Abstract

Before 1998, extracts of kava kava, *Piper methysticum*, were considered to be very safe alternatives to anxiolytic drugs and to possibly exert a wide range of other benefits. Major reviews published through the end of 2002 continued to confirm kava’s safety and efficacy. Nevertheless, by January 2003 kava extracts had been banned in the entire European Union and Canada, and were subject to cautions and advisories by the US FDA as a result of 11 cases of hepatic failure leading to liver transplants, including four deaths. A total of 78 cases of hepatotoxicity reputedly linked to kava ingestion are available for review from various databases. Of these adverse events, four probably are linked to kavalactones taken alone and another 23 are potentially linked to kava intake, but also involve the concomitant ingestion of other compounds with potential hepatotoxicity. Three possible mechanisms for kavalactone hepatotoxicity are known: inhibition of cytochrome P450, reduction in liver glutathione content and, more remotely, inhibition of cyclooxygenase enzyme activity. The direct toxicity of kava extracts is quite small under any analysis, yet the potential for drug interactions and/or the potentiation of the toxicity of other compounds is large. Presently, kava toxicity appears to be “idiosyncratic.” The risk-to-benefit ratio of kava extracts, nevertheless, remains good in comparison with that of other drugs used to treat anxiety.

Keywords: Kava; *Piper methysticum*; Kavalactones; Kava pyrones; Hepatotoxicity; Cytochrome P450; Glutathione; Cyclooxygenase; Anxiety

1. Introduction

Pharmacological studies of kava kava, *Piper methysticum*, date back to the early 1960s. As a result of these and clinical trials, until very recently, kava extracts were accepted as being characterized by a high degree of safety (Singh and Singh, 2002; Singh, 1992). Such findings appeared to be supported by an historically safe use of the herb. Direct European knowledge of kava extends only as far back as the voyages of Cook to the South Pacific in the Eighteenth Century, yet subsequently it has been established that kava consumption not only has been widespread throughout this area in the relatively modern period (Cawte, 1985), but also that its ceremonial employment, at least, may go back perhaps thousands of years (Hocart et al., 1993; Loew, 2002). Because of its historic use and modern scientific data demonstrating safety and efficacy, the German Commission E or expert committee of the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, normally abbreviated as BfArM), in a publication dating to 1990 approved kava preparations as nonprescription drugs for the treatment of nervous anxiety.
disorders, stress and restlessness (Blumenthal et al., 1998). More recent reviewers of kava’s efficacy and safety have found kava extracts to be superior to placebo for the treatment of anxiety and, likewise, based on the evidence of major trials, have determined that reported adverse events were “mild, transient and infrequent” (Pittler and Ernst, 2002; Loew, 2002).

In a remarkable reversal of fortune, as of January 2003, kava preparations are banned in most of their major markets. According to a press release from the UK Medicines Control Agency (MCA) dated December 20, 2002, medicinal products containing kava will be prohibited in the UK as of January 13, 2003. Similarly, “in the EU, all licensed kava–kava products have been removed from the market while in Canada, investigations have concluded that there is insufficient evidence to support the products’ safety and they have also been withdrawn from the market. In Australia products have been voluntarily removed from the market while an investigation is conducted and in the USA consumers have been warned of the risk of liver toxicity pending the outcome of an investigation by the FDA” (http://www.mca.gov.uk/ accessed January 1, 2003).

Are these recent bans and health alerts justified? The Morbidity and Mortality Weekly Report issued by the US Centers for Disease Control (2002) indicates that 11 patients using kava products have suffered liver failure and undergone subsequent liver transplants. A combination of other sources suggests that 78 documented adverse event reports (AERs) involving liver toxicity existed as of December 2002. On the one hand, evidence of this magnitude argues strongly for a reappraisal of kava’s safety. On the other hand, the quality of these reports repeatedly has been challenged.

A connection between massive kava consumption and liver toxicity was established more than a decade ago (Mathews et al., 1988), but work successfully identifying possible mechanisms involved has appeared only since 1999. It remains to be established whether reports of liver toxicity can be explained by these mechanisms. Current cases raise many issues. For example, the nature of the reporting itself may skew results. Second, mechanisms either established or as yet unknown may lead to instances of toxicity with or without the advent of other factors. Third, reports of toxicity may prove to be idiosyncratic. A final consideration is whether kava, even if proven to be linked to cases of hepatotoxicity, nevertheless remains an acceptably safe drug for the treatment of anxiety and related disorders when compared with alternatives.

2. Pharmacology

The pharmacology of kava and its extracts plays a significant role in the evaluation of toxicity reports both because the AERs are confined to very concentrated extracts and because of the complexity of kava’s components. For instance, a water-soluble extract of kava, at least in the mouse model, is mildly analgesic, but does not induce sleep, whereas the lipid-soluble extract exerts more robust analgesia and induces sleep (Jameson et al., 1989). Sedative action of the lactones per se has been demonstrated in animals (Hansel, 1996). The rather broad range of uses for more traditional style extracts which would have included water- and lipid-soluble components given in the British Herbal Pharmacopoeia (1983) is indicative of the differences between the two sets of components: “Cystitis, Urethritis, Rheumatism, and Infection of the genito-urinary tract.” Similarly, one or more of the proposed mechanisms of toxicity described below apply to the lipid-soluble fractions, but not to the water extract.

2.1. Bioactivity of the kavalactones

Researchers have isolated eighteen kavalactones (also termed kava pyrones) in kava root extract. Total kavalactone content ranges from 3% to 20% on a dry weight basis (He et al., 1997). Four chiral and two achiral enantiomers are considered to be the most important of these lactones and consist of yangonin, desmethoxyyangonin (5,6-dehydrokawain), methysticin, 7,8-dihydromethysticin, kawain, and 7,8-dihydrokawain (Hsu et al., 1994; Haberlein et al., 1997). (Fig. 1) Together they account for approximately 96% of lipidic extracts (Lebot and Levesque, 1989). It has been reported the individual administration of the lactones does not induce the same degree of pharmacologic activity as does whole kava extract (Lebot et al., 1992, 1997). Some authors have suggested that this is indicative of mod-
ulation of transport and/or metabolism (Mathews et al., 1988).

Kavalactones and metabolites are eliminated via the urine and feces. Peak plasma levels appear 1.8 h after ingestion; the half-life is 9 h (Ang-Lee et al., 2001). Whether this pattern varies in the cases of purported hepatotoxicity has not yet been established.

2.2. Mechanisms of action

Most of the mechanisms proposed to explain the observed benefits of kava appear to be quite remote from physiological interaction with the liver. The anxiolytic actions of the drug are centrally mediated and are speculated to involve a reduction in the excitability of the limbic system, particularly the amygdala complex. The pharmacological properties of kava are postulated to include blockade of voltage-gated sodium ion channels, enhanced ligand binding to gamma-aminobutyric acid (GABA) type A receptors, diminished excitatory neurotransmitter release due to calcium ion channel blockade, reduced neuronal re-uptake of noradrenaline (norepinephrine), reversible inhibition of monoamine oxidase B and suppression of the synthesis of the eicosanoid thromboxane A2, which antagonises GABA(A) receptor function (Jamieson and Duffield, 1990a; Jussofie et al., 1994; Boonen and Haberlein, 1998a; Singh and Singh, 2002). It should be noted that the kavalactones themselves exhibit no or inconsistent binding to GABA and benzodiazepine receptors (Davies et al., 1992; Holm et al., 1991). Similarly, the analgesic effects of kavalactones do not appear to be dependent upon the binding of opioid receptors (Jamieson and Duffield, 1990a).

Several other benefits and mechanisms are explored in the literature. Of these, the inhibition of cyclooxygenase enzyme activity has been linked in other therapeutic drugs to irregularities in liver function. An indirect link to liver function also may be indicated by kavalactones’ effects upon dopamine in the brain. Preliminary evidence suggests that sedative
effects may reflect dopamine antagonism and that in some patients this antagonism may rise to the level of clinical significance (Schelosky et al., 1995; Boonen et al., 1998b; Meseguer et al., 2002; Bilia et al., 2002).

This mechanism also may be responsible for observed disturbances in vision and arise from alterations in brain oxidant status resulting from changes in liver glutathione and aldehyde processing. Both of these lines of argument are discussed in the subsequent text.

2.3. Clinical trial indications of safety

Clinical studies of kava extracts generally have suffered from the same shortcomings as found with many other trials of natural products. Samples sizes for the most part have been small, the periods of treatment have been short (usually 4–8 weeks and ranging, exceptionally, up to 24 weeks), and the patient populations ill-defined (Siegers et al., 1992; Saletu et al., 1989; Möller and Heuberger, 1989; Gessner and Cuoto, 1994; Herberg, 1991, 1992, 1997; Lehmann et al., 1996; Scherer, 1998; Abadi et al., 2001). To some extent, these failings have been corrected in the most recent trials. Contemporary reviewers of kava’s efficacy and safety have found kava extracts to be superior to placebo for the treatment of anxiety and characterized by few and mild adverse events (Pittler and Ernst, 2002; Loew, 2002).

The limitations of these clinical trials with regard to establishing safety are much the same as with regard to establishing efficacy (Ernst, 2002). A further limitation with regard to establishing safety is that these trials can only very poorly predict the fate of kava extracts in real world settings where patients ingest multiple drugs, alcohol and other compounds, often for extremely extended periods of time, and perhaps while taking many times the indicated dosages for kava and/or one or more of these compounds.

To be sure, two post-marketing observational studies have been conducted in Germany, each of which involved more than 3000 respondents. These showed a small, but definite dose-dependent increase in the rate of adverse events, including gastrointestinal complaints, allergic skin reactions, headaches and photosensitivity. At a daily intake of 105 mg kavalactones, the rate of adverse events was 1.5% in 4049 patients after 7 weeks; at a daily intake of 240 mg kavalactones, the rate of adverse events climbed to 2.3% in a patient population of 3029 after 4 weeks (Pittler and Ernst, 2000; Bilia et al., 2002). Each of these surveys potentially is skewed to some degree in the pool of respondents and in physician judgments, hence must be used with caution.

2.4. Preparations and dosages

Just as there are differences in availability and efficacy between the concentrated kavalactones and the same lactones taken in the form of a whole herb extract, so also the bioavailability of kava constituents varies substantially depending on the method of extraction (Loew, 2002). The German-speaking market, which until the ban was the single largest market, relied largely on highly concentrated kavalactone extracts. Two methods predominate in the production of these concentrates. In the first, kava is dissolved in an ethanol–water mixture to obtain extracts containing approximately 30% kavalactones. An alternate procedure employs an acetone–water mixture to obtain extracts containing approximately 70% kavalactones. Variations on these extraction methods and the starting materials may influence the relative ratios of the major kavalactones. To complicate the picture still further, there are also products on the market that contain synthetic racemic kavain. (Denham et al., 2002)

The suggested intake by the German Commission E is the equivalent of 60–120 mg kavalactones per day for not more than 3 months without medical evaluation (Blumenthal et al., 1998). However, many clinical trials used 70 mg kavalactones taken 3 times per day (such as in the form of the extract designated WS 1490), hence these trials were based on an intake of 210 mg per day (Volz and Kieser, 1997). The reported effective range of kavalactones from clinical trials runs from 60 to 240 mg per day.

3. Hepatotoxicity

Adverse effects attributed to kava use generally were considered to be mild or negligible, except for the occurrence of a skin lesion, before a spate of liver-related AERs began to surface in 1998. Negative reports regarding impaired vision, including reduced near-point accommodation, enlargement of the pupils and disturbances in oculomotor equilibrium are in-
dicated in the German Commission E monograph and can be found in earlier literature (Blumenthal et al., 1998; Garner and Klinger, 1985). Other neurologic reports include exacerbation of Parkinson’s disease (Meseguer et al., 2002) and interactions with CNS depressants, including benzodiazepines (Stevinson et al., 2002; Almeida and Grimse, 1996). Experimentally, it has been demonstrated that ethanol in quantity markedly potentiates both the sedative/hypnotic actions of kava and its toxicity (Jamieson and Duffield, 1990b; Foo and Lemon, 1997). Moreover, although kavalactones have been reported to exert neuroprotective effects against several forms of neurotoxicity, two researches have shown that “while the kavapyrone (+−) kavain is neurotoxic only at high concentrations when exposed alone to the developing hippocampus, it appears to adversely affect neuronal recovery following excitotoxic insults” (Mulholland and Prendergast, 2002).

The reversible kava-related skin disorder, kava dermopathy, usually occurs only with prolonged use of large amounts of kava (Guro-Razuman et al., 1999). It is of interest in light of concerns regarding hepatotoxicity because some authorities feel that kava extracts may interfere with cholesterol metabolism (Norton and Ruze, 1994). Among male kava drinkers in the Tonga Islands who consumed the beverage daily, one study found that 29 out of 200 exhibited prominent kava dermopathy (Ruze, 1990); hence it would appear that under some conditions this side effect is not uncommon. In European experience, prolonged intake of more than 600 mg kavalactones daily is frequently associated with this skin change (Ernst, 2000).

The significance of the information concerning kava’s possible hepatotoxicity prior to 1998 is unclear. Enough crude evidence existed to suggest rather weakly that kava might interfere with liver functions under certain conditions. Nevertheless, actual adverse events appeared to be limited to the chronic consumption of enormous amounts of the kava beverage far in excess of any dosage that might be considered in Western practice (Chanwai, 2000).

3.1. Genesis of current concerns

A complete overview of the development of the current crisis can be found in HerbalGram: The Journal of the American Botanical Council (Blumenthal, 2002). The report of hepatotoxicity that set off the chain of events leading to the current bans and warnings appeared only in 1998 after almost a decade of widespread use of kava extracts in Europe (Strahl et al., 1998; Russmann et al., 2001a). It was followed by a highly publicized death (Brauer et al., 2001).

3.2. Elevation of γ-glutamyltransferase and other liver enzymes

Elevated levels of γ-glutamyltransferase in aboriginal chronic kava consumers were reported more than a decade ago (Mathews et al., 1988). More recently in a 14-year old girl with fulminant hepatic failure requiring transplant after ingesting a kava preparation for 3 months, this pattern was repeated. Liver function tests revealed multiple marked abnormalities in these areas: alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase, total bilirubin, ammonia, and prothrombin time, plus mixed inflammatory infiltrates (Campo et al., 2002). A very similar range of liver marker disturbances was reported for a 50 year old man who had consumed 210–280 mg per day (Laitan from Schwabe Pharma AG) for 2 months in Switzerland. Again, a transplant was required and histological analysis showed severe hepatocellular necrosis and infiltration with lymphocytes and eosinophils (Escher et al., 2001).

The elevation of liver enzymes, of course, is not a mechanism of toxicity, but rather is a marker for such toxicity. What is typical of these and other cases is not only the indications of stress upon the liver, but also the presence of inflammatory infiltrates.

3.3. Inhibition of human cytochrome P450

Cytochrome P450 issues with regard to kava and hepatotoxicity were initially brought up in 1998 (Strahl et al., 1998). A report of a Swiss woman who consumed 210 mg per day kavalactones for 3 weeks (Laitan from Schwabe Pharma AG) leading to hepatotoxicity which appeared in 2001 also focused on the issue of the inhibition of cytochrome P450.
Similarly to the cases discussed above, there were various inflammatory infiltrates plus elevations in the aminotransferase and bilirubin, although prothrombin time was normal. Liver enzymes returned to normal 8 weeks after withdrawal of the drug (Russmann et al., 2001b). The authors showed that this patient displayed poor cytochrome P450 metabolism secondary to a deficiency in CYP2D6.

Subsequent to this report, more direct evidence emerged of the inhibition of cytochrome P450 by kava extracts, with significant inhibition of the activities of CYP1A2 (56% inhibition), 2C9 (92%), 2C19 (86%), 2D6 (73%), 3A4 (78%), and 4A9/11 (65%) under experimental conditions (Mathews et al., 1988). Interestingly, these authors were able to outline a good deal of previous work suggestive of cytochrome P450 inhibition. They note that Meyer in 1962 had demonstrated a dramatic increase in hexobarbital sleep time, possibly indicative of CYP2C inhibition, following administration of kavalactones to mice. They further draw attention to the fact that methysticin analogs present in kava extract contain a methylenedioxyphenyl group which has been shown, after metabolic activation, to inhibit multiple cytochrome P450 enzymes through the formation of metabolic intermediate complexes (Hodgson and Philpot, 1974; Murray et al., 1983; Murray and Reidy, 1989). Another teams of researchers has published results similar to those of the Mathews group (Unger et al., 2002). Sufficient interference with the cytochrome mechanism itself is known to lead to necrosis (Kaplowitz, 1997).

The obvious implication of these demonstrations of the inhibition of cytochrome P450 is that one might expect significant interactions with a number of drugs (Fromm et al., 1997). Inhibition of the activities of CYP2D6 is not itself a toxic effect, hence this mechanism would not lead to a clear dose-dependent increase in reports of adverse events. Instead, one would find toxic reactions limited to poor metabolizers, on the one hand, and to apparently idiosyncratic responses, on the other hand. Of quite possible significance here is the fact that CYP2D6 deficiency, which has a prevalence of 7%–9% in European groups (Poolsup et al., 2000; Schmid et al., 1985), is rare in Polynesian and Asian populations, being found is roughly 1% (Poolsup et al., 2000; Wanwimolruk et al., 1998). This suggests that history of safe use in the South Pacific may not be predictive of safety in those of European descent.

It is of special interest that the recent demonstration of kava’s inhibitory effects upon a range of P450 enzymes implies that a low genotypic expression of CYP2D6 alone may not be required to explain several of the hepatic AERs. Moreover, reports linking lethargy and coma to concomitant use of benzodiazepines or other CNS depressants, likewise, may be indicative of inhibition of CYP2D6 expressed at normal levels (Mathews et al., 1988).

3.4. Cyclooxygenase inhibition

Not only the antioxidant and free radical-scavenging activities of some kavalactones, but also the ability to inhibit cyclooxygenase enzymes COX-1 and COX-2 has been demonstrated (Wu et al., 2002). These effects are usually cast in a very positive light and may explain some of the observed benefits of kava. Nevertheless, the picture is actually much more complicated than this. COX-2-derived mediators serve an important hepato-protective function and COX inhibition may contribute to the risk of drug-induced liver injury, possibly through both nonimmunological and immunological pathways (Keily et al., 2001). Moreover, hepatotoxicity is a not uncommon finding with a number of drugs that inhibit cyclooxygenase (Ben-Zvi et al., 1990; Knight et al., 1996).

Inasmuch as immunologic pathways appear to be involved in many of the reports of kava-induced hepatotoxicity, it would be prudent to explore the possible role of cyclooxygenase inhibition in these cases. As with the inhibition of cytochrome P450, an involvement of the COX-1 and COX-2 pathways might initially lead to the appearance that AERs of hepatotoxicity are adventitious or “idiosyncratic.”

3.5. Reduction of liver glutathione

One other possible mechanism of hepatotoxicity, that of glutathione depletion, is discussed at length by Whitton, Whitehouse and Evans (Appendix 1 in Denham et al., 2002). As reported there, kavalactones may cause hepatic stress if not mediated by glutathione, and are usually metabolized in the liver by lactone hydrolases (Schmidt et al., 1999). The argument by Whitton et al. is that glutathione has an essential role in the phase II conversion of kavalactones into excretable waste products, and thus glutathione...
is relevant in excess dosage of kavalactones. It can be demonstrated in vitro that the kavalactones combine with glutathione in a pH dependent reaction. The issue arises as to whether the high concentration of kavalactones introduced by concentrated standardized extracts has the potential to saturate the enzymatic detoxification pathways and thereby place undue stress on the liver. In extracts in which there is one part plant material to one part solvent, the ratio of glutathione to kavalactones may be as high as 2.2:1. With the use of traditional processing, the ratio still would normally be 1:1, whereas in the concentrated extracts typically used in Europe, the ratio may be 0.0003:1 or less. Hence, the use of high lactone kava extracts has the potential to deplete liver glutathione and open the way to liver damage.

This line of argument remains largely speculative, yet suggestive indirect evidence does exist. For instance, liver enzyme readings in cases of hepatotoxicity associated with antipyretic drugs are similar to those reported with kava and glutathione depletion in the former is a typical mechanism of toxicity (Benson, 1983; van Bree et al., 1989). Visual disturbances are common with overdoses of nonsteroidal anti-inflammatory drugs (Smolinske et al., 1990). Odd parallels also exist with alcohol poisoning. Alcohol consumption increases brain acetaldehyde levels, alters brain dopamine turnover, and interferes with visual discrimination (Heap et al., 1995). Glutathione depletion in the liver would be expected to increase levels of circulating acetaldehyde and, inasmuch as acetaldehyde crosses into the brain, to increase brain levels, as well.

Dopamine antagonism by kavalactones has been postulated as possibly leading to Parkinson-like effects (Schelosky et al., 1995; Stevinson et al., 2002), but this has been disputed as not being compatible with the pharmacological properties of the kavalactones. It is at least worth considering that this issue may be partially resolved through an indirect mechanism. It may not be the case that kavalactones themselves directly alter dopamine activity in the brain, yet it may nevertheless be true that (a) kava toxicity/side effects are exacerbated by alcohol and, (b) kavalactones may reduce liver glutathione through one or more mechanisms, leading to (c) the visual side effects noted with the excessive consumption of kava extracts as a downstream effects of the impact of kavalactones on the liver similar to those found with alcohol, i.e. brain acetaldehyde accumulation.

4. Adverse event reports (AERs)

The majority of AERs known regarding kava are derived from the files of the BfArM. Several sets of authors have already undertaken to evaluate these and other reports, with the most thorough and up-to-date likely being the work of Mathias Schmidt and Adolf Nahrstedt of the University of Münster. Originally published in the Deutsche Apotheker Zeitung in February 2002 (Schmidt and Nahrstedt, 2002a, b), a much expanded version of this article is available on the Internet in an updated English translation at http://www.uni-muenster.de/chemie/pb/kava/analyse.html under the title, “Is kava really hepatotoxic?” The Internet version (Schmidt and Nahrstedt, 2002a, Internet) is particularly valuable because it not only analyzes more and very recent cases (78 cases versus 36 cases in the original version), but also includes the actual case reports for the years 1990–2002. Two other valuable evaluations are those of Donald P. Waller (prepared for the American Herbal Products Association as of February 15, 2002) and of Alison Denham and co-authors (Denham et al., 2002) prepared on behalf of the UK Traditional Medicines Evaluation Committee.

4.1. The direct toxicity model

It is not our purpose here to repeat the analysis available in Schmidt and Nahrstedt (2002a, b), which appears to be both comprehensive and valid in most of its judgments regarding individual case reports. According to the authors, their database consists of 37 case reports from the German BfArM (plus five duplicate/triplicate entries of otherwise identical case reports), five cases from the Swiss SWISSMEDIC (formerly Interkantonale Kontrollstelle or IKS), two case reports published in the German public press, five cases from the medical literature, 20 case reports from the US FDA (Food and Drug Administration, 2002), two case reports from the British MCA (Medicines Control Agency), one from the Australian TGA (Therapeutic Goods Administration), three from Canada, two from the France and one case from the Pharma-
The Schmidt and Nahrstedt evaluation is unproblematic in its judgment of these particulars:
1. Of the 78 reports, 5 appear to be double or triple entries.
2. 14 have no connection to kava usage.
3. 29 cannot be assessed due to the insufficiency of the documentation.

Of the cases showing a "possible connection," only one appears to involve use in strict conformity with German Commission E recommendations of no more than 120 mg kavalactones per day for 3 months or less. Three other cases are "plausible," although in two of these three higher dosage and longer term treatment may have been employed. Using their very narrow criteria for inclusion, Schmidt and Nahrstedt conclude that only 4 out of the 78 cases constitute reasonably acceptable AERs against kava. By this is meant that a model of direct toxicity, as opposed to a model of the potentiation of the toxicity of other drugs. The direct toxicity model, of course, is the model which is reflected in the safety data of the clinical trials discussed earlier running from 4 to 24 weeks in length. Under the restricted conditions of these trials, kava extracts appear to be quite safe. Similarly, very short term trials of high kavalactone intake have not demonstrated toxicity: 300–600 mg per day acetone extract for 1 week (Johnson et al., 1991), 600 mg per day acetone extract for 1 week (Mińi et al., 1993; Heinze et al., 1994), or 240 mg per day alcohol extract for 2 weeks (Herberg, 1996).

As several authors have noted, the range of hepatotoxic reactions found in the AERs is not compatible with the usual results of adverse drug interactions. Reports include necrosis, drug-induced hepatitis, and cholestatic hepatitis, that is, a pattern more indicative of a range of causes than of a single modality (Humbertson et al., 2001; Denham et al., 2002). Such a conclusion, if warranted, does not, however, mean that kava should be taken as being free of causality in the AERs.

4.2. The indirect toxicity model

The model of direct toxicity may not be the proper frame of reference. Already three mechanisms of potential toxicity have been uncovered that would normally lead to hepatic issues only under special—but not necessarily unusual—circumstances. The inhibition of human cytochrome P450, interactions with cyclooxygenase activities and the reduction of liver glutathione all potentially present serious threats to health under appropriate conditions even though in themselves they may lead to hepatotoxicity only as exceedingly rare events. Researchers involved with uncovering the P450 inhibition already have observed that a number of accounts provide indirect indications of this linkage (Mathews et al., 1988).

Schmidt and Nahrstedt judge eight reports as having doubtful connection to kava usage. The doubtful category consists of cases with abnormalities in reported laboratory testing, improbable temporal relations between ingestion of the drug and the adverse event, the presence of pre-existing disease conditions and/or use of other drugs or chemicals more likely to explain the events. This leaves 23 reports as being probably connected to concomitant medications.

It is this category of 23 reports probably connected to concomitant medications which eludes easy judgment and, indeed, may not be subject to proper evaluation given the present state of knowledge and the available records. Schmidt and Nahrstedt conclude that our current data point to an idiosyncratic-immunologic mechanism of liver toxicity. These authors are able to demonstrate, furthermore, that in a number of identical cases the BfArM, MCA and EMEA expert panels rendered strikingly conflicting evaluations (Schmidt and Nahrstedt, 2002a, Internet). Therefore, the prima facie evidence with regard to many of the cases is that there is either no consensus as to what standards of evaluation should be employed or, if such standards exist, they are difficult in practice even for experts to apply. This type of difficulty is more common than we would normally like to think (Kaplowitz, 2001; Lucena et al., 2001).

One problem is that an indirect potentiation of hepatotoxicity by kavalactones likely would manifest as just the idiosyncratic mechanism of liver toxicity referred to by Schmidt and Nahrstedt or, for that matter, the UK Medicines Control Agency in its December 2002 announcement. Moreover, the range of possible untoward interactions with even common OTC preparations, such as acetaminophen, is quite high. Most commentators on the AERs have taken the stand that
these overstate the number of cases of toxicity. This is true in the sense that a clouding of the data with concomitant medications is found in most of the AERs. Nevertheless, in reporting more generally there is a risk that the reverse is also true (Izzo and Ernst, 2001). In cases involving co-medication with drugs of known toxic impact on the liver, it quite possible that reactions have been reported as resulting from these drugs and the interactions with kava overlooked. This is to say that the AERs may underestimate the number of cases that should be examined, although there would seem to be no way of readily determining whether or to what extent this is true after the fact.

Would even more thorough clinical trials have solved the issue kava’s safety with regard to the liver before kava extracts were widely marketed? Probably not. It is widely accepted that most hepatic drug reactions involve only a small proportion of individuals. This fact makes it difficult to detect even direct hepatotoxicity at the time of drug development (Larrey, 1997, 2002).

4.3. The risk-to-benefit ratio

Certainly in the US, it is quite common for those ingesting herbal products to not inform their doctors. Depending on the region and the survey, between 50% (Martin et al., 2002) and 63% (Oldendick et al., 2000) of patients do not inform their doctors of herb use. FDA research suggests that <1% of the severe adverse events that occur with the use of dietary supplements are reported to FDA (Walker, 2000). Moreover, in general data collected on non-prescription drugs, including AERs, differs in quality from data collected on prescribed medications. Therefore, an aura of uncertainty surrounds comparisons of risk-to-benefit ratios between these two classes of drugs. Nevertheless, an assessment of kava’s safety would seem to require at least a glancing examination of the known risks of the drugs that would replace it.

A worst-case scenario accepts that all 78 cases presently available be included and the rate of adverse events be calculated against the best available data on intake, in this case 250 million daily doses over the last 10 years as derived from the figures of the German Institute of Medicinal Statistics. According to this analysis, the rate of incidence is 0.3 cases per one million daily doses (Schmidt and Nahtstedt, 2002a, Internet). This compares extremely favorably with the benzodiazepines, where the rate of hepatic adverse effects per million daily doses is 0.90 for bromazepam, 1.23 for oxazepam, and 2.12 for diazepam (Schulte et al., 2001). Similarly, the nonsteroidal anti-inflammatory drugs have rates of hepatotoxicity of 3%–5% (acetosalicylic acid), of which 3% again are potentially life-threatening (Rahmovitz and Van Thiel, 1992; O’Brien, 1986; Schmidt and Nahtstedt, 2002a, Internet). Acetaminophen-containing products are another case in point, accounting for more than 56,000 emergency room visits per year in the US and 258 cases of acute liver failure in the period 1998–2000 (Wooltorton, 2002).

It should be stressed again that there appears to be general agreement at this point that kavalactones are efficacious for treating anxiety. Moreover, even the safest of the preferred prescription drugs appear to exhibit a hepatic adverse event rate at least three times that of the kavalactones. Therefore, a quite strong argument can be made that kavalactones should be returned to the market, perhaps as prescription drugs, for the treatment of anxiety.

5. Conclusion

Evidence is beginning to emerge that kavalactones may influence both the phase I and II liver detoxification pathways through, respectively, inhibition of cytochrome P450 activity and a reduction in liver glutathione. Of possible, but unknown importance with regard to potential hepatotoxicity is the inhibition of cyclooxygenase enzyme activity by kavalactones. Implicit in these findings is the probability that kava extracts have a high potential for drug interactions.

Investigators have yet to clearly identify factors that might allow the reliable prediction of which individuals are at risk for adverse reactions after usage of kavalactones. Liver toxicity associated with kava consumption is rare and its appearance is idiosyncratic. Of the 78 AERs known at the time of this writing, only one seems definitely and only three others seem likely linked to kava consumption alone. Evidence of direct toxicity under German Commission E recommendations appears to be limited to one case.

Some 23 other reports exhibit possible connections, yet include the confounding usage of drugs which
themselves may have untoward effects upon liver function. Despite the emergence of knowledge of mechanisms by which kavalactones may promote and intensify the hepatotoxicity of other drugs, it is not possible at this stage to show definitively either how many of or to what extent these 23 AERs are the result of kava ingestion. The indirect promotion of hepatotoxicity of drugs, alcohol, etc. by concentrated kavalactones, although very probable, cannot as of yet be properly evaluated.

Finally, it remains true that kava extracts show good efficacy in the treatment of anxiety. In comparison with prescribed anxiolytics and even many OTC products, moreover, kava extracts continue to demonstrate a far better risk-to-benefit ratio.

References


