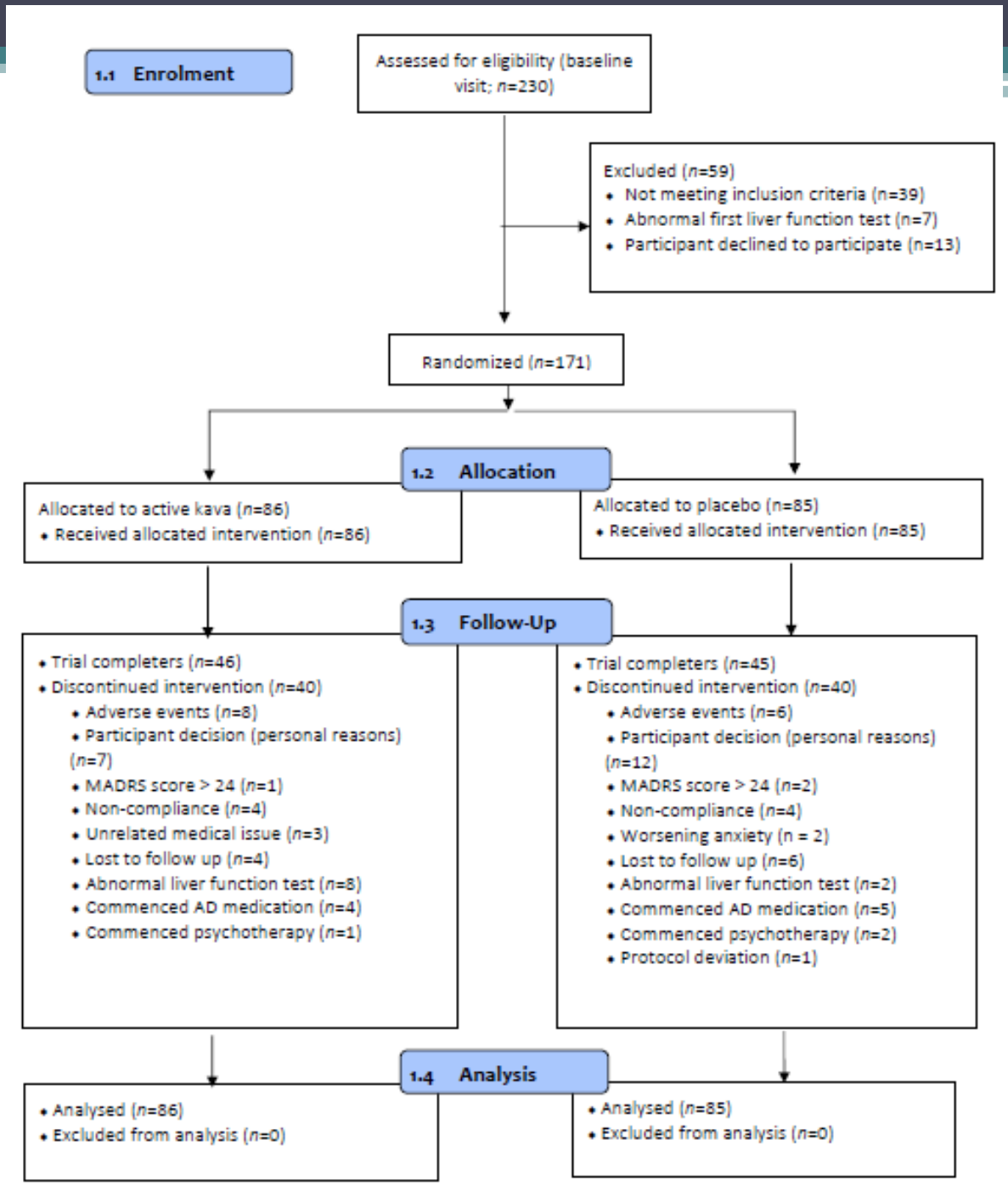
Summary Trial Design

- A 16-week (+ 2-week placebo run-out), 2-arm, double-blind, multi-centre RCT testing the effect of a standardised pharmaceutical-grade water-soluble extract of kava (240mg of kavalactones per day) versus placebo in adults with diagnosed GAD

- N=171 (pharmacogenetics: *n*=100, imaging: *n*=40)

- Adults aged 18-70 years
- DSM-5 diagnostic criteria for GAD
- Currently anxious (scoring ≥ 18 on the HAMA)
- fMRI, MRS (GABA levels in ACC), gene expression and GABA-T SNPs



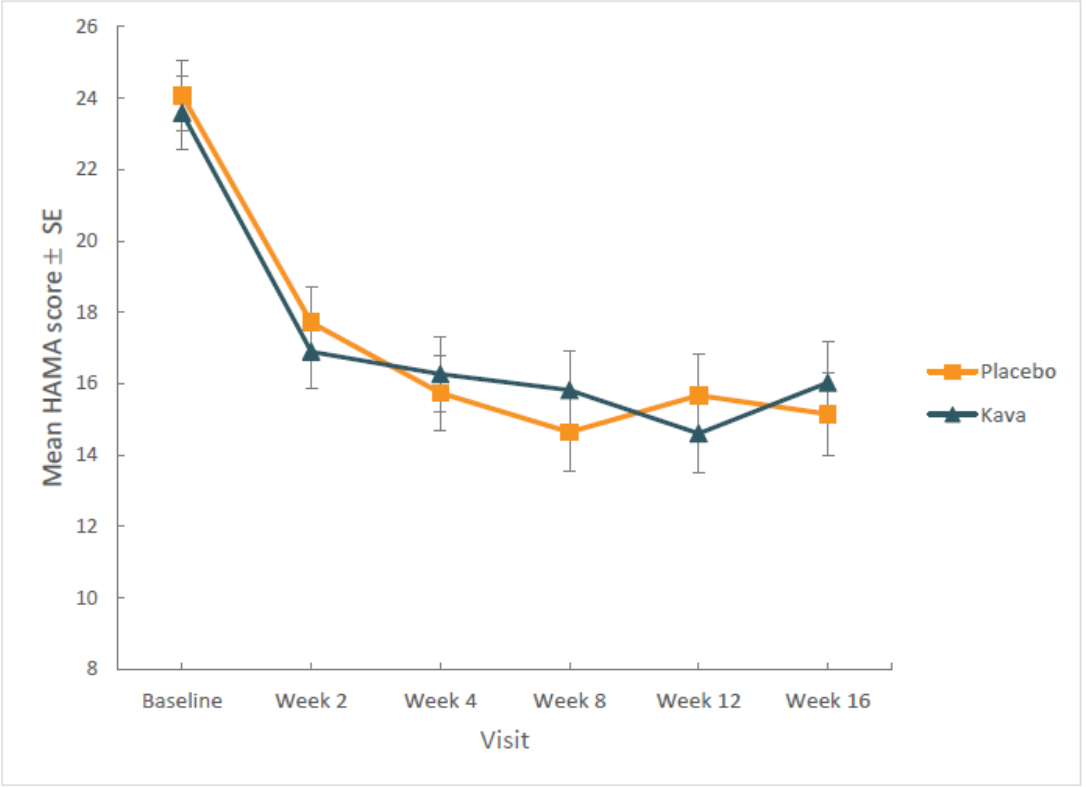

1.1 Enrolment
Assessed for eligibility (baseline visit; n=230)
Excluded (n=59)
• Not meeting inclusion criteria (n=39)
• Abnormal first liver function test (n=7)
• Participant declined to participate (n=13)
Randomized (n=171)
1.2 Allocation
Allocated to active kava (n=86)
• Received allocated intervention (n=86)
Allocated to placebo (n=85)
• Received allocated intervention (n=85)
1.3 Follow-Up
• Trial completers (n=46)
• Discontinued intervention (n=40)
• Adverse events (n=8)
• Participant decision (personal reasons) (n=7)
• MADRS score > 24 (n=1)
• Non-compliance (n=4)
• Unrelated medical issue (n=3)
• Lost to follow up (n=4)
• Abnormal liver function test (n=8)
• Commenced AD medication (n=4)
• Commenced psychotherapy (n=1)
• Trial completers (n=45)
• Discontinued intervention (n=40)
• Adverse events (n=6)
• Participant decision (personal reasons) (n=12)
• MADRS score > 24 (n=2)
• Non-compliance (n=4)
• Worsening anxiety (n = 2)
• Lost to follow up (n=6)
• Abnormal liver function test (n=2)
• Commenced AD medication (n=5)
• Commenced psychotherapy (n=2)
• Protocol deviation (n=1)
1.4 Analysis
• Analysed (n=86)
• Excluded from analysis (n=0)
• Analysed (n=85)
• Excluded from analysis (n=0)

ANZJP

Australian & New Zealand Journal of Psychiatry
2020, Vol. 54(3) 288–297
DOI: 10.1177/0004867419891246

Kava for generalised anxiety disorder: A 16-week double-blind, randomised, placebo-controlled study

Jerome Sarris[1,2], Gerard J Byrne[3], Chad A Bousman[4,5], Lachlan Cribb[2], Karen M Savage[2,6], Oliver Holmes[6], Jenifer Murphy[2], Patricia Macdonald[3], Anika Short[3], Sonia Nazareth[3], Emma Jennings[6], Stuart R Thomas[7], Edward Ogden[6], Suneel Chamoli[8], Andrew Scholey[6] and Con Stough[6]



HAMA = Hamilton Anxiety Rating Scale; Group x Time interaction $p = 0.25$

An explorative qualitative analysis of participants' experience of using kava versus placebo in an RCT

Australian Journal of Medical Herbalism **2010** 22(1)

Jerome Sarris MHSc PhD*
Jon Adams MA PhD
David J Kavanagh MA PhD

Major domains
Relief of stress and anxiety from kava
Effects of kava on mood
Effect of kava on sleep
Kava's effect on physical signs of anxiety
Physiological side effects possibly from kava
Effect of being on placebo compared with kava

KAVA

- I have been more relaxed in the past week . . and I am able to cope a lot easier. My usual anxiety symptoms have decreased or disappeared (participant 55)
- I have been able to handle stress in a more positive light . . mind has stopped ticking so late in the evening (participant 59)
- Found it easy to accomplish day to day activities without getting worked up. I had a pretty hectic week but didn't feel too concerned or nervous about anything (participant 18)
- Felt more calm especially in the evening. Not as fearful of the worst happening (participant 52)

PLACEBO

- No noticeable effects on anxiety and stress quite bad, in fact a little worse than usual (participant 1)
- My stress and anxiety stayed elevated, still poor concentration, and motivation, feeling of nervousness in general (participant 18)
- No positive effect occurred. Felt quite fearful and anxious (participant 52)
- Very apprehensive, not a good feeling, free floating anxiety like first week of trial (placebo week). Haven't felt that restless before (participant 13)

Kava for the Treatment of Generalized Anxiety Disorder RCT: Analysis of Adverse Reactions, Liver Function, Addiction, and Sexual Effects

PHYTOTHERAPY RESEARCH
Phytother. Res. (2013)

J Sarris,[1,2,3]* C Stough,[2,3] R Teschke,[4] ZT Wahid,[2,3] CA Bousman,[1,2,5,6] G Murray,[7] KM Savage,[2,3] P Mouatt,[8] C Ng[1] and I Schweitzer,[1]

SAFETY & ADDICTION

- No serious adverse effects, no hepatoxicity
  - However, one 18 yr old male had raised GGT from kava
- No significant difference in the number of participants in the kava group [6/25 (24%)] compared to the placebo group [6/25 (24%)] wanting to increase their tablets
- A total of 1/25 (4%) in the kava group took more tablets than instructed, compared to 2/25 (8%) for placebo

Kava for the Treatment of Generalized Anxiety Disorder RCT: Analysis of Adverse Reactions, Liver Function, Addiction, and Sexual Effects

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Phytother. Res. (2013)

J Sarris,[1,2,3]* C Stough,[2,3] R Teschke,[4] ZT Wahid,[2,3] CA Bousman,[1,2,5,6] G Murray,[7] KM Savage,[2,3] P Mouatt,[8] C Ng[1] and I Schweitzer,[1]

SEXUAL EFFECTS

- Results on the Arizona Sexual Experience Scale (ASEX) showed that kava caused no diminishment of sexual performance /enjoyment
- **IN FACT…** amongst females there was an indication an improvement of sexual function for the kava group (not for men)
- **FURTHER…** Kava was found to significantly increase women's sex drive (ASEX sub-domain)
- The relationship between anxiety reduction and ASEX score for combined genders revealed a significant positive correlation between anxiety reduction and improved sexual effects from kava

My personal perspective- considering the science, and safety, and cultural importance