RESPONSE TO CALL FOR SUBMISSIONS

URGENT PROPOSAL P1057 – Review of the Kava Standard

ABOUT FIJI KAVA

Fiji Kava Ltd, is an Australian-Fijian medicinal kava health & wellness company, producing natural 'noble kava' products for the complementary medicine and functional beverage markets in the USA, Australia and Asia. Fiji Kava is the first and only foreign company with approval from the Fijian Government to operate in the kava industry. We have established a leading sustainable and 100% traceable supply chain of 'noble kava' with a number of collection hubs and two HACCP accredited processing facilities in the Fiji Islands.

FIJI KAVA LTD PRODUCTS IN AUSTRALIA

Kava is the traditional drink in many South Pacific Island nations. It has had a long history of safe use when consumed as a beverage. Fiji Kava only produces the highest grade of kava known as "Noble Kava". Fiji Kava is focussed on expanding the availability of noble Kava products in western markets to provide a natural alternative to prescription medicines to promote sleep, soothe and calm the nerves, support muscle relaxation and relax the mind as well as functional beverages that are an alternative to alcohol for relaxation and recreation.

Our products are currently sold in capsule form online and through a variety of Australian retailers including Coles and Chemist Warehouse. We are also a leading global supplier of medicinal grade kava powder for other branded products to customers including the Blackmores Group. Since the inception of the pilot commercial import program we have also sold a 50g Drinking Kava SKU in Coles supermarkets. We offer a range of Drinking Kava products on our online store: www.fijikava.com

THE ECONOMIC BENEFITS OF KAVA IMPORTATION TO AUSTRALIA ARE MORE IMPORTANT THAN EVER

The economic impact of COVID-19 as well as China's increased presence in the South Pacific has made it more important than ever for Australia to maintain close ties with our South Pacific neighbours.

Kava is an important cash crop, the growth of which can at least partly offset emerging rural poverty. As Commonwealth backed not for profit aid organisations such as PHAMA Plus have identified, it is also a crop with high social benefits, and which results in high cash yields per hectare with relatively low requirements for costly fertilisers or damaging pesticides and herbicides.

We believe that all the original reasons the Prime Minister and Department of Foreign Affairs and Trade identified for initiating trials of commercial importation of Kava have only become more pressing and that all relevant government departments and bodies should work constructively to ensure the success of the program and to maintain food safety.

ONLY ALLOWING NOBLE KAVA VARIETIES IS OF CRITICAL IMPORTANCE

There are different grades of Kava available throughout the Pacific. The highest grade of Kava is known as "Noble Kava" which has a certain chemical composition suitable for consumption as food beverages and has historically been used in ceremonies. All other Kava varieties are known as "Narafala Kava" and should not be sold or exported for human consumption as a food beverage. Various medical studies have concluded there are no adverse impacts from long term consumption of Noble Kava. Furthermore, a Codex Standard adopted by the Food and Agriculture Organisation (FAO) and the United Nations and World Health Organisation (WHO) has significantly strengthened the framework suitable for guiding the regulation of the Pacific Noble Kava market to bring higher-quality and safer kava to international markets and excludes other kava varieties such as Tudei Kava. The standard provides mandated procedures and controls for the growth, harvesting and processing of Kava with the key benchmarks for international exports of Kava including at a minimum being the exclusive use of Noble Kava and produced to relevant Food Safety Standards.

Fiji Kava Limited Strongly Supports the requirement that only Noble Kava varieties be imported

PROVIDING REGULATORY CERTAINTY IS KEY TO ENSURING THE SUCCESS OF THE PILOT PROGRAM

In January 2019 during a visit to Vanuatu Prime Minister Scott Morrison announced a pilot program to ease some of the limitations on the importation of Kava in order to boost economic links with South Pacific Nations. In November 2020 [redacted],

[redacted] During the briefing he indicated by the end of 2021 the Federal Government would commence a pilot program to allow the commercial importation of Kava in limited quantities, however this would require co-operation from the State and Territory Governments. Regulatory bodies thus had around 2 years to prepare for the program.

Fiji Kava understands Department of Health was consulting with key stakeholders as well as the State and Territory Governments in order to specifically progress the pilot program for more than 6 months prior to the announcement of the pilot trial commencement date.

The announcement of the expedited review of regulations for kava, very shortly after the announcement of the initiation of the pilot commercial kava importation trial, caused significant business impacts on companies who had prepared for more than 2 years and reasonably expected that any regulatory changes would take place prior to the announcement of the trial commencement and the opening of applications for importation licenses. In particular, uncertainty around labelling requirements meant that normal business activities, such as printing of packaging was delayed. Furthermore, negotiations with retail partners, in light of an active review of regulations was also a challenge that companies need not have faced.

Further changes in labelling or other regulatory requirements at the mid-point of the pilot trial period would place an unreasonable and unnecessary burden on importing companies.

However, appropriate post market surveillance may improve compliance. In particular, we believe that all Kava imports should be subject to random batch testing by a recognised facility such as the Analytical Research Laboratory at Southern Cross University in Lismore, NSW and regulated through Food Safety Australia New Zealand (FSANZ), and

Further steps should be taken to ensure that all importers of drinking kava should be able to provide appropriate evidence to Food Safety Australia New Zealand (FSANZ) of current compliance with HACCP accreditation requirements for facilities preparing and packaging kava imported into Australia, especially where those facilities are overseas.

THE HEALTH BENEFITS OF KAVA ARE WELL ESTABLISHED AND SUPPORT FUNCTIONAL CLAIMS

In addition to kava's traditional use for cultural, social, and religious occasions, the plant is employed also as a medicine, and has been used in Western society for its beneficial effects on reducing anxiety (Bilia, Gallon et al. 2002). Kava use in Western countries has been popularised since the 1990s, with dozens of kava products being sold for anxiety and sleep

disorders. While antidepressants and benzodiazepines are effective first-line pharmacological treatments of anxiety disorders (Rickels and Rynn 2002), side effects may occur from both agents, thus plant medicines such as kava offer a valuable additional option in medicinal and in food formats.

The pharmacodynamic mechanism for kava's anxiolytic (anxiety-reducing) action is thought to be due to the lipophilic constituents known as kavalactones (Figure 1) (Bilia, Gallon et al. 2002). Collectively, kavalactones are concentrated mainly within the rhizomes, roots and root stems of the plant (Singh and Singh 2002, Raduege, Kleshinski et al. 2004). The aerial parts of the plant may contain toxic alkaloids such as pipermethystine, and are not used in traditional consumption (Nerurkar, Dragull et al. 2004). Collectively, there has been identified to date 18 different kavalactones, with approximately 96% of the total pharmacological activity being attributed to the presence of six kavalactones: methysticin, dihydromethysticin, kavain, dihydrokavain, demethoxyyangonin, and yangonin (Lebot and Lévesque 1989, Singh and Singh 2002).

Several preclinical studies have documented a wide spectrum of pharmacological effects of kava including anxiolytic (Kinzler, Kromer et al. 1991), hypnotic (Wheatley 2001), anticonvulsant (Gleitz, Tosch et al. 1996), anti-stress (Kinzler, Kromer et al. 1991), sedative (Gleitz, Tosch et al. 1996), analgesic (Jamieson and Duffield 1990), muscle-relaxant (Singh 1983), and neuroprotective (Gleitz, Tosch et al. 1996) activity. Numerous test tube and animal studies suggest possible mechanisms which may mediate the actions of kava extract and specific kavalactones including (Sarris, LaPorte et al. 2011):

- Blockade of voltage-gated sodium ion channels
- Reduced excitatory neurotransmitter release due to blockade of calcium ion channels
- Enhanced ligand binding to gamma-aminobutyric acid (GABA) type A receptors
- Reversible inhibition of monoamine oxidase B
- Reduced neuronal reuptake of noradrenaline and dopamine.

Given the strong structure and function evidence for the medicinal benefits of kava FSANZ should allow limited claims for kava products presented as foods, in line with the established body of clinical evidence. For drinking kava this may include "soothing the nerves", "supporting relaxation", "natural sleeping aid" or "stress relief". A short review of this evidence is presented in the following pages:

Evidence of Efficacy for Reducing Anxiety

A Cochrane review has been undertaken of 11 RCTs of rigorous methodology using kava monopreparations (60mg–280mg of kavalactones) in anxiety (Pittler and Ernst 2003). Results revealed kava's anxiolytic activity compared with placebo in all but one trial. A meta-analysis of seven randomised controlled trials (RCTs) using the Hamilton Anxiety Rating Scale (HAMA) demonstrated that the plant reduced anxiety significantly over placebo, with a strong clinical effect. There was moderate differences in respect to the type of extract used (acetone, ethanol, and type of standardisation), dosage used (60mg–280mg kavalactones), and the sample treated (pre-operative anxiety, climacteric anxiety, state–trait or generalised anxiety disorder (GAD) diagnoses). Similar findings were also demonstrated in another meta-analysis conducted by Witte et al. (2005) (Witte, Loew et al. 2005), that included six placebo-controlled, randomised trials using a standardised kava extract WS1490 in non-psychotic anxiety disorders (assessed via HAMA).

In one 8-week 3-arm double-blind RCT involving 129 adults with GAD, kava demonstrated equivalent efficacy to synthetic agents, buspirone and opipramol (Boerner, Sommer et al. 2003). In respect to the use of acetone and ethanol formulations of whole kava extracts in anxiety, several studies have been conducted since 1995. Four out of six studies reviewed revealed a positive outcome. Of the two studies with negative results on primary outcomes, a four week RCT involving 141 people by Gastpar and Klimm (2003) using a standardised extract of kava versus placebo in neurotic anxiety revealed equivocal effects between the treatments on the Zung Anxiety Inventory (Gastpar and Klimm 2003). Another four-week RCT by Connor and Davidson using a standardised extract of kava versus placebo in 37 adults with DSM-IV diagnosed Generalised Anxiety Disorder (GAD) (Connor and Davidson 2002), revealed no difference between the treatments (however recruitment for this study was stopped early). Of the four positive studies, a four week RCT involving 58 adults by Lehmann and colleagues (1996) using 300mg of a standardised kava extract on general anxiety, revealed a significant effect in favour over placebo, and a strong clinical effect. An RCT conducted by Geier and Konstantinowicz (2004) using a standardised kava extract (150mg of kavalactones per day) versus placebo over four weeks in 50 patients with DSM-III-R non-psychotic anxiety, found on per-protocol analysis a significant effect in favour of kava on HAMA (Geier and Konstantinowicz 2004). A larger 25-week study by Volz et al. (1997) using a standardised extract of kava in 101 participants with non-psychotic anxiety found superiority of the extract over placebo from week 8 onwards (Volz and Kieser 1997).

The Kava Anxiety Depression Spectrum Study (KADSS) was a 3-week placebo-controlled, double-blind, crossover trial that recruited 60 adult participants with one month or more of elevated generalised anxiety (Sarris, Kavanagh et al. 2009). The results revealed that the aqueous extract of kava (standardised to 250mg of kavalactones per day) significantly reduced participants' anxiety ($p<0.001$) on the HAMA with a very large clinical effect (see Figure 2). A significant reduction ($p<0.01$) of depression also occurred on the Montgomery-Asberg Depression Rating Scale (MADRS). Baseline depression level on the Beck Inventory Scale (BDI-II) was also discovered to predict the degree of change on HAMA in the group who first took Kava ($p=0.012$). This reveals that it is likely that the higher level of depression the participants in the first group had, the greater the drop in anxiety. response (Figure 3). The aqueous extract (supplied by MediHerb) was found to be safe and well-tolerated, with no serious adverse effects, and no clinical liver toxicity.

In a subsequent 6-week double-blind RCT (consisting of a 1-week placebo run-in and a 1-week placebo run-out) (Sarris, Stough et al. 2013) involving 75 participants with diagnosed GAD (58 randomised to 120 mg daily kavalactones titrated to 240 mg for non-response), a significant Group X Time interaction was found ($p=0.046$) for a reduction in HAMA scores in favour of kava over placebo. Further, kava significantly reduced participant anxiety by 4.2 points, representing a moderate clinical effect size (Cohen's $d=0.63$). Participants with moderate-

to-severe level anxiety (assessed via the MINI Plus diagnostic interview), had a greater treatment effect (p=0.020), with a larger effect size (d=0.80). The effects were still significant after controlling for baseline Beck Anxiety Inventory (BAI) anxiety (p=0.05) and Montgomery-Åsberg Depression Rating Scale (MADRS) depression (p=0.01), in addition to thyroid function (p=0.02), and weekly caffeine use (p=0.03). Further sub-analysis of participants with 'pure GAD' and no other DSM-IV diagnosed co-morbid anxiety disorder (i.e. social phobia, panic disorder, post-traumatic stress disorder or obsessive-compulsive disorder), revealed a significant Group X Time interaction (p=0.020; d=1.28), with a reduction of 8.5 points for Kava on the HAMA compared to only 2.3 points for placebo (Figure 4). Results also showed no significant differences between groups for liver function tests, withdrawal or perceived addiction; while no significant adverse reactions occurred in the kava group (Sarris, Stough et al. 2013). Interesting, kava significantly increased female's sexual drive compared to placebo (p = 0.040) on a sub-domain of the Arizona Sexual Experience Scale (ASEX), with no negative effects seen in males. Further, a highly significant correlation was found between ASEX reduction (improved sexual function and performance) and anxiety reduction in the whole sample.

Evidence on the Qualitative Human Experience of Taking Kava

A qualitative research component (in the form of semi-structured and open ended written questions) was incorporated into the above KADSS RCT to explore the experiences of those taking Kava (Sarris, Adams et al. 2010).The written questions were provided to participants after randomisation and after each controlled phase, with the data being analysed in a blinded fashion. Two open-ended questions were posed to elucidate their experiences from taking either kava or placebo. Thematic analysis found that the key themes participants reported after the kava phases were: a reduction in anxiety and stress, and calming or relaxing mental effects. Other themes related to improvement in sleep and in somatic anxiety symptoms. The vast majority of participants reported positive experiences in the week they took kava. Participants explained that they experienced a reduction of perceived stress or anxiety, an elevation in mood, improvement in sleep pattern and a reduction of somatic symptoms of stress. The reported positive effects on stress, anxiety or mood are consistent with the highly significant reductions on quantitative depression and anxiety outcome measures that were revealed in the study.

EFFECTS ON MENTAL FUNCTION AND DRIVING

Eleven clinical trials have explored the acute (8 studies) and chronic (3 studies) effects of kava on cognition (LaPorte, Sarris et al. 2011). All trials conducted used similar cognitive tests, which primarily assessed various domains including: visual attention, memory retrieval and psychomotor function. Four out of ten studies suggest improved accuracy and performance on visual attention and working memory measures (Saletu, Grunberger et al. 1989, Munte, Heinze et al. 1993, Heinze, Münte et al. 1994, Thompson, Ruch et al. 2004), while five out of ten studies found that kava had little or no negative effect on cognitive processes (Russell, Bakker et al. 1987, Mathews, Riley et al. 1988, Prescott, Jamieson et al. 1993, Foo and Lemon 1997, Cairney, Clough et al. 2003). The remaining study revealed that kava impaired reaction time (Cairney, Maruff et al. 2003). From this, the current evidence suggests that kava has a

positive or benign effect on cognition, while potentially impairing motor skills at higher dosages.

Acute RCTs have suggested that kava may enhance some aspects of cognitive performance. For example, Thompson and colleagues (2004) reported that kava improved performance in the ability of selective attention, visual processing speed and increased the efficiency of memory retrieval (Thompson, Ruch et al. 2004). Response accuracy was also significantly increased, indicating again that kava may have beneficial effects on working memory and retrieval processes. This study however found that reaction time was reduced by 40% in comparison to placebo, indicating a potentially negative effect on motor-skill based tasks such as driving.

An Australian RCT compared the acute neurocognitive, anxiolytic, and thymoleptic effects of a medicinal dose of kava to a benzodiazepine (oxazepam), and explored for the first time specific genetic polymorphisms, which may affect psychotropic activity (Sarris, Scholey et al. 2012). Twenty-two moderately anxious adults (who were “kava naïve”) aged between 18-65 years were randomized to receive a small medicinal acute dose of kava (180mg of kavalactones), oxazepam (30mg), and placebo one week apart in a cross-over design trial. Results revealed that after exposure to cognitive tasks, a significant interaction was revealed between conditions on STAI-State anxiety ($p=0.046$). In the oxazepam condition there was a significant reduction in anxiety ($p=0.035$), whereas there was no change in anxiety in the kava condition, and an increase in anxiety in the placebo condition. Kava was found however to have no negative effect on cognition, whereas the oxazepam condition had a reduction of alertness. It is considered from this, that a small medicinal dose of kava both has no detrimental effects on cognition and is not an effective anxiety-reducing interventions in people who have never taken it before.

Increasing concerns over the prescriptive and medicinal use of sedative drugs such as benzodiazepines while people are driving have been raised (Drugs and Crime Prevention Committee, 2007); however kava may also potentially impair motor skills and cognitive attributes required to operate a motor vehicle safety. No epidemiological studies have assessed the relationship of kava on driving safety, however two studies have assessed the potential effects of kava on driving ability. Herberg (1991) conducted a randomized, double-blind, placebo-controlled trial which investigated the effects of 300mg of kava daily (higher medical dose) over 15 days on driving ability. Participants were subjected to a battery of tests including measures of concentration, vigilance, optical orientation, motor co-ordination and reaction time under stress. Results showed that kava had no effect on measures of driving performance.

An Australian RCT by Sarris et al. 2012(Sarris, Laporte et al. 2013) compared the acute effects of kava versus the benzodiazepine oxazepam and placebo using a driving simulator in 22 adults aged between 18-65 years. After being randomly administered an acute medicinal dose of kava (180mg of kavalactones), oxazepam (30mg), and placebo one week apart in a cross-over design trial, participants undertook a 15 minute computerised driving simulator. Results revealed no impairing effects on driving outcomes after kava administration compared to placebo. On specific driving outcome domains, results revealed the oxazepam group as having significantly slower breaking reaction time compared to placebo($p=0.002$) and kava ($p=0.003$). The kava group had significantly less lapses of concentration compared to oxazepam ($p=0.033$). No significant differences were found between groups for steering deviation, speed deviation, and number of crashes. Results were not modified by driving experience. Important future research now centres on studying a "recreational dose" of kava as used commonly by Pacific Island communities, who consume sometimes 10 to 20 "bowls" of kava beverage containing up to 2g of kavalactones (Sarris, LaPorte et al. 2011). This can determine whether higher doses of the plant impose a risk when driving. At present, caution is advised when driving or operating heavy machinery under the influence of high kava consumption.

While evidence for impairment of driving is mixed at best, Fiji Kava Limited has voluntarily added a warning related to driving and operating heavy machinery to all our drinking kava products which we consider to be best practice for companies selling drinking kava products.

LIVER TOXICITY CONCERNS DO NOT RELATE TO DRINKING NOBLE KAVA IN AQUEOUS SOLUTION

Traditionally, kava has not been noted to cause any health issues with the liver, and it was very surprising to Pacific Island people when it was withdrawn by the EU in 2002 due to dozens of reported cases of kava-associated liver toxicity. It should be noted that many kava formulations previously studied and sold are no longer currently used due to being withdrawn from production after the 2002 ban of kava in the EU. To date over 100 cases of hepatotoxicity have been identified whereby kava maybe implicated (Teschke 2010). In many of these case reports it was unclear whether kava was responsible for the toxic effects on the liver, particularly in those involving concomitant ingestion of other compounds with potential hepatotoxicity (e.g. other medications and/or alcohol), and in some cases a higher than recommended dose (Coulter 2007). In most cases formulations using potentised extract methods (via acetone or ethanol) were used. Factors potentially responsible for hepatotoxic

effects include hepatic insufficiency to metabolise kavalactones, preparations low in glutathione, and use of aerial parts or root peelings (higher in alkaloids), acetonic or ethanolic kava extraction media, or incorrect cultivar (medicinal, tudie or wichmanni varieties) (Sarris, Teschke et al. 2010). Currently, there is speculation that some raw kava material (incorrect cultivar, poor storage and manufacture) may be responsible for the cases of hepatotoxicity. Issues that may affect kava quality and potentially cause poor kava material include:

- Lack of correct pharmaceutical standards for storage and processing of raw material
- Lack of standardisation of the best kava cultivar/s to be used for kava products
- Absent standardisation of minimum age of kava plant at the time of harvest
- Absent declaration of the type of solvents and solubilisers used in certain kava products
- Failure of standardisation of the analytical method to quantify kavalactones in extracts
- Undefined percentage content and profile of individual kavalactones in kava extracts
- Lack of prescriptive advice for kava administration
- Inappropriate surveillance at the level of farmers and manufacturers

The WHO commissioned a report assessing the risk of kava products (Coulter 2007). Recommendation 2.1.3 suggested that products from water-based suspensions should be studied and used preferentially over acetone and ethanol extracts. In Australia only the use of water-soluble extracts are allowed (<250mg of kavalactones per day) for medicinal use, and are available over the counter. Current drinking kava legislation also provides for products using kava and water only. This approach is supported theoretically by evidence of safety from traditional use, and aqueous extracts being rich in hepatoprotective glutathione (Whitton, Lau et al. 2003). Even so, in the USA where a large variety of kava products are sold as dietary supplements reports liver damage at less than one in one million doses in that market (public FDA pharmacovigilance and safety data).

Fiji Kava Limited does not believe the current evidence for products allowed for sale in Australia warrants a liver toxicity warning, given no evidence for this risk being present for dried kava prepared in aqueous solutions and consumed in moderation (per current labelling requirements).

References

- Bilia, A. R., S. Gallon and F. F. Vincieri (2002). "Kava-kava and anxiety: growing knowledge about the efficacy and safety." Life Sci **70**(22): 2581-2597.
- Boerner, R. J., H. Sommer, W. Berger, U. Kuhn, U. Schmidt and M. Mannel (2003). "Kava-Kava extract
- LI 150 is as effective as Opipramol and Buspirone in Generalised Anxiety Disorder--an 8-week randomized, double-blind multi-centre clinical trial in 129 out-patients." Phytomedicine **10 Suppl 4**: 38-49.
- Cairney, S., A. R. Clough, P. Maruff, A. Collie, B. J. Currie and J. Currie (2003). "Saccade and cognitive function in chronic kava users." Neuropsychopharmacology **28**(2): 389-396.
- Cairney, S., P. Maruff, A. R. Clough, A. Collie, J. Currie and B. J. Currie (2003). "Saccade and cognitive impairment associated with kava intoxication." Hum Psychopharmacol **18**(7): 525-533.
- Clouatre, D. L. (2004). "Kava kava: examining new reports of toxicity." Toxicol Lett **150**(1): 85-96.
- Connor, K. M. and J. R. Davidson (2002). "A placebo-controlled study of Kava kava in generalized anxiety disorder." Int Clin Psychopharmacol **17**(4): 185-188.
- Coulter, D. (2007). "Assessment of the risk of hepatotoxicity with kava products." WHO appointed committee:.
- Foo, H. and J. Lemon (1997). "Acute effects of kava, alone or in combination with alcohol, on subjective measures of impairment and intoxication and on cognitive performance." Drug Alcohol Rev **16**(2): 147-155.
- Gastpar, M. and H. D. Klimm (2003). "Treatment of anxiety, tension and restlessness states with Kava special extract WS 1490 in general practice: a randomized placebo-controlled double-blind multicenter trial." Phytomedicine **10**(8): 631-639.
- Geier, F. P. and T. Konstantinowicz (2004). "Kava treatment in patients with anxiety." Phytother Res **18**(4): 297-300.
- Gleitz, J., C. Tosch, A. Beile and T. Peters (1996). "The protective action of tetrodotoxin and (+/-)-kavain on anaerobic glycolysis, ATP content and intracellular Na+ and Ca2+ of anoxic brain vesicles." Neuropharmacology **35**(12): 1743-1752.
- Heinze, H. J., T. F. Münte, J. Steitz and M. Matzke (1994). "Pharmacopsychological effects of oxazepam and kava-extract in a visual search paradigm assessed with event-related potentials." Pharmacopsychiatry **27**(6): 224-230.
- Herberg, K. W. (1991). "Fahrtüchtigkeit nach Einnahme von Kava-Spezial-Extrakt WS 1490, Doppelblinde, placebokontrollierte Studie [in German]." Z Allgemeinmed **13**: 842-846.
- Hirunsatit, R., R. Ilomaki, R. Malison, P. Rasanen, E. Ilomaki, H. R. Kranzler, T. Kosten, A. Sughondhabirom, N. Thavichachart, S. Tangwongchai, J. Listman, A. Mutirangura, J. Gelernter and J.
- Lappalainen (2007). "Sequence variation and linkage disequilibrium in the GABA transporter-1 gene (SLC6A1) in five populations: implications for pharmacogenetic research." BMC Genet **8**: 71.
- Jamieson, D. D. and P. H. Duffield (1990). "The antinociceptive actions of kava components in mice." Clin Exp Pharmacol Physiol **17**(7): 495-507.
- Kinzler, E., J. Kromer and E. Lehmann (1991). "[Effect of a special kava extract in patients with anxiety-, tension-, and excitation states of non-psychotic genesis. Double blind study with placebos over 4 weeks]." Arzneimittelforschung **41**(6): 584-588.
- LaPorte, E., J. Sarris, C. Stough and A. Scholey (2011). "Neurocognitive effects of kava (Piper methysticum): a systematic review." Hum Psychopharmacol **26**(2): 102-111.
- Lebot, V. and J. Lévesque (1989). "The origin and distribution of kava (*Piper methysticum Forst. f. and Piper wichmannii C. DC., Piperaceae*): a phytochemical approach." Allertonia **5**: 223-280.

- Lehmann, E., E. Kinzler and J. Friedemann (1996). "Efficacy of a special Kava extract (Piper methysticum) in paitents with states of anxiety, tension and excitedness of non-mental origin- A double-blind placebo-controlled study of four weeks treatment." Phytomedicine **III(2)**: 113-119.
- Mathews, J. D., M. D. Riley, L. Fejo, E. Munoz, N. R. Milns, I. D. Gardner, J. R. Powers, E. Ganygulpa and B. J. Gununuwawuy (1988). "Effects of the heavy usage of kava on physical health: summary of a pilot survey in an aboriginal community." Med J Aust **148**(11): 548-555.
- Munte, T. F., H. J. Heinze, M. Matzke and J. Steitz (1993). "Effects of oxazepam and an extract of kava roots (Piper methysticum) on event-related potentials in a word recognition task." Neuropsychobiology **27**(1): 46-53.
- Nerurkar, P. V., K. Dragull and C. S. Tang (2004). "In vitro toxicity of kava alkaloid, pipermethystine, in HepG2 cells compared to kavalactones." Toxicol Sci **79**(1): 106-111.
- Pittler, M. H. and E. Ernst (2003). "Kava extract for treating anxiety." Cochrane Database Syst Rev(1): CD003383.
- Prescott, J., D. Jamieson, N. Emdur and P. Duffield (1993). "Acute effects of kava on measures of cognitive performance, physiological function and mood." Drug Alcohol Rev **12**(1): 49-57.
- Raduege, K. M., J. F. Kleshinski, J. V. Ryckman and J. E. Tetzlaff (2004). "Anesthetic considerations of the herbal, kava." J Clin Anesth **16**(4): 305-311.
- Rickels, K. and M. Rynn (2002). "Pharmacotherapy of generalized anxiety disorder." J Clin Psychiatry **63 Suppl 14**: 9-16.
- Russell, P. N., D. Bakker and N. N. Singh (1987). "The effects of kava on altering and speed of access of information from long-term memory." Bulletin of the Psychonomic Society **25**(4): 236-237.
- Saletu, B., J. Grunberger, L. Linzmayer and P. Anderer (1989). "EEG-Brain mapping, psychometric and psychophysiological studies on central effects of kavain - A kava plant derivative." Human Psychopharmacology **4**: 169-190.
- Sarris, J., J. Adams and D. Kavanagh (2010). "An explorative qualitative analysis of participants' experience of using kava versus placebo in an RCT." Aust J Med Med Herbalism **22**(1): 12-16.
- Sarris, J., D. Kavanagh, G. Byrne, K. Bone, J. Adams and G. Deed (2009). "The Kava Anxiety Depression Spectrum Study (KADSS): A randomized, placebo-controlled, cross-over trial using an aqueous extract of Piper methysticum." Psychopharmacology (Berl) **205**(3): 399-407.
- Sarris, J., E. Laporte, A. Scholey, R. King, A. Pipingas, I. Schweitzer and C. Stough (2013). "Does a medicinal dose of kava impair driving? A randomized, placebo-controlled, double-blind study." Traffic Inj Prev **14**(1): 13-17.
- Sarris, J., E. LaPorte and I. Schweitzer (2011). "Kava: a comprehensive review of efficacy, safety, and psychopharmacology." Aust N Z J Psychiatry **45**(1): 27-35.
- Sarris, J., C. Ng and I. Schweitzer (2011). ""Omic" Genetic Technologies for Herbal Medicines in Psychiatry." Phytother Res **In Press**.
- Sarris, J., A. Scholey, I. Schweitzer, C. Bousman, E. LaPorte, C. Ng, G. Murray and C. Stough (2012). "The Acute Effects of Kava and Oxazepam on Anxiety, Mood, Neurocognition, and Genetic Correlates: A Randomized, Placebo-controlled, Double-Blind Study." Human Psychopharm **Accepted**.
- Sarris, J., A. Scholey, I. Schweitzer, C. Bousman, E. Laporte, C. Ng, G. Murray and C. Stough (2012). "The acute effects of kava and oxazepam on anxiety, mood, neurocognition; and genetic correlates: a randomized, placebo-controlled, double-blind study." Hum Psychopharmacol **27**(3): 262-269.
- Sarris, J., C. Stough, C. A. Bousman, Z. T. Wahid, G. Murray, R. Teschke, K. M. Savage, A. Dowell, C. Ng and I. Schweitzer (2013). "Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study." J Clin Psychopharmacol **33**(5): 643-648.

- Sarris, J., C. Stough, R. Teschke, Z. T. Wahid, C. A. Bousman, G. Murray, K. M. Savage, P. Mouatt, C. Ng and I. Schweitzer (2013). "Kava for the treatment of generalized anxiety disorder RCT: analysis of adverse reactions, liver function, addiction, and sexual effects." Phytother Res **27**(11): 1723-1728.
- Sarris, J., R. Teschke, C. Stough, A. Scholey and I. Schweitzer (2010). "Re-introduction of Kava (Piper methysticum) to the EU: Is There a Way Forward?" Planta Med.
- Schosser, A. and S. Kasper (2009). "The role of pharmacogenetics in the treatment of depression and anxiety disorders." Int Clin Psychopharmacol **24**(6): 277-288.
- Singh, Y. N. (1983). "Effects of kava on neuromuscular transmission and muscle contractility." J Ethnopharmacol **7**(3): 267-276.
- Singh, Y. N. and N. N. Singh (2002). "Therapeutic potential of kava in the treatment of anxiety disorders." CNS Drugs **16**(11): 731-743.
- Teschke, R. (2010). "Kava hepatotoxicity - a clinical review." Ann Hepatol **9:in press**
- Teschke, R., J. Sarris and V. Lebot (2010). "Kava hepatotoxicity solution: A six-point plan for new kava standardization." Phytomedicine **In Press**.
- Thompson, R., W. Ruch and R. U. Hasenohrl (2004). "Enhanced cognitive performance and cheerful mood by standardized extracts of Piper methysticum (Kava-kava)." Hum Psychopharmacol **19**(4): 243-250.
- Volz, H. P. and M. Kieser (1997). "Kava-kava extract WS 1490 versus placebo in anxiety disorders--a randomized placebo-controlled 25-week outpatient trial." Pharmacopsychiatry **30**(1): 1-5.
- Wheatley, D. (2001). "Stress-induced insomnia treated with kava and valerian: singly and in combination." Hum Psychopharmacol **16**(4): 353-356.
- Whitton, P. A., A. Lau, A. Salisbury, J. Whitehouse and C. S. Evans (2003). "Kava lactones and the kava-kava controversy." Phytochemistry **64**(3): 673-679.
- Witte, S., D. Loew and W. Gaus (2005). "Meta-analysis of the efficacy of the acetonic kava-kava extract WS1490 in patients with non-psychotic anxiety disorders." Phytother Res **19**(3): 183-188.