

## Tropical Medicine Rounds

**Kava dermopathy in Fiji: an acquired ichthyosis?\***Sarah Hannam<sup>1</sup>, MBBS, Michael Murray<sup>2</sup>, B Pharm (Hons I), PhD, Dsc, Lucia Romani<sup>3</sup>, MSD, Meciusela Tuicakau<sup>4</sup>, MBBS, DDM, and Margot J Whitfeld<sup>5,6</sup>, MBBS, FACD, DTM&H

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**Summary**

Kava dermopathy is a common cutaneous effect of regular or heavy use of Kava, a psychoactive beverage consumed widely throughout the Pacific. In Fiji in 2012, over 1000 study participants underwent full skin examination, and kava dermopathy was a common cutaneous finding. The clinical manifestations of kava dermopathy share similarities with the spectrum of autosomal recessive congenital ichthyoses, predominantly lamellar ichthyosis. The pathogenesis of Kava dermopathy may be associated with a functional defect in one or more cytochrome P450 enzymes implicated in epidermal integrity, thus mimicking the genetic defect as seen in lamellar ichthyosis type 3.

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**Introduction**

Kava, a psychoactive beverage prepared from the root of the pepper plant, *Piper methysticum*, has been consumed for thousands of years throughout the Pacific Islands.<sup>1</sup> It is known for its sedating, anxiolytic, local anesthetic, antithrombotic, and anticonvulsant properties, as well as strong traditional importance in the everyday life of many Pacific Islanders.<sup>2</sup> There is a wide spectrum of reported health effects, and one commonly documented is kava dermopathy, well known to Fijians as kanikani.<sup>3</sup> Kava dermopathy is characterized by a spectrum of cutaneous manifestations, ranging from a powdery dryness of the limbs and upper back to a widespread ichthyosiform eruption.<sup>1</sup> Very few images in the literature demonstrate this phenomenon. Multiple theories exist regarding its pathogenesis.<sup>4–10</sup> In this article, we explore a brief history of kava, from its origin to modern day and review the literature on kava dermopathy, which we speculate may be associated with a functional defect in one or more cytochrome P450 enzymes, mimicking the genetic defect and cutaneous findings observed in lamellar ichthyosis type 3 (LI3).

**Background**

Kava is the term used to describe both the psychoactive beverage and the plant from which it is derived.<sup>1</sup> The kava plant (Fig. 1), *P. methysticum*, is a member of the black pepper family (*Piper* being Latin for Pepper, and *methysticum* being Greek for intoxicant, thus translating to intoxicating pepper). The plant has the appearance of an upright shrub with long wooden stems and large, dark green, heart-shaped leaves. There are multiple varieties of this perennial plant, which reaches maturity about 3–5 years after planting, when it is usually cultivated, at approximately 2–2.5 m tall.<sup>3</sup>

**Traditional and modern day uses**

Kava has been used widely for thousands of years throughout the Pacific in a medicinal, as well as a ceremonial and social capacity. Different parts of the plant have been believed to have varying healing properties, being utilized for ailments such as asthma, headaches, muscle pains, cystitis, gonorrhoea, and syphilis.<sup>2</sup> The social and ceremonial importance of kava is still actively present today throughout the islands of Micronesia, Polynesia,



**Figure 1** The kava plant in Fiji

and Melanesia, and in many places, it is used on a daily basis.<sup>11</sup>

Kava is traditionally consumed as a beverage created by diffusing the crushed, dried root of the mature kava plant in water or less commonly coconut milk.<sup>2,3,11</sup> Traditionally, it is the young male members of the community that pound the root into a powder using metal cylinders and poles as large makeshift mortars and pestles. This fine powder is then placed in a muslin cloth, diffused, and mixed in a large communal bowl of water. The resultant brown, turbid, astringent liquid is then served to individuals, typically in order of social rank, out of communal cups often made from coconut shell. Traditionally, the strength of the mixture is determined by whoever drinks the first bowl, which is usually a Chief or head of the family/clan. Upon drinking, the community member and his server perform ritual hollow clapping patterns. This process is ongoing as cups continue to be refilled and served, and commonly people consume at least a dozen rounds of the beverage throughout the day and/or night (pers. comm. Dr. Meciusela Tuicakau).

Upon drinking kava, the consumer experiences an immediate partial anesthesia to the tongue and palate. It is believed to exert a pleasant, calming sense of relaxation and tranquility.<sup>3</sup> Kava was introduced to Arnhem Land Aboriginal communities in the Northern Territory in the early 1980s, partially as an intended substitute to alcohol, and became widely consumed,<sup>12</sup> however, often in large quantities and in combination with alcohol.<sup>13–15</sup>

Pharmaceutical preparations of the herb extracts became widely available in Western countries in the 1990s, marketed in health stores for natural treatment of anxiety, depression, insomnia, and premenstrual syndrome.<sup>3</sup> Popularity grew in the USA, particularly with annual sales reaching approximately \$15 million in 2001.<sup>16</sup>

International concerns have been raised in the last 10–20 years, however, regarding the safety of kava, with

reports of hepatotoxicity and deaths from liver failure associated with consumption of kava products. A direct causal relationship, however, has been difficult to establish in the majority of cases. Nonetheless, this has led to its withdrawal or restriction in many countries since 2002.<sup>13</sup> In June 2007, the Australian Government banned all commercial importation of Kava in an attempt to combat kava abuse and significant associated health problems in Indigenous communities.<sup>17</sup> The Therapeutic Goods Administration in Australia placed a limit on the maximum amount of *P. methysticum* permitted per dosage form (for example, tablets or teabags) in 2003.<sup>18</sup>

### Pharmacology and pharmacokinetics

Over 40 compounds have been isolated from *P. methysticum*, including a group of pyrone derivatives, known as kavalactones. Nineteen have been identified, with only six suggested as being active constituents in the reported biological effects of kava.<sup>19</sup> These are metabolized by the cytochrome P450 system (CYP450) with a subgroup, typified by methysticin and dihydromethysticin, containing an aromatic methylenedioxyphenyl (MDP) substituent.<sup>13,20</sup> Such methylenedioxyphenyl-containing natural products are frequently associated with prolonged inhibition of CYP450 activities because they undergo biotransformation to reactive intermediates that generate tight-binding complexes with the cytochromes.<sup>21</sup> The concentration of kavalactones generally decreases progressively towards the aerial part of the plant. Potency of kavalactones may vary in accordance with plant subtype and method of preparation. This lack of standardization contributes to the difficulty of direct comparison between the effects and outcomes of kava consumption.<sup>11</sup>

Multiple *in vivo* and *in vitro* studies in animals and humans have assessed the pharmacological properties of kavalactones. These have been hypothesized to include blockade of voltage-gated sodium ion channels, enhanced ligand binding to gamma-aminobutyric acid type A receptors, diminished excitatory neurotransmitter release due to calcium ion channel blockade, reduced neuronal reuptake of norepinephrine, reversible inhibition of monoamine oxidase B, and suppression of the synthesis of the eicosanoid thromboxane A<sub>2</sub>, which antagonizes gamma-aminobutyric acid type A receptor function.<sup>3,22,23</sup>

Information on the pharmacokinetics of kava and kavalactones is sparse. Studies in rodents have indicated that the kavalactone kawain has a relatively short half-life of approximately 1.5 hours.<sup>24</sup> However, issues pertinent to the disposition of kavalactones on prolonged exposure, such as the volume of distribution, which may influence kavalactone accumulation in epidermal tissues, remain unresolved.

### Health effects of kava

Aside from the desired tranquility and relaxation attained from consuming kava, as well as perceived therapeutic benefits, reported adverse general health effects of chronic kava consumption have included headaches, impaired coordination, cognitive impairment, sexual dysfunction, loss of appetite, gastritis, pupillary dilatation and red, watery eyes, increased high-density lipoprotein cholesterol, lymphopenia, hypoalbuminemia, and liver function derangement.<sup>3,2,5,27</sup>

### Kava dermopathy

A common effect of chronic heavy kava consumption (defined as > 310 g/week)<sup>3</sup> is kava dermopathy.<sup>2,6</sup> Kava dermopathy has been reported in approximately 45% of regular consumers, and up to 78% of heavy kava consumers.<sup>12</sup> The condition is characterized by an ichthyosiform eruption that occurs gradually, often beginning as a powdery dryness of the arms (Fig. 2) and upper back. It then develops into a desquamating keratosis, manifest as a generalized dry, fine, polygonal scale, lacking erythema (Fig. 3). Palmar and plantar keratoderma are common<sup>27</sup> and photo-accentuation of the rash has been recognized (Fig. 4). It is widely documented to be a reversible phenomenon upon cessation or reduction of intake.<sup>1</sup>

### Kava dermopathy in Fiji

On a recent medical visit to Fiji in 2012, over 1000 study participants underwent a full skin examination. Among the adult male population, the characteristic features of kava dermopathy were a common finding. The skin changes known as kanikani are widely recognized by the Fijians and in the past have been perceived as a sign of nobility or privilege, as kava was only served to Chiefs.<sup>1</sup> This concept has now changed as kava is consumed by



**Figure 2** Fine powdery dryness of the upper arm



**Figure 3** Fine dry scale on the chest, lacking erythema



**Figure 4** Photo-accentuated pattern on the feet

all. It is most commonly seen in men, but now women are also affected. Because kanikani is so common and people are aware of the causative factors, medical treatment is usually not sought. Sufferers concerned about the rash either reduce or cease kava consumption, use traditional moisturizers such as coconut oil, and exfoliate the dry skin off in water (pers. commun. Dr. Meciusela Tuicakau).

### Theories on the pathogenesis of kava dermopathy

While the pathogenesis of the cutaneous rash is not established, several theories have been proposed. These include allergic systemic/contact dermatitis,<sup>4–6</sup> accumulation of kavalactones,<sup>7</sup> or flavopigments,<sup>8</sup> a sebotropic reaction,<sup>9</sup> a persistent photosensitivity reaction<sup>1</sup> – although the rash is not limited to sun-exposed areas, and a pellagra-like dermatosis.<sup>10</sup> Ruze tested the hypothesis that the dermopathy may be a result of niacin deficiency, either as a result of kava interfering with tryptophan metabolism or a dietary deficiency in kava drinkers, but outcomes were not supportive of this.<sup>27</sup>



More recently, it has been suggested that mast cell activation might have a mechanistic role in producing kava-related skin inflammation,<sup>28</sup> as mast cells have an active role in delayed hypersensitivity reactions,<sup>29</sup> a proposed explanation of kava dermatopathy.<sup>5,29</sup> Additionally, while ichthyoses involve disrupted keratin synthesis,<sup>30</sup> some studies indicate that mast-cell-derived factors can influence keratinocyte functions.<sup>31,32</sup>

#### **Potential role of defective cytochrome P450 isoenzymes in the pathogenesis of kava dermatopathy**

We note that kava dermatopathy shares multiple characteristic clinical features with LI, an autosomal recessive congenital ichthyosis (ARCI). ARCI is a heterogeneous group of genetic disorders of keratinization, with a spectrum of clinical subtypes ranging from large dark polygonal scales and little or no erythema, to fine, lighter scales, often with prominent erythema.<sup>33</sup> Within this spectrum exist multiple intermediate phenotypes.<sup>34</sup> The similarities between LI and kava dermatopathy include hyperlinearity of the palms and soles, as well as a dry scale – ranging from fine, powdery dryness to an adherent, pigmented, and polygonal scale, particularly on the back and chest, distinctly lacking erythema. LI<sub>3</sub> is an ARCI that has recently been found to be associated with a defect in a recently described gene, FLJ39501, which is also known as the CYP450 gene CYP4F22,<sup>35</sup> that is within a gene cluster on chromosome 19p13. CYP4F22 is expressed in epidermal tissues and, although its function remains somewhat unclear,<sup>36</sup> it shares significant sequence relatedness to other members of the CYP4F subfamily that mediate the conversion of arachidonic acid and arachidonic acid-derived mediators to further oxidized products. Arachidonic acid is an abundant polyunsaturated fatty acid that is not only a critical structural component of phospholipids within the membranes of epidermal keratinocytes but also undergoes biotransformation to intermediates that are essential for skin hydration. Defects in other enzymes that participate in these biotransformation pathways have also been linked to the Sjögren–Larsson syndrome, an ichthyosis in which there is a defect in the enzyme aldehyde dehydrogenase 3A2.<sup>37</sup>

Kavalactones have been shown to inhibit and generate reactive metabolites that elicit tight-binding complexes with a number of human CYP450 enzymes, including CYP4A11 and CYP2C9,<sup>38</sup> which are structurally similar to CYP4F22, and mediate arachidonic acid biotransformation.<sup>33,39</sup>

We propose that the CYP450 enzymes that are readily inhibited by kavalactones are structurally very similar to those involved in the pathogenesis of LI and likely share functional similarities in arachidonic acid metabolism.

Involvement of the CYP450 pathway in the pathogenesis of kava dermatopathy may be further supported by the fact that multiple medications have been documented to induce an acquired ichthyosis, including cholesterol-lowering agents, such as niacin and triparanol, which disrupt the critical components of the lipid barrier of the skin and, like kava, are metabolized by CYP450 enzymes.<sup>40</sup>

The clinical similarities between kava dermatopathy and LI, as well as the common involvement of the CYP450 pathway lead us to suggest that kava dermatopathy should be renamed kava ichthyosis and that further alterations in CYP450 metabolism be explored with the other ichthyoses.

#### **Conclusion**

We propose that the cutaneous effects of kava may be a result of a functional defect in one or more CYP450 isoenzymes leading to an acquired ichthyosis that is biologically similar to the genetic defect of CYP4F22 gene as seen in LI<sub>3</sub>. Further investigation is required to understand this condition, which remains highly prevalent throughout the Pacific. In addition, research into kava ichthyosis may help in improving our knowledge of some of the other ichthyoses, which are still poorly understood today.

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