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A Single Dose of Kudzu Extract Reduces Alcohol Consumption in a Binge Drinking Paradigm

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Abstract

Background—Overconsumption of alcohol has significant negative effects on an individual's health and contributes to an enormous economic impact on society as a whole. Pharmacotherapies to curb excessive drinking are important for treating alcohol use disorders.

Methods—Twenty (20) men participated in a placebo-controlled, double-blind, between subjects design experiment (n=10/group) that tested the effects of kudzu extract (Alkontrol-Herbal™) for its ability to alter alcohol consumption in a natural settings laboratory. A single dose of kudzu extract (2 grams total with an active isoflavone content of 520 mg) or placebo was administered 2.5 hours before the onset of a 90 minute afternoon drinking session during which participants had the opportunity to drink up to 6 beers *ad libitum*; water and juice were always available as alternative beverages.

Results—During the baseline session, the placebo-randomized group consumed 2.7 ± 0.78 beers before treatment and increased consumption to 3.4 ± 1.1 beers after treatment. The kudzu group significantly reduced consumption from 3.0 ± 1.7 at baseline to 1.9 ± 1.3 beers after treatment. The placebo-treated group opened 33 beers during baseline conditions and 38 following treatment

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Conflict of Interest Drs. Lukas and Lee hold a patent for kudzu extract to treat alcohol abuse and dependence. McLean Hospital has licensed the production of kudzu extract (NPI-031) to Natural Pharmacia International (NPI), Inc. that markets it as Alkontrol-Herbal™. Dr. Lee has a financial interest in NPI, Inc. Other authors have no conflicts of interest to declare.

Contributors Drs. Lukas, Lee, and Penetar designed the experiment. Ms. Toto and Dr. Penetar conducted the experiment and analyzed the data. All authors contributed to and have approved the final manuscript.

whereas the kudzu-treated group opened 32 beers during baseline conditions and only 21 following treatment. Additionally, kudzu-treated participants drank slower.

Conclusion—This is the first demonstration that a *single* dose of kudzu extract quickly reduces alcohol consumption in a binge drinking paradigm. These data add to the mounting clinical evidence that kudzu extract may be a safe and effective adjunctive pharmacotherapy for alcohol abuse and dependence.

Keywords

kudzu; isoflavone; alcohol; binge drinking

1. INTRODUCTION

Excessive alcohol consumption is a leading cause of illness worldwide (Shield et al., 2013) and has a significant impact on the health of millions people. Over the past two decades, alcohol abuse has affected the national economy and is on the rise as analysis of the estimated cost of alcohol abuse in the US has risen from $148 billion in 1992 (Harwood et al., 1998) to $184.6 billion in 1998 (Harwood, 2000), and to $223.5 billion in 2006 (Bouchery et al., 2011). The impact of excessive alcohol consumption results in increased healthcare costs, loss of productivity, alcohol-related crime (including assault and sexual abuse), and motor vehicle accidents.

Patterns of alcohol consumption vary, but one of the more pervasive types in the younger population is binge drinking. Binge drinking is defined as the consumption of 5 or more drinks for men, and 4 or more drinks for women, in a 2-hour period (National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2015). (A standard drink in the US is defined as containing 14 grams of alcohol, an amount found in 12 oz of beer, 5 oz of wine, and 1.5 oz of 80-proof liquor.) This pattern of rapid drinking typically produces a blood alcohol level above the legal driving limit of 0.08%, and is associated with many alcohol-related problems (including accidents, injuries, crime, and lost productivity; Bouchery et al., 2011; Center for Disease Control and Prevention (CDC), 2004; NIAAA, 2000). The CDC reports that in 2001, binge drinking was responsible for approximately half of the alcohol-related deaths and two-thirds of the economic costs (as measured in years of potential life lost; CDC, 2004). A recent government survey found that 23% (58.6 million) of persons 12 years of age and older engaged in binge drinking in the 30 days prior to the survey (Substance Abuse and Mental Health Services Administration (SAMSHA), 2011). Other surveys have found that 17% of adults engage in a binge drinking episode 4 times per month and consume ~8 drinks per episode (CDC, 2012) and 50% of college-aged drinkers report binge drinking in the past two weeks (NIAAA, 2014).

There are currently three FDA-approved medications for alcohol use disorders: disulfiram (Antabuse®), naltrexone (in both an oral formulation [ReVia®] and a sustained-release injectable formulation [Vivitrol®]), and acamprosate (Campral®) (Friedmann, 2013; Williams, 2005). All are available only by prescription. While they are effective for some individuals, they are not universally useful or well tolerated for all patients. Currently, we do not know which treatment strategy is useful for an individual patient population (Kranzler,

2000) and the many side effects often limit their acceptance and adherence (Edwards et al., 2011). There are no over-the-counter medications or preparations that are proven to reduce alcohol consumption, and no medication has been evaluated specifically to treat binge drinking patterns of consumption.

Readings of historical Chinese texts (Li, 1590–1596; Sun, circa 600 AD) reveal that extracts of the kudzu root have been used to treat alcoholism and drunkenness since at least 600 AD. Recent analysis of the kudzu root has revealed it contains 3 active isoflavones that have antidipsotropic activity: daidzin, daidzein, and puerarin. Studies with these components demonstrated significant reductions in alcohol consumption in animal models. Heyman et al. (1996) showed that daidzin-treated rats had a dose-related decrease in lever pressing reinforced by oral alcohol consumption. Keung and co-workers showed the effectiveness of daidzin and daidzein to suppress ethanol consumption in Syrian golden hamsters (Keung et al., 1995, 1993). Lin et al. (1996) showed dose-related reductions in alcohol consumption of 40 to 65% with oral ingestion of puerarin (100–300 mg/kg/day). Benlhabib et al.'s (2004) work with puerarin showed not only a 50% reduction in alcohol intake, but a suppression of alcohol withdrawal symptoms in alcohol preferring rats.

Our laboratory has been involved in assessing an extract of the kudzu root (*Pueraria lobata*) for its ability to reduce alcohol consumption in humans. In the first, kudzu extract was administered for 7 days and acute binge drinking was suppressed (Lukas et al., 2005). In the second, participants who were treated for 4 weeks with kudzu extract significantly reduced their alcohol consumption during weeks 2 through 4 of the study (Lukas et al., 2013). We have subsequently shown that puerarin is the major active isoflavone because 7 days treatment with this compound alone (1,200 mg/day) produced a similar reduction of binge drinking as the extract (Penetar et al., 2012). Given that a week of preplanning is unlikely before a binge drinking episode or opportunity, we built on our previous findings to explore in the present experiment if a *single dose* of kudzu extract taken shortly before a drinking session would reduce alcohol consumption.

2. MATERIAL AND METHODS

2.1 Participants

A total of 32 participants (28 men, 4 women) between the ages of 21–40 years old were recruited through advertisements in local newspapers and on the internet (e.g., CraigsList and local University websites) to participate in this study. Inclusion criteria included good physical and mental health, a body mass index (BMI) between 18 and 30, ages between 21 and 40 yrs, and a self-reported drinking pattern of 15 drinks per week or incidences of binge drinking 2 or more times per week. Exclusion criteria included a diagnosis of an Axis I disorder (as assessed through the Structured Clinical Interview for DSM disorders (DSM-IV-TR; First et al., 2002), psychoactive prescription medication, current or past alcohol dependence, cigarette consumption greater than 5 per day, and heavy caffeine use (defined as greater than 500 mg of consumption per day). Four participants failed to meet inclusion criteria and 8 participants dropped out of the study before completion (1 after the first drinking session and was lost to follow-up; 7 due to schedule conflicts with work, school or family emergencies and were not interested in continuing). Twenty men (18 Caucasian [1

Hispanic] and 2 multiracial) completed both sessions of the study and were used in the analysis. They were physically and mentally healthy individuals, 23.6 ± 3.6 years old, with a BMI between 22 and 30 (M = 25.4 ± 2.5) and reported drinking on average 3.4 ± 0.9 days/week and consumed on average 18.5 ± 6.2 drinks per week with an average of 5.7 ± 2.0 drinks per drinking day (demographics reported in Table 1). All participants were primarily beer drinkers, only occasionally consuming other types of alcoholic drinks. None of the participants met criteria for alcohol abuse or dependence, nor had current psychiatric disorders. Seven were light cigarette smokers (less than 1 to 4 cigarettes per day), 13 used marijuana recreationally (up to 2 times per month), and none were heavy users of caffeinated beverages. The McLean Hospital Institutional Review Board reviewed and approved the study and related documents (advertisements, informed consent, protocol). Participants provided written informed consent and were financially compensated for their time.

2.2 Materials and Medication

Drinking sessions were conducted in a modified laboratory room decorated to simulate a dormitory or small apartment (the `natural settings') room and included carpeting, wall hangings, an overstuffed reclining chair, end tables, lamp, television with satellite connections, DVD player and stereo equipment, and bookcases. The room contained a small sink with an under-the-counter refrigerator where the beverages (beer, juice, and water) were kept.

Kudzu extract was administered in gelatin capsules containing 500 mg of extract (Alkontrol-Herbal™; NPI-031) prepared by Natural Pharmacia International, Inc., Burlington, MA. The extract contained 26% (130 mg) active isoflavones (20% puerarin, 4% daidzin, 2% daidzein; an improved HPLC analysis revealed that the total puerarin content includes both puerarin and 3-methoxypuerarin.). Participants were randomized on a blind basis to receive either 4 capsules of the extract (for a total of 520 mg isoflavones) or placebo (sugar beet filler) 2.5 hours before the start of an afternoon drinking session. This pretreatment time was selected based on our pharmacokinetic study of puerarin absorption and elimination (Penetar et al., 2006).

Drinking was recorded using a custom built end table that contained a digital scale beneath a ceramic tile insert in the tabletop (Ohaus model #B10P with I5S controller). Participants were instructed to always keep the beer glass on the table except when taking a sip. The scale was connected to a computer in an adjacent room that ran a customized program that sampled the scale at 5 Hz and detected any weight changes that exceeded 1 gm. This rapid sampling of the weight permitted a real time assessment of drinking topography that included gross measures of volume and number of beers consumed but also provided details on a more micro level and included the number and size of sips taken, latency to opening a beer, and consumption time of each beer. Additional details and photos of the device can be found in Lukas et al. (2005). Breath alcohol levels were assessed using an Alco-Sensor FST breathalyzer (Intoximeter, Inc., St. Louis, MO) both before and after the drinking session; values were not collected during the active alcohol acquisition period to avoid interacting with the participant and allowing natural drinking patterns to emerge.

2.3 Assessments

The primary measure of drinking was the number of beers (bottles or cans) opened and consumed. Additional analyses included the amount (weight in grams converted to volume in ounces) of the beverage consumed in a sip by sip analysis, latency from the beginning of the session to opening each drink, and the time to consume each drink. Because the alcohol content of individual brands of beer varies slightly, a calculation and analysis of the absolute amount of alcohol consumed (in grams) was also performed. The use of `beers' as the primary measure is based on the manner in which beer (and other standard drinks) is served and consumed, and how drinking behavior is often defined in the addiction field and understood by the general public. Just prior to the beginning of the drinking session, participants completed the Alcohol Urge Questionnaire (AUQ; Bohn et al., 1995), an 8-item 7-point Likert scale questionnaire assessing three domains of the urge to drink (desire to drink, expectation of positive effects, and inability to avoid drinking; Drummond et al., 2002; Farren et al., 1999); the Profile of Mood States (POMS; McNair et al., 1971); and a series of visual analog scales (VAS) to rate subjective behavioral responses from `not at all' to `extremely' on drunk, floating, dizzy, clumsy, anxious, feeling effects of alcohol, uncomfortable, high, desire to use, desire to avoid, muddled, slurred speech, nauseated, sleepy, terrible, great, happy, and stimulated. The POMS was administered again at the end of the drinking session. The visual analog scales were administered again after the drinking session and at 1, 1.5, 2 and 2.5 hours (8:30 pm) after the session.

2.4 Procedure

A between subjects design was used and participants were randomly assigned to the placebo or active medication group. Each person participated in two drinking sessions separated by at least 7 days. The first was a familiarization/baseline session (no medication given); the second was the medication administration session during which kudzu extract or placebo was given in a double-blind fashion. Participants arrived individually at the laboratory for an afternoon drinking session that began at 4:30 pm. They were required to abstain from consuming alcoholic beverages from 10 pm the night before and were cautioned not to have drunk heavily (if at all) the night before (no more than two alcoholic beverages). No caffeine was permitted after 9 am on the study day. After verification of no recent use of drugs of abuse (negative urine screen), a negative breath sample for alcohol, and carbon monoxide below 10 ppm, they were escorted to a waiting room. Medication was administered 2.5 hours before the second drinking session. Fifteen minutes before the beginning of a drinking session, they were escorted into the natural settings room and completed computerized presentations of the AUQ, POMS, and VAS. At the appropriate time, the refrigerator was unlocked and they were free to read, watch television, listen to music, or watch movies (movie choices were available from a list of titles that did not include any blatant or recurrent alcohol or drug using themes). They were instructed that if they wanted a drink, they were to go to the refrigerator, open a bottle or can of their beverage of choice, pour it completely into the mug, and place the mug on the center of the table's ceramic tile. The mug was to remain on the table at all times except when they picked it up to take a sip, and they were instructed to place the mug back on the table after the final sip. The drinking session lasted 1.5 hours (until 6 pm). During that time they had the opportunity to consume up to 6 bottles or cans of beer in addition to bottles of water and juice. Participants chose

their beer preference from common named brand beers with an alcohol content between 3.2% and 5.9%, and drank the same brand of beer for both drinking sessions. They did not have to finish the entire contents of a beverage, but they could have only one drink open at any one time. No food was permitted during the drinking session. At the end of the session, they provided a breath sample for alcohol, filled out questionnaires, were provided dinner, and were free to relax (read, watch television/movies) until at least 2.5 hours after the conclusion of the session. When their breath alcohol levels were below 0.04% and they passed a field sobriety test, they were released to go home. Taxicab transportation was provided to and from the laboratory.

Data were analyzed using a linear mixed model analysis of variance (with subjects as random and fixed factors of drinking session and medication treatment) with drinks per week and drinks per drinking day reported at intake as covariates, and standard correlational (Pearson) and regression analyses (IBM SPSS, version 19 for Mac OS). Counts of beers opened were compared using the Wilcoxon Rank Sum Test with an exact testing procedure (coin package in R for Mac OS), which is more powerful for small datasets with a high frequency of ties (Hothorn et al., 2006, 2008). A significance level of $p<0.05$ was set.

3. RESULTS

3.1 Alcohol Consumption

The average alcohol content for the beers consumed by the placebo group was 4.7% and 4.4% for the kudzu group [$t(18)=1.448$, ns]. During baseline conditions, the average number of beers consumed overall was 2.8 ± 1.3 beers with the placebo group drinking 2.7 ± 0.78 beers and the kudzu group drinking 3.0 ± 1.7 beers (Figure 1). The placebo-treated group increased their consumption slightly to 3.4 ± 1.1 beers while the kudzu-treated group decreased their consumption to 1.9 ± 1.3 beers. There was a significant session by treatment interaction [$F(1,36)=4.987$, $p=0.032$] indicating that the changes between the two drinking sessions differed for placebo vs. kudzu treatment. Specifically, when comparing the change from baseline in the kudzu group to the corresponding change in the placebo group, the difference is −1.78 beers (95% CI: −3.40, −0.16). Fewer kudzu-treated participants opened the available beers than the placebo-treated participants (Figure 2). During baseline conditions there was no difference in the number of beers opened by either group (33 vs. 32 for the placebo- versus kudzu-treated groups, respectively). Following treatment, placebo-treated individuals opened a total of 38 beers while kudzu-treated individuals opened only 21 beers ($Z=2.3841$, $p=0.0186$). (The number of beers opened but not fully consumed accounted for the slight discrepancy between the count of beers opened and the average number of beers/amount consumed). The group difference following medication administration is also reflected in the total amount of beer consumed (Figure 3, upper panel). Average amount of beer consumed for the placebo-treated group was 39.80 ± 13.5 ounces versus 23.1 ± 15.5 ounces [significant session X treatment interaction: $F(1,36)=4.753$, $p=0.036$]. Absolute amount of alcohol consumed was calculated for each individual participant. During baseline, the placebo-randomized group consumed 35.08 ± 11.7 gm while the kudzu-randomized group consumed 37.7 ± 22.8 gm. Following treatment in the second drinking session, the placebo-treated group consumed 44.7 ± 20.2 gm while the

kudzu-treated group consumed 23.5 ± 16.8 gm [significant session X treatment interaction: F(1,36)=4.227, p=.047]. The individual consumption amounts were correlated with their breath alcohol levels taken at the end of the drinking period. For both groups, there was a significant correlation between the two measures (Placebo r = 0.853, p=0.002; Kudzu r = 0.931, p<0.001). These correlations were not significantly different (Z=0.0745, ns). Breath alcohol measurements taken shortly after the drinking session revealed that the kudzu-treated individuals had significantly lower estimates of blood alcohol levels (30 ±0.01 mg/dL) than placebo-treated individuals (73 ±0.014 mg/dL) [significant treatment effect: F(1,18)=5.919, p=0.026] (Figure 3, middle panel).

The average time to consume a full beer in the second drinking session was longer in the kudzu-treated group - 28.1 ± 3.8 minutes – compared to placebo-treated participants – 22.4 ± 3.4 minutes [significant treatment effect: F(1,16)=4.680, p=0.046] (Figure 3, lower panel). Latency to opening the first beer was at approximately 7 minutes into the session, and then at 15-20-minute intervals if a participant drank subsequent beers (data not shown). The slight difference between opening the 1st beer for the placebo-treated individuals (5.3 ± 2.5 min) and the kudzu-treated individuals (8.8 ± 6.0 min) in the second drinking session was not significant [F(1,17)=0.314, ns]. The number of sips taken to drink a beer was not significantly different between the groups averaging approximately 10 sips per beer for both groups (data not shown).

3.2 Behavioral and Subjective Effects

Analysis of the self-rated scores on the VAS for the second drinking session (when medication was given) revealed significant before and after drinking interactions for the scales of drunk [F(1,36)=11.841, p=0.001], floating [F(1,36)=4.826, p=0.035], dizzy [F(1,36)=10.322, p=0.003], clumsy [F(1,36)=5.124, p=0.030], and feel effects of alcohol [F(1,36)=20.694, p<0.001]. There were no significant changes in scores for the other scales. The time course of effects for four scales is shown in Figure 4. Scores on the Alcohol Urge Questionnaire were similar for both groups before the treatment drinking session (session 2). The placebo group had an average score of 24.8 ± 8.9 and the kudzu-treated group had an average score of 21.4 ± 4.8; these were not significantly different and scores before the first drinking session were similar. An analysis of ratings on the POMS for the second drinking session revealed a significant main effect of time before vs. after drinking with increases in confusion [F(1,36)=8.161, p=0.007] and a trend towards degreased vigor [F(1,36)=3.559, p=0.067] in both groups. There was no significant medication effect or interaction.

4. DISCUSSION

Previous studies conducted in our laboratory have shown that one week and four weeks of kudzu extract administration are effective in reducing alcohol consumption by non-treatment seeking, heavy social drinkers (Lukas et al., 2005, 2013) and that puerarin alone, the major component of the extract, is similarly effective (Penetar et al., 2012). The present study provides further evidence that extracts of the kudzu root are effective in reducing alcohol consumption but unlike any other medication (other than disulfiram) it does so after a single dose was taken shortly before a binge drinking opportunity. And, contrary to disulfiram

treatment, the drinking that did occur after kudzu administration did not result in any noxious side effects, increases in subjective ratings of nausea, uncomfortable, or feeling terrible. The reduction in drinking was evident rather quickly as it was apparent for the second through sixth beers and no kudzu-treated participant drank five or six beers, which suggests that binge drinking was curtailed.

Although the number of sips taken per beer did not significantly increase in this study – contrary to what was found in our previous study (Lukas et al., 2005) - we did observe an increase in the time taken to consume a beer which is consistent with our previous study. This change in drinking topography was not secondary to alterations in the subjective effects of alcohol as kudzu-treated individuals still reported positive feelings (e.g., drunk, floating) without any change in the negative effects (e.g., clumsy, dizzy). The apparently lower magnitude of subjective effects compared to the placebo treated group (Figure 4) is due most likely to the fact that the kudzu-treated individuals drank less alcohol during the session, which was reflected in significantly lower breath alcohol levels. When given equal amounts of alcohol, kudzu- and placebo-treated individuals respond similarly (Penetar et al., 2011).

One limitation of this study is the lack of a dose-response assessment. Although the dose used in the present study has been vetted in prior studies, testing multiple doses would be helpful to fully explore the magnitude of effects of the kudzu root extract and determine if an even greater reduction in drinking is possible with a higher dose. The complete lack of side effects would favor the conduct of such studies. Our previous studies indicate that the dose used here is producing measurable levels of puerarin in the blood (Penetar et al., 2006), but the concentrations of other isoflavones (e.g., daidzin and daidzein) are unknown as we currently lack a standard biochemical assay for human blood. Although daidzin and daidzein have been shown to reduce alcohol consumption in animal models (Heyman et al., 1996; Keung et al., 1993; Lin et al., 1996), their contribution to the antidipsotropic properties of the kudzu extract in humans is unknown as only puerarin can be studied in humans at the present time (under IND #102,425). Other limitations of the present study are the use of a rather narrow aged male population who drink only at moderate levels. Therefore, the generalizability of the present findings to women, populations of different ages and degrees of dependence and in treatment-seeking individuals is currently unknown and so future studies aimed at these populations will be needed in order to fully assess the role of kudzu extract in treating alcohol abuse/dependence.

In spite of the compelling preclinical and clinical evidence of its efficacy, the precise mechanism of action of kudzu in reducing alcohol consumption is not currently known. Prior studies of its antidipsotropic effect have focused on taste-aversion, alterations in alcohol metabolism or effects on neurotransmitters. Overstreet et al.'s (1998) study provides cursory evidence that a taste aversion mechanism is not likely. Other investigators have focused on possible alterations in alcohol metabolism through a blockade of aldehyde dehydrogenase (ALDH) activity as, at least one of the major isoflavone components of kudzu, daidzin, is a reversible inhibitor of the ALDH2 enzyme (Keung et al., 1993). A subsequent study by the same group demonstrated that a simple increase in acetaldehyde, which can cause a disulfiram-type reaction following alcohol consumption when ALDH is

inhibited, is unlikely to be the mechanism, at least in nonhumans, for reducing alcohol intake (Keung et al., 1995). More recent evidence suggests that at least one of the major isoflavones contained in kudzu extract, daidzin, and its analogs may alter central serotonergic and catecholaminergic pathways that are important for the reinforcing effects of alcohol (Gao et al., 2001; Keung, 2003; Rooke et al., 2000). Through its inhibition of mitochondrial ALDH2, daidzin blocks the pathway of serotonin metabolism to 5-hydroxyindole acetic acid (5-HIAA) and dopamine to 3,4 dihydroxyphenyl acetic acid (DOPAC) and produces an accumulation of their respective intermediates, 5-hydroxyindole acetaldehyde (5-HIAL) and 3,4 dihydroxyphenyl acetaldehyde (DOPAL). Increases in 5-HIAL have been shown to be correlated with decreased alcohol consumption in hamsters (Keung et al., 1995). Kudzu's alteration of alcohol consumption may be through direct effects at brain benzodiazepine receptors on the $GABA_A$ complex. Both puerarin and daidzein have been shown to inhibit benzodiazepine binding at this site (Overstreet et al., 2003; Shen et al., 1996), and because alcohol's effect are modulated, in part, by the chloride channel present at this site in the $GABA_A$ receptor complex, there may be an important interaction between the presence of isoflavones, $GABA_A$ receptor activity, and the subjective effects of alcohol that alters consumption.

All of the above mentioned mechanisms, with the exception of a disulfiram-like one, require repeated administration and time to develop. Since consuming alcohol while taking kudzu extract is not aversive, another explanation is necessary to account for the extremely fast onset of action observed in the present study. The most obvious is one that involves alcohol pharmacokinetics. The correlational analysis of absolute amount of alcohol consumed and breath alcohol levels in this study indicates that the physiological effects and the rate of elimination of ingested alcohol are not altered by kudzu administration. This was demonstrated in our previous study (Penetar et al., 2011) where pharmacokinetic parameters such as peak concentration and elimination time were not affected by kudzu. In that study, however, we did find evidence of an initial more rapid rise in blood alcohol levels in kudzu-treated individuals, suggesting that isoflavones may alter *bioavailability* of alcohol to the brain during the ascending alcohol absorption phase. This interpretation of kudzu's possible mechanism of action was also suggested by Wong et al. (2011) who postulated that kudzu alters peripheral and cerebral blood flow. Puerarin, one of the most abundant isoflavones in kudzu root extracts, is a known vasodilator and is approved for such use in China following coronary infarction and stroke (Wu et al., 2014).

The ability of puerarin and related isoflavones to facilitate alcohol's entry into the brain has not been systematically studied. For this mechanism to be plausible, the more rapid penetration of alcohol into the brain would have to trigger a satiety mechanism rather quickly such that the desire for the next drink is delayed—thus interrupting a binge episode. This is precisely what was observed in the present study as kudzu's effects were evident after a single dose within a few hours of administration. Of course, it is entirely possible that any of the above mechanisms may *also* develop with repeated administration and complement the immediate altered absorption effect that likely explains kudzu's rapid onset of action.

Regardless of the mechanism of action, the present finding that a modest, single dose of kudzu extract reduces binge drinking has profound implications as it offers a unique

opportunity for early intervention for problem drinkers. As an herbal plant extract, kudzu can be made available without a prescription. While it does not completely eliminate drinking, it is clearly effective in significantly reducing intake, which offers individuals an opportunity to engage in more responsible drinking patterns. As a safe, over-the-counter preparation, kudzu may be used alone in initial attempts to curb alcohol consumption, but it may also become a useful adjunct to the currently available prescription medications. This latter scenario might very well permit the use of lower doses of prescription medications and thus reduce the incidence of side effects. Furthermore, because kudzu extract exerts its beneficial effects within hours of the first dose, it could be administered along with a prescription medication and provide "coverage" until the other medication begins to work.

This study provides additional evidence that an extract of the kudzu root significantly reduces alcohol consumption by human participants and confirms that this botanical medication may be a safe and effective adjunct pharmacotherapy for treating alcohol use disorders.

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- Isoflavone containing compounds have traditionally been studied to alleviate alcohol problems
- An extract of the kudzu root is shown to significantly reduce alcohol consumption
- A single pretreatment dose of the kudzu root may reduce binge drinking

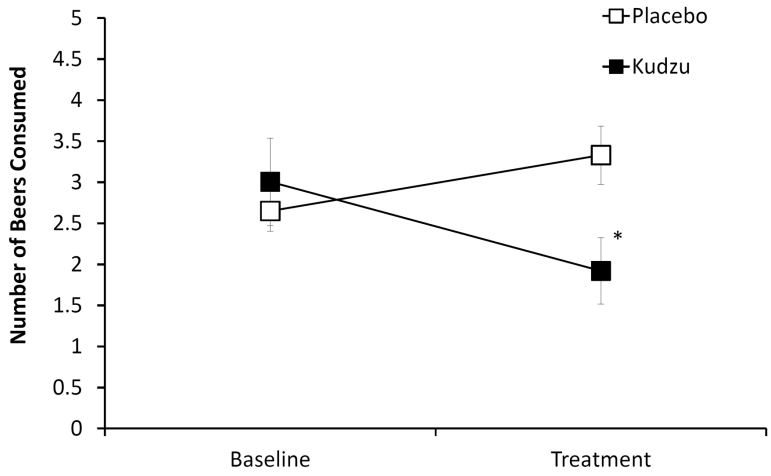

Figure 1.

Number of beers consumed by group for the 1st (baseline) session where no medication was given, and for the 2nd (treatment) session where kudzu or placebo was administered 2.5 hours before the session. Plotted points are averages ± SEM, n=10 per group. *Kudzu-treated participants significantly decreased their drinking.

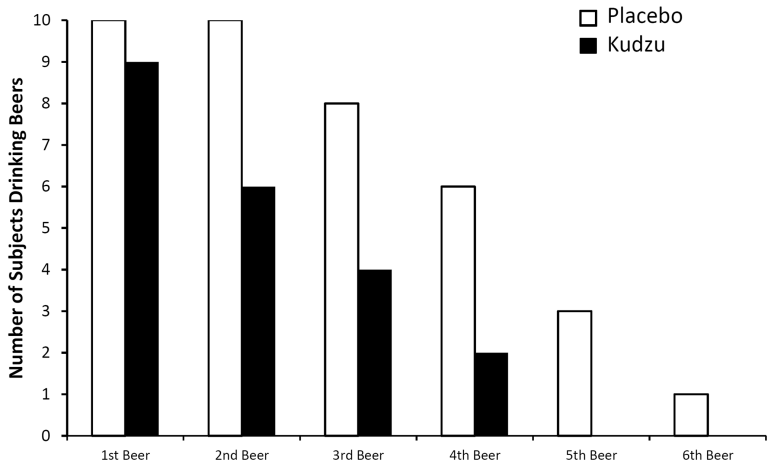

Figure 2.

The number of participants who drank each available beer during the 1.5 hour drinking session following administration of placebo or kudzu. No kudzu-treated participant drank a 5^{th} or 6^{th} beer.

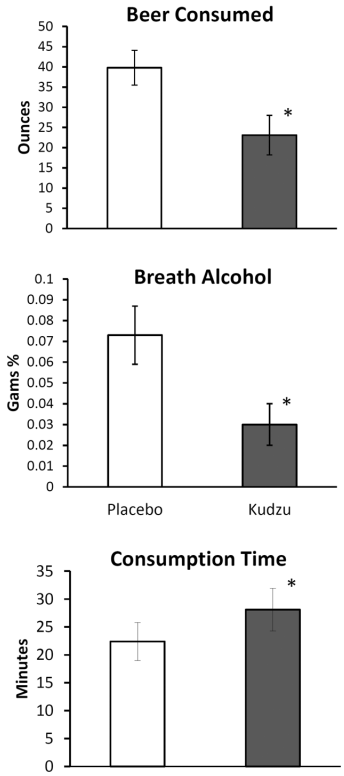

Figure 3.

Measures of drinking for the 2nd (treatment) session. Total volume of beer consumed (upper panel); Breath Alcohol Levels immediately after the drinking session ended (middle panel); and Time to consume beers (lower panel). Bars are averages ± SEM, n=10 per group. *Significantly different from placebo.

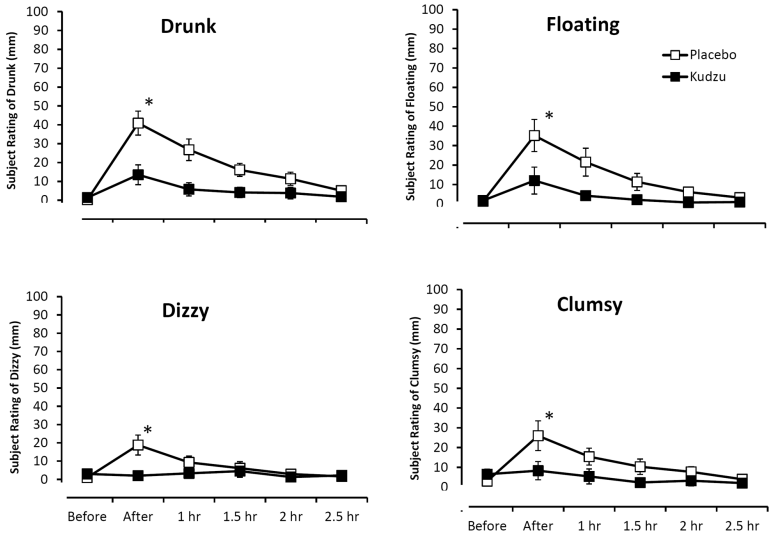

Figure 4.

Ratings on four Visual Analog Scales on a scale of 0 – `not at all' to 100 – `extremely'. Ratings were taken during the second (treatment) drinking session before the drinking session started, immediately after the drinking session ended, and at additional times, as indicated. *Significant interactions indicate that placebo group changes are greater than kudzu group changes. Plotted points are averages ± SEM, n=10 per group.

Table 1

Demographic profiles of participants. Values are averages ± sd

	Placebo (n=10)	**Kudzu (n=10)**	***p* value**
Age (years)	24.6 ± 3.3	22.6 ± 3.7	0.785
Weight (pounds)	181.3 ± 9.5	176.3 ± 22.5	0.529
Body Mass Index (BMI)	26.1 ± 2.2	24.6 ± 2.6	0.192
Race (Ethnicity)	9 Caucasians; 1 Multiracial	9 Caucasians; 1 Multiracial; (1 Hispanic)	
Age of first drink	16.2 ± 2.0	16.2 ± 1.9	> 0.99
Years drinking regularly	5.3 ± 3.5	4.6 ± 3.5	0.661
# drinks/week	15.8 ± 5.6	21.1 ± 5.8	0.054
# drinking days/week	3.4 ± 0.94	3.5 ± 0.96	0.817
# drinks/drinking day	4.9 ± 1.6	6.5 ± 2.1	0.068
Tobacco smokers[1]	0	1	
Marijuana users[2]	6	7	

[1] Those reporting daily smoking (participant reported smoking ~4 cigarettes/day)

[2] All users reported 2 times per month or less