Date: June 15, 2012

RE: Kava Has No Acute Effect on Anxiety but May Prevent It


Kava (*Piper methysticum*) has been extensively used for ceremonial purposes by people in the South Pacific. Traditionally, kava has been used as a relaxant, an anesthetic, and in the treatment of urinary tract problems and asthma. Kava has shown a wide range of neurophysical effects on sodium ion channels, neurotransmitters, and enzymes. Previous clinical trials support the use of kava for anxiety; however, the clinical trials examining the acute use of kava on cognitive function are inconclusive. Also, correlations of neurobiological and liver function genetic polymorphisms to the use of kava, or the benzodiazepine oxazepam, are largely unexplored. This randomized, placebo-controlled, double-blind, crossover study investigated the acute effects of kava and oxazepam on anxiety, cognitive function, and potential correlations of genetic polymorphisms associated with anxiety or drugs for anxiety, as well as liver metabolism.

The study took place at the Centre for Human Psychopharmacology, Swinburne University, Melbourne, Australia, and included adult subjects between the ages of 18-65 years that suffered from "mild to moderate" anxiety as determined by the Hamilton Anxiety Scale (HAMA) model. Subjects were excluded if they had more severe mental illness, depression, or history of suicide attempts; were taking associated medications, including St. John's wort (*Hypericum perforatum*); had drug or alcohol problems; had an allergy to kava or benzodiazepines, or had regularly used these agents in the prior year or more than once a week during the past month; were pregnant or trying to become pregnant; were smokers; had liver problems; or had HAMA scores outside the targeted range.

For 3 weeks, included subjects were randomized to take 1 dose of treatment with a period of a week in between treatments. The treatments consisted of 3 tablets along with 1 capsule. Those in the kava group took 3 kava tablets with 1 oxazepam placebo capsule, while those in the oxazepam group took 3 kava placebo tablets with 1 oxazepam capsule. The placebo group took 3 kava placebo tablets along with 1
oxazepam placebo capsule. The kava treatments were manufactured by MediHerb Pty Ltd.; Warwick, Australia. Kava tablets were made from the dried water extract of the peeled root and standardized to 60 mg of kavalactones in 1 tablet. Oxazepam capsules contained 30 mg of the drug and all treatments and placebos were manufactured to appear identical. Serious adverse side effects were assessed via checklist.

The primary outcome was the assessment of kava and oxazepam treatments on stress and anxiety. This was determined using the State-Trait Anxiety Inventory-State (STAI-S) with the State-Trait Cheerfulness Inventory-Short version (STCI-S) for the assessment of moods. The Bond-Lader Visual Analogue Scales served to gauge the alertness, calmness, and contentedness of subjects. [Note: For all these scales, lower scores indicate lower levels.] These tests, similar to the scaling concept of the HAMA, were conducted at the beginning and end of the treatment period. The cognitive function of subjects was measured using Computerized Mental Performance Assessment tests consisting of Simple Reaction Time (RT), Digit Vigilance Task, Choice RT, Numeric Working Memory, Rapid Visual Information Processing (RVIP), and Corsi Blocks. Testing took place at the end of the acute treatment period, including a brief practice before treatment administration. In addition, liver function was assessed using a blood test at baseline and after the treatment period. Blood samples were used to measure genetic polymorphisms. Those investigated were gamma-aminobutyric acid (GABA) transporters (SLC6A1) and receptors, noradrenaline transporters (NAT), catechol-O-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), serotonin transporter (SLC6A4), cytochrome P450 2D6 (CYP2D6), and cytochrome P450 3A4 (CYP3A41b).

The study enrolled 22 subjects and all of them finished the crossover study protocol of all treatments. The average age was 33.3 ± 13.0 years, with 15 subjects being female. Of the total subjects, 19 agreed to a genetic analysis of CYP2D6 genes showing that 2 subjects were "poor metabolizers," 6 were "intermediate metabolizers," and 11 were "extensive metabolizers" [Note: It is unclear whether this refers to total gene or protein expression.]. There was a significant interaction found with STAI-S anxiety (P=0.046). In addition, when subjects were taking the placebo treatment, they had significantly greater anxiety during the cognitive tests than when they were taking oxazepam (P=0.035). Calmness also significantly increased in the oxazepam group (P=0.002). The interaction between group and time had a significant effect on alertness (P=0.032), and subject alertness when taking oxazepam significantly decreased over time (P<0.001), with no effect on alertness when taking kava or placebo.

With the cognition assessment, the Choice RT score in the oxazepam group was significantly higher when oxazepam was taken compared to placebo (P=0.005). When taking oxazepam or kava, subjects did significantly better on the RVIP test as compared to when they took the placebo (P=0.002); however, when subjects took the placebo, they scored significantly higher on the Digit Vigilance RT than when taking kava (P=0.016).

Regarding the genetic polymorphisms measured in those taking kava, there were significant correlations between the NAT rs3785157 T-allele and the decrease in Bond-Lader scores for contentedness (P=0.016), and between the NAT rs2242446 T-allele and an increase in the STCI-S seriousness score (P<0.01). When subjects took oxazepam, a decrease in STCI-S bad mood score was significantly correlated with the GABA receptor, alpha 4 (GABRA4) rs2229940 A-allele (P<0.01), while a higher Bond-
Lader contentedness score was significantly correlated with the NAT rs998424 T-allele (P=0.008). Also, the Digit Vigilance RT test was significantly correlated with both the COMT rs737865 T-allele (P<0.01) and the SLC6A1 rs2697153 G-allele (P<0.01) when subjects consumed oxazepam. There were no shared correlations between the kava and oxazepam treatments. None of the markers measured for liver function showed any significant difference between any of the treatments, and of the adverse side effects reported (including fatigue, headaches, and dizziness), there were also no significant differences between groups.

Although acute administration of oxazepam significantly reduced anxiety, there was no effect observed on anxiety from acute kava consumption; however, a trend increase in anxiety that was seen in the placebo group was absent from the kava group, suggesting a preventative effect of kava. This result could also be due to the lower, but not statistically relevant, baseline anxiety of the placebo group. Also, no acute effects on mood were seen with kava intake, and it is suggested that this may be due to dosage, the stress of the cognitive testing, or the necessity of multiple doses. Another factor discussed is the variation between kava cultivars; as different cultivars may vary in the content of active phytochemicals, this may have affected the results.

In summary, the investigation of correlations between endpoints and genetic polymorphisms is an interesting approach that will, ideally, be incorporated in future clinical studies of medicinal plants; however, in this study these results are difficult to interpret as only one is correlated with a significantly different endpoint. Future clinical studies should incorporate various cultivars of kava, as well as different treatment lengths to fully elucidate the efficacy of kava for anxiety.

—Amy C. Keller, PhD

References


The American Botanical Council has chosen not to reprint the original article.