

Evaluation of the effects of Kava on the Liver

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Introduction

Although kava has been consumed on regular occasions by oceanic people for over two centuries^(1, 2,3,4), its pharmacological property^(4,5,6,7,8) clinical effects^(2,3,4,5,6,7,9,10,11,12,13,14,15) and therapeutic uses have concentrated mainly upon its cerebral and anti-anxiety properties. There is limited literature regarding the gastrointestinal effects and side-effects of kava. In fact, there has been little pressure until recently to perform research into the liver complication of kava.

Over the past century, Health Departments throughout the Pacific islands have not been alerted to the possible adverse effects of kava on the body, particularly no strong link to liver disease. Kava consumption however has increased over the years, both in its traditional consumption and later, during the past few years, in its tablet and herbal extract format.

Since its first recorded consumption in 1777, there has been no significant concern on the health effects of kava until 1988 when a comprehensive report on 98 heavy Aborigines kava drinkers was published. Later in 2001, Escher and Desmeules reported a case of a 50 YO man with hepatic necrosis following consumption of kava tablets and later requiring liver transplant. Since that time, 31 cases have been reported to the German and Swiss health authorities. The direct link of kava to liver diseases in these cases are still in question but nevertheless has raised significant question as to the safety of kava consumption and mainly kavalactone extracts.

Of the total of 33 case reports (including one study) on the liver complications of kava, only one is related to consumption of kava powder and 32 are related to consumption of herbal kava-extracts. The single report on the kava powder group showed a significant elevation in GGT enzymes on very heavy kava drinkers, which may indicate kava effect on the liver. The report however did not specify further whether this group of people did have chronic liver disease or liver failure.

Traditional versus Herbal Kava Extract

It is important to distinguish between two major categories of kava consumption. The first group involves the consumption of powdered kava

whilst the second group involves the consumption of kavalactone herbal tablets. Although the two groups are different in many ways, even individual factors within a group can be quite different.

The first category may be classified under “traditional preparation” and this is consumed widely throughout the pacific islands. The preparation differs in different countries like Vanuatu, Pohnpei (Micronesia), Fiji, Tonga and Samoa. The population that frequently consume this traditional preparation, are generally different from the people who consume the Herbal Kava Extract (second category) in many ways. They have different racial and genetic makeup, different social existence, nutritional status may be different, underlying associated diseases are different, less likely to be on other medications, take a much higher dose of kava and have different reasons for consuming kava. These differences does not only exist between the “traditional” and “herbal extract” groups but there is also different social and genetic makeup within a group (e.g., Vanuatu vs Samoa).

Although mild to moderate kava drinkers of kava are not known to have significant gastrointestinal complications, recent adverse effects have involved mainly heavy kava drinkers ^(16,17,18). There has also been speculation about association of kava drinkers and weight loss ⁽¹⁶⁾. The possible causes of this have included poor food intake ⁽¹⁹⁾, malnutrition and the possibility of malabsorption ⁽¹⁶⁾.

The “herbal kava extract” group also differs since the kava extract is consumed in different format including liquid form (tea and coffee) and tablets, which may be pure kava extract, or in combination with other herbs (e.g., Kava Kava capsule contains Kava Kava 1000mg, Jamaica Dogwood 300mg, Oats 200mg, Californian Poppy 150mg, Passionflower 100mg, St. John’s Wort). The cases implicated in the German reports had taken kava herbal products marketed as Neuronika, Laitan, Phyto-Geriatrikum, Limbao, Kavatino and Antares. In one case-report ⁽²⁰⁾ however, a 50-year-old man who had been taking a reasonable dose of a well-regarded kava product for 2 months, experienced liver failure and requiring liver transplant. The recent worldwide concern on kava has been triggered by reports of 31 cases of possible liver disease in association with herbal kava tablet consumption according to German authorities.

During this recent concern on the hepatotoxic effects of kava, it is important from the health point of view that an independent and scientific evaluation is carried out both retrospectively and also prospectively. Retrospective data would mean the evaluation of medical reports and data on health issues concerning kava over the past 3 centuries where major health issues have not been a concern. This would include both the analysis medical of reports from

1776 (first documented record of kava consumption by James Cook) and also the post 1988 era which would include the 1988 report on a series of heavy Aborigines kava drinkers and the series reported to the German and Switzerland Health Authorities.

History and pharmacology of Kava

Kava is prepared and consumed differently in the Pacific island countries like Fiji⁽⁴⁾, Pohnpei⁽¹⁷⁾, Vanuatu, Tonga and Samoa. The different preparations of kava in these countries combined with the specific phenotype of the kava plant (table one), contribute to the different concentration, strength and physical effects of the brew.

By the end of the 1800, kava-based pills were available in German herbal shops. The use of kava made its way into the European Pharmaceutical Codex. Kava was listed in the British Pharmacopoeia as “kava rhizome” in 1914, and in 1950 it appeared in the US Dispensary as treatment of both gonorrhoea and nervous disorders⁽¹⁵⁾.

Over the past 100 years, extensive analytical investigations of the kava root have revealed that the active ingredients of kava, the kavalactones, comprise 15% of the root. Since then many investigators have added to our knowledge of the constituents of kava. About 50% of the dry kava root is starch. The compounds responsible for the pharmacological effects of kava drinking make up only 3-8% of the kava root^(21,2). The standard phytopharmaceutical preparations used in clinical research in Europe however contains 70% kavalactones⁽⁶⁾. The percentage of the pharmacologically active ingredients depends on the age of the root and the kava variety⁽²²⁾.

Of the 15 kavalactones isolated from kava, there are six major kavalactones known to provide psychoactive activity: kawain, methisticin, demethoxy-yaconin, dihydrokawain, dihydromethicin and yaconin (clinical and experimental pharmacology, 1992, 18:571).

All kavalactones are physiologically active although it is the fat-soluble kavalactones derived from kava resin that convey the main psychoactive activity. Slight differences in the structures of these alpha-pyrone make significant differences in activity; some are pharmacologically inactive whereas others as noted above cause sedative effects⁽²⁾. Different cultivars vary as to which alpha pyrones predominate and this is one of the major factors in the various strength of the brew. The ratio of the wild form, *Piper witchmanni* to the cultivated form *Piper methisticum* vary in different countries (table one). *Piper*

methysticum contain more of the clinically active kavalactones and Fiji does not have the wild form piper witchmanni.

Recent work in the comparative chemistry of various kava plants indicates different cultivars have different mixtures of kava pyrones. Research by Lebot and Le'vesque indicated morphological characteristics of the plant are a good indicator of the type, quantity, and composition of its active ingredients ⁽²³⁾. In order to define various cultivar chemotypes, Lebot and Lev'esque divided the active ingredients of piper methysticum into major and minor kavalactones. After demonstrating the major kava lactones comprised 96% of the lipid extract, they numbered and used only these constituents to define the chemotypes (1= desmethoxyyaqonin, 2= dyhydrokavain, 3 = yaqonin, 4 = kavain, 5= dihydromethisticin, 6= methisticin) ⁽²³⁾. The composition of each cultivar was then coded by listing the proportion of the six major kava lactones in decreasing order of content (521364, for example , indicates dihydroxymethisticin was in the highest proportion in the cultivar, followed by dihydrokavain, etc.). Comparison of the chemotypic analysis with the ethnobotanical data demonstrated a strong correlation between traditional use of a cultivar and its chemical composition. Chemotype 256431, the infamous tudei ("two day" because it makes the drinker feel drunk for two days) and most of the P. witchmanni cultivars (chemotype 521634), for example were largely avoided due to the unpleasant nausea they caused owing to their high proportion of dihydromethysticin and dihydrokavain. Cultivars traditionally used for medicinal and exchange purposes belonged to the chemotype 265431 ⁽²³⁾. While there is some cultural variability concerning which cultivars were the most highly prized, generally those with high percentage of kavain and a low percentage of dihydromethysticin (cultivars beginning 426, 462 and 246) were the most sought after ⁽²⁴⁾. The chemotypes are divided into group A-I according to chemotypes and table one indicates the chemotypes in some areas in Fiji compared to Tonga and Hawaii.

Table one: Chemotype group I ⁽²³⁾

Chemotype group I	Place of origin
642351	Oahu, Hawaii
643251	Vanua Levu, Fiji
643251	Taveuni, Fiji
624531	Tongatapu, Tonga
246513	Taveuni, Fiji
624531	Taveuni, Fiji
642351	Vitilevu, Fiji
642351	Vanua Levu, Fiji

Sources: Lebot and Lev'sque 1989; Aradhya, and Manshardt 1991.

Other compounds isolated from piper methysticum include alkaloids (2 from the roots and one, piper methisticin from leaves), flavokawins, an alcohol, a phytosterol, ketones and organic acids⁽²³⁾.

The absorption in the gastrointestinal tract is remarkably rapid, so that the effects are felt almost immediately (kava Kava-piper methysticum). The peak plasma level occurs about 1.8 hours after an oral dose and elimination occurs primarily by renal excretion (both unchanged and changed metabolites) and in the feces. It is also metabolized by the liver cytochrome P-450 system and may have the potential to interact with other herbs or drugs⁽¹⁰⁾.

Studies on the Gastrointestinal Effects of Kava

There is limited scientific study to date that properly evaluates the gastrointestinal effects of kava in humans. A study in normal subjects and patients was conducted by Pfeiffer et al⁽²⁰⁾ in 1967 and there was little noted on the gastrointestinal effects of kava. A comprehensive evaluation was conducted in 1988 by the Menzies School of Health Research in Darwin⁽¹⁶⁾ who conducted an epidemiological survey of 97 aboriginal kava drinkers. The finding of this survey indicated that heavy kava drinkers were more likely to suffer from general ill-health, skin rash, shortness of breath, malnutrition (with 20% loss of body weight and 50% loss of body fat), liver damage and biochemical changes in red and white blood cells and platelets similar to those caused by large doses of alcohol.

This study however was conducted on very heavy kava drinkers but who had stopped consuming alcohol for a number of years. Although the significant increase in GGT in very heavy kava drinkers is most likely related to heavy kava intake, the study did not further comment on other evidence to support chronic liver disease. Although low albumin level is an indicator of liver disease, the possibility of malnutrition contributing to this abnormality in these cases is a strong possibility. It is important to take this factor into consideration since people who are very heavy kava drinkers may continue drinking kava for a few days with very little food consumption. Even when they do eat, the quality of food may be high in starch and low in protein and vitamins.

In a case report, Escher and Desmeules⁽²⁰⁾ described severe hepatic necrosis in a 50-year-old man following the consumption of kava capsules (210-280mgs lactones daily) and eventually requiring a liver transplant. The detail and background of this case was not provided and it would be difficult to comment on the direct effect of kava. Frater described kava as a purgative by some people in Fiji although this is disclaimed by others⁽¹⁹⁾. From his observation, he did not appreciate any strong association between kava and weight loss. Problems with

undernutrition in some areas may be attributed to the fact that kava is usually drunk before eating (particularly in Fiji but not in Tonga and other pacific islands) and when the drinking is finished, the person may prefer immediate sleep to eating.

Recent reports on the hepatotoxic effects of kava

The recent international concern has emanated from 32 case reports indicating hepatotoxic effects of **herbal kava extracts** ranging up to liver failure, hepatitis or cirrhosis. Not having access to the full case reports, it is difficult to make any proper conclusion as to the direct effect of kava on the liver.

It is however well known in medicine that the liver has a major role in metabolism of substances both exogenous (taken from outside the body) and also endogenous (produced by the body). A large amount of medications are metabolized through the various enzyme systems in the body. Kava is thought to be metabolized by the P450 enzyme system, which also metabolise a large amount of drugs. It is understood that some of these patients (24 patients) had also been on other medications.

When considering the recent concern about possible hepatotoxicity of kava products, and the subsequent regulatory action taken by various European countries, there are a series of issues that must be addressed and kept in mind.

- 1) The strengths and limitations of our knowledge about the use of kava over many centuries in the Pacific islands. This includes the extensive experience of apparent safety, but also the possibility that occult liver disease could be a problem in the Pacific, but has not been systematically sought so could have escaped detection.
- 2) The details of the formulations of kava as used in the Pacific and as used in the preparations marketed in Western countries.
- 3) Detailed consideration of the possibility that kava extracts might have a different toxicological profile in comparison to “native” kava as consumed in the Pacific.
- 4) The details of the cases of apparent liver toxicity reported to the regulatory authorities in Germany and other European countries. This includes an objective clinical assessment of the likelihood in each case that the toxicity was caused by the kava.
- 5) The fact that pharmacovigilance is an inexact science, and draws on a variety of knowledge and information bases to draw conclusions about drug toxicity.
- 6) The fact that toxicological assessment of new kava preparations has not been as rigorous as would have been the case had they been

classed as new drugs. This is because they were classed as herbs, and therefore escaped full toxicological assessment on the basis that experience with the use of kava as a herb was sufficiently extensive to lessen concern about possible toxicity.

Conclusion

Although kava has been consumed for centuries, concerns for the liver toxicity of kava has become a health concern only since 1988. Since that time 32 reports have suggested the involvement of kava in liver disease. Out of those reports, 3 have been published in major medical journals and 31 were reports forwarded to the German and Switzerland health authorities. Of the 32 reports, only one is involved with traditional consumption of kava and 31 involved herbal kava extracts.

In analyzing the only report (1988 on Aborigines Heavy Kava drinkers) on traditional kava consumption, it does show evidence of raised GGT in very heavy kava drinkers. Although the clinical significance of this elevated GGT needs to be interpreted with caution, it does raise the important issue that with heavy kava drinkers, there is a rise in GGT. The study however did not provide any further information to support evidence of chronic liver disease nor did it provide any other parameter of liver cell injury. This study does show that Very Heavy Kava Drinkers had evidence of malnutrition (low BMI), which may also account for the low serum albumin. There has also been claim by some investigators that kava cause a transient rise in GGT. Whether this transient rise in GGT indicates ongoing liver damage leading to chronic liver disease has not been established.

In Fiji and other pacific island countries, kava is consumed heavily during funerals, weddings and other traditional gatherings. We have not seen a rise in acute liver injury nor have any clinical suspicion of a direct link of kava with chronic liver disease following these gatherings. However, no formal study has been done to confirm this observation. There is however a high prevalence of chronic liver disease in the pacific island countries. Although this has been attributed to hepatitis B infection, the recent suggestion of possible liver effects of kava would make it important that a proper study is performed to evaluate this possibility.

The large number of case reports concerning herbal kava extract and liver toxicity is concerning since this effect is not seen with the traditional kava consumption. These reports need to be properly evaluated since the evidence so far points to the consumption of herbal extract and to a smaller extent to the

consumption of traditional kava powder. It is also unlikely to be related to the dose of kava since the herbal extract doses used in the reported cases are relatively smaller compared to kava consumed in the pacific islands. If however, there is a reasonable suggestion of liver toxicity, then it is of utmost importance that the claimed herbal kava extract cases are properly evaluated to see if there is an idiosyncratic hepatotoxic effect, interaction with other drugs, P450 enzyme deficiency in some cases, coincidental liver disease, herbal extract preparation or the change in chemotypes are the important factors.

There is no recorded idiosyncratic effect of kava on the liver observed in pacific islanders and Europeans traveling into the pacific islands over the past 3 centuries. Interaction with other drugs is a possibility but there are many pacific islanders who consume kava while taking antihypertensive, cardiac and diabetic and other medications. A deficiency in P450 enzyme that metabolises kava is a possibility but its clinical manifestation should also have been observed in pacific islanders or Europeans consuming kava over the past century. A recently new chemotype of kava extract and also its preparation method needs to be properly evaluated since this concern has come to light since the recently new herbal extract preparation.

Summary points

1. There is no convincing evidence so far indicating direct kava toxicity to the liver when consumed using traditional methods.
 - There is however evidence that there are health problems associated with very heavy kava consumption including poor nutrition and rise in liver enzymes.
2. There is a concern regarding liver toxicity when using herbal kava extract as reported to the German and Switzerland Health Authorities.
 - The evidence concerning #2 needs to be clearly evaluated.
 - Based on evidence on the pacific population, it is probably not the kavalactone but the preparation
 - It would be unlikely to be dose related since herbal kava extract dose is relatively smaller compared to that consumed in the pacific.
 - It is impossible to make any conclusion from the cases reported in Germany until more information is known about the details of individual cases.
3. There is an urgent need to examine the gastrointestinal effects of kava using a properly designed study.

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