Table 2 Case reports of hepatotoxicity with kava: additional data (continued)

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
74	14723	FDA	Phytopharm 2.6.17 (EMEA 51)	F	44	Celecoxib, citalopram		
75	1939507	Brazil		F	44	Diclofenac, famotidine		Toxic hepatitis
76	2380373	WHO		F	46	Not recorded	Onset > 1 yr after stopping	
77	47	MCA		F	47	Not recorded		
78	28	Stickel		F	49	'Regular alcohol'		Necrotising hepatitis
79	14951	FDA	Phytopharm 2.4.20 (EMEA 59)	F	51	Omega-3		
80	15267	FDA	Phytopharm 2.4.25 (EMEA 62)	F	51	Not recorded		
81	8119572	WHO	Canada, Phytopharm 2.5.5 (EMEA 66)	F	53	Alcohol		
82	10	Literature (10)		M	55	None		Haemorrhagic necrosis
83	14	Stickel		F	57	Candesartan, oestrogen		Lobular hepatitis
84	2001	Weekly Magazine	Phytopharm 2.4.18; similar to case 18 (literature (8)/ Phytopharm 2.6.23)	F	60	Not recorded		
85	14538	FDA	Phytopharm 1.6.19 (EMEA 50)	F	60	Capecitabine, chaparral	Secondaries in liver? Chemo restarted & OK	
86	3	Literature (1, 2)	Phytopharm 2.4.31	F	14	None		Hepatocellular necrosis / chemical hepatitis
87	7	Literature (7), TGA		F	56	Passiflora incarnata		Severe acute hepatitis, massive necrosis.
88	2	MCA		F	-	Alcohol, fluoxetine		
89	15319	FDA	Phytopharm 2.7.9 (EMEA 57)	M	63	Enalapril, hydrochlorothiazide	History of hepatitis C	
90	67	Canada (EMEA id)	Phytopharm 2.4.27 (EMEA 67)	M	38	Not recorded		
91	15250	FDA	Phytopharm 2.4.23 (EMEA 54)	F	-	Multivitamins, 'moderate alcohol'	Phytopharm records as male	
92	13198	FDA		F	52	>60 herbs, alcohol		Chronic alcoholic liver disease
93	15252	FDA	Phytopharm 2.4.24 (EMEA 61)	F	-	Dexatrim Green Tea		

Table 3 Hepatic events reported in association with kava

Hepatic event	Count	%
Hepatitis	22	23.7
Hepatitis cholestatic	9	9.7
Hepatitis fulminant	3	3.2
Hepatitis toxic	2	2.2
Hepatic failure	11	11.8
Hepatic necrosis	6	6.5
Jaundice	9	9.7
Hepatocellular liver injury	8	8.6
Liver injury	1	1.1
Hepatic function abnormal	18	19.4
Cirrhosis	2	2.2
Not described	2	2.2
Total	93	100.3

Table 4 Case reports of hepatotoxicity with kava: histological data

No	Histology	Hepatic event	Outcome
19	Acute necrotising hepatitis	Hepatic necrosis	Recovered
07	Autoimmune hepatitis un-changed after > 4 months	Hepatitis	Recovered
45	Cholestatic hepatitis	Jaundice	Recovered
35	Cholestatic hepatitis	Hepatitis cholestatic	Recovered
53	Cholestatic hepatitis	Hepatocellular liver injury	Recovered
29	Cholestatic hepatitis	Hepatitis cholestatic	Unknown
11	Cholestatic hepatitis. Pronounced necrosis.	Hepatic necrosis	Liver transplant, Died (6 months)
92	Chronic alcoholic liver disease	Cirrhosis	Unknown
54	Drug induced hepatitis	Hepatitis	Recovered
31	Drug-induced cell necrosis and fibrosis	Hepatic failure	Liver transplant
43	Drug-induced hepatitis	Hepatitis cholestatic	Recovered
82	Haemorrhagic necrosis	Hepatitis	Recovered
86	Hepatocellular necrosis / chemical hepatitis	Hepatitis fulminant	Liver transplant
83	Lobular hepatitis	Hepatitis	Recovered
18	Necrosis & intrahepatic cholestasis	Hepatic failure	Liver transplant
23	Necrosis liver cells	Hepatic failure	Liver transplant, Died [Stickel]
12	Necrotising hepatitis	Hepatic necrosis	Liver transplant
27	Necrotising hepatitis	Hepatic failure	Died
51	Necrotising hepatitis	Hepatic necrosis	Recovered
52	Necrotising hepatitis	Hepatitis	Recovered
65	Necrotising hepatitis	Hepatic necrosis	Recovered
78	Necrotising hepatitis	Hepatic necrosis	Recovered
87	Severe acute hepatitis, massive necrosis.	Hepatic failure	Liver transplant, Died
56	Subfulminant hepatic necrosis	Hepatitis cholestatic	Liver transplant
75	Toxic hepatitis	Hepatitis fulminant	Liver transplant
34	Toxic hepatopathy	Hepatic failure	Died
55	Toxic-cholestatic liver damage	Hepatitis cholestatic	Recovered
47	Toxic-necrotic hepatitis	Hepatitis toxic	Liver transplant

Table 5 Case reports of hepatotoxicity with kava: significant concomitant medicines

No	Sex	Age	Rel	OPS	Concomitant
05	F	59	3	Yes	Lisinopril, phenobarbital, fenofibrate
06	F	39	3	Yes	Tetracycline, alcohol
07	F	21	4	Yes	Paracetamol, pantoprazole, MDMA
08	M	35	3	Yes	'Regular alcohol'
10	F	69	3	Yes	Bemetizid, pentoxifyllin
11	F	22	3	Yes	COC (Pramino)
12	M	32	3	Yes	Valerian
13	F	35	3	Yes	Paracetamol
15	F	46	3	Yes	COC (Klimonorm)
17	F	47	3	Yes	Fish oil
18	F	60	3	Yes	Piretanide
19	F	39	2	Yes	Paroxetine, COC (Pramino)
20	F	-	6	Yes	Omeprazole, estradiol, losarten
22	M	39	3	Yes	Interferon-beta
23	F	50	3	Yes	COC (Gravistat), glimepiride, metformin
26	F	56	3	Yes	Esberitox, omeprazole
27	F	61	3	Yes	Bemetizid, omeprazole
28	F	32	6	Yes	COC (Marvelon)
30	F	26	3	Yes	Diclofenac, sulfasalazine, MPA
32	F	33	3	Yes	Cisapride
34	F	81	3	Yes	Alcohol, hydrochlorothiazide, nitrendipin
35	M	55	6	Yes	Glibenclamide
36	F	41	6	Yes	COC (Diane)
41	F	72 / 75	3	Yes	Vitamin A
44	F	37	4	Yes	Diclofenac, COC (Microdiol)
45	F	39	3	Yes	COC (Gravistat)
46	F	46	3	Yes	Hydrochlorothiazide, valsartan
47	M	50	3	Yes	'Moderate alcohol' (BfArM, Denham 18)
49	F	57	3	Yes	Silybum
50	F	59	3	Yes	Celecoxib
52	M	38	3	Yes	Penicillin V, 'regular alcohol' (Stickel 12)
54	F	50	3	Yes	Terfenadine, furosemide
56	F	45	3	Yes	Rabeprazole
57	M	24	3	Yes	Chromium piccolinate, vanadyl sulphate
58	F	70	6	Yes	Lisinopril, warfarin
59	M	72	6	Yes	Valerian
63	F	28	6	Yes	Fluoxetine
64	F	30	3	Yes	Passiflora
65	M	33	6	Yes	'Regular alcohol'
66	F	33	6	Yes	COC (LoEstrin), chemotherapy
69	F	39	3	Yes	Yes (drug not stated)
70	F	39	3	Yes	Unspecified possibly hepatotoxic drugs
71	M	40	3	Yes	Alcohol
73	F	43	3	Yes	Beta blocker, anaesthetic
74	F	44	6	Yes	Celecoxib, citalopram
75	F	44	3	Yes	Diclofenac, famotidine
78	F	49	6	Yes	'Regular alcohol'
79	F	51	3	Yes	Omega-3
81	F	53	3	Yes	Alcohol
83	F	57	3	Yes	Candesartan, oestrogen
85	F	60	3	Yes	Capecitabine, chaparral
87	F	56	3	Yes	Passiflora incarnata
88	F	-	3	Yes	Fluoxetine
89	M	63	3	Yes	Enalapril, hydrochlorothiazide
91	F	-	3	Yes	Multivitamins, 'moderate alcohol'
92	F	52	6	Yes	>60 herbs, alcohol
93	F	-	3	Yes	Dexatrim Green Tea

Table 6 Case reports of hepatotoxicity with kava: concomitant therapy not suspect

No	Sex	Age	Hepatic event	Outcome	Rel	OPS	Products not suspect
03	F	27	Jaundice	Recovered	2	NS	Psyllium, vitamins B6 & E, St John's Wort, phytoestrogen mix (Mex yam, black cohosh, dong quai)
21	F	34	Hepatitis	Recovered	2	NS	Jodthyrox (Levothyroxine, potassium iodide)
31	F	47	Hepatic failure	Transplant	6	NS	Sylmarin, Polilevo (arginine, ornithine, citrullin), Gelum (mineral supplement), Rheumeda (antirheumatic homeopathic preparation).
37	F	59	Hepatocellular damage	Recovered	2	NS	Buscopan
39	F	45	Hepatitis	Recovered	2	NS	Artichoke extract (taken occasionally)
43	F	33	Cholestatic hepatitis	Recovered	2	NS	Exepta (homeopathic combination product)
55	F	68	Hepatitis cholestatic	Recovered	3	NS	St John's Wort, Maaloxan (magnesium and aluminium hydroxide)
68	M	38	Hepatitis	Unknown	6	NS	St John's Wort

Table 7 Case reports of hepatotoxicity with kava: summary of outcomes

Outcome	Count	%
Died	7	7.5
Transplant	14	15.1
Recovered	50	53.8
Improved	3	3.2
Not recovered	4	4.3
Unknown	19	20.4

Table 8 Case reports of hepatotoxicity with kava: cases with 'probable' relationships

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
03	F	27	Kava tea	Water	2400	kava lactones	(180)	Jaundice	NS	Y	N	Recovered	2
04	F	55	Kava traditional drink	Water	2571	kava lactones	35	Hepatocellular liver injury	No	Y	N	Recovered	2
19	F	39	Kava	Ethanol	60	kava lactones	194	Hepatic necrosis	Yes	Y	R	Recovered	2
21	F	34	Kava ratiopharm	Ethanol	120	kava lactones	(90)	Hepatitis	NS	Y	N	Recovered	2
37	F	59	Limbao	Ethanol	240	kava lactones	120	Hepatocellular liver injury	NS	Y	X	Recovered	2
39	F	45	Maoni	Ethanol	45	kava lactones	(120)	Hepatitis	NS	Y	N	Recovered	2
43	F	33	Laitan	Acetone	210	kava lactones	(21)	Hepatitis cholestatic	NS	Y	N	Recovered	2
82	M	55	Kava		750		90	Hepatitis	No	Y	N	Recovered	2

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
03	15281	FDA	Phytopharm 2.5.4 (EMEA 55)	F	27	None suspect		
04	11.2	Literature (11)		F	55	None		
19	5	Literature (5)	Phytopharm 2.2.1, Denham 10	F	39	Paroxetine, COC (Pramino)	Rechallenge of kava only. Poor metaboliser.	Acute necrotising hepatitis
21	1003089	BfArM	WHO 2851368, MCA 25, Phytopharm 2.4.4 (EMEA 24), Denham 22	F	34	None suspect		
37	2223603	WHO	BfArM 99500453, Denham 11, Phytopharm 2.4.3 (EMEA 17)	F	59	None suspect		
39	1010536	BfArM	Phytopharm 2.4.8 (EMEA 37)	F	45	None suspect		
43	4	Literature (4)	Denham 16, Phytopharm 2.3.1 (EMEA 7), WHO 2639336, IKS 2000-0014	F	33	None suspect	Poor metaboliser	Drug-induced hepatitis
82	10	Literature (10)		M	55	None		Haemorrhagic necrosis

Table 9 Case reports of hepatotoxicity with kava: 'possible' relationships showing concomitant therapy

No	Sex	Age	Dur	Dech	Rech	Concomitant	Outcome
02	F	37	(24)	Y	X	(Unknown herbals)	Improving
05	F	59	28	Y	N	Lisinopril, phenobarbital, fenofibrate	Recovered
06	F	39	180	Y	X	Tetracycline, alcohol	Recovered
08	M	35	56	Y	N	'Regular alcohol'	Recovered
10	F	69	56	Y	X	Bemetizid, pentoxifyllin	Recovered
11	F	22	120	Y	N	COC (Pramino)	Transplant, Died (6 months)
12	M	32	(75)	Y	N	Valerian	Transplant
13	F	35	57	Y	N	Paracetamol	Recovered
15	F	46	(105)	Y	N	COC (Klimonorm)	Recovered
16	F	46	(28)	Y	N	Not recorded	Recovered
17	F	47	(30)	N	N	Fish oil	Recovered
18	F	60	(365)	Y	N	Piretanide	Transplant
22	M	39	210	Y	X	Interferon-beta	Recovered
23	F	50	(195)	Y	N	COC (Gravistat), glimepiride, metformin	Transplant, Died
26	F	56	-	Y	R	Esberitox, omeprazole	Recovered
27	F	61	(90)	X	X	Bemetizid, omeprazole	Died
29	M	45	(90)	Y	X	Not recorded	Unknown
30	F	26	6	Y	N	Diclofenac, sulfasalazine, MPA	Recovered
32	F	33	(120)	Y	R	Cisapride	Recovered
33	F	62	-	Y	R	Not recorded	Recovered
34	F	81	(300)	Y	N	Alcohol, hydrochlorothiazide, nitrendipin	Died
41	F	72 / 75	(730)/ (180)	Y	X	Vitamin A	Recovered
42	F	-	60	Y	X	Not recorded	Unknown
44	F	37	(60)	Y	Neg	Diclofenac, COC (Microdiol)	Recovered
45	F	39	106	Y	X	COC (Gravistat)	Recovered
46	F	46	(135)	Y	N	Hydrochlorothiazide, valsartan	Recovered
47	M	50	30	Y	N	'Moderate alcohol' (BfArM, Denham 18)	Transplant
49	F	57	30	Y	X	Silybum	Recovered
50	F	59	(21)	Y	N	Celecoxib	Recovered
51	M	36	46	Y	N	Not recorded	Recovered
52	M	38	21	Y	X	Penicillin V, 'regular alcohol' (Stickel 12)	Recovered
53	M	39	14	Y	X	None	Recovered
54	F	50	75	Y	X	Terfenadine, furosemide	Recovered
55	F	68	730	Y	X	None suspect	Recovered
56	F	45	56	Y	X	Rabeprazole	Transplant
57	M	24	24	Y	N	Chromium piccolinate, vanadyl sulphate	Died
64	F	30	60	Y	N	Passiflora	Died
69	F	39	(60)	Y	N	Yes (drug not stated)	Recovered
70	F	39	(60)	Y	X	Unspecified possibly hepatotoxic drugs	Recovered
71	M	40	90	Y	X	Alcohol	Recovered
73	F	43	14	X	X	Beta blocker, anaesthetic	Transplant
75	F	44	119	Y	N	Diclofenac, famotidine	Transplant
79	F	51	(120)	Y	X	Omega-3	Recovered
80	F	51	(60)	Y	R	Not recorded	Recovered
81	F	53	-	Y	X	Alcohol	Recovered
83	F	57	150	X	X	Candesartan, oestrogen	Recovered
85	F	60	-	Y	X	Capecitabine, chaparral	Recovered
86	F	14	105	Y	N	None	Transplant
87	F	56	(90)	Y	N	Passiflora incarnata	Transplant, Died
88	F	-	(60)	X	X	Fluoxetine	Not recovered
89	M	63	(42)	Y	X	Enalapril, hydrochlorothiazide	Improved
90	M	38	(14)	Y	X	Not recorded	Recovered
91	F	-	(730)	Y	X	Multivitamins, 'moderate alcohol'	Recovered
93	F	-	(90)	Y	N	Dexatrim Green Tea	Improving

Table 10 Case reports of hepatotoxicity with kava: reports with positive rechallenge

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
19	F	39	Kava	Ethanol	60	kava lactones	194	Hepatic necrosis	Yes	Y	R	Recovered	2
26	F	56	Kava Ratiopharm	Ethanol	-		-	Hepatitis	Yes	Y	R	Recovered	3
32	F	33	Kavatino	Ethanol	180	kava lactones	(120)	Hepatitis toxic	Yes	Y	R	Recovered	3
33	F	62	Kavatino	Ethanol	60	kava lactones	-	Hepatocellular liver injury	NR	Y	R	Recovered	3
80	F	51	Kava		-		(60)	Hepatic function abnormal	NR	Y	R	Recovered	3

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
19	5	Literature (5)	Phytopharm 2.2.1, Denham 10	F	39	Paroxetine, COC (Pramino)	Rechallenge of kava only. Poor metaboliser.	Acute necrotising hepatitis
26	2851799	WHO		F	56	Esberitox, omeprazole		
32	99006005	BfArM	WHO 2598102, Phytopharm 2.6.4 (EMEA 20), Denham 14	F	33	Cisapride		
33	99003911	BfArM	Denham 13, Phytopharm 2.4.2 (EMEA 19)	F	62	Not recorded		
80	15267	FDA	Phytopharm 2.4.25 (EMEA 62)	F	51	Not recorded		

Table 11A Case reports of hepatotoxicity with kava: patients with liver transplant (basic data)

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
11	F	22	Antares	Ethanol	240	kava lactones	120	Hepatic necrosis	Yes	Y	N	Died 6 months after transplant	3
12	M	32	Antares	Ethanol	240	kava lactones	(75)	Hepatic necrosis	Yes	Y	N	Transplant	3
18	F	60	Antares	Ethanol	480-1200	kava lactones	(365)	Hepatic failure	Yes	Y	N	Transplant	3
23	F	50	Kava Ratiopharm	Ethanol	60	kava lactones	(195)	Hepatic failure	Yes	Y	N	Transplant, Died	3
31	F	47	Kavasporal forte	Ethanol	-		-	Hepatic failure	NS	X	X	Transplant	6
36	F	41	Limbao	Ethanol	-		-	Hepatic failure	Yes	X	X	Transplant	
47	M	50	Laitan	Acetone	210-280	kava lactones	30	Hepatitis toxic	Yes	Y	N	Transplant	3
56	F	45	Combination NOS		150	kava lactones	56	Hepatitis cholestatic	Yes	Y	X	Transplant	3
66	F	33	Kava		-		-	Jaundice	Yes	X	X	Transplant	6
73	F	43	Kava		-		14	Hepatic failure	Yes	X	X	Transplant	3
75	F	44	Kava		200		119	Hepatitis fulminant	Yes	Y	N	Transplant	3
84	F	60	Kava		-		(90)	Hepatic failure	NR	X	X	Transplant	6
86	F	14	Kava (2 products)		-		105	Hepatitis fulminant	No	Y	N	Transplant	3
87	F	56	Kava 1800 Plus		180	kava lactones	(90)	Hepatic failure	Yes	Y	N	Transplant, Died	3

Table 11B Case reports of hepatotoxicity with kava: patients with liver transplant (additional data)

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
11	8627	Literature (3)	WHO 2767171. Phytopharm 2.5.3 (EMEA 23), BfArM 8627	F	22	COC (Pramino)		Cholestatic hepatitis. Pronounced necrosis.
12	1006229	BfArM	WHO 2852999, Phytopharm 2.4.6 (EMEA 31), Denham 30	M	32	Valerian		Necrotising hepatitis
18	8	Literature (8)	Phytopharm 2.6.23 (EMEA 5), similar to case 85 (Weekly Magazine)	F	60	Piretanide	Overdose	Necrosis & intrahepatic cholestasis
23	6	Literature (6)	Denham 20, Stickel, Phytopharm 2.6.6 (EMEA 22), BfArM 5994	F	50	COC (Gravistat), glimepiride, metformin		Necrosis liver cells
31	2003010	BfArM	Phytopharm 2.7.4 (EMEA 46)	F	47	None suspect		Drug-induced cell necrosis and fibrosis
36	15320	FDA	Phytopharm 2.4.26	F	41	COC (Diane)		
47	9	Literature (9)	Denham 18, Phytopharm 2.3.2 (EMEA 9), WHO 2458938, IKS 2000-3502	M	50	'Moderate alcohol' (BfArM, Denham 18)	Paracetamol just before transplant.	Toxic-necrotic hepatitis
56	15035	FDA	FDA 15274, Phytopharm 2.6.18 (EMEA 53)	F	45	Rabeprazole		Subfulminant hepatic necrosis
66	14810	FDA	Phytopharm 2.7.7 (EMEA 52)	F	33	COC (LoEstrin), chemotherapy		
73	275	Press report	Phytopharm 2.7.5	F	43	Beta blocker, anaesthetic		
75	1939507	Brazil		F	44	Diclofenac, famotidine		Toxic hepatitis
84	2001	Weekly Magazine	Phytopharm 2.4.18; similar to case 18 (literature (8)/Phytopharm 2.6.23)	F	60	Not recorded		
86	3	Literature (1, 2)	Phytopharm 2.4.31	F	14	None		Hepatocellular necrosis / chemical hepatitis
87	7	Literature (7), TGA		F	56	Passiflora incarnata		Severe acute hepatitis, massive necrosis

Table 12 Case reports of hepatotoxicity with kava: patients who died

No	Sex	Age	Product	Extract	Dose	DoseType	Dur	Hepatic event	OPS	Dech	Rech	Outcome	Rel
11	F	22	Antares	Ethanol	240	kava lactones	120	Hepatic necrosis	Yes	Y	N	Transplant, Died (6 months)	3
23	F	50	Kava Ratiopharm	Ethanol	60	kava lactones	(195)	Hepatic failure	Yes	Y	N	Transplant, Died	3
27	F	61	Kava Ratiopharm	Ethanol	120	kava lactones	(90)	Hepatic failure	Yes	X	X	Died	3
34	F	81	Kavatino	Ethanol	120	kava lactones	(300)	Hepatic failure	Yes	Y	N	Died	3
57	M	24	Hard Gainers 6		200	product (6 herbs)	24	Hepatic failure	Yes	Y	N	Died	3
64	F	30	Kava		200		60	Hepatitis fulminant	Yes	Y	N	Died	3
87	F	56	Kava 1800 Plus		180	kava lactones	(90)	Hepatic failure	Yes	Y	N	Transplant, Died	3

No	Report Id	Source	Other sources	Sex	Age	Concomitant	Comment	Histology
11	8627	Literature (3)	WHO 2767171. Phytopharm 2.5.3 (EMEA 23), BfArM 8627	F	22	COC (Pramino)		Cholestatic hepatitis. Pronounced necrosis.
23	6	Literature (6)	Denham 20, Stickel, Phytopharm 2.6.6 (EMEA 22), BfArM 5994	F	50	COC (Gravistat), glimepiride, metformin		Necrosis liver cells
27	2001135	BfArM	BfArM 2002378, Phytopharm 2.6.14 (EMEA 40)	F	61	Bemetizid, omeprazole		Necrotising hepatitis
34	98004297	BfArM	Denham 9, Phytopharm 2.7.1 (EMEA 16)	F	81	Alcohol, nitrendipin, hydrochlorothiazide	Cirrhosis preceded kava	Toxic hepatopathy
57	11444	FDA		M	24	Chromium piccolinate, vanadyl sulphate		
64	2003422	Brazil		F	30	Passiflora		
87	7	Literature (7), TGA		F	56	Passiflora incarnata		Severe acute hepatitis, massive necrosis

Table 13 Potential drug interactions with kava: alphabetical listing by drug

Drug	ATC code
abciximab	B01AC
acenocoumarol	B01AA
acetaminophen	N02BE
acetophenazine	N05AB
adinazolam	
alfentanil	N01AH
alprazolam	N05BA
alteplase	B01AD
amantadine	N04BB
amiodarone	C01BD
amisulpride	N05AL
amlodipine/atorvastatin	
amobarbitol	N05CA
anagrelide	N05CA
ancrod	B01AD
anisindione	B01AA
anistreplase	B01AD
anithrombin iii	B01AB
aprobarbital	N05CA
ardeparin	B01AB
argatroban	B01AE
aspirin	N02BA
aspirin/dipyridamole	
atorvastatin	C10AA
azathioprine	L04AX
becaplermin	D03AX
benperidol	N05AD
bentazepam	N05BA
bivalirudin	B02BD
bromazepam	N05BA
bromocriptine	N04BC
brotizolam	N05CD
butobarbital	N05CA
butalbital	N02BE
calusterone	L02AX
carisoprodol	M03BA
carmustine	L01AD
cerivastatin	C10AA
certoparin	B01AB
chlordiazepoxide	N05BA
chlordiazepoxide/amitriptyline	
chlorpromazine	N05AA
chlorprothixene	N05AF
chlorzoxazone	M03BB
cilostazol	B01AC
clobazam	N05BA
clonazepam	N03AE
clopidogrel	B01AC
clorazepate	N05BA
clorgyline	
codeine	R05DA
dalteparin	B01AB
danaparoid	B01AB
danazol	G03XA
dantrolene	M03CA
defibrotide	B01AX
delorazepam	N05BA

Drug	ATC code
dermatan	
desirudin	B01AE
dextromethorphan/morphine	
diazepam	N05BA
diclofenac	S01BC
diclofenac/misoprostol	
dicumarol	B01AA
dihydroergotamine/heparin	
dipyridamole	B01AC
dixyrazine	N05AB
enoxaparin	B01AB
epoprostenol	B01AC
eptifibatide	B01AC
estazolam	N05CD
eterobarb	
ethanol	V03AZ
ethopropazine	N04AA
ezetimibe/simvastatin	
fentanyl	N01AH
fluconazole	D01AC
flunitrazepam	N05CD
fluoxymesterone	G03BA
fluphenazine	N05AB
flurazepam	N05CD
flutamide	L02BB
fluvastatin	C10AA
fondaparinux	B01AX
halazepam	N05BA
haloperidol	N05AD
heparin	B01AB
hydrocodone	R05DA
hydromorphone	N02AA
ibuprofen	M01AE
iloprost	B01AC
isocarboxazid	N06AF
isoniazid	J04AC
itraconazole	J02AC
ketazolam	N05BA
ketoconazole	D01AC
lamifiban	B01AX
lazabemide	N04BD
lepirudin	B01AE
levodopa	N04BA
levodopa/benserazide	
levodopa/carbidopa	
levodopa/carbidopa/entacapone	N02AF
levorphanol	N05CD
loprazolam	N05BA
lorazepam	N05CD
lormetazepam	C10AA
lovastatin	N05BA
medazepam	N02AB
meperidine	N03AA
mephobarbitol	N05BC
meprobamate	L01BB
mercaptopurine	N05AC
mesoridazine	N05BA
metadazepam	M03BB

Table 13 Potential drug interactions with kava: alphabetical listing by drug (continued)

Drug	ATC code
metaxalone	
methdilazine	R06AD
methenolone	M03BA
methocarbamol	L04AX
methotrexate	A03FA
metoclopramide	N05CD
midazolam	N06AG
moclobemide	N05AE
molindone	N02AA
morphine	N05AC
nadroparin	B01AB
nandrolone	A14AB
niacin	C04AC
niacin/lovastatin	
nitrazepam	N05CD
oxandrolone	A14AA
oxazepam	N05BA
oxycodone	N02AA
oxymetholone	A14AA
oxymorphone	N02AA
parnaparin	B01AB
pentobarbital	N05CA
pentosan polysulfate sodium	C05BA
perazine	N05AB
pergolide	N04BC
periciazine	N05AC
perphenazine	N05AB
perphenazine/amitriptyline	
phenelzine	N06AF
phenindione	B01AA
phenobarbital	N03AA
phenprocoumon	B01AA
pimozide	N05AG
pinazepam	N05BA
pioglitazone	A10BG
pipotiazine	S01BC
piroxicam	L01DC
plicamycin	N04BC
pramipexole	C10AA
pravastatin	N05BA
prazepam	N03AA
primidone	N05AB
prochlorperazine	N05AA
promazine	R06AD
promethazine	N05CM
propiomazine	N02AC
propoxyphene	N05CD
quazepam	N01AH
remifentamil	B01AD
reteplase	B01AB
reviparin	N04BC
ropinirole	A10BG
rosiglitazone	
rosiglitazone/metformin	N05CA
secobarbital	N04BD
selegiline	B10AC
sibrafiban	C10AA
simvastatin	A14AA

Drug	ATC code
stanozolol	B01AD
streptokinase	
sufentanil	N01AH
sulfinpyrazone	M04AB
sulodexide	B01AB
tacrine	N06DA
temazepam	N05CD
tenecteplase	B01AD
terbinafine	D01BA
testosterone	G03BA
tetrazepam	N05BA
thiopental	N01AF
thioridazine	N05AC
ticlopidine	B01AC
tinzaparin	B01AB
tirofiban	B01AC
tramadol/acetaminophen	
tranylcypromine	N06AF
treprostinil	B01AC
triazolam	N05CD
trifluoperazine	N05AB
triflupromazine	N05AA
troglitazone	A10BG
urokinase	B01AD
valproic acid	N03AG
warfarin	B01AA
xemilofiban	

(From DrugDex 2005)

Table 14 Potential kava-drug interactions by ATC code

Drug	ATC	Drug	ATC
metoclopramide	A03FA	anistreplase	B01AD
pioglitazone	A10BG	reteplase	B01AD
rosiglitazone	A10BG	streptokinase	B01AD
troglitazone	A10BG	tenecteplase	B01AD
oxandrolone	A14AA	urokinase	B01AD
oxymetholone	A14AA	argatroban	B01AE
stanozolol	A14AA	desirudin	B01AE
nandrolone	A14AB	lepirudin	B01AE
acenocoumarol	B01AA	defibrotide	B01AX
anisindione	B01AA	fondaparinux	B01AX
dicumarol	B01AA	lamifiban	B01AX
phenindione	B01AA	bivalirudin	B02BD
phenprocoumon	B01AA	amiodarone	C01BD
warfarin	B01AA	niacin	C04AC
antithrombin iii	B01AB	pentosan polysulfate sodium	C05BA
ardeparin	B01AB	atorvastatin	C10AA
certoparin	B01AB	cerivastatin	C10AA
dalteparin	B01AB	fluvastatin	C10AA
danaparoid	B01AB	lovastatin	C10AA
enoxaparin	B01AB	pravastatin	C10AA
heparin	B01AB	simvastatin	C10AA
nadroparin	B01AB	fluconazole	D01AC
parnaparin	B01AB	ketoconazole	D01AC
reviparin	B01AB	terbinafine	D01BA
sulodexide	B01AB	becaplermin	D03AX
tinzaparin	B01AB	fluoxymesterone	G03BA
abciximab	B01AC	testosterone	G03BA
cilostazol	B01AC	danazol	G03XA
clopidogrel	B01AC	itraconazole	J02AC
dipyridamole	B01AC	isoniazid	J04AC
epoprostenol	B01AC	carmustine	L01AD
eptifibatide	B01AC	mercaptopurine	L01BB
iloprost	B01AC	plicamycin	L01DC
sibrafiban	B01AC	calusterone	L02AX
ticlopidine	B01AC	flutamide	L02BB
tirofiban	B01AC	azathioprine	L04AX
alteplase	B01AD	methotrexate	L04AX
ancrod	B01AD	ibuprofen	M01AE
carisoprodol	M03BA	dixyrazine	N05AB
methocarbamol	M03BA	fluphenazine	N05AB
chlorzoxazone	M03BB	perazine	N05AB
metaxalone	M03BB	perphenazine	N05AB
dantrolene	M03CA	prochlorperazine	N05AB
sulfinpyrazone	M04AB	trifluoperazine	N05AB
thiopental	N01AF	mesoridazine	N05AC
alfentanil	N01AH	periciazine	N05AC
fentanyl	N01AH	pipotiazine	N05AC
remifentanil	N01AH	thioridazine	N05AC
sufentanil	N01AH	benperidol	N05AD
hydromorphone	N02AA	haloperidol	N05AD
morphine	N02AA	molindone	N05AE
oxycodone	N02AA	chlorprothixene	N05AF
oxymorphone	N02AA	pimozide	N05AG
meperidine	N02AB	amisulpride	N05AL
propoxyphene	N02AC	alprazolam	N05BA
levorphanol	N02AF	bentazepam	N05BA
aspirin	N02BA	bromazepam	N05BA
acetaminophen	N02BE	chlordiazepoxide	N05BA

Drug	ATC	Drug	ATC
butalbital	N02BE	clobazam	N05BA
mephobarbital	N03AA	clorazepate	N05BA
phenobarbital	N03AA	delorazepam	N05BA
primidone	N03AA	diazepam	N05BA
clonazepam	N03AE	halazepam	N05BA
valproic acid	N03AG	ketazolam	N05BA
ethopropazine	N04AA	lorazepam	N05BA
levodopa	N04BA	medazepam	N05BA
amantadine	N04BB	metaclazepam	N05BA
bromocriptine	N04BC	oxazepam	N05BA
pergolide	N04BC	pinazepam	N05BA
pramipexole	N04BC	prazepam	N05BA
ropinirole	N04BC	tetrazepam	N05BA
lazabemide	N04BD	meprobamate	N05BC
selegiline	N04BD	amobarbital	N05CA
chlorpromazine	N05AA	anagrelide	N05CA
promazine	N05AA	aprobarbital	N05CA
triflupromazine	N05AA	butobarbital	N05CA
acetophenazine	N05AB	pentobarbital	N05CA
secobarbital	N05CA	quazepam	N05CD
brotizolam	N05CD	temazepam	N05CD
estazolam	N05CD	triazolam	N05CD
flunitrazepam	N05CD	propiomazine	N05CM
flurazepam	N05CD	isocarboxazid	N06AF
loprazolam	N05CD	phenelzine	N06AF
lormetazepam	N05CD	tranylcypromine	N06AF
midazolam	N05CD	moclobemide	N06AG
nitrazepam	N05CD	tacrine	N06DA
codeine	R05DA		
hydrocodone	R05DA		
methdilazine	R06AD		
promethazine	R06AD		
diclofenac	S01BC		
piroxicam	S01BC		
ethanol	N05BA		
adinazolam			
amlodipine/atorvastatin			
aspirin/dipyridamole			
chlordiazepoxide/ amitriptyline			
clorgyline			
dermatan			
dextromethorphan/ morphine			
diclofenac/misoprostol			
dihydroergotamine/ heparin			
eterobarb			
ezetimibe/simvastatin			
levodopa/benserazide			
levodopa/carbidopa			
levodopa/carbidopa/ entacapone			
methenolone			
niacin/lovastatin			
perphenazine/ amitriptyline			
rosiglitazone/metformin			
tramadol/acetaminophen	B01AC		
treprostinil			
xemilofiban			

Table 15 Potential kava-drug interactions by ATC groups

ATC	Count	Drug Type
N05A Antipsychotics		
N05AA	3	phenothiazine (aliphatic) antipsychotics
N05AB	7	phenothiazine (piperazine) antipsychotics
N05AC	4	phenothiazine (piperidine) antipsychotics
N05AD	2	butyrophenone derivatives antipsychotics
N05AE	1	indole antipsychotics
N05AF	1	thioxanthine antipsychotics
N05AG	1	diphenylbutylpiperidine antipsychotics
N05AL	1	benzamide antipsychotics
N05B Anxiolytics		
N05BA	17	benzodiazepine anxiolytics
N05BC	1	carbamate anxiolytics
N05C Hypnotics and sedatives		
N05CA	6	barbiturates
N05CD	11	benzodiazepine hypnotics & sedatives
N05CM	1	other hypnotics and sedatives
B01A Antithrombotic agents		
B01AB	12	heparin group
B01AC	10	platelet aggregation inhibitors (excl heparin)
B01AD	7	enzymes
B01AA	6	vitamin K antagonists
B01AX	3	other antithrombotic agents
B01AE	3	direct thrombin inhibitors
C10A Cholesterol and triglyceride reducers		
C10AA	6	HMG CoA reductase inhibitors
N01A Anaesthetics, general		
N01AF	1	barbiturate anaesthetics
N01AH	4	opioid anaesthetics
N02A Opioids		
N02AA	4	natural opium alkaloids
N02AB	1	phenylpiperidine opioids
N02AC	1	diphenylpropylamine opioids
N02AF	1	orphinan opioids
N02B Other analgesics and antipyretics		
N02BE	2	anilide analgesics
N02BA	1	alicylic acid & derivatives
N03A Antiepileptics		
N03AA	3	barbiturate antiepileptics
N03AE	1	benzodiazepine antiepileptic
N03AG	1	fatty acid antiepileptic
N04A Anticholinergic agents		
N04AA	1	tertiary amine anticholinergic
N04B Dopaminergic agents		
N04BA	1	dopa & dopa derivatives
N04BB	1	adamantane dopaminergic agents
N04BC	4	dopamine agonists
N04BD	2	MAO B inhibitors
N06A Antidepressants		
N06AF	3	MAO inhibitors
N06AG	1	MAO A inhibitor
N06D Antidementia drugs		
N06DA	1	anticholinesterase anti-dementia
A10B Oral blood glucose lowering agents		
A10BG	3	thiozolidinediones (glitazones)
A14A Anabolic steroids		
A14AA	3	androstan anabolic steroids
A14AB	1	estren anabolic steroid
M03B Muscle relaxants, centrally acting agents		
M03BA	2	carbamic acid esters centrally acting muscle relaxants
M03BB	2	oxazol, thiazine & triazine centrally acting muscle realaxants
M03C Muscle relaxants, directly acting agents		
M03CA	1	dantrolene directly acting muscle relaxant

Table 16 Case reports of hepatotoxicity with kava: excluded cases

Source	Sex	Age	Medicine	Extract	Dose	Dur	Hepatic	Other	Dech	Rech	Outcome	Rel
EMEA	F	54	Kava		120	-	Gall bladder pain	Yes	X	X	Unknown	6
France	F	60	Kava		-	(365)	GGT increased	NR	Y	X	Recovered	6
BfArM	F	68	Laitan 100	Acetone	210	(60)	Hepatic enzymes increased	NR	X	X	Unchanged	4
BfArM	M	27	Kavacur	Ethanol	120	2	Faeces discoloured	Yes	X	X	Unknown	6
WHO	M	48	Kava		-	-	GGT increased	Yes	Y	N	Improving	3
FDA	M	53	Nature Pharma Kava		-	-	Pain right hypochondrium	NR	X	X	Unknown	6

Sex	Age	Source	Report Id	Other sources	Comment	Concom	Histology
F	54	Phytopharm (EMEA id)	38	Phytopharm 2.7.13 (EMEA 38)	Not hepatic	Enalapril, Triamterene	
F	60	France (EMEA id)	63	Phytopharm 2.5.6 (EMEA 63)	Non-specific	NR	
F	68	BfArM	93.0351	Denham 3	Abnormal LFTs before kava.	NR	
M	27	BfArM	2001776	Phytopharm 2.6.15 (EMEA 42)	Non-specific	HIV treatment	
M	48	WHO	8098467		On kava 8 years & GGT elevated over that time.	Bendroflumethiazide	
M	53	FDA	15249		Not specifically hepatic	NR	

Discussion

There are differences between the case review findings of this report for WHO and that of others. The valuable, detailed, comprehensive and most recent review is that of Schmidt (2003). This contains follow-up information not available to earlier reviewers such as Waller (2002) and Denham (2002). Some of the differences between this WHO review and that of Schmidt are discussed below, but similar comments are applicable to some of the findings of Waller and Denham.

The Schmidt review records 20 cases that are said to be 'unrelated to kava intake'. The conclusions about the relationship of the hepatic events to the kava products taken are generally at variance with this WHO report. The comparisons are summarized in Table 17. Apart from four cases excluded because they are clinically irrelevant, none of these 20 cases were regarded as 'unrelated' to the outcome in our review. They were either 'possible' or 'unassessable' because of insufficient information. If unassessable, they cannot be classified as 'unrelated' (or related).

Table 18 compares the cases coded as probable in this report with the assessments of Schmidt.

Table 17 Cases considered 'unrelated to kava intake' by Schmidt (2003)

Key: 'Schmidt ref' refers to the case reference used by Schmidt (2003), 'Case No.' refers to the case number of this (WHO) report and 'Rel' refers to the relationship assigned in this report (3=possible, 6=unassessable) (see table 1).

Schmidt ref	Case No.	Rel	Comment
3.1	34	3	The patient had pre-existing liver disease, but it is possible that kava made the condition worse and induced liver failure.
3.2	17	3	Considered by Schmidt as unrelated because there was recovery with stopping co-medication and continuing kava, but an interaction was possible with the co-medication which was stopped. Therefore coded as 'possible'.
3.3	-	-	Excluded from this review (table 16)
3.4	54	3	Had liver abnormalities before kava, but whatever the cause of the abnormality, if kava is hepatotoxic, then it may have made the abnormality worse. Kava-drug interaction is also 'possible'.
3.5	31	6	Unassessable because of insufficient data. This means the causality of the event cannot be assessed and so it should not be included in the 'unrelated' group.
3.6	73	3	There is a question over pre-existing liver disease. If present, it could have been aggravated by the kava product. Therefore 'possible'.
3.7	92	6	As for 3.5.
3.8	66	6	As for 3.5
3.9	-	-	Excluded from this review (table 16)
3.10	91	3	Took kava for 2 years. LFTs returned to normal on withdrawal. Schmidt attributes the problem to obesity, but there is no record of weight reduction associated with the LFT recovery. Therefore 'possible'.
3.11	68	6	As for 3.5.
3.12	89	3	History of hepatitis C, but this does not exclude kava as contributory or causal. LFTs improved to near normal (ALT 997 ⊠ 46 IU) 5 weeks after withdrawal of kava.
3.13	-	-	Excluded from this report.
3.14	59	6	Unassessable. Pre-existing hepatitis C does not exclude hepatic damage by kava as claimed by Schmidt.
3.15	57	3	Other medications may have affected the liver, but this does not exclude kava as a cause. Hepatitis C could not be completely excluded.
3.16	74	6	As in 3.5.
3.17	36	6	As in 3.5.
3.18	6	3	Considered by Schmidt to be 'hepatitis caused by tetracycline' (even though 'the data is insufficient'), but this does not exclude kava as an interacting agent. Apparently there was a negative rechallenge to kava alone, not indicated in earlier report details.
3.19	88	3	Probably alcoholic (Schmidt). Alcohol &/or fluoxetine could have caused liver problems, but this does not exclude kava either as an interacting agent or as contributory to the event.
3.20	-	-	Excluded from this report (table 16).

Table 18 Cases coded 'probable' in this report compared with the evaluation of Schmidt (2003)

Schmidt ref	Case No.	Rel	Comment
5.4	3	2	'Doubtful' causality by Schmidt because of other possible components of 'Sleepy tea', one of two kava containing products taken. However, this case fulfils the key criteria for 'probable': recovery on withdrawal and no other identifiable suspect cause.
-	4	2	Not included in Schmidt's review.
7.1	19	2	'Probable' relationship agreed.
6.4	21	2	Regarded by Schmidt as unassessable because, 'There is no information on the differential diagnostics, virus serology and ethanol consumption.' However, the basic pharmacovigilance data for a 'probable' relationship are present. Recovery on withdrawal of kava suggests the absence of virus and alcohol problems.
6.3	37	2	Same comment. Schmidt states that the outcome was unknown. If this is correct then the relationship should be 'possible', but the WHO database report states that the 'reaction abated' on withdrawal.
6.8	39	2	Schmidt suggests that the taking of an artichoke extract might mean that the patient was suffering from pre-existing 'hepatic insufficiency' and that the case was 'unassessable'. This is a vague assumption and the basic pharmacovigilance data for a 'probable' relationship are present. She was investigated in hospital for causes other than kava and none found.
8.1	43	2	'Probable' relationship agreed.
-	82	2	Not included in Schmidt's review.

The reviewers of the case reports of hepatotoxicity linked with kava have to date taken a purely clinical approach with the examination of each report individually and have largely neglected the epidemiological type of assessment used in pharmacovigilance and pharmacoepidemiology. While clinical assessment is essential, it must be supported by epidemiological assessment. In pharmacovigilance, the clinical data is usually incomplete and imperfect, as has been found with the kava case reports, but there are other means, as demonstrated in this review, of evaluating the strength of a signal or validating a causal association when looking at the aggregation of reports as a whole. In pharmacovigilance there are frequent intra- and inter-individual inconsistencies in the relationship (causality) assessment of individual case reports. These assessments, though important, are seldom anything more than provisional and their main value is in establishing a plausibility for a suspected causal association which may lead to further investigation.

Whatever the individual assessments of the case reports, probably the most important finding of this review is that amongst an aggregation of 93 worldwide case reports of hepatotoxicity associated with the use of kava, there are differences between the extracts which provides scientific evidence that this association is not a random phenomenon. This evidence suggests that the organic extracts of kava are associated with a higher rate of hepatic events than synthetic products. It might be thought that the possibility of a small number of unidentified duplications in the case reports arising from Stickel's case series (up to four) could affect these statistical comparisons of the extracts, but this is not so. None of the unmatched case reports from Stickel et al. (2003) provided the name of the product used or type of extract and so they were not included in the statistical comparisons.

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Section III Regulatory issues

Regulation / registration of kava products

Table 1 Country status of kava usage before the ban in Europe

Country	Food Supplements (yes/no)	Medicine (yes/no)	Approved use
Australia	yes	no	Traditional form and food supplements
Austria	no	yes	Treatment for anxiety
Belgium	no	yes	As drugs (treatment for anxiety)
Brazil	no	yes	As drugs (treatment for anxiety)
Canada	yes	yes	Food supplement and as treatment for anxiety
Denmark	yes	no	Food supplement
Finland	yes	no	Food supplement
France	yes	no	Food supplement
Germany	no	yes	As drugs to treat anxiety disorders
Greece	yes	no	Food supplement
Ireland	yes	yes	As food supplements and as treatment for anxiety
Italy	yes	no	As food supplements
Liechtenstein	yes	no	As food supplements
Netherlands	yes	no	As food supplements
New Zealand	yes	no	As food supplements and traditional form
Norway	yes	no	As food supplements
Portugal	no	yes	Licensed drug for anxiety treatment
Singapore	yes	no	As food supplements
Spain	yes	no	As food supplements
Sweden	yes	no	As food supplements
Switzerland	no	yes	Treatment for anxiety
UK	yes	yes	As food supplements and as treatment for anxiety
USA	yes	no	As food supplements + traditional form

In the Pacific Islands, people have used kava as a traditional drink before and after the ban. Only water extracts have been used in the Pacific Islands whereas the countries mentioned in the table above have principally used organic solvent extracts such as either ethanol or acetone extracts.

Regulatory actions on kava containing products

Table 2 outlines the regulatory actions taken by various countries around the world from the year 2000 after concerns about hepatotoxicity were first raised in Germany.

The total number of worldwide reports of suspected liver toxicity associated with kava-containing products was 68 in June 2002. Of the 68 reports, there were three deaths and six liver transplants.

While the United States of America has issued numerous warnings to both consumers and physicians, the herb is still available for sale throughout the country.

Table 2 Regulatory actions on kava containing products

Year	USA	Canada	Germany	Australia	France	UK
2000			Small number of cases of liver damage reported to the German regulatory authority (BfArM).1, 2			
2001	In a letter issued by the Food and Drug Administration (FDA) on December 18, the agency stated it is investigating whether kava-containing products are a health concern. The FDA noted 26 cases of liver toxicity in Germany and Switzerland, including one fatality and one liver transplant that were reportedly associated with kava products.3		In November, Germany's Federal Institute for Drugs and Medical Development (BfArM) reported 24 recent kava-related cases of liver damage, including one death. BfArM asked kava manufacturers to respond to the reports and stated that licenses to market the herb could be withdrawn.1		Two non-serious liver case reports were filed with regulatory authorities.1 However, no kava product was registered for sale in France because it is traded as a food supplement. On January 8, the French Agency for the Safety of Health Products halts kava sales for one year based on German and Swiss reports.4	The Committee on Safety of Medicines (CSM) first considers safety of kava. The Medicines Control Agency (MCA) and CSM call for a voluntary suspension of kava-containing products.1 MCA said it knows of 68 cases of liver problems worldwide suspected to be associated with kava kava, including liver failure resulting in six transplants and three deaths.12
2002	US Centers for Disease Control and Prevention issued a report on hepatotoxicity associated with kava-containing products. On March 25, the FDA warned that kava is linked to serious liver damage, including hepatitis, cirrhosis, and at least four urgent liver transplants in other countries. A letter was also issued urging healthcare professionals to review cases of liver toxicity to determine if they were associated with kava.	On January 16, Health Canada begins safety assessment of kava and advises consumers not to use kava-containing products. The investigation found that as of August 21, three cases of liver toxicity associated with kava were reported. A stop-sale order was issued for all kava-containing products.1	Forty cases of severe liver damage were reported to BfArM from 1999-2002. Of the forty cases, three were fatal and six patients required transplants.5	On August 15, kava-containing products were recalled by the Therapeutic Goods Administration (TGA). The recall was sparked after a reported death of a woman from complications of fulminant hepatic failure associated with the use of a kava-containing medicine.1,6	There is no evidence that kava was allowed back on the shelves, all reports say it is still banned.	Three reports of liver toxicity (none fatal) were reported to the MCA up to June. On July 18, the MCA considers proposal that prohibits the supply of kava in unlicensed medicinal products.7
2003	As of March, the FDA advised that 21 adverse event reports had been received in the U.S.A Five stated some type of liver disorder.3			In January, the TGA established a committee, called the Kava Evaluation Group (KEG) to review the safety of kava products.6		The Committee on Safety of Medicines and the Medicines Commission found evidence linking kava to cases of liver toxicity. The MCA noted 70 worldwide reports of adverse liver reactions, In January, the Medicines and Healthcare products Regulatory Agency (MHRA), bans kava-containing products.7
2004						
2005	Kava products remain available for purchase.		Germany is giving consideration to making kava a prescription drug.			MHRA is reviewing the ban on kava. (If the regulatory agency can find evidence that kava is safe, the herb may enter the United Kingdom market once again.) 8

Table 2 Regulatory actions on kava containing products (continued)

Year	Portugal	Switzerland	Singapore	Austria	Ireland	New Zealand
2000		In September 2000, the government warned marketers of safety concerns related to kava, based on four case reports.1				
2001		Health authorities, (Swissmedic) issued a safety protocol.1,4				
2002	Portugal followed France and suspended all kava-containing products for one year. 1,4 There were no local reports of hepatotoxicity.		In January, the country's Health Sciences Authority (HSA) warned consumers of the potential adverse effects of kava. On July 25, kava was banned. While no adverse effects associated with kava were reported in Singapore, HAS prohibited the importation and sale of kava products in the country based on German and Swiss case reports.1	Following the German ban of kava, Austria banned kava. The recall of all kava products followed a single case of liver failure associated with kava consumption.	On February 4, the Irish Medicines Board while acknowledging that there were no reports of liver ADRs associated with kava in Ireland, issued a voluntary recall of kava products in conjunction with the industry, based on the reports in Germany and Switzerland.11	On January 16, the New Zealand Ministry of Health announced that it was investigating overseas concerns about kava and liver damage. The ministry noted that available evidence is poor because of additional liver-affecting factors, such as alcohol consumption. On August 16, the NZ Food Safety Authority issued a warning to consumers about the safety of kava-containing products.4 No case reports of hepatotoxicity.1,4
2003		In February, the Swissmedic banned the sale of kava-containing products.1				
2004						
2005						

Year	New Caledonia	South Africa	Wales	South America	Asia
2000					
2001					
2002	On January 11, the Health and Social Department announced a ban on the sale of kava-containing products sold in pharmacies. Traditional kava preparations and kava products sold in supermarkets were exempt from the ban.1 Two cases of hepatic injury with recovery associated with traditionally prepared kava drink.13	In November 2002, the South African Medicines Control Council (MCC) issued a drug alert, stating that kava may cause irreversible liver damage. No cases of liver damage were reported to the MCC.1	The National Assembly for Wales bans all kava-containing products under The Kavakava in Food (Wales) Regulations 2002 in December 2002.		April-May—Japan: begins action on kava.
2003			The National Assembly for Wales reversed a two-year ban on the sale of kava-containing products. The decision went into effect in October.10	Brazil- Two cases of hepatotoxicity reported.	
2004					
2005			Fresh regulations to ban kava were proposed but an appeal is currently under consideration by the court. 14		

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Section IV Conclusions and recommendations

Background

Kava is a perennial shrub native to some islands of the South Pacific that has been cultivated for centuries. Water-based extracts of its rhizoma are used traditionally to prepare a psychoactive beverage and acetonic and ethanolic extracts of kava have been used in considerable quantity as a herbal anxiolytic in many countries. Until the ban of kava products in 2002, kava was available in Europe as an herbal medicine. Kava is still available for use in the United States of America and some other countries as a dietary supplement.

Warnings about the safety of the plant were initiated in the late 1990s when several cases of hepatotoxicity including liver failure and death were reported to regulatory agencies mainly in the European Union (EU) in 1998 after almost a decade of widespread use of kava extracts in Europe (Strahl et al. 1998; Russmann et al. 2001a). The first reported cases were presented to the Federal Institute for Drugs and Medical Devices (BfArM) in Germany, where out of 76 spontaneous adverse drug reaction (ADR)- reports on kava, 24 were associated with impaired liver function or symptoms that could be linked to impaired liver function. One out of four reports of liver dysfunction from Switzerland was of fulminant liver failure and required liver transplantation. Other hepatic events were hepatitis, jaundice, cirrhosis of the liver, and elevated liver enzyme and bilirubin concentrations. There was also a highly publicized death (Brauer et al. 2001).

Suddenly other agencies in different countries started documenting cases of hepatotoxicity possibly induced by kava preparations available in the market at the time. By late 2001 and early 2002 both the Medicines Control Agency (MCA) in the UK and the Food and Drug Administration (FDA) in the USA received 3 and 17 reports of liver toxicity in association with kava. Four published cases of hepatic injury associated with kava were reported in Canada in February 2002. A total of 82 documented adverse event reports involving liver toxicity existed as of December 2002. As a result kava products were banned by individual countries in the EU such as Germany, Switzerland, France and Spain, and the controversy began.

More recently two cases of fulminant hepatitis (one death) suspected to be related to kava consumption were reported to the Brazil regulatory agency late in 2003. Other cases of liver toxicity particularly hepatitis have been reported in Spain, Australia and Switzerland (Bujanda 2002; Gow 2003; Russman 2003).

I. Ralph Edwards, Director of the WHO Collaborating Centre for International Drug Monitoring (*the* Uppsala Monitoring Centre) has stated, *'There are valid arguments on both sides about the level of attribution that can be ascribed to kava products as causing liver damage. This is common in drug safety according to where one applies the benefit of any doubt. When there are more than a few suspected cases, and when the outcome is serious (liver transplantation and death), I believe there is a 'case to answer''.*

Possible mechanisms

Toxicological and clinical studies vary in their results addressing kava hepatotoxicity, but experimental studies and clinical trials suggest that water extracts are devoid of toxic effects on the liver. Several factors analysed in this report have been implicated in the apparent cause-effect relationship between ingestion of acetonic or ethanolic (organic) kava extracts and the liver toxicity observed in the case reports, but the exact mechanism of toxicity (if any) remains unknown. In a few reports there is a suggestion of an idiosyncratic immune mediated process and in two cases, a metabolic abnormality with CYP 2D6 enzyme deficiency. Further research is necessary to determine all the chemical constituents of kava in the different types of preparation and their exact metabolic pathways. In terms of drug-drug interactions, kava appears to inhibit or induce multiple CYP 450 enzymes.

Differing opinions

As described in Section IIA, some experts consider kava to be a medicinal plant with a very favourable risk profile and to have at the same time, excellent efficacy in the treatment of anxiety and as a muscle relaxant, mood enhancer and sedative. As a reaction to the ban of kava products in Germany, the scientists in the official German expert group for phytotherapy (Commission E) publicly stated that according to their point of view the ban of kava was an overreaction. They disagreed with the ban and reiterated their view in July 2002 that they were *'convinced of the presented scientific data on the efficacy of Kava and consider the benefit-risk ratio and the therapeutic benefit for the patient positive'*. According to some experts (Hagemann 2003; Corrigan 2005) this is an extremely important fact because it has been stated that the German ban was as a consequence of an assumed lack of kava efficacy.

Incidence

It has also been claimed that the majority of case reports were probably not related to kava and that the benefit-risk ratio for kava is positive when compared with other available treatments for anxiety disorders. According to Mathias Schmidt (2003) *'from the cases where a causal relationship seemed probable, an incidence rate of less than 0.02 cases per one million daily doses is calculated, corresponding to less than one case in 50 million days of application. This incidence calculation is far below the liver risk for diazepam with one case on 472,000 days of application'*. In addition, some experts have pointed to an imbalance in the benefit-risk analysis resulting in an underestimation of efficacy and an overestimation of risk.

However, estimates of the incidence of adverse events based on spontaneous reporting are usually much lower than the true incidence, because, with modern pharmaceuticals, only 5% or less of all adverse reactions are reported. Adding to the uncertainty of Schmidt's estimate is the fact that the reporting rate for herbal medicines is very much lower than

for modern pharmaceuticals. Therefore the true incidence of adverse events related to kava is not known, but it appears to be quite low. A true incidence figure can only be ascertained by a proper epidemiological study.

Clinical trials

In the reviewed clinical trials serious adverse events related to kava are listed as non-existent or negligible. There have not been any case control studies for relative risk determination. *'Based on empirical data from other benefit-risk evaluations, it can be stated that severe liver damage caused by Kava-Kava occurs only very rarely'* (Corrigan 2005)

Would even more thorough clinical trials before kava extracts were widely marketed have solved the issue of kava's safety with regard to the liver? 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 (Gruenwald 2003), but it may be worth evaluating this problem in future clinical trials and in prospective observational cohort studies (cohort event monitoring).

Causality

When case reports of hepatic side effects are discussed, a range of potential causes has to be taken into consideration. Drug-induced hepatic diseases are only one of the possibilities in differential diagnosis, and would account for less than 5% of all hepatic illness. It is well established that alcohol abuse and viral infections are still the leading causes of hepatic diseases.

In general, drug-induced disease mimics non-iatrogenic disease and examination of the clinical characteristics recorded in case reports will often not assist in differential diagnosis. Many of the clinical and histological features in the kava case series would be consistent with viral hepatitis, but the evidence as outlined in the section on differential diagnosis, largely points to their exclusion.

As with many different types of ADR, reliance must be placed on the closeness of the association between drug and disease and the collective characteristics of the reports. Eight reports met the requirements of having a probable relationship. A probable relationship means that there was a new (or worsening) hepatic event within a plausible time period after the administration of kava, that there was no other plausible reason identified for the event and that the patient recovered soon after withdrawal of kava. In addition to the probable reports, there were five reports with a positive rechallenge. Although these contained confounding elements that prevented their classification as 'certain', a positive rechallenge with the suspect agent is a strong indication of cause and effect. Further evidence for a causal relationship comes from the reports classified as possible. These were classified according to strict criteria and the absence of information on dose, duration, dechallenge or outcome, or the presence of a potentially hepatotoxic drug, prevented their classification as probable even though the association of drug and event was otherwise strong. Some of the concomitant drugs had a very low likelihood of causing a hepatic reaction e.g. phenoxymethylpenicillin and some had been used continuously for several years without problems, but with the hepatic event occurring only after the administration of kava. It is of note that the reports stated that there was no other therapy in seven and in eight others the concomitant therapy mentioned is assessed as not causing hepatotoxicity.

Benefit-risk

A comprehensive assessment of the safety of kava preparations would have to weigh the claimed relative benefits of kava against its perceived (or, ideally measured) comparative risk. In future, new studies evaluating the mechanism of toxicity, or data on product characteristics, manufacturing and quality control, as well as post-marketing surveillance studies, will contribute to this assessment. Appropriate study outcomes and biological assays may have to be developed. The issue of the synergistic effect of multiple plant constituents, part of the plant used in the preparation of the extracts and type of extraction method should also be considered when evaluating both safety and efficacy of kava preparations (Spinella 2002). Hagemann (2003), states that a complete evaluation also has to take into consideration the possible effects of regulatory decisions such as cancelling a license or banning a product a priori without an evidence-based justification. Such decisions must not result in a shift to therapeutic alternatives that may be even less researched, or whose application entails greater or more severe risks, or that may be more costly.

Several initiatives have been established to address these and other important issues. The most recent is that of the MHRA agency in the UK that has called stakeholders to participate in a review process of available kava evidence. The final report 'Report of the Committee of Safety of Medicines Expert Working Group on the Safety of kava' is available from the website: www.mhra.gov.uk.

Post-marketing surveillance

Current cases of adverse events associated with kava raise many new (and controversial) issues. However, according to our literature review, alcohol and acetone extracts appear acceptable and safe for the treatment of anxiety and related disorders. But a lot of uncertainties remain. Good post-marketing surveillance studies are essential and should not rely exclusively on spontaneous reporting. Case-control studies and prospective observational cohort studies are essential, but because the putative hepatotoxicity appears rare, the cohort studies would need to be large. The accumulation of large cohorts of kava users, taking a variety of kava products, should provide many opportunities for scientific study, including real incidence, differences between extracts, ethnic or regional differences, identification of risk factors, case-control studies, identification of interactions and pharmacogenetic studies.

Toxicological research

Further comparative toxicity studies among kava users, both in indigenous populations and Western populations are required. Further evidence-based research should focus on the safety of all the different types of kava preparations (organic extracts, synthetic and water based) used in clinical practice. Controlled clinical and non-clinical studies are necessary to determine the possible mechanisms of liver toxicity of the various kava lactones and other chemicals identified.

Such studies may then lead to the development of less toxic kava products, to the identification of a subpopulation of individuals that should not use kava or to additional mandatory cautionary requirements, including label claims and warnings, if needed (Anke and Ramsan 2004). In the meantime physicians and patients should continue to be alert to possible hepatotoxic side effects in the course of kava treatment, to stop the treatment at first suspicion and to undertake a careful diagnostic work-up ruling out all other causes (Teschke 2003). Further research into kava products is necessary to gain information about the pharmacokinetics, particularly distribution, metabolism, and hepatic elimination mechanisms as well as the mechanism of liver toxicity itself.

Quality control

Of primary importance on the producer side, is the development of adequate quality control and regulated production. Standards for the cultivation and processing of kava before its pharmaceutical processing need to be established and enforced. It would appear that the 'correct' cultivar(s) and plant parts for medicinal use are known. The use of other cultivars or similar species, or aerial parts of the plant, could increase the risk of toxic effects. Raw kava produced for manufacture should be certified according to the standards set and pharmaceutical companies have a responsibility for using only those sources that meet these standards.

Clinical review of case reports

Preceding comments derive from the literature review. With a pharmacovigilance and pharmaco-epidemiological approach, there is evidence that there is a greater risk of hepatotoxicity with the organic extracts than with synthetic or water products. The case report analysis suggests a likelihood that kava products of any type can be harmful to the liver and that this can be serious. This problem appears to occur rarely, but there is no good information on incidence. While there is evidence that some of the cases are due to direct toxicity, there is evidence that other factors may, perhaps more often, be responsible. These include pre-existing liver disease e.g. hepatitis C, or alcohol related liver problems, kava-drug or kava-herb interactions, idiosyncratic responses either immune mediated or metabolic, and overdose. The use of kava with known hepatotoxic drugs should be avoided. In terms of potential interactions, kava should not be used with antipsychotics, other anxiolytics and anticoagulants. Where pharmacogenetic testing is available, it would be desirable to determine the presence or absence of enzyme abnormalities in the cytochrome P450 system. Some pharmacogenetic laboratories have developed straightforward and cheap methods of doing this without reliance on blood samples.

Interactions

Kava products have a high propensity to cause kava-drug, and probably kava-herb interactions. Over 200 possible or potential kava-drug interactions have been listed (Section IIB tables 13-15). Some of these will affect the liver. Co-medication with anxiolytics, antipsychotics and antithrombotics should be avoided and a decision on the use of other drugs with kava should only be undertaken after the potential for interaction has been checked. Use with other potentially hepatotoxic drugs should be avoided.

Pharmacoepidemiology

Using denominator data in the form of daily doses of various kava products sold, it has been possible to compare rates of hepatic events by extract type. The results suggest that there is a higher rate of hepatotoxicity with acetonic and ethanolic extracts than with synthetic products. This is a key finding, although the rates are based on sales figures only and numbers are small. The results also show that the differences are independent of age, gender, dose, duration of use, concomitant therapy and alcohol use and are unlikely to be confounded by other disease states. This suggests, at least in part, that the liver toxicity is not due to the kava lactone content, but other chemicals extracted that are not present in the synthetic product and not bioavailable in water suspensions of kava. It is impossible to make a comparison of rates with water-based products.

Risk factors

In the absence of epidemiological studies it is difficult to identify risk factors for hepatic reactions with certainty. However there is evidence for the following:

- Acetonic and ethanolic extracts
- Alcohol
- Co-medication with potentially hepatotoxic medicines
- Co-medication with potentially interacting medicines: kava has been shown to inhibit a variety of cytochrome P450 enzymes.
- Pre-existing liver disease
- Significant overdose (see section on liver transplants), but within the usual range, there is no evidence that higher dose carries increased risk
- Genetic polymorphisms of cytochrome P450 enzymes. 2D6 deficiency has been associated with cases, but there may be others that are significant.

Pharmacovigilance versus clinical trials

It might be considered that the findings of the review of case reports are inconsistent with the findings of the review of clinical trials and experimental studies. However, this apparent incompatibility is a common situation. Clinical trials usually involve insufficient numbers of patients and do not continue for a sufficient length of time to reliably detect rare reactions. In addition, they are generally designed to assess efficacy and while they collect safety information, the methodology is not primarily aimed at detecting potential toxic effects. Many common or serious reactions have been missed in good quality clinical trials and have been revealed only through effective pharmacovigilance, prospective observational cohort studies such as cohort (prescription) event monitoring, published case reports in the literature or case control studies following signal identification. The absence of reports of hepatotoxicity in clinical trials does not mean that these reactions do not occur.

Recommendations

Should kava products be used as medicines, then the following are recommended in terms of safety:

- Ethanolic and acetonic extracts should be avoided.
- Synthetic products should be available.
- Products should be developed from water-based suspensions of kava.
- A pharmacopoeial standard for kava products should be created.
- Further research should be undertaken on the identification and toxicology of the chemical constituents of acetonic and ethanolic extracts.
- Cohort event monitoring studies should be undertaken on all products, including those that are synthetic and water-based.

Overall summary

Conclusions

1. The case reports of liver injury associated with the use of kava products provide a significant concern of a causal relationship in the absence of other identifiable risks of liver disease.
2. The chemical component(s) of kava products responsible for hepatotoxicity have not been identified.
3. The strong potential for kava-drug interactions, genetic differences in the cytochrome P enzyme system, heavy alcohol use and previous liver disease are potential risk factors for hepatotoxicity with kava. In addition, the cultivar of *Piper methysticum* used and the plant part are relevant to safety.
4. Other mechanisms proposed for hepatotoxic effects are immune mediated idiosyncrasy, the presence of the alkaloid pipermethystine in organic solvent extracts and loss of the protective effect on the liver of glutathione with the organic solvent extracts.
5. The incidence of hepatotoxicity with kava is unknown. Published estimates are unrealistically low. Nevertheless, the incidence is likely to be uncommon or rare.
6. There is some evidence of a higher risk of hepatotoxicity with acetonic and ethanolic extracts. This suggests that hepatic events occurring with products prepared from these extracts are non-random.
7. Alcoholic and acetonic extracts of kava may include toxic substances e.g. alkaloids, not present in synthetic products, or not bioavailable in water extracts.
8. On present knowledge, synthetic products and water extracts should have a lower risk of hepatotoxicity.
9. A variety of cultivars of *Piper methysticum*, and some other similar species have been used by pharmaceutical companies for the preparation of medicinal kava. A variety of plant parts has also been used.
10. The chemical composition of raw material from different species, cultivars and plant parts is not equivalent and in some instances has not been investigated.
11. Clinical trials of kava have not revealed hepatotoxicity as a problem.
12. Most experimental studies have failed to demonstrate a toxic effect on liver cells by kava.

Summary of findings

1. Of the 93 case reports of hepatotoxicity that have been collected and analysed there were seven fatalities and 14 liver transplants.
2. Eight cases were classified as having a probable relationship between the use of kava and liver disorder. This means that there was no factor present other than kava that was likely to cause liver injury.
3. There were 53 cases classified as having a possible relationship. Some of these cases will have a causal relationship with kava and some will not.
4. Five patients had a positive rechallenge, presumably to kava alone.
5. All seven deaths were classified as having a possible relationship with the use of kava, as were 10 of the 14 liver transplants. By definition of the term 'probable' in pharmacovigilance practice, deaths and transplants cannot be coded as such. It is likely that some of these cases were related to kava use.
6. Five of the case reports were from the use of water 'extracts' (but only two were prepared in the traditional manner); two were coded as probable and three possible.

Summary of recommendations

1. Further research into kava products is necessary, in particular to identify and gain information about the toxicology of the non-kava lactone constituents. This needs to include any differences between root and rhizome.
2. Should any kava product be considered for approval by regulatory authorities, the following should be important considerations:
   - 2.1. Post-marketing surveillance and research
     - 2.1.1. A risk management plan should be drawn up early in the approval process. This plan would include suggestions for pharmacoepidemiological studies, in particular cohort event monitoring, preferably with international collaboration. These studies should be undertaken on all products, including synthetic and water-based. Reliance should not be placed on spontaneous reporting alone for post-marketing surveillance.
     - 2.1.2. Pharmacogenetic studies should be undertaken to determine differences in cytochrome P450 metabolic enzyme activity and any relationship to hepatotoxicity. This could be undertaken using case control studies, ideally nested case control studies of cohorts of users of kava from cohort event monitoring studies.
     - 2.1.3. Products from water-based suspensions and further synthetic preparations should be developed and tested in clinical trials and consideration given to using these in preference to acetonic and ethanolic extracts.
   - 2.2. Conditions of use
     - 2.2.1. It would seem advisable that all kava products prepared as pharmaceuticals be available on prescription only in order to better monitor their use and apply necessary controls.
     - 2.2.2. Kava should not be used in patients with liver disease or a history of such, nor in patients who take excessive alcohol.

2.2.3. Warnings should be made available about the extensive risk of interactions with other drugs or herbal preparations. In particular, kava should not be used with antipsychotics, other anxiolytics or antithrombotics because of the risk of interactions which could include effects on the liver.

2.3. Standards

2.3.1. A pharmacopoeial standard for kava should be created. This should address the issues of quality, plant parts, dosage and methods of preparation. The findings of this review indicate that:

2.3.2. Only the root or rhizome of *Piper methysticum* G Forst should be used for preparation of medicinal kava. No other species and no aerial parts should be used. Agreement should be reached on the appropriate cultivar(s).

2.3.3. Adequate quality control measures standardized across the producing countries with agreed standard operating procedures, should be instituted for growth, harvesting and processing of the raw kava root or rhizome.

Opinion on key question

1. Evidence from our review of case reports suggests that kava lactones in any type of product may rarely cause hepatic adverse reactions because of kava-drug interactions, excessive alcohol intake, metabolic or immune mediated idiosyncrasy, excessive dose or pre-existing liver disease.
2. In addition to this background incidence, products made from acetonic and ethanolic extracts appear to be hepatotoxic on rare occasions, seemingly from non-kava lactone constituents. The incidence is unknown, but is more significant than the background effect in '1'.

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Information sources

A listing of information sources is attached. The references have been sorted by type e.g. case reports; general reviews. The list is by no means complete, but we have attempted to include significant sources of information used as background in preparation of the report, as well as those referenced in the text. There are no doubt errors, but we have made strenuous efforts to avoid such and hope that these are minimal.

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Assessment of the risk of hepatotoxicity with kava products

There has been international concern over the association of kava products and serious hepatotoxicity. Regulatory action banning these products in Europe has been controversial. This report investigates the possibility of hepatotoxicity with kava. It is aimed to be comprehensive but does not represent an authoritative statement regarding the safety of all kava preparations available.

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