

ARTICLE

Liver Function Test Abnormalities in Users of Aqueous Kava Extracts

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ABSTRACT

Introduction. Hepatic toxicity from manufactured herbal remedies that contain kava lactones has been reported in Europe, North America, and Australia. There is no evidence for serious liver damage in kava-using populations in Pacific Island societies or in Indigenous Australians who have used aqueous kava extracts. This article presents evidence that liver function changes in users of aqueous kava extracts appear to be reversible. Data from one Arnhem Land community [Northern Territory (NT), Australia] with 340 indigenous people older than 15 years of age in 2000 are used. *Methods.* This study was a cross-sectional study with 98 participants, 36 of whom had never used kava. Among 62 kava users, 23 had discontinued kava at least 1 year before the study. Continuing users had not used kava for 1 to 2 months ($n = 10$) or 1 to 2 weeks previously ($n = 15$). Some ($n = 14$) had used kava within the previous 24 hr. Liver function tests were compared across these groups, taking into account differences due to age, sex, alcohol, and other substance use. *Results.* The average quantity of kava powder consumed was 118 g/week, and median duration of use was 12 years (range, 1–18 years). Kava usage levels were less than one-half of those found in previous studies. More recent kava use was independently associated with higher levels of liver enzymes gamma-glutamyl transferase (GGT) ($p < 0.001$) and alkaline phosphatase (ALP) ($p < 0.001$), but not with alanine aminotransferase or bilirubin, which were not elevated. In those who were not heavy alcohol users, only those who used kava within the previous 24 hr showed GGT levels higher than nonusers ($p < 0.001$), whereas higher ALP levels occurred only in those who last used kava 1 to 2 weeks ($p = 0.015$) and 24 hr previously ($p = 0.005$). *Discussion.* Liver function changes in users of aqueous kava extracts at these moderate levels of consumption appear to be reversible and begin to

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return to baseline after 1 to 2 weeks abstinence from kava. No evidence for irreversible liver damage has been found.

Key Words: Hepatic toxicity; Kava; Aqueous extracts; Indigenous Australian.

INTRODUCTION

Since the late 1990s, several countries have reported serious irreversible liver damage in people using herbal products that contain ethanol or acetone extracts of kava lactones (1–3). Consequently, manufactured kava-based products have become subject to medical alerts or bans on their sale in Europe (4), North America (5,6), and Australasia (7).

In the Pacific Islands region where the kava plant (*Piper methysticum* Forst. f.) was domesticated, people have used it for centuries in a manner consistent with local cultural practices primarily in the form of aqueous emulsions of the crushed fresh or dried roots or lower stems (8–12). Long-term observers of kava used in this customary manner in the Pacific stress that no reports of permanent liver injury have emerged (8,13).

Indigenous Australians in Arnhem Land [Northern Territory (NT)] acquired the practice of kava drinking from Fijians and Tongans, and so have consumed kava powder mixed with water since 1982 when it was first imported for local use (14–16). Although there remains ongoing concern about kava's health effects (17–21), no clinical record or research has reported irreversible liver damage associated with kava use in this population either.

However, there is some evidence to suggest that liver function changes do occur in users of aqueous kava extracts. A March 2000 survey in an Arnhem Land community found gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels above the reference range in 61% and 50% of kava users, respectively. A 1987 survey conducted in another Arnhem Land community reported that "heavy" (310 g/week of kava powder) and "very heavy" (440 g/week) kava users showed decreased levels of total protein, albumin, and bilirubin and increased GGT when compared with "occasional" (100 g/week) users and non-users (21). The researchers concluded that the apparent hepatic toxicity of kava was possibly greater than alcohol, although the relative effects of alcohol and other substance use were not clarified (8,22). However, ongoing clinical observations from the 1990s in Arnhem Land indicate that abnormal liver function tests return to normal after 1 to 2 months abstinence from kava with no evidence for long-term effects (23), while earlier limited evidence suggested that GGT became normal 8 months after discontinuing kava (24).

Kava's mood altering and muscle relaxing qualities with few known side effects stand in contrast to the possible serious effects of liver toxicity. This article focuses on liver function changes in users of aqueous kava extracts, their temporal relationships with kava consumption and their possible improvement after kava is discontinued.

METHODS

Study Participants

The survey from which the data reported here are drawn investigated a wide range of possible health effects of kava (23). The study compared a group of "current" users, who had used kava during the preceding month, with a group of "recent" users, who had not used it for at least 1 month and these were compared with a group who had never used kava (23). Among the "recent" users, 23 people had, in fact, discontinued kava at least 1 year before they were assessed, and this provided the opportunity to compare liver function tests with continuing kava users who had last consumed kava 1 to 2 months ($n=10$) or 1 to 2 weeks ($n=15$) before the study. Finally, another group of continuing users had used kava during the previous 24 hr ($n=14$). It was possible to compare these kava-using groups with a control group who had never used kava ($n=36$).

In the community studied, from 52% to 77% of men and 11% to 20% of women were using kava (25). Procedures for the opportunistic selection of participants have already been described (23). Sixty-five people (52 males, 13 females) had a history of kava use, and 36 (13 males, 23 females) had never used it. For three of the 65 kava drinkers, it was not possible to determine the last kava use occasion so these were excluded, leaving 62 kava users in a sample of 98 participants.

Setting

The community is located in central-east Arnhem Land in the "Top End" of the NT (Australia), 530 km east of Darwin and 120 km west of the nearest regional center. Kava has been used continuously in some Arnhem Land localities (16), and in this community (23,25),

from 1982. Approximately 55 g of kava powder per liter of cold water is usually consumed in the local drinking style (16). Aboriginal people do not use manufactured herbal remedies (16). Alcohol has been available since the early 1970s from outlets in the regional center (25). Kava use declined from 1998 when it became illegal (25), and a recent rise in cannabis use in Arnhem Land has become evident (25,26). A background of petrol sniffing is common because petrol sniffing was widespread throughout the region during the late 1980s and early 1990s (25,27). This pattern of substance misuse posed considerable challenges to identifying independent effects of kava (25).

Assessing Exposure to Kava Use

All participants were interviewed about their substance use behaviors and categorized according to the time since they last used kava (never used, more than 1 year ago, 1–2 months ago, 1–2 weeks ago, within the past 24 hr). Kava powder was available in the community in 75-g bags with a kava lactone content of ~8 g (16). Quantities consumed per week were estimated from the number of 75-g bags reported used. Participants were also asked when in their lives they commenced using kava and for how long they had used it. Pictorial representations were used in interviews conducted in a clinic setting with local health workers assisting. Knowledgeable senior Aboriginal health workers, who are also community members, confirmed self-reported kava use by consensus classification (21,28). Chart review using community health clinic files assisted to confirm health worker consensus.

Heavy, episodic alcohol drinking is well known in Indigenous Australian populations (19,29,30). In this study, health workers reported 31 out of 47 alcohol users in the sample known to drink in this way including 29 males and 2 females. However, average alcohol consumption reported was found to be equivalent to just 318 g/month of pure alcohol (25), with a maximum of 576 g/month. This is from one-quarter to one-third of the average quantity consumed per capita in indigenous communities across the “Top End” of the NT (25) and somewhat less than the average alcohol consumption considered to be harmful in Australia, which is 40 g/day (males) or 20 g/day (females) (31). Heavy users within this group of apparently moderate alcohol users were therefore described as those who reported using >318 g of pure alcohol per month, who were known to health workers as heavy users and who had used alcohol within the previous year. The heavy users so defined had used alcohol from 2 to 32 years in their

lifetime, and all were continuing users. One man had used alcohol for 18 years and was known as a past heavy user, but had ceased drinking 5 years before the study. He was not included in the heavy-using group. The others who were not classified as heavy users ($n=15$) had commenced alcohol use recently, within the preceding year.

Tobacco smokers who reported using 25 cigarettes/day (one pack) or more (Table 1) were classified by health workers as heavy users. Cannabis was periodically available (25) and consumed in hand-made “bucket bong” using “cones” containing ca. 4 mg of THC (unpublished data). Those who used >5 cones/week were described by health workers as heavy cannabis users (Table 1). There were no active petrol sniffers. A history of petrol sniffing was exclusive to males, and 42% said they had sniffed petrol (Table 1).

In Arnhem Land, there are high rates of hepatitis B infection (21). However, community screening data were not available for this study. Inspection of clinic charts did not reveal evidence of chronic liver disease in any of the participants. Systematic data on compliance with medication regimes were not available.

Blood tests were performed measuring alanine aminotransferase (ALT), GGT, ALP, total protein, albumin, and bilirubin. All blood tests were performed by a commercial laboratory that provides pathology services to Royal Darwin Hospital and community health clinics.

Data Analysis

Significance levels for trends across groups were calculated from logistic regression models for dichotomous outcomes or ranked qualitative traits. For quantitative traits, significance levels for linear trends after one-way analyses of variance were calculated using the method described by Altman (1991) (32). Backward stepwise regressions, using the 95% CI criterion for removing variables, were performed with each outcome measure as the dependent variable and with measures of exposure to kava use, age, and other substance use as independent variables. Positively skewed data were log-transformed before analysis. Analyses were performed using Stata version 7.0 (33).

Ethics

A memorandum of understanding between the local Aboriginal community Council and Menzies School of Health Research guided the research (23). Ethical approval was provided by the Joint Institutional Ethics Committee of the Royal Darwin Hospital and the



Table 1. Kava use and other substance use in an indigenous community in Arnhem Land (NT, Australia).

Outcome measure	Never used kava, <i>n</i> = 36 (<i>m</i> = 13, <i>f</i> = 23)	Kava user: time since last kava use				<i>p</i>
		>1 year, <i>n</i> = 23 (<i>m</i> = 14, <i>f</i> = 9)	1–2 months, <i>n</i> = 10 (<i>m</i> = 9, <i>f</i> = 1)	1–2 weeks, <i>n</i> = 15 (<i>m</i> = 14, <i>f</i> = 1)	≤ 24 hr, <i>n</i> = 14 (<i>m</i> = 12, <i>f</i> = 2)	
<i>Other substance use</i>						
Tobacco use	26 (72%)	20 (87%)	10 (100%)	12 (80%)	13 (93%)	0.282
None	10	3	0	3	1	
<25 cigarettes/day	4	3	1	2	0	0.647
≥ 25 cigarettes/day	22	17	9	10	13	
Years used mean (SD)	18 (12)	18 (11)	14 (7)	17 (11)	21 (7)	0.140
Alcohol use	4 (11%)	12 (52%)	9 (90%)	13 (87%)	9 (64%)	<0.001
None	31	11	1	2	5	
≤ 318 g pure alcohol/month	2	8	3	5	5	<0.001
>318 g pure alcohol/month	1	4	5	6	2	
Years used median (range)	0 (0–3)	1 (0–32)	8 (0–20)	13 (0–30)	1 (0–32)	0.001
Heavy alcohol use	1 (3%)	10 (43%)	5 (50%)	10 (67%)	5 (36%)	<0.001
Cannabis use	5 (15%)	12 (55%)	8 (89%)	6 (43%)	6 (43%)	<0.001
None	29	10	1	8	8	
≤ 20 mg THC/week	5	9	5	5	4	0.007
>20 mg THC/week	0	3	3	1	2	
Years used median (range)	0 (0–4)	1.5 (0–20)	1 (0–14)	0 (0–16)	0 (0–20)	0.373
Petrol sniffing history	4 (11%)	8 (35%)	4 (40%)	5 (33%)	5 (36%)	0.118

Menzies School of Health Research, which has an Aboriginal subcommittee and which works to guidelines of the National Health and Medical Research Council of Australia. All participants gave written informed consent. Study procedures were explained with the assistance of Aboriginal health workers.

RESULTS

Time Since Last Kava Use, Other Substance Use, and Associated Characteristics

Males were more likely to be kava users than females (age adjusted OR = 6.8, 2.7–17.2, $p < 0.001$) and to have used it within the previous 1 to 2 months (age adjusted OR = 15.5, 4.5–53.7, $p < 0.001$). Quantity of kava powder consumed averaged 118 g/week and ranged from <40 g/week to >195 g/week. This was equivalent to ~12 g/week of kava lactones (range 4 g–20 g/week), a level which is from 5 to 24 times greater than recommended therapeutic dosages in manufactured

kava products (16). This is less than 368 g/week (38 g/week kava lactones) reported earlier in other Arnhem Land communities, a level that is 45 times greater than recommended therapeutic dosages (16,21). Median duration of kava use was 12 years (range, 1–18 years). One-quarter of kava users had used kava continuously for 16 years or more (data not shown). Among the kava users, time since last kava use and quantity consumed were not associated (likelihood ratio $\chi^2 = 0.66$, $p = 0.882$). However, duration of kava use was longer in more recent kava users ($|t| = 2.4$, $df = 58$, $p = 0.009$, one-sided).

Table 1 summarizes kava and other substance use within the community. Kava users, when compared with non-users and adjusted for age; were more likely to also use alcohol (OR = 19.1, 5.7–63.9, $p < 0.001$), cannabis (OR = 14.1, 3.7–53.9, $p < 0.001$), and tobacco (OR = 3.0, 1.0–8.0, $p = 0.042$); and were more likely to have sniffed petrol (OR = 5.5, 1.6–19.0, $p = 0.003$). In males, alcohol and kava use remained strongly associated (OR = 8.8, 2.2–34.5, $p = 0.001$), but not in females (OR = 0.9, 0.8–1.1, $p = 0.162$). Heavy alcohol users were also more likely to use kava (OR = 32.1, 4.1–

Table 2. Kava use and liver function tests: comparison of values in an indigenous community in Arnhem Land (NT, Australia).

Outcome measure	Never used kava, <i>n</i> = 36 (<i>m</i> = 13, <i>f</i> = 23)	Kava user: time since last kava use				<i>p</i>
		>1 year, <i>n</i> = 23 (<i>m</i> = 14, <i>f</i> = 9)	1–2 months, <i>n</i> = 10 (<i>m</i> = 9, <i>f</i> = 1)	1–2 weeks, <i>n</i> = 15 (<i>m</i> = 14, <i>f</i> = 1)	≤ 24 hr, <i>n</i> = 14 (<i>m</i> = 12, <i>f</i> = 2)	
<i>Blood tests</i>						
Bilirubin (umol/L) (<20) median (range)	8 (5–14)	8 (6–16)	8.5 (6–12)	8 (7–12)	8 (6–11)	0.662
Total protein (g/L) (62–80) median (range)	80 (3.9)	80 (4.8)	81 (3.0)	80 (5.2)	81 (5.2)	0.534
Albumin (g/L) (35–50) mean (SD)	44 (2.0)	45 (2.4)	46 (2.1)	45 (1.6)	45 (2.4)	0.642
ALT (U/L) (<40) median (range)	24 (11–71)	24 (9–81)	24.5 (16–30)	21 (13–38)	25.5 (14–37)	0.437
GGT (U/L)M (<60)F (<40) median (range)	34 (7–184)	29 (16–195)	49 (14–165)	88 (23–178)	78 (44–257)	<0.001
ALP (U/L) (35–135) median (range)	109 (61–240)	105 (77–152)	130 (86–163)	123 (99–212)	165 (102–204)	<0.001

250.2, $p = < 0.001$), compared with those not classified as heavy users.

Abnormally High Values of Gamma-Glutamyl Transferase and Alkaline Phosphatase and Time Since Last Kava Use

Almost one-half (48%) of the kava users showed GGT above a normal reference range (OR = 2.6, 1.0–6.5, $p = 0.034$), with 37% having abnormally elevated ALP (OR = 3.4, 1.2–10.1, $p = 0.017$) (data not shown). There was no association between duration of kava use and abnormally elevated liver enzymes. However, quantity consumed per week was associated with an abnormally elevated ALP (likelihood ratio test, $\chi^2 = 9.33$, $p = 0.009$). In those who were not heavy alcohol users, when adjusted for age, the quantity consumed per week, and the duration of kava use, the tendencies for an association between time since last kava use and abnormally high GGT (likelihood ratio test, $\chi^2 = 5.0$, $p = 0.291$) and ALP (likelihood ratio test, $\chi^2 = 3.61$, $p = 0.461$) were not significant.

Liver Function Tests: Associations with Time Since Last Kava Use

In a univariate analysis, there was a significant association between time since last kava use and observed levels of both GGT and ALP but not ALT,

albumin, bilirubin, or total protein (Table 2). Those with more recent exposure to kava use showed higher GGT and ALP. One-third of kava users had elevated total protein, with values generally elevated across groups but not associated with time since last kava use (Table 2).

The tendency for higher GGT with more recent kava use remained statistically significant ($p < 0.001$) in multiple regression, including independent variables such as age, tobacco use, cannabis use, and a history of petrol sniffing. In those who were not heavy alcohol users, the association remained significant ($p < 0.001$). In heavy alcohol users, the association was weaker ($p = 0.046$), although still statistically significant. When analyzing the separate groups, only those who were not heavy alcohol users and who had used kava within the previous 24 hr showed GGT higher than nonusers ($|t| = 4.0$, $df = 35$, $p < 0.001$, one-sided) (Fig. 1). Data were not sufficient for this comparison in heavy alcohol users.

The association between ALP and more recent kava use also remained statistically significant in multiple regression ($p < 0.001$) with the association remaining statistically significant in heavy alcohol users ($p < 0.001$), as well as in those who were not heavy alcohol users ($p < 0.001$). Those who were not heavy alcohol users and who last used kava 1 to 2 weeks prior to the study ($|t| = 2.3$, $df = 35$, $p = 0.015$, one-sided) and those who used it within the preceding 24 hr ($|t| = 2.7$, $df = 39$, $p = 0.005$, one-sided) had ALP levels significantly greater than nonusers (Fig. 2).

Conversely, among those who were not heavy alcohol users, participants who had never used kava did not



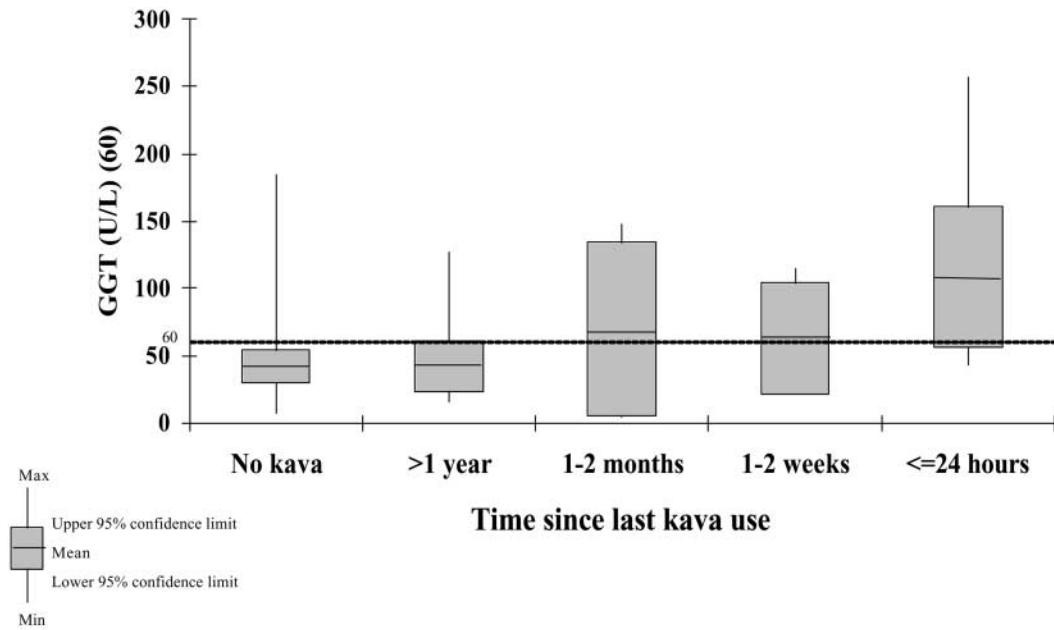


Figure 1. Increase in GGT with more recent kava use in those who were not heavy alcohol users in an Indigenous community in Arnhem Land (NT, Australia) and comparisons with a normal reference range (broken line).

have statistically significant differences in ALP levels compared with those who had abstained from kava for 1 to 2 months ($|t| = 0.7$, $df = 35$, $p = 0.242$, one-sided), and

they also did not have statistically significant differences in GGT levels compared with those who had abstained for 1 to 2 weeks ($|t| = 1.3$, $df = 35$, $p = 0.096$, one-sided).

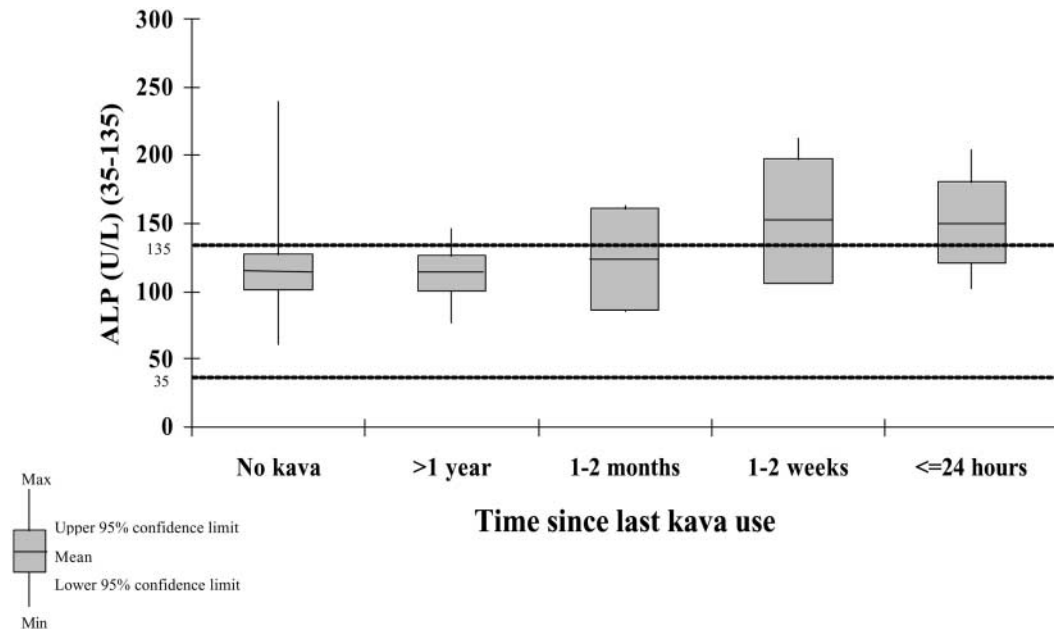


Figure 2. Increase in ALP with more recent kava use in those who were not heavy alcohol users in an Indigenous community in Arnhem Land (NT, Australia) and comparisons with a normal reference range (broken lines).

Liver Function Tests: Associations with Other Measures of Kava Use

The comparative effects of different measures of exposure to kava use on levels of GGT and ALP in those who were not heavy alcohol users were assessed using multiple regression. Using a backward stepwise approach with ALP as the dependent variable, time since last kava use remained statistically significant ($p=0.001$), whereas duration of kava use and quantity consumed per week were not significant. A similar result was found with GGT as the dependent variable ($p<0.001$). Time since last kava use was therefore a key variable accounting for variation in observed levels of GGT and ALP.

Liver Function Tests: Associations with Other Substance Use

In the univariate analysis, there were no associations between measures of exposure to cannabis use and any of the outcome measures. Although alcohol users as a whole had a higher GGT ($|t|=2.4$, $df=93$, $p=0.010$, one-sided), they did not have higher ALP ($|t|=2.2$, $df=93$, $p=0.410$, one-sided). Similarly, heavy alcohol users had higher GGT ($|t|=1.9$, $df=93$, $p=0.031$, one-sided), but not ALP ($|t|=0.6$, $df=93$, $p=0.271$, one-sided). Regression of outcome measures with number of years of alcohol use as an independent variable showed no associations except for a trend for increased ALP ($r=0.27$, $df=46$, $p=0.067$). Because there was no strong effect of heavy alcohol use on the outcome measures, it seems unlikely that it was an important confounder of the effects of kava use.

DISCUSSION

These results confirm limited previous data showing that aqueous kava extracts can cause elevation of the liver enzymes GGT and ALP. Importantly, however, these liver function changes appear reversible (23), with improvements evident from 1 to 2 weeks of abstinence from kava use at the moderate usage levels reported in this study. The majority of kava users had ALP and GGT levels return to normal levels after 1 to 2 months and 1 year of abstinence, respectively. These effects occur independently of effects of alcohol or other substance use. Most important, the use of aqueous kava extracts in this study was not associated with elevation of ALT. This is in contrast to the case reports of hepatic toxicity with fulminant hepatitis associated with herbal kava

products used at much lower kava lactone dosages and with exposure occurring over just a few months in contrast with use for 1 to 18 years found in kava drinkers in this study (3,6).

The small sample size and lack of a random sample were unavoidable weaknesses of the study. Improved measures of exposure to kava use and time since last kava use in follow-up studies will assist to quantify more precisely the temporal relationships between development of liver function changes in kava users and their improvement when kava is discontinued (28). One advantage of this study was that possible confounding effects of alcohol and other substance use were quantified and controlled for, whereas these were not clearly delineated in an earlier (1987) study (8,21–23).

Would these same results be observed at higher average levels of kava consumption and could the amount of kava consumed become a more important factor for irreversible liver injury at some critical level? Kava was used more heavily by Indigenous Australians in Arnhem Land in the recent past, but mortality data available for that time do not give cause for concern about death from liver damage in kava users. For the period 1985 to 1997, the period of heaviest kava use (34), the Australian Bureau of Statistics reported 9 deaths (5 males and 4 females older than 15 years of age) in Indigenous people in eastern Arnhem Land with chronic liver disease as the primary cause (ICD9-code-571). When directly standardized to the 1991 Australian resident population, these deaths represent an annual rate (per 100 000 population) of 18 (males) and 12 (females). Although numbers of deaths are too small for meaningful comparisons, rates are within ranges of age-adjusted death rates (per 100 000 population) for chronic liver disease in indigenous people in the rest of the NT (5–91 in males, 6–39 in females) for a similar period (1982–1995) (35). Furthermore, close clinical surveillance of kava use within Arnhem Land, estimated by us as 30 000 person-years of moderate to heavy kava consumption (unpublished data), has not documented any cases of severe hepatic toxicity, which could be possibly attributed to kava.

It seems likely that the abnormal ALP and GGT seen with consumption of aqueous kava extracts reflects a different process to the hepatic toxicity documented from herbal products (3,6). It is possible that the ethanol or acetone extraction of kava lactones used in herbal products results in potentially hepatotoxic compounds not present in traditional aqueous extracts. It is also possible that genetic differences in liver metabolism between population groups may be important in determining whether hepatic toxicity occurs with various kava products.

In conclusion, the data confirm previous research and clinical observations that liver function test changes do occur in those who use kava in the form of aqueous extracts. However, the changes appear to only be in GGT and ALP and begin to return to normal after 1 to 2 weeks abstinence. There is currently no evidence for long-term liver damage from use of "traditional" preparations, even when people have used kava for 12 years or more. The reversibility of liver function changes outlined in this article, together with the lack of reports of long-term liver damage in both Indigenous Australian and Pacific Island populations, are compelling. However, given consistent evidence for liver function changes in Arnhem Land, and because it is uncertain whether these effects are reversible at higher levels of consumption, the possibility for long-term liver damage cannot be ruled out. Accordingly, until research further elucidates these issues, the promotion of moderate kava use with clinical surveillance is required.

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