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An Extract of the Chinese Herbal Root Kudzu Reduces Alcohol Drinking by Heavy Drinkers in a Naturalistic Setting

[Neurobiological, Behavioral, and Environmental Relations to Drinking]

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Abstract

Background: Of the available medications for treating alcohol-related problems, none are universally effective, and all have side effects that may limit their use. Extracts of kudzu containing a variety of isoflavones have been shown to reduce alcohol drinking in rats and hamsters.

Methods: The present study was designed to test the efficacy of a kudzu extract in a clinical population. Male and female "heavy" alcohol drinkers were treated with either placebo or a kudzu extract for 7 days and then given an opportunity to drink their preferred brand of beer while in a naturalistic laboratory setting. Participants served as their own controls, and order of treatment exposure was counterbalanced. Drinking behavior was monitored by a digital scale that was located in the top of an end table.

Results: Kudzu treatment resulted in significant reduction in the number of beers consumed that was paralleled by an increase in the number of sips and the time to consume each beer and a decrease in the volume of each sip. These changes occurred in the absence of a significant effect on the urge to drink alcohol. There were no reported side effects of kudzu treatment.

Conclusion: These data suggest that an extract of this leguminous plant may be a useful adjunct in reducing alcohol intake in a naturalistic setting.

Ethyl alcohol is the most widely used psychoactive drug in the world, and alcohol-related problems contribute to approximately 100,000 deaths annually in the US alone (McGinnis and Foege, 1993; Naimi et al., 2003). There are no uniformly effective pharmacotherapies for treating alcohol abuse/dependence, and only three medications have been approved in the US for treating alcoholism—disulfiram (Antabuse™, Florham Park, NJ), naltrexone (ReVia™, Wilmington, DE), and recently acamprosate (Campral EC™, New York, NY). In addition, many gaps remain in our understanding of which medications are most effective for particular subpopulations (Kranzler, 2000). Because of the multifaceted nature of alcoholism, it is not surprising that drugs from a number of different pharmacological

classes have been tested as possible treatments (Kranzler and Orrok, 1989; Liskow and Goodwin, 1987; Litten and Allen, 1991). Liskow and Goodwin (1987) and Swift (1997, 1999) reviewed and identified agents used to treat alcoholism as belonging to one of six categories: (1) agents to treat withdrawal, (2) anticraving agents, (3) aversive agents, (4) agents to treat concomitant psychiatric problems, (5) agents to treat concomitant drug abuse, and (6) amethystic (reversing or antidrunkenness) agents.

The use of herbal plants to treat alcohol-related diseases dates back to 600 AD. One such Chinese herbal medicine, XJL (NPI-028), has long been used to reduce the inebriation that results from alcohol consumption. NPI-028 contains the extracts of several plants including *Pueraria lobata* (kudzu) and *Citrus reticulata*, which were recorded in an ancient Chinese materia medica entitled Ben Cho Gang Mu (Li, 1590–1596 AD) and have long been used to lessen alcohol intoxication (antidrunkenness) (Sun, circa 600 AD). However, it is difficult to assess the real efficacy of kudzu based on these writings because they are primarily anecdotal in nature.

As a group, the isoflavones are benzo-[gamma]-pyrone derivatives that are found in all leguminous plants. About 500 varieties are known, many of which were studied extensively in the 1950s and found to have weak estrogenic activity (Cheng et al., 1955). These polyphenolic compounds also possess a number of other pharmacological effects such as inhibiting enzymes (Havsteen, 1983; Keung and Vallee, 1993a), scavenging for free radicals (Bors et al., 1990), and reducing inflammation (Di Perri and Auteri, 1988). In addition, isoflavones appear to have antifebrile, antihypertensive, antioxidant, and antidysrhythmic properties (Harada and Ueno, 1975; Nakamoto et al., 1977). The legume kudzu (*Pueraria montana*) was introduced to the US in 1876 as a method of controlling soil erosion. As many residents of the southeastern states of the US know, kudzu spread rapidly and engulfed many farms and buildings. Its thick long roots (up to 20 ft in length) dig deep into the soil, and its large leaves overshadow other crops such that it has been branded "the vine that ate the South." A total of seven isoflavonoids have been isolated from kudzu including puerarin, daidzin, daidzein, 3'-methoxypuerarin, and genistein.

In one of the first empirical studies of kudzu, Niiho et al. (1989) found that plasma ethanol and acetaldehyde levels were lower in mice that had received oral doses of an isoflavonoid fraction of the flower of the kudzu plant *Pueraria flos*. Ethanol's effects on spontaneous locomotor activity also were attenuated in the treatment group. Subsequently, it was shown that NPI-028 could significantly reduce alcohol intake in two strains of alcohol-preferring rats under a range of conditions without the development of tolerance. Low doses of NPI-028 also were effective in alcohol-preferring vervet monkeys in a 24-hr free-choice drinking paradigm (Overstreet et al., 1996, 1998). The effects of certain components of kudzu on suppressing alcohol intake have been reported by several laboratories. Keung and Vallee (1993a,b) demonstrated that daidzin and daidzein were the active herbal components isolated from *Pueraria radix* that suppressed alcohol intake in Syrian golden hamsters. The degree of reduction was more than 50%, and the effects appeared within 1 day of treatment; drinking resumed once the treatment stopped. These researchers also verified that the isoflavones daidzin and daidzein were present in this extract and that intraperitoneal injections of these agents also decreased ethanol

intake (Keung and Vallee, 1994). The experimental design involved a choice procedure of ethanol versus water, and because water intake by the hamsters was unaffected by the isoflavone treatment, they concluded that the isoflavones were selectively reducing ethanol consumption. A recent book (Keung, 2002) was dedicated to reviewing the chemistry and pharmacology of a number of *Pueraria* species, and it is remarkable that these species have such a wide range of effects.

The Chinese herbal medicine (NPI-028) and two of its derivatives suppressed ethanol intake in alcohol-preferring Fawn-Hooded rats (Overstreet et al., 1996). This preparation contains a number of different herbs including kudzu. Ethanol intake was reduced rather abruptly after introduction of NPI-028, while water as well as food intake was essentially unaffected. Lin et al. (1996) found that three isoflavonoids isolated from kudzu (daidzin, daidzein, and puerarin) decreased alcohol consumption by female alcohol-preferring rats by 75%, 50%, and 42%, respectively. These data were observed in the absence of any effects on liver alcohol dehydrogenase and aldehyde dehydrogenase. Heyman et al. (1996) used a two-lever choice procedure to demonstrate that daidzin decreased ethanol consumption in rats as well.

In summary, although the mechanism of action remains unclear, it is widely accepted that the isoflavones found in kudzu are effective in reducing alcohol intake in a number of nonhuman mammalian models. To our knowledge, only one clinical trial using kudzu to treat alcoholism has been reported previously (Shebek and Rindone, 2000), and the researchers found no effect of kudzu on drinking patterns or craving for alcohol among the veterans who participated in the trial. Shebek and Rindone (2000) did not report the concentration of active isoflavones in their kudzu extract. The concentration of isoflavones in the natural product is less than 1%, and our initial attempts using raw kudzu root were not successful in demonstrating any effect on alcohol-induced intoxication (Lukas et al., unpublished observations, 2004). We subsequently developed a more concentrated extract of kudzu that contained 25% isoflavones (Lukas, 2002).

In the present study, we tested whether short-term treatment with an extract of kudzu root containing the three major isoflavones (puerarin, daidzin, and daidzein) reduced alcohol drinking by heavy drinkers. Secondary aims were to determine how drinking patterns were affected during the sessions of free availability of alcohol and to assess the safety of this herbal product.

MATERIALS AND METHODS

Participants

This study received full institutional review board approval, and all participants provided verbal as well as written informed consent. All individuals were first screened for alcohol dependence using the DSM-IV. Because alcoholic beverages were made available in this study, dependent persons, recently detoxified persons, or persons seeking treatment were not allowed to participate and were referred to a treatment program. A total of 14 (11 male) volunteers (mean age ± SD, 24.54 ± 1.05 years; range, 21-32 years) who reported

drinking 25.08 ± 1.97 alcoholic beverages per week were recruited to participate. Participants first tried alcohol at 13.77 ± 1.08 years of age and first drank alcohol on a regular basis at 17.50 ± 0.40 years of age. Lifetime use of marijuana averaged 10.31 ± 3.72 joints. Only one participant smoked tobacco (two cigarettes per day), and weekly caffeine intake was 5.06 ± 1.71 cups of coffee.

All participants were selected with a body mass index of between 19 and 24 kg/m^2 (average ± SD, 22.31 ± 0.30 kg/m^2) to decrease drug response variability due to absorption and redistribution differences (Reed and Kalant, 1977). Individuals who were currently taking any prescription or over-the-counter medications were excluded, and participants were asked to avoid aspirin-containing products because plasma alcohol levels are higher in individuals who have taken aspirin (Roine et al., 1990).

All women received a pregnancy test during the physical examination and just before each drinking session. Pregnant women were not permitted to participate, and any woman who became pregnant before finishing all of her visits was removed from the study, informed to stop drinking, and received counseling to seek medical advice. All women of childbearing potential had to use medically approved methods of contraception. Women who take oral contraceptives have higher plasma acetaldehyde levels after ethanol intake (Jeavons and Zeiner, 1984); therefore, only women who did *not* use oral contraceptives were recruited. Women were studied only during their follicular phase, verified by plasma progesterone levels.

Only individuals with a negative family history of alcoholism were recruited. Family history was determined using criteria initially established by Schuckit (Schuckit and Irwin, 1988). As part of the initial screening for family history of alcoholism, all participants completed the Family Tree Questionnaire for assessing family history of drinking problems (Mann et al., 1985). In completing the Family Tree Questionnaire, the participants had to initially indicate the drinking history of each of the following family members in their family tree: grandparents, parents, aunts, uncles, brothers, and sisters. Each family member was rated as being (a) an abstainer (never drank alcohol), (b) a nonproblem drinker, or (c) a problem drinker (known to have a drinking problem). Abstainers were grouped with nonproblem drinkers for a dichotomous ranking. Family history of alcoholism was calculated using a variation of the family density methods described by McCaul et al. (1991) and Hill and Steinhauer (1993), by crediting participants with 1 point for the father, 0.5 point for each sibling or grandparent, and 0.25 point for each aunt or uncle who was family history positive. An individual was labeled as family history positive if his or her accumulated score equaled 0.75 point or more. Similarly, a participant was labeled as family history negative if he or she scored 0.25 point or fewer. Participants with a score of 0.5 point were excluded from the study to secure a clear differentiation between family history positive and family history negative status. In addition, participants who reported that their biological mothers have (or had) alcohol-related problems were excluded to prevent confounders due to possible in utero exposure to alcohol.

Study Design and Procedure

This experiment was designed to determine if pretreatment with a kudzu extract alters alcohol consumption among participants in a “natural” setting. The volunteers served as their own controls and came to the laboratory a total of four separate times. Each self-administration session was conducted in a natural setting laboratory. This laboratory resembles a small studio apartment complete with satellite TV, audio equipment, VCR, and movies. Four video cameras and intercoms provided visual and audio contact as participants were monitored by staff in the adjacent control room. The natural laboratory was furnished with a recliner chair, end tables, bookshelf, and entertainment center and was decorated with pictures on the wall and small art pieces. It also included a small kitchen area with a refrigerator that was stocked with their preferred brand of beer and a variety of other nonalcoholic beverages such as juices and bottled water. Drinking patterns were measured via a custom-built end table/digital scale (see below). Participants arrived at the laboratory at approximately 4:30 PM and provided a urine specimen and breath sample that were tested for illicit drugs and alcohol, respectively; women also received a urine pregnancy test. Only participants who had negative test results were permitted to continue with the study. Participants were permitted to watch TV or movies or listen to music, but they were not permitted to do their homework or other work. Free access to beverages began at 5:00 PM (only one beverage at a time), and they were permitted to drink the beers as fast or as slow as they desired during the 1.5-hr drinking session. Participants were given the opportunity to consume up to six beers of their preferred brand but were required to set the beer mugs on the custom end table that had a scale built into the tile top (Fig. 1) so that their drinking patterns could be monitored. Once the drinking session was over, participants were served a light dinner, and vital signs and intoxication levels were monitored until it was safe for them to return home via taxicab.

Fig. 1. The custom-designed end table with ceramic tile top is shown with a mug of beer in place (left). The scale is hidden under the ceramic tile top and serves as a base for the scale (right). This view shows that the digital scale is hidden inside the table. The view is from behind the table that normally abuts the wall and so is not typically seen by the participants.

Participants were studied one at a time and came to the laboratory on four separate occasions. The first visit was used to allow them to become familiar with the natural setting laboratory and the protocol. Upon completing this session, they were given double-blind medication to take for the next 7 days. At the end of the first treatment period, participants returned to the laboratory for their second drinking session. They were then given a "washout period" of 2-3 weeks after which time another drinking session was scheduled to determine if they had returned to their baseline drinking levels. After that drinking session had ended, the other medication was then started (counterbalanced for order) and continued for 7 days. The fourth drinking session was then scheduled to take place at the end of the second treatment period.

Treatment

Double-blind medication was administered for 1 week. Each 500-mg capsule of kudzu extract (NPI-031, Natural Pharmacia Int., Inc., Research Triangle Park, NC) contained sugar beet–based filler and 19% puerarin, 4% daidzin, and 2.0% daidzein. Participants were instructed to take two 500-mg capsules three times daily. Gelatin capsules (650 mg per capsule) served as the matched placebo treatment. To preserve the double-blind medication, both capsules (#0 size) were repacked into #00 size opaque capsules. Riboflavin (25 mg) was added to the morning and evening doses of both preparations to measure compliance. During the trial, participants came to the laboratory two times a week to provide urine specimens to be tested for riboflavin (both placebo and kudzu) and puerarin (kudzu only) levels. The urine samples were exposed to ultraviolet light in a dark room and would fluoresce if riboflavin were present. Normal endogenous levels of riboflavin do not fluoresce, and participants were instructed to not take multivitamin complexes while participating in the study. Because riboflavin is cleared from the body rather quickly, a positive test indicates compliance for the past 18-24 hr. Three blood samples were collected during the course of the study (baseline, midweek of kudzu treatment, and midweek of placebo treatment) and analyzed for puerarin levels using an assay that was recently developed in our laboratory (Ma et al., submitted).

Apparatus

A custom-built end table was equipped with a digital scale upon which a ceramic tile was supported (Fig. 1). The output of the scale was fed directly to a computer that recorded each time the glass beer mug was removed and replaced on the table. Participants were instructed to place the mugs on the tile surface after taking a sip and were not permitted to walk around with the mug. The digital scale reader was located in the adjacent control room. The output was sent via a serial cable to the computer. The scale was connected to a reader station that recorded the weight of the mug and beer via a customized computer program that sampled the scale output at 5 Hz. The program was structured to detect any weight change that exceeded 1 g and reported the value to the screen for review by study staff. Data were automatically stored for later analysis. In this manner, a "sip-by-sip" measure of their drinking patterns was obtained during the session. Thus, this table provided both macro and micro measures of drinking behavior.

The scale contains a load cell mechanism so that there is no movement when the mug is placed on or removed from the tile base. This prevents the participants from knowing that the device is actually a scale. They are told only that hospital policy requires that glass mugs be kept on a table at all times and that they are not permitted to walk around with the mugs.

Assessments

Dependent variables were derived primarily from the data collected using the custom-built scale table. These included total number of beers and volume consumed, number of sips per beer, time to consume each beer, and latency to each beer. In addition, participants were asked to complete the Alcohol Urge Questionnaire that provides a composite measure of desire to drink (Bohn et al., 1995). The Alcohol Urge Questionnaire is a series of eight questions that are coded using a 7-point Likert scale with anchors of "strongly disagree" and "strongly agree." The scores are summed to provide a composite score that encompasses three domains of urge to drink including desire to use, expectancy of positive effects, and inability to avoid use (Drummond and Phillips, 2002; Farren et al., 1999). This questionnaire was administered just before the participants were escorted into the natural setting laboratory to participate in the four drinking sessions.

Data Analysis

Three participants were not included in the final analyses because they either did not drink at all during the study ($n = 1$) or did not complete all four sessions ($n = 2$). Dependent variables were analyzed as repeated measures using a linear mixed model with a fixed effect for drug treatment and a random intercept for participant (Jones and Kenward, 2003). Analysis of drinking topography also included a fixed effect for drink order. Changes in topography between the first and second drink were tested by linear contrasts in a model with a drug × order interaction. Drinking urge questionnaires were analyzed using a generalized linear model for ordinal multinomial response to properly accommodate the 7-point Likert scale used in this questionnaire with correlation between repeated measures estimated by generalized estimating equations.

RESULTS

No participant had a negative test for riboflavin, and urine and blood samples from all kudza-treated participants contained puerarin, which is indicative of a 100% compliance rate. Further, no placebo-treated participants had a positive puerarin test. On four occasions, a blood sample could not be obtained from a participant and on all but one of those, the urine specimen was positive. We were unable to obtain either a blood or urine sample on only one visit for one participant. The plasma puerarin levels averaged 0.0296 ± 0.0279 μg/ml and ranged from 0.006 to 0.084 μg/ml. In addition, no participant reported any side effects during either placebo or kudzu treatment. Analysis of the weekly vital signs and urine and blood samples revealed that kudzu did not alter any variable including liver function, hematology, and blood chemistry findings.

Figure 2 shows the effects of the 1-week treatment on alcohol drinking behavior. Compared with placebo, kudzu treatment resulted in significantly fewer beers consumed (Fig. 2A) and a smaller total volume of alcohol consumed (Fig. 2B) during the session. In fact, only one participant actually opened a fifth beer while receiving kudzu treatment, and no one drank all six beers. In contrast, when these same participants were treated with placebo, two of them drank all six beers during the session.

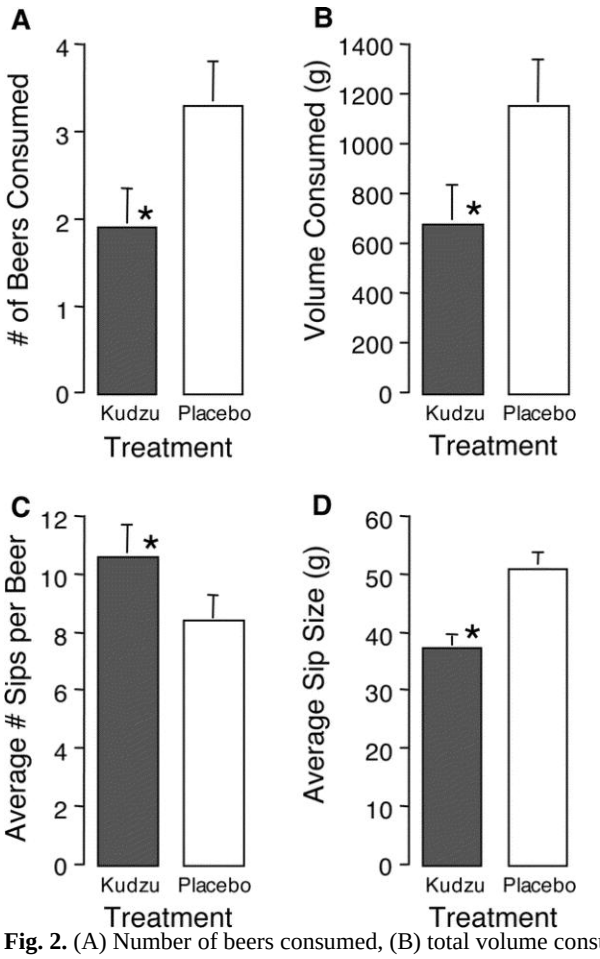

Fig. 2. (A) Number of beers consumed, (B) total volume consumed, (C) average number of sips per beer, and (D) average sip size during a 1.5-hr session after 7 days of either kudzu or placebo treatment. All data were collected using the custom-built scale table. *Significantly different from placebo; *p* ranges from <0.0001 to 0.019. Error bars represent standard deviations.

A more detailed view of this effect was explored by analyzing the drinking topography data that were collected from the scale table. Analysis of the average number of sips (Fig. 2C) and the average sip size (Fig. 2D) revealed that the participants took significantly more but smaller sips to finish each beer while receiving kudzu treatment. Thus, while receiving kudzu treatment, they took nearly 2.5 more sips to finish a beer because each sip was about 14 g smaller.

Table 1 presents the estimated kudzu treatment effect for all of the dependent variables that relate to alcohol drinking. Although many measures of drinking topography were significantly altered by kudzu treatment, some were unaffected. These included the total time to consume each beer, latency to each sip, time between each sip, and time to open each beer. The number of drinks consumed, total volume of beer consumed, number of sips to consume each beer, sip volume, and latency to open each beer were all significantly altered by kudzu pretreatment. Latency to open each beer was, on average, 8 min longer after kudzu pretreatment, but this was not statistically significant.

Table 1. Summary of Treatment Group Differences

Response	Mean (95% CI)		*F* (ndf/ddf)	*p*
	Kudzu	Placebo		
No. of drinks consumed	1.52 (1.05–3.25)	2.59 (2.23–4.36)	6.71 (1/9)	0.029
Volume of beer consumed (ml)	532 (366–1142)	906 (777–1528)	6.49 (1/9)	0.031
Time to consume (min)	21.4 (15.4–27.3)	18.9 (13.9–24.0)	1.42 (1/8)	0.267
Sips to consume (no.)	8.77 (6.57–11.0)	7.32 (5.31–9.33)	7.18 (1/8)	0.028
Sip latency (sec)	104 (49.8–158)	91.7 (46.9–137)	0.38 (1/8)	0.556
Time between sips (sec)	170 (118–223)	167 (119–214)	0.06 (1/8)	0.807
Sip volume (ml)	38.1 (25.4–50.9)	46.3 (33.9–58.8)	22.31 (1/8)	0.002
Time to open (min)	58.1 (44.8–71.4)	50.2 (38.9–61.4)	3.29 (1/8)	0.107

Treatment group differences included least-squares means with 95% CIs for each treatment group and the *F* statistic for the treatment group comparison with associated numerator and denominator degrees of freedom and *p* value from a linear mixed model.
ndf, numerator degrees of freedom; ddf, denominator degree of freedom

Table 1. Summary of Treatment Group Differences

Figure 3 depicts a time course of the sip latency and number of sips per beer to demonstrate how these changed during the session. Although there was little effect on the first beer (Fig. 3, top), the latency to the second beer under both treatments was longer than the first, and kudzu treatment appeared to delay the latency to the first sip of the second beer; however, the difference was not statistically significant. The topography of the number of sips per beer is depicted in Fig. 3 (bottom) and demonstrates that kudzu treatment increased the number of sips during most of the session. Because only one kudzu-treated participant started (but did not finish) the fifth beer, the number of sips data for this fifth beer are not plotted. Each beer in the sequence is plotted against the time the beer was opened in Fig. 4 to provide additional insight to the altered drinking topography induced by kudzu treatment. The typical “binge” drinking pattern seen in the placebo-treated condition was no longer present when the participants were treated with kudzu. Only one kudzu-treated participant opened a fifth beer (and he did not finish it). Kudzu treatment extended the drinking intervals such that the participants drank only four beers in the time that they drank six beers after placebo treatment.

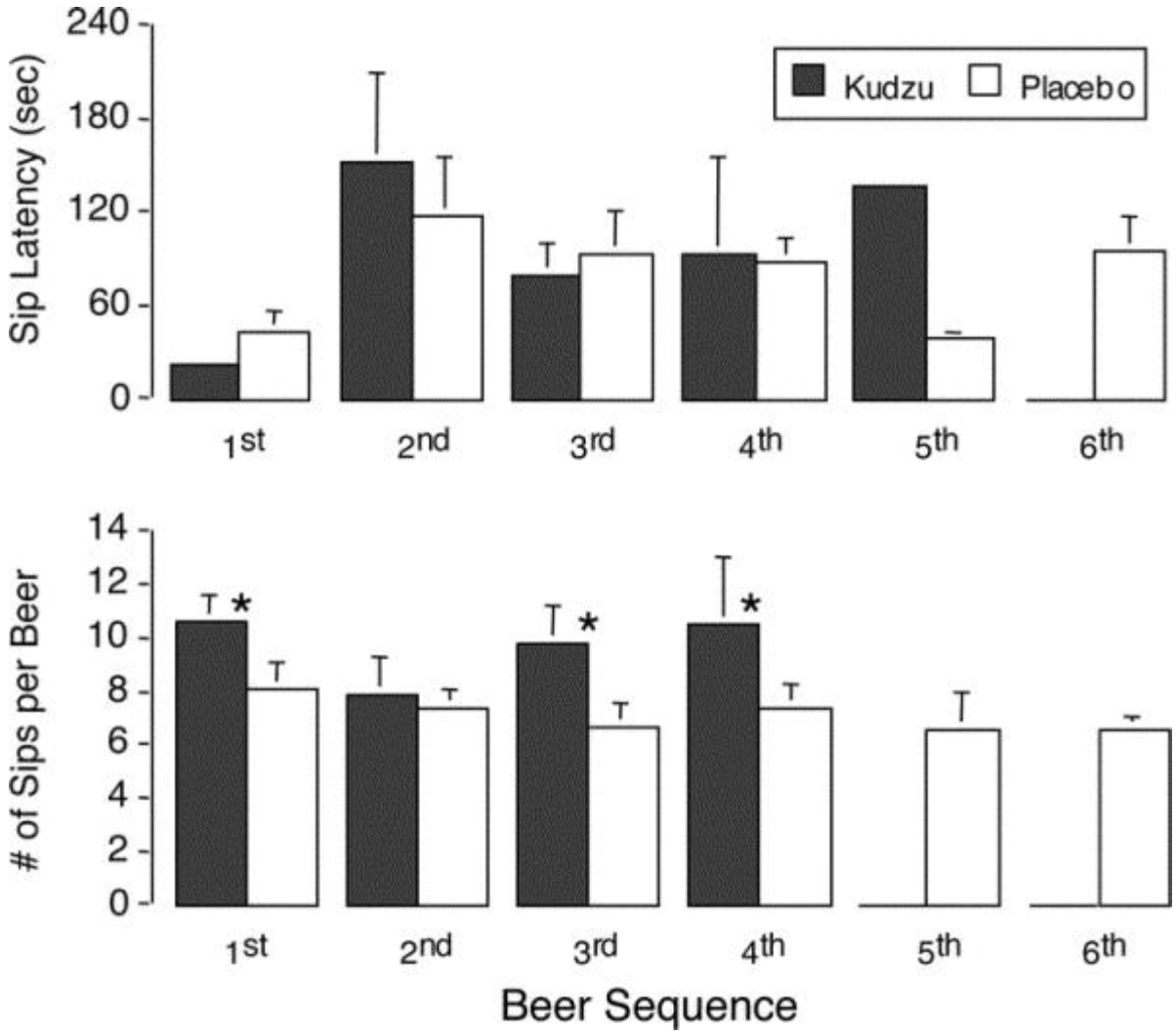

Fig. 3. (Top) Latency to the first sip for each of the six available beers during a single drinking session. (Bottom) Number of sips taken to finish each of the six available beers. *Values that are significantly higher than the placebo condition; *p* varies from 0.0086 to 0.0456. Error bars represent standard deviations.

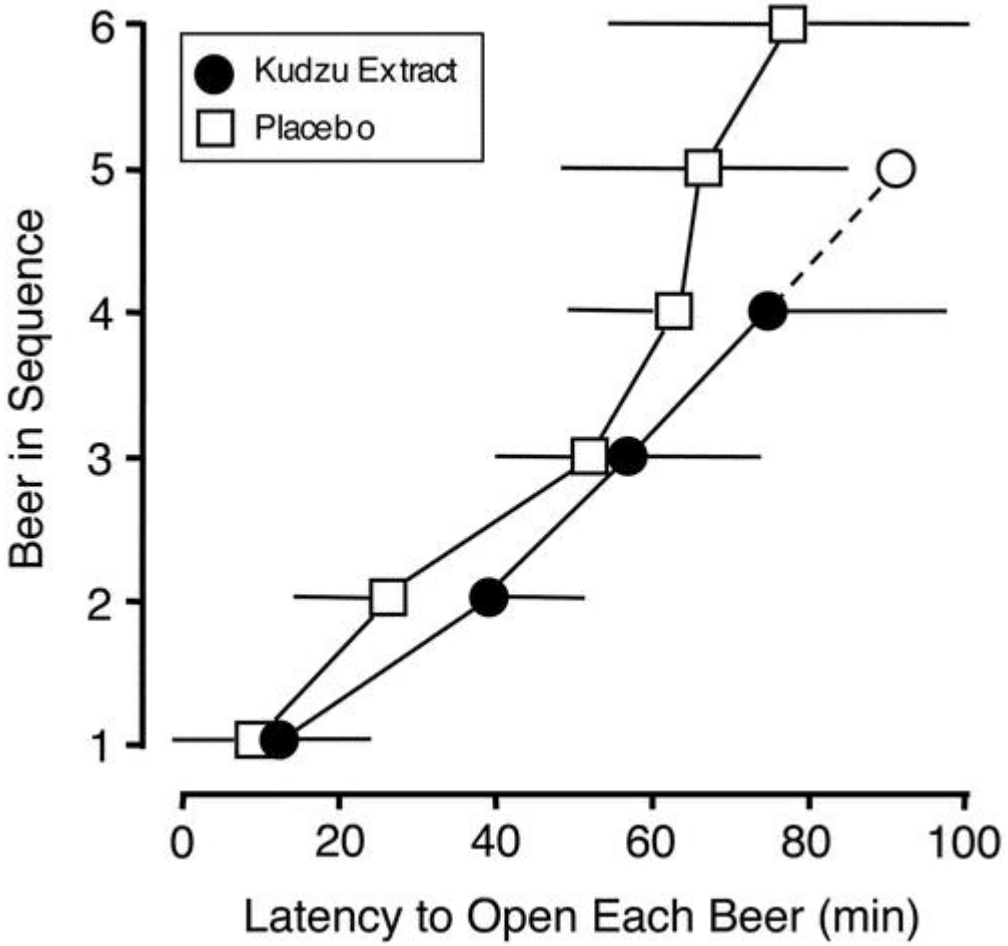

Fig. 4. Cumulative latency to open each beer in sequence during the drinking session. Lines connect sequential beers, and each beer is labeled as 1 (first) to 6 (sixth) along the ordinate. Note that none of the kudzu-treated participants consumed a sixth beer, and only one person started (but did not finish) the fifth beer. Horizontal bars are standard deviations of the latency to open each beer.

Finally, analysis of participant's response to the Alcohol Urge Questionnaire showed that although there was a slight reduction in participants' overall urge to drink alcohol, this effect was not statistically significant (difference = -1.23; 95% CI, 6.98-4.52; $p = 0.64$). In addition, there was no significant effect even when the questions were analyzed on the basis of the three domains of desire, expectancy, and avoidance.

DISCUSSION

This study demonstrates that 1 week of treatment with a kudzu extract results in a significant reduction in the number of beers consumed in a simulated natural environment. This scenario is analogous to a person coming home from work or school and relaxing in his or her living room. The results are strengthened by the fact that each participant served as his or her own control and so received both placebo and kudzu

under double-blind conditions and in random order. Of the 11 participants who completed all four sessions, 8 drank fewer beers while receiving kudzu versus placebo treatment, 2 drank the same number of beers, and 1 drank 1 more beer. However, this is a rather gross measure of intake, and the analysis afforded by the custom-built scale table revealed that there were important kudzu-induced differences in drinking topography.

To our knowledge, there has been only one previously reported controlled clinical trial of kudzu as a treatment for alcohol abuse (Shebek and Rindone, 2000). The investigators reported no effect of kudzu in promoting sobriety or reducing alcohol craving among US military veterans. However, this study had a number of weaknesses (many of which the researchers noted) that limit the impact of their negative findings. These included a large dropout rate (48–53%), small sample size, low statistical power, unsupervised completion of the questionnaires, and only one assessment per month. However, most dropouts in the first month were in the placebo-treated group, which suggests that kudzu may have been having an effect after all. Another procedural problem was that there were no measures of medication compliance; therefore, it was unknown whether their participants actually took the kudzu. A related problem is that while the dosage was stated as being 1.2 g twice daily, no information was provided on the isoflavone concentration that the participants received. Because it is the isoflavones in the kudzu plant that are believed to be the active ingredients (Keung, 2002; Keung and Vallee, 1993a,b), it is imperative to ensure that the isoflavone concentration of the preparation is biologically active—a fact that is never reported on the labels of over-the-counter preparations of kudzu. We have analyzed a variety of commercial kudzu preparations and found them to vary widely in their isoflavone concentration, even within the same manufacturer. None of the preparations contained more than 2% isoflavones, and most contained less than 1%. Although the original 1993 report of Keung and Vallee (1993b) was the first well-controlled study demonstrating that kudzu reduces alcohol intake in an animal model, it is important to note that the Syrian hamsters received a concentrated injection of the kudzu root—a dose that is difficult to achieve in humans using the supplements available in health food stores. Because all of the noted weaknesses in the previous study were avoided in the present investigation, we believe that a concentrated formulation of the kudzu plant is necessary to alter alcohol intake in humans, just as it has done in hamsters and rats.

The mechanism of action of these isoflavones on alcohol consumption is difficult to determine from the data collected in the present study. Data on subjective mood effects and breath alcohol levels after consuming each beer were not collected so that the participants would be free to drink as they might normally do in this simulated naturalistic home environment. Had we interrupted the participants to collect objective measures of intoxication or breath samples, we might have introduced additional variance in the self-administration data and made it difficult to detect and/or interpret meaningful differences in drinking behavior.

In the present study, the “desire” to drink alcohol just before the drinking sessions began was not significantly altered during kudzu treatment, although there was a slight reduction in the composite craving score. This assessment was collected just before the onset of the drinking session, and despite the lack of change in desire for alcohol, their

altered mood state was reflected in their subsequent drinking behavior. A more detailed description of their drinking was revealed via the analysis of the drinking topography using the data collected from the customized scale table. These data suggest that kudzu is probably not acting to block alcohol's effects but instead may be prolonging or enhancing the acute effects of the first drink. Apparently, this effect is sufficient to delay or eliminate the desire to drink subsequent beers and, in particular, may be effective in reducing "binge" drinking such as that seen in the present study. This effect was most clearly observed in the reduction in the total number of beers and total volume consumed but was also evident in the sip-by-sip analysis. Kudzu pretreatment resulted in a marked change in that the sip volume was reduced while the total number of sips per beer was increased. This altered drinking pattern may indicate that these kudzu-treated individuals "titrated" their alcohol intake to a lower amount, perhaps because the first one to two beers had satiated their desire for alcohol.

It is interesting that, in this naturalistic setting, participants consumed nearly 1.5 fewer beers (in only 90 min) after kudzu treatment than after placebo treatment and that this effect occurred after a relatively brief treatment period (1 week). The results from our earlier pilot studies indicated that participants who had been treated with this kudzu extract reported feeling more "tired," "floating," and "intoxicated" after consuming a standard alcohol drink (Lukas et al., 2000); their blood alcohol levels increased at a slightly faster rate as well. This enhanced action of kudzu on alcohol's effects is similar to the purported mechanism of naltrexone in that the first drink is often consumed but the desire for subsequent drinks is reduced (O'Malley and Froehlich, 2003). Nevertheless, the major impact that kudzu may have is to minimize the chance that a "slip" will result in a full "relapse," and the reduction in total daily alcohol intake clearly fits in with a harm reduction position on alcohol abuse. Thus, kudzu may help heavy or binge drinkers to reduce their consumption during each drinking episode.

Although there were a number of statistically significant changes in beer drinking after kudzu treatment, the magnitude of the decrease in drinking was still modest (approximately one to two beers over a 1.5-hr period). However, placed in the context of binge drinking that often exceeds 10 to 12 beers per episode, this small, but significant, decrease in consumption could have important implications. This is especially true because there was a complete lack of any side effects, and no participant could identify that they had taken any medication. It is also significant that there were no changes in vital signs and blood chemistry, liver function, or urinalysis findings during the course of kudzu treatment. We are presently studying individuals after 4 weeks of treatment with this kudzu extract and have not observed any side effects or changes in blood or urine chemistry profiles. The complete lack of side effects of the dose used in this study suggests that higher doses may exhibit greater efficacy and may also be well tolerated. Moreover, a much better than average compliance with this therapy might be expected among heavy drinkers, even during long-term treatment, because there are no side effects.

In conclusion, this kudzu extract may be a useful adjunct in managing excessive alcohol consumption in a population of moderately heavy drinkers. One limitation of the present

study is that alcohol-dependent persons or treatment seekers were not included; these subpopulations will need to be studied to determine if kudzu extract is effective in these individuals as well. In the future, it may be worth examining whether kudzu extract can be used in pregnant women, adolescents, and other vulnerable populations where a lack of medication toxicity is not only desirable but also necessary.

REFERENCES

Bohn MJ, Krahn DD, Staehler BA (1995) Development and initial validation of a measure of drinking urges in abstinent alcoholics. Alcohol Clin Exp Res 19:600–606.

Bors W, Heller W, Michel C, Saran M (1990) Flavonoids as antioxidants: Determination of radical-scavenging efficiencies. Methods Enzymol 186:343–355.

Cheng EW, Yoder L, Story CD, Burroughs CD (1955) Estrogenic activity of some naturally occurring isoflavones. Ann NY Acad Sci 61:652–658.

Di Perri T, Auteri A (1988) Action of S 5682 on the complement system. In vitro and in vivo study. Int Angiol 7:11–15.

Drummond DC, Phillips TS (2002) Alcohol urges in alcohol-dependent drinkers: Further validation of the Alcohol Urge Questionnaire in an untreated community clinical population. Addiction 97:1465–1472.

Farren CK, O'Malley S, Grebski G, Maniar S, Porter M, Kreek MJ (1999) Variable dose naltrexone-induced hypothalamic-pituitary-adrenal stimulation in abstinent alcoholics: A preliminary study. Alcohol Clin Exp Res 23:502–508.

Harada M, Ueno K (1975) Pharmacological studies on pueraria root. I. Fractional extraction of pueraria root and identification of its pharmacological effects. Chem Pharm Bull (Tokyo) 23:1798–1805.

Havsteen B (1983) Flavonoids, a class of natural products of high pharmacological potency. Biochem Pharmacol 32:1141–1148.

Heyman GM, Keung WW, Vallee BL (1996) Daidzin decreases ethanol consumption in rats. Alcohol Clin Exp Res 20:1083–1087.

Hill SY, Steinhauer SR (1993) Postural sway in children from pedigrees exhibiting a high density of alcoholism. Biol Psychiatry 33:313–325.

Jeavons CM, Zeiner AR (1984) Effects of elevated female sex steroids on ethanol and acetaldehyde metabolism in humans. Alcohol Clin Exp Res 8:352–358.

Jones B, Kenward MG (2003) *Design and Analysis of Cross-Over Trials.* 2nd ed. Chapman & Hall, Boca Raton.

Keung WM ed (2002) *Pueraria: The Genus Pueraria.* Taylor & Francis, New York. Keung WM, Vallee BL (1993a) Daidzin: A potent, selective inhibitor of human mitochondrial aldehyde dehydrogenase. Proc Natl Acad Sci USA 90:1247–1251.

Keung WM, Vallee BL (1993b) Daidzin and daidzein suppress free-choice ethanol intake by Syrian Golden hamsters. Proc Natl Acad Sci USA 90:10008–10012.

Keung WM, Vallee BL (1994) Therapeutic lessons from traditional Oriental medicine to contemporary Occidental pharmacology, in *Toward a Molecular Basis of Alcohol Use and Abuse* (Jansson B, Jömvall H, Rydberg U, Terenius L, Vallee BL eds), pp 371–381, Birkhãuser Verlag, Basel.

Kranzler HR, Orrok B (1989) The pharmacotherapy of alcoholism, in *Review of Psychiatry* (Tasman A, Hales RE, Frances AJ eds), pp 359–379, American Psychiatric Press, Inc., Washington, DC.

Kranzler HR (2000) Pharmacotherapy of alcoholism: Gaps in knowledge and opportunities for research. Alcohol Alcohol 35:537–547.

Li SC (1590–1596 AD) Ben Cho Gang Mu.

Lin RC, Guthrie S, Xie C-Y, Lee DY, Lumeng L, Li T-K (1996) Isoflavonoid compounds extracted from *Pueraria lobata* suppress alcohol preference in a pharmacogenetic rat model of alcoholism. Alcohol Clin Exp Res 20:659–663.

Liskow BI, Goodwin DW (1987) Pharmacological treatment of alcohol intoxication, withdrawal and dependence: A critical review. J Stud Alcohol 48:356–357.

Litten RZ, Allen JP (1991) Pharmacotherapies for alcoholism: Promising agents and clinical issues. Alcohol Clin Exp Res 15:620–633.

Lukas SE (2002) Human studies of kudzu as a treatment for alcohol abuse, in *Pueraria: The Genus Pueraria* (Keung WM ed), pp 159–179, Taylor and Francis, New York.

Lukas SE, Lachance M, Ke Y, Lundahl LH, Lee DY, Renshaw PF (2000) The Chinese herb, kudzu, differentially alters brain and plasma ethanol levels in human subjects (abstract). Drug Alcohol Depend 60S:S132. [Context Link]

Ma Z, Wu Q, Lee DYW, Tracy M, Lukas SE Determination of puerarin in human plasma by high performance liquid chromatography. J Chromatogr B Biomed Appl (submitted). [Context Link]

Mann RE, Sobell LC, Sobell MB, Pavan D (1985) Reliability of a family tree questionnaire for assessing family history of alcohol problems. Drug Alcohol Depend 15:61–67.

McCaul ME, Turkkan JS, Svikis DS, Bigelow GE (1991) Familial density of alcoholism: Effects on psychophysiological responses to ethanol. Alcohol 8:219–222.

McGinnis J, Foege W (1993) Actual causes of death in the United States. JAMA 270:2208.

Naimi TS, Brewer RD, Mokdad A, Denny C, Serdula MK, Marks JS (2003) Binge drinking among US adults. JAMA 289:70–75.

Nakamoto H, Iwasaki Y, Kizu H (1977) [The study of aqueous extract of Puerariae Radix. IV. The isolation of daidzin from the active extract (MTF-101) and its antifebrile and spasmolytic effect (author's translation)]. Yakugaku Zasshi 97:103–105.

Niiho Y, Yamazaki T, Nakajima Y, Itoh H, Takeshita T, Kinjo J, Nohara T (1989) [Pharmacological studies on puerariae flos. I. The effects of puerariae flos on alcoholic metabolism and spontaneous movement in mice]. Yakugaku Zasshi 109:424–431.

O'Malley SS, Froehlich JC (2003) Advances in the use of naltrexone: An integration of preclinical and clinical findings. Recent Dev Alcohol 16:217–245.

Overstreet DH, Lee YW, Rezvani AH, Pei YH, Criswell HE, Janowsky DS (1996) Suppression of alcohol intake after administration of the Chinese herbal medicine, NPI-028, and its derivatives. Alcohol Clin Exp Res 20:221–227.

Overstreet DH, Yee Y-W, Chen YT, Rezvani AH (1998) The Chinese herbal medicine NPI-028 suppresses alcohol intake in alcohol-preferring rats and monkeys without inducing taste aversion. J Perfusion 11:381–389.

Reed TE, Kalant H (1977) Bias in calculated rate of alcohol metabolism due to variation in relative amounts of adipose tissue. J Stud Alcohol 138:1773–1776.

Roine R, Gentry T, Hernandez-Munoz R, Baraona E, Lieber CS (1990) Aspirin increases blood alcohol concentrations in humans after ingestion of ethanol. JAMA 264:2406–2408.

Schuckit MA, Irwin M (1988) Diagnosis of alcoholism. Med Clin North Am 72:1133–1153.

Shebek J, Rindone JP (2000) A pilot study exploring the effect of kudzu root on the drinking habits of patients with chronic alcoholism. J Altern Complement Med 6:45–48.

Sun SM (circa 600 AD) Beiji-Quianjin-Yaofang.

Swift RM (1997) The pharmacological treatment of alcohol dependence. N Engl J Med 80:91–93.

Swift RM (1999) Drug therapy for alcohol dependence. N Engl J Med 340:1482–1490.

[END]
