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Is Kava Safe to Be Used by the Public?

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The use of botanical products in the United States and European countries is extensive. While the original intention of the Dietary Supplements and Health Education Act of 1994 (DSHEA) by the US Congress was to use these products for the purpose of "supplementing" the diet, however many consumers use them for managing their disease states. Among the dietary supplements that have been popular among individuals who suffer from anxiety or insomnia is kava (*Piper methysticum* Frost F.) (The word "*methysticum*" is Greek for intoxicant, and "*Piper*" is for pepper. Taken together, kava is an "intoxicating pepper") [1]. The herb is native to South Pacific region (Melanesia, Micronesia, Polynesia, and Hawaii) where it has been in use for centuries as a traditional beverage. The natives prepare kava drink by masticating the rhizomes which are further diluted with either coconut milk or water [2]. South Pacific islanders use the drink to connect to their gods and ancestors through religious and ceremonial gatherings, to alleviate fatigue, and as a relaxant [3]. The word kava when used by the natives refers to both the shrub itself and the psychoactive drink that is made from its rhizomes [2]. Kava beverage has a bitter and acrid taste which is known by the natives as 'awa' [2].

In 2002, kava's import and use in Europe was greatly hindered by the health authorities citing toxicity concerns. In the same year, the US Food and Drug Administration (FDA) issued a consumer advisory (dated March 25, 2002) concerning the use of kava and its association with liver toxicity [4]. The FDA stated that

"Kava-containing products have been associated with liver-related injuries – including hepatitis, cirrhosis, and liver failure -- in over 25 reports of adverse events in other countries. Four patients required liver transplants. In the U.S., FDA has received a report of a previously healthy young female who required liver transplantation, as well as several reports of liver-related injuries" [4].

In the same advisory, the FDA acknowledged the fact that "liver damage appears to be rare" and that "persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should consult a physician before using kava-containing supplements" [4]. The European decision and US FDA warning concerning kava had major economic implications on the nations that exported kava to the West. For example, the Pacific Island kava producers claimed an annual loss of $US 200 million over kava restriction [5]. This ban was later reversed in many EU member countries including Germany and France. Poland remains the only EU member that outright bans the use of kava within its territories [6]. Unfortunately, kava is not the sole known offender in this area as more than 900 drugs, herbs, and toxins are documented to cause liver damage in human [7].

Kava rhizomes contain many active ingredients known collectively as kavalactones or kavapyrones (most important ones are kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and demethoxyyangonin) [3,8]. The rhizomes also contain components known as chalcones (mainly three flavokavins A, B, and C) and a volatile oil [3,8]. Kavalactones are metabolized by cytochrome P-450 (CYPs)mixed function monooxygenase systems in the liver (Phase I metabolic pathways), in particular CYP2D6, and by conjugation to glutathione (GSH) during Phase II metabolic systems [9]. Lactone hydrolases found in the serum also are involved in kavalactones metabolism [9]. The presence of normal enzymatic pathways is essential for avoiding the hepatotoxicity associated with Kava [9]. In clinical studies, kava extract's effect on the permeability of glycoprotein (P-gp) functions and on various CYP activities was not of significance, except for CYP2E1 and CYP1A2 where the extract demonstrated an inhibitory effect on their functions [10]. Kavalactones were shown to modulate both sodium and calcium channels, to reduce neuronal re-uptake of adrenaline and dopamine, to cause reversible inhibition of monoamine oxidase B in platelets, to enhance substrate binding to gamma-aminobutyric acid (GABA-α) receptors, and to activate GABAergic neurotransmission [8].

Although the exact reason by which kava extract exerts its damaging effect on the liver remains elusive, various theories have been suggested to explain it. The presence of aflatoxin in kava as a contaminant has been advocated to be the culprit to this hepatotoxicity as this mold is known to be hepatotoxic [11,12]. Another hypothesis proposed that the organic solvents used in the preparation of the extract were perhaps themselves the culprits for the toxicity in kava products sold in the West [13]. However, this does not seem to be plausible as hepatotoxicity cases have been documented with preparations made with aqueous and organic solvents alike [13]. The presence of specific hepatotoxic components in the herbal extract was also suggested to be the cause of this toxicity. Specifically, flavokawain B was shown to be toxic to liver cells grown in cell culture and in experimental animals [14]. This toxicity was reversed by the introduction of exogenous GSH [14]. Interestingly, kava extracts prepared with organic solvents (e.g., acetone or 96% ethanol solution) were found to lack any GSH in their content, whereas those prepared with diluted ethanol solutions (25% v/v) or water contained a significant quantity of GSH [9]. Moreover, individuals with low reserve of GSH in their system tend to deplete this reserve rather quickly when challenged with high doses of kavalactones, and this in turn can lead to hepatotoxicity [9]

It appears that the hepatotoxicity of kava may be avoided if the product itself supplies GSH along with kavalactones. The possibility of the kava product being contaminated with the mold alfatoxin remains a worrisome issue at this junction until it is fully ruled out. Thus, regulatory agencies have the obligation to assure the public that kava products available on their market are free from any alfatoxin contamination and contain an adequate amount of GSH in their formula. Unless these two requirements are met, safety issues of kava

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preparations will continue to be a reality and caution must be exercised when recommending kava products for therapeutic use.

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