

## Kava hepatotoxicity with Western herbal products: does it occur with traditional kava use?

*Differences in kava extraction methods may affect hepatotoxicity*

IN THIS ISSUE OF THE Journal, Gow and colleagues (*page 442*) report the first Australian case of fulminant hepatic failure attributed to a herbal product containing kava,<sup>1</sup> while Moulds and Malani (*page 451*) note the cultural and economic importance of kava for Pacific island nations, and provide a balanced overview on kava safety and availability.<sup>2</sup> For centuries kava has been widely consumed in Pacific island countries as a ceremonial beverage and for its mood-altering and stress-relieving properties. It is prepared as an aqueous emulsion of the crushed fresh or dried roots or lower stems of the kava shrub *Piper methysticum* ("intoxicating pepper").<sup>3</sup> Pharmacological properties, such as anxiolytic activity, are attributed to a poorly characterised group of compounds termed kavalactones.<sup>3,4</sup>

In 1982, kava was introduced to some Arnhem Land Aboriginal communities from Pacific island countries, in part to reduce the harmful effects of alcohol.<sup>5</sup> Kava use continued to rise during the 1980s and 1990s, supplied by a lucrative black market. Concerns about adverse health, social and economic effects of widespread heavy consumption resulted in the Northern Territory Kava Management Act in May 1998, which made the possession of more than 2 kg of kava illegal unless in accordance with a licence. However, an illegal trade continued, with profiteering by those distributing kava imported from several Pacific island countries. In October 2000, the Kava Management Act was amended to incorporate harm reduction objectives and a system of licensed kava supply, controlled by local Aboriginal community organisations.

Over the last decade, there has been an expanding global market for herbal preparations made in Western countries and containing kava extracts.<sup>4</sup> These products have been marketed for the treatment of anxiety, insomnia, premenstrual syndrome and stress, and sold over the counter as complementary medicines or dietary supplements.<sup>6</sup> Since 1999, cases of severe hepatic toxicity in people using kava-containing herbal products have been reported from Europe and the United States.<sup>6,7</sup> Subsequently, kava-based herbal products have been banned in some European countries, including the United Kingdom. In Australia, a practitioner alert and consumer advice were issued in February 2002 by the Therapeutic Goods Administration (TGA) concerning hepatotoxicity possibly related to kava-containing products. By late 2002, eight cases of liver transplantation after hepatic failure associated with use of kava-containing products had been reported from Europe, and two from the United States.<sup>6</sup> The patient reported by Gow et al died soon after liver transplantation.<sup>1</sup> As a result of this case, the TGA initiated a voluntary recall of all complementary medicines containing kava extracts on 15 August 2002.<sup>8</sup> The TGA has 87 products containing kava on its Australian Register of Therapeutic Goods.<sup>8</sup>

*Kava-based herbal products have been banned in some European countries*

Although details are sketchy for many of the at least 68 cases of suspected kava hepatotoxicity,<sup>4</sup> with the herbal products sometimes containing additional ingredients, the increasing number of well documented cases<sup>1,6,7</sup> make it likely that kava extracts are responsible for occasional severe progressive hepatotoxicity. However, the mechanism of this toxicity remains to be determined. Histological examination has shown portal inflammation with lymphocytes and eosinophils,<sup>6,7,9</sup> and an idiosyncratic immune response to a reactive metabolite has been suggested as a possible cause.<sup>9</sup> In two patients, phenotyping of the activity of cytochrome P450 isoform CYP2D6 showed that they were "poor metabolisers", and it was postulated that genetic differences in liver metabolism of kavalactones may be important.<sup>9</sup>

Moulds and Malani discuss the paradox that fulminant hepatic failure has not been documented with traditional kava use in Pacific countries.<sup>2</sup> Kavalactones in herbal products are usually extracted with ethanol or acetone,<sup>6</sup> and may differ critically from the aqueously extracted kavalactones used in Pacific countries and Aboriginal communities.

Of note is an early study of the health effects of kava use in Aboriginal communities, which documented consistent abnormalities in liver function tests in heavy kava drinkers.<sup>5</sup> A recent study in Arnhem Land has confirmed these findings, with abnormal serum levels of  $\gamma$ -glutamyl transferase (GGT) and alkaline phosphatase (ALP) in 61% and 50% of kava users, respectively.<sup>10</sup> However, serum levels of alanine aminotransferase (ALT) were not raised in any kava drinkers. Furthermore, the abnormalities in liver function usually return to normal within 1–2 months of stopping kava use.<sup>10</sup> The raised GGT and ALP levels combined with normal ALT levels in Aboriginal kava users do not suggest acute inflammation and are not consistent with the changes documented in the cases of hepatotoxicity associated with herbal products, where aminotransferase levels are especially high.<sup>1,6,7</sup> Clinical surveillance in the Northern Territory over 20 years has not documented any cases of fulminant hepatic failure attributable to kava use. This is despite Aboriginal kava drinkers consuming kavalactones in doses estimated to be 10–50 times the recommended therapeutic doses for herbal products.<sup>3</sup> However, the recent study confirmed adverse effects of kava, such as kava dermatopathy and lymphocytopenia,<sup>10</sup> which were documented in the 1980s.<sup>5</sup>

Although a rigorous systematic review found kava to be an effective symptomatic treatment option for anxiety,<sup>4</sup> herbal preparations should not be used until the mechanism for hepatic toxicity is clearly ascertained. The abnormal but reversible GGT and ALP levels seen in heavy kava drinkers does not reflect the same pathological process. Whether the

apparently idiosyncratic fulminant hepatic failure documented with herbal kava preparations can also occur with traditional aqueous extracts requires further surveillance. Close monitoring for this and other potential adverse effects of kava use in Aboriginal communities and Pacific countries is recommended, in addition to initiatives encouraging moderation in consumption.

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## Childhood obesity: modernity's scourge

*The overarching cause is energy imbalance*

THE HEALTH AND WELLBEING of Australia's children and adolescents, now and in the future, is under threat. In 2002–2003, the most prevalent child health issues affecting children are preventable: obesity, dental disease, emotional and behavioural problems, bullying and learning delays. These problems often present as comorbidities.

Overweight and obesity affect about 23% of Australian children and adolescents, with 6% being obese.<sup>1</sup> These are conservative estimates, as there has been no systematic monitoring of the prevalence of overweight and obesity in Australian children and adolescents since 1995. However, over the previous decade, the prevalence of overweight children almost doubled, and the prevalence of obese children more than tripled.<sup>1,2</sup> There is no reason to believe that the rapid rise in prevalence rates has not continued. Studies of historical datasets have also revealed that the prevalence of overweight and obesity in children and adolescents doubled over the period 1985–1997, a far greater rate of increase than in the preceding 16 years.<sup>3</sup>

Health inequalities related to overweight and obesity are evident. There is a higher incidence of overweight and obesity in children of parents of particular backgrounds,<sup>3</sup> and maternal education is the strongest social determinant of overweight and obesity in childhood.<sup>4</sup> Although there are limited national data, and combined New South Wales, Victorian and National Nutrition datasets<sup>1</sup> failed to find a rural/urban difference, Victorian epidemiological data show a statistically significant, higher proportion of overweight and obese boys in metropolitan areas, but this difference was not found for girls (Ms K Hesketh, NHMRC PhD Scholar, Centre for Community Child Health, Melbourne, VIC, personal communication).

The health consequences of overweight and obesity are substantial, although Australian data remain unclear in certain areas.<sup>5</sup> At least in the United States, obesity carries more stigma in children than any physical disability, and this

is evident across all socioeconomic and ethnic groups.<sup>6</sup> Issues of social acceptance, athletic competence and physical appearance are well known to obese children and affect their sense of social and psychological wellbeing. Obese children with decreasing self-esteem are more likely to smoke and drink alcohol compared with those whose self-esteem increases or remains the same.<sup>7</sup> Obese children and adolescents may also have a range of medical conditions including hypertension, dyslipidaemia, and even type 2 diabetes. Other problems, such as musculoskeletal discomfort, obstructive sleep apnoea, heat intolerance, asthma and shortness of breath, greatly affect their lifestyle.<sup>8</sup>

Implications for the future can be gathered from longitudinal studies. Combined cohort studies indicate that relative body weight is sustained from childhood to adulthood, and, once children or adolescents are overweight or obese, their weight is unlikely to track backwards.<sup>5</sup> If this is not sufficient reason for concern, reflect that these studies (of the long-term consequences of child and adolescent obesity) were all performed before the worldwide obesity epidemic developed. What, then, will be the outcome, in 10 or 20 years' time, of large numbers of children and adolescents entering adulthood, already with abdominal obesity and well established risk factors for cardiovascular disease and type 2 diabetes?

Focusing on children highlights their contribution to contemporary society and future populations. Addressing the determinants of health and wellbeing for children and adolescents will improve population health and wellbeing overall. The overarching cause of the obesity epidemic is energy imbalance — a relative increase in energy intake (food intake) together with a decrease in energy expenditure (decreased physical activity and increased sedentary behaviour). Identifying the most important predictive determinants of each of these behaviours, as well as the most effective and sustainable remedial strategies, is complex and involves