Potential for interaction of kava and St. John’s wort with drugs

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Abstract

The present interest and widespread use of herbal remedies has created the possibility of interaction between them and pharmaceutical drugs if they are used simultaneously. Before the recent reports of apparent hepatotoxicity associated with its use, kava (*Piper methysticum* Forst. F.) was one of the top 10 selling herbal remedies in Europe and North America. This adverse effect was not previously encountered with the traditional beverage which was prepared as a water infusion in contrast to the commercial products which are extracted with organic solvents. Kavalactones, the active principles in kava, are potent inhibitors of several of the CYP 450 enzymes, suggesting a high potential for causing pharmacokinetic interactions with drugs and other herbs which are metabolized by the same CYP 450 enzymes. Furthermore, some kavalactones have been shown to possess pharmacological effects, such as blockade of GABA receptors and sodium and calcium ion channels, which may lead to pharmacodynamic interactions with other substances which possess similar pharmacological proprieties. St. John’s wort (*Hypericum perforatum* L.) used extensively for the treatment of mild to moderate clinical depression, has long been considered safer than the conventional pharmaceutical agents. However, its ability, through its active constituents hypericin, pseudohypericin and hyperforin, to induce intestinal *P*-glycoprotein/MRD1 and both intestinal and hepatic CYP3A4 enzyme, could markedly reduce the distribution and disposition of their co-substrates. In addition, St. John’s wort is a potent uptake inhibitor of the neurotransmitters serotonin, noradrenaline and dopamine all of which have a role in mood control. Consequently, the very real potential for a pharmacodynamic interaction between the herb and pharmaceutical drugs which share this mechanism of action and, like St. John’s wort, are used for mood elevation. However, presently there is very little evidence to substantiate actual pharmacokinetic and/or pharmacodynamic interaction between drugs and kava or St. John’s wort. This review provides a brief overview of the existing data on interactions of kava and St. John’s wort with pharmaceutical agents and as a result reveals the urgent need for detailed investigations to identify clinically significant interactions for these herbal remedies that have the potential to cause adverse effects.

Keywords: St. John’s wort; *Piper methysticum*; Kava; *Hypericum perforatum*

1. Introduction

During the last decade, a dramatic increase in the use of herbs and herbal remedies has been witnessed in many parts of the world, in particular in Europe and North America (Brevoort, 1998; Blumenthal, 1999). While such products had been used with apparent safety in traditional societies for many centuries, their introduction into western countries, where they are being combined with pharmaceutical agents, poses the possibility of potential interaction between the two groups of substances. Although often promoted as natural and therefore safe and harmless, the clinical and adverse effects of herbal remedies have not been investigated thoroughly enough for them to be considered effective or completely safe. In many countries they may be marketed without proof of safety and efficacy which are required by national health agencies for medicinal drugs.

For instance, in the United States, there are no standards set for quality control nor prior approval of supplements is required before they enter the market (Radimer et al., 2000). While manufacturers may not make claims on efficacy for treating a disease, they may state a product’s pharmacological effects. Hence the consumer has to rely on the manufacturers to provide reliable information on effectiveness, safety, contraindications and interactions (Valli and Giardina, 2002).
A major safety concern associated with the use of herbal therapies is the risk of interactions with prescription medications (e.g., Izso and Ernst, 2001; Brazier and Levine, 2003; Williamson, 2003). Reports indicate that about 15–20% of individuals on prescription medications also use herbal supplements and less than 40% of patients disclose to their physicians their usage of herbal remedies, even if they experience severe side effects—because of the fear of censure or rebuke (Eisenberg et al., 1998; Kaufman et al., 2003). The problem is further compounded by the fact that many physicians are themselves not always familiar with the potential for herb–drug interactions (Klepser et al., 2000).

This article highlights some of the observed and potential clinical interactions between two common herbal remedies, kava and St. John’s wort, and prescribed medications for the treatment of some common disorders.

2. Kava

The kava beverage, prepared as a water infusion from the roots and rhizomes of the kava plant (Piper methysticum Forst. F.), has been used by the Pacific Islanders for many centuries as a traditional drink and as part of their material culture (Singh, 1992; Singh, 2004). In the past few decades, kava has gained popularity in the Western countries as a herbal preparation because of its anxiolytic, antistress and sedative properties (Singh and Singh, 2002). The psychoactive activity in kava is contained in a series of about 18 compounds called kavalactones of which six (kavain, yangonin, methysticin, dihydrokavain, desmethoxyyangonin and dihydromethysticin) account for about 95% of the lipid extract and the activity (Lévesque, 1985). However, about 3–4 years ago, reports of alleged hepatotoxicity associated with commercial kava preparations caused alarm in the medical community and the media and forced several countries to either ban the products or to issue health advisories.

These actions effectively removed most of these products from the market. However, the traditional kava beverage continues to be consumed in the Pacific Islands and the kava root is still available and used for this purpose in many Western countries, especially by Pacific Island immigrants. The kava producing countries of the Pacific find the controversy surprising given the long history of apparent safe use in the Pacific and are making a concerted effort to identify the origins of the alleged hepatotoxicity. The International Kava Conference, held in Suva, Fiji in late 2004, was an integral part of this effort.

Various hypotheses that have been proposed for the origins of the toxicity include the method of extraction in that the commercial preparations use organic solvents while the traditional beverage is a water infusion, the use of bark and other parts of the plant which may contain toxic substances, in particular pipermethystine (Nerurkar et al., 2004), pre-existing liver and kidney dysfunction, overdosage, kava–drug interaction and genetic differences between Europeans and Pacific Islanders which may impact the rate of metabolism of the kavalactones (Singh et al., 2004).

The effect of simultaneous intake of a kava extract (WS 1490) with ethanol was evaluated by Herberg (1993) on seven safety-related performance variables in a double-blind, placebo-controlled, randomized trial of 40 volunteers. In general, there were no negative performance effects of combining kava with ethanol compared to kava alone. In a similar study, Foo and Lemon (1997) assessed in 10 subjects the impact of ethanol or kava separately and in combination on subjective measures of impairment and intoxication and on cognitive performance. Kava consumption produced no significant effects on perceived or measured competence, while alcohol caused motor and cognitive impairments. However, when alcohol and kava were combined, kava potentiated both the perceived and measured impairment produced by alcohol alone. This potentiation effect is in agreement with the findings of Janieson and Duffield (1998) on the positive interaction of ethanol and kava resin in mice.

Another double-blind, randomized, cross-over study examined the effect of combining a kava extract with a benzodiazepine (Herberg, 1996). Eighteen subjects daily received either 800 mg of a kava extract or 9 mg bromazepam or both for 14 days each. Results from a battery of performance tests indicated no significant differences between bromazepam alone and the combination with kava. Tiredness was the most common complaint, reported by 4 subjects taking kava, 11 with bromazepam and 14 with the combination.

The case of a purported interaction between kava and alprazolam that may have caused a semicomatose state in a 54-year-old man was described by Almeida and Grimsley (1996). The man had been taking alprazolam, cimetidine and terazosin and, for 3 days prior to his hospitalization, he self-medicated himself with kava as well. When admitted to the hospital, he was in a lethargic and disoriented state. Tests showed that his vital signs and laboratory values were normal, alcohol was negative and a positive drug screen for benzodiazepines, presumably from alprazolam. Few details, such as dosage of any of the medications or kava, were reported. The authors suggested that kavalactones and the alprazolam had additive effects because both act on the same GABA receptors, hence undergoing a pharmacodynamic interaction. Kavalactones, like benzodiazepines, do indeed interact strongly with GABA A receptors which are plentiful in the hippocampus and amygdala (Jussofie et al., 1994), and which could well account for the observed interaction leading to the exaggerated effect.

Potentially the most significant interaction between kava and pharmaceutical drugs could occur through an inhibition by kavalactones of the cytochrome P 450 (CYP 450) enzymes, resulting in pharmacokinetic interaction. Since these enzymes are responsible for the hepatic metabolism of a large number of pharmaceutical agents and xenobiotics, their inhibition could elevate the plasma levels of these drugs to concentrations that are toxic to various organs and tissues. In a study on the actions of the six major kavalactones...
on cDNA-derived CYP450 enzymes, Zou and coworkers (2002) found that the most potent inhibition of CYP1A2 occurred with desmethoxyyangonin (DMY) (IC₅₀ 1.70 μM); of CYP2C19 with dihydromethysticin (DHM) (0.43 μM), DMY (0.51 μM) and methylcristin (0.93 μM); of CYP3A4 with methylcristin (1.49 μM) and DHM (2.49 μM). Potent inhibitors in this test were considered to be compounds with IC₅₀ values \( \leq 10 \mu M \). What is most notable in the data is that kavain, the most potent anxiolytic kavalactone, dihydromethysticin and yangonin were largely ineffective in the highest concentrations tested.

The inhibition of CYP450 enzymes by whole kava extract (containing 100 μM total kavalactones) and individual kavalactones was also investigated in human liver microsomes (Mathews et al., 2002). The extract caused significant inhibition of the activities of CYP1A2 (56% inhibition), 2C9 (92%), 2C19 (86%), 2D6 (73%), 3A4 (78%) and 4A9/11 (65%). CYP2A6, 2C8 and 2E1 activities were unaffected. The activities of CYP2C9, 2C19, 2D6 and 3A4 were measured with kavain, DMY, methylcristin and DHM, each at 10 μM. While kavain did not inhibit these enzymes, there was significant inhibition of CYP2C9 by DMY (42%), methylcristin (58%) and DHM (69%); of 2C19 by DHM (76%); of 2D6 by methylcristin (44%); of 3A4 by DMY (40%), methylcristin (27%) and DHM (54%). Unger et al. (2002) tested several ethyl acetate extracts of kava for inhibitory effects of CYP3A4. They observed a 70–80% inhibition of the enzyme by the different fractions with kavain, DHK, methylcristin, DHM and DHY being the main inhibitory principles.

These data collectively indicate that kava has a high potential for causing herb-drug interactions through inhibition of CYP450 enzymes responsible for the majority of the metabolism of pharmaceutical agents used currently. Co-ingestion of kava with prescription medications or over-the-counter products, including other herbal remedies that are metabolized with one or more of these enzymes, might result in elevated and potentially toxic concentrations of the co-administered agents or their metabolites (Anke and Ramzan, 2004). Some common pharmaceutical agents that are metabolized by these enzymes include, for 1A2: amitryptiline, caffeine, diazepam, warfarin; 2C9: aspirin, phenytoin, tolbutamide, warfarin; 2C19: amitryptiline, diazepam, imipramine, propranolol; 2D6: fluoxetine, haloperidol, morphine, many β-blockers; 3A4: amitryptiline, many calcium channel blockers, midazolam, several antifungal agents. In the earlier report (Almeida and Grimley, 1996), a possible interaction of kava with alprazolam to produce a semicoma state may also in part have been pharmacokinetic in nature with kava inhibiting CYP enzymes and hence increasing plasma alprazolam concentrations to toxic levels.

Genetic polymorphism of many CYP enzymes, leading to interindividual variation in drug metabolism, may be another important factor in the marked discrepancy in hepatotoxic response to kava of Caucasians from Europe, North America, Australia and New Zealand on the one hand and the Pacific Islanders on the other. CYP2D6 is one of the most extensively studied genetically polymorphic enzymes. It is thought to cause much of the interindividual variations seen in drug responses, adverse effects and interactions with drugs (Poolus et al., 2000). Individuals may be poor (slow), intermediate, extensive (fast), or ultrarapid metabolizers. In a Caucasian population, 7–9% of individuals were homozygous deficient in CYP2D6 and thus are poor metabolizers (Poolus et al., 2000). On the other hand, the incidence of CYP2D6 deficiency was almost 0% in persons of pure Polynesian descent and about 1% in Asian populations (Wanowriilnik et al., 1998). Since this enzyme is a major metabolizer of kavalactones, it is tempting to assume that the genetic difference between Caucasian kava users and the Pacific Islanders may be a significant contributory factor. It may also explain why the descendants of Asian migrants to the Pacific, like the authors’ family members who have been habitual kava users, have supposedly not experienced kava hepatotoxicity. However, the genetic polymorphism of CYP2D6 or of other CYP enzymes for Melanesians of Fiji, Vanuatu and other kava consuming nations in the Pacific is yet to be determined.

### 3. St. John’s Wort

St. John’s wort (Hypericum perforatum L.) has been used medicinally for over 2000 years, variously as a diuretic, in the treatment of neuralgic conditions, sciatica and poisonous snake bites, wounds, bruises, strains, anxiety, hysteria and neurasthenia (Bilia et al., 2002). In the past two decades, it has become increasingly popular in Europe and North America for the treatment of mood disorders, especially in cases of mild to moderately severe depression.

Depression is a serious psychological problem encountered in medical practice with about one person in five experiencing an episode of major depression in his or her life. About 75% of all cases of depression are of mild to moderate severity and are normally treated in primary care settings. Pharmacotherapy and psychotherapy represent the most widespread therapeutic approaches for the management of depression. However, severe side effects from the use of antidepressants have limited their true efficacy and acceptance by the patients and often lead to non-compliance in a very short time. Thus, successful treatment of clinical depression with currently available drugs is achieved in about 65–75% of cases and only between 40–50% achieve complete recovery (Keith and Matthews, 1993; Müller and Volz, 1996).

Because of the above limitations, there has been renewed interest in alternative therapies, such as St. John’s wort (SJW), which may have comparable efficacy to prescription medications while lacking their severe side effects (Bilia et al., 2002). In the last decade, several standardized extracts of SJW have been approved in Europe for the treatment of mild to moderate depression and such preparations are also freely available over-the-counter in most other western countries. A total sales figure of about US$ 6 billion for 1998 in Europe
alone attests to the popularity of this herb for treating depression (Harrison, 1998).

Commercial SJW preparations consist of dried flowers or dried aerial parts of the plant which grows well in Europe, Asia, North Africa and North America. The major active constituents are the naphthodianthrones hypericin and pseudohypericin and the chlorogranular derivative hyperforin. The European Pharmacopoeia (2001) requires not less than 0.08% naphthodianthrones calculated using UV spectroscopy whereas for the United States Pharmacopoeia (1999) the standardized extract should contain not less than 0.2% of hypericin and pseudohypericin combined and not less than 3.0% of hyperforin, all calculated by HPLC. The HPLC assay method is generally considered to be more selective, accurate and reproducible than UV analysis and so is preferable. The inclusion of hyperforin is especially significant as it is now postulated to be the major active ingredient in SJW. However, all three compounds are fairly unstable towards light and temperature and so shelf life and method of storage may be critical factors in preserving activity (Bergonzi et al., 2001).

SJW is probably the most studied herb with respect to its efficacy, safety and tolerability in patients with mild to moderate depressive symptoms. Its popularity in mild to moderate depression is primarily attributable to its favorable risk–benefit profile. Adverse effects are mild and generally have a similar incidence to that for placebo and lower compared to conventional antidepressants. On the other hand, it has been demonstrated to be more efficacious than placebo and as efficacious as many synthetic antidepressants (e.g., Kim et al., 1999a; Brenner et al., 2000; Whiskey et al., 2001). These and many other findings are in direct contrast to a recent study that found that neither SJW nor the standard treatment sertraline, a selective serotonin reuptake inhibitor (SSRI), was superior to placebo in achieving a better response (HDTSG, 2002). This report has been widely criticized for flaws in its protocol, in particular that the subjects were suffering from moderate to severe depression for which SJW is not recommended (e.g., American Botanical Council, 2002).

Despite its widespread use and purported efficacy, the mechanism of action for SJW is still uncertain. Most currently used antidepressants work primarily by blocking the reuptake of the monoamine neurotransmitters norepinephrine, dopamine and, in particular, serotonin. The older agents also act at muscarinic, histaminergic and adrenergic receptors, leading to numerous side effects such as sedation, dry mouth, constipation, orthostatic hypotension and sexual dysfunction. The lack of similar side effects with SJW suggests it has minimal activity at muscarinic or adrenergic receptors.

SJW itself has been shown to inhibit monoamine neurotransmitter uptake in several biologic systems. Several in vitro studies have shown that SJW and hyperforin specifically inhibit synaptosomal uptake of serotonin, norepinephrine and dopamine with potency comparable to that of conventional antidepressants such as imipramine and fluoxetine (Chatterjee et al., 1998; Müller et al., 1998; Butterweck, 2003). This mechanism of action of SJW creates a marked possibility of an interaction between it and a wide range of drugs that are potent inhibitors of the uptake of serotonin, norepinephrine and dopamine if co-administered with it. Drugs and drug groups with which the risk of interaction is the greatest include the SSRIs, such as fluoxetine, sertraline and paroxetine, the tricyclic antidepressants, such as imipramine, which also inhibit reuptake of serotonin, and venlafaxine, which inhibits reuptake of both serotonin and norepinephrine. Interactions between SJW and drugs that inhibit serotonin uptake could be especially troublesome because the resulting elevated levels of the transmitter can cause “serotonin syndrome” whose clinical symptoms typically include akathisia-like restlessness, muscle twitches and myoclonus, hyperreflexia, sweating, penile erection, shivering and tremor as prelude to more severe intoxication, with seizures and coma (Sternbach, 1991).

Recent studies show that, in addition to the above mentioned inhibition of transmitter uptake, interaction between SJW and conventional drugs may also be due to induction of certain CYP enzymes although inhibition of others has been proposed (Fugh-Berman, 2000; Biffignandi and Bilia, 2000). Clinical reports indicate that SJW consistently decreases alprazolam and midazolam plasma levels in healthy volunteers (Markowitz et al., 2003). These observations are likely to be due to the reported potent induction by SJW and its constituents of a number of hepatic enzymes. For instance, in human studies, an SJW extract produced a clear induction of 3A4 expression in intestinal mucosal microsome preparations and roughly doubled its hepatic activity in near clinical doses, as evaluated by the erythromycin breath test, as well as enhanced the activities of other enzymes such as CYP1A2, 2D6 and 2C9. By acting in this manner, SJW was found to reduce the serum level of a number of drugs and chemicals in the clinical setting (Durr et al., 2000; Dresser et al., 2003). Bilia et al. (2002) cite such effects with cyclosporine leading in some cases with acute transplant rejection (eight cases), digoxin (one), indinavir (eight), nevirapine (five), SSRIs (five), combined oral contraceptives (three), theophylline (one) and warfarin (seven).

Another mechanism by which drug combinations can result in deleterious effects is by drug induction of P-glycoprotein (P-gp)/MDR1. It is becoming increasingly clear that the expression of this drug transporter plays an important role in the disposition and pharmacological activity of a broad range of compounds (Kim et al., 1999b; Fromm et al., 1999; Hennessy et al., 2002). It is the product of the multidrug resistance (MDR) genes and functions to reduce drug efflux and hence the intracellular concentrations of many P-gp substrates. In a number of recent studies, SJW was shown to produce significant inducing effects on the expression of intestinal P-gp/MDR1 (Durr et al., 2000; Hennessy et al., 2002; Dresser et al., 2003; Weber et al., 2004).

These effects on the expression of intestinal P-gp/MDR1 and CYP3A4 and function of hepatic CYP3A4 provide a mechanistic explanation for the interactions of SJW with
the drugs and chemicals mentioned above and others cited in the literature. The inducing effects would decrease their intestinal absorption and so increase hepatic first pass clear-
ance of P-gp/MDR1 and CYP3A4 substrates. The resulting additive decrease of the overall oral bioavailability through altered drug absorption and disposition could thus explain the observed adverse interactions between SJW and the compounds.

In conclusion, the studies and observations cited in this paper suggest that there could possibly be significant interactions between herbal remedies and drugs and between herbs themselves if taken together in very much the same way as the well recognized and cited drug-drug interactions. Since herbal supplements are usually intended to be taken over an extended period of time, there is, beside enzyme induh-
ion and other chronic effects, ample opportunity for enzyme induction and activation. Hence, without exaggerating the negative properties of the herbal supplements as occurs in the public media, there is need for greater vigilance of any adverse effects and more research in the mechanisms of action and unwanted activities they may produce.

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