21 November 2017
EMA/HMPC/450587/2016
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Piper methysticum* G. Forst., rhizoma

Final

The European Medicines Agency acknowledges that copies of the underlying works used to produce this monograph were provided for research only with exclusion of any commercial purpose.

Abu N, Akhtar MN, Yeap SK, Lim KL, Ho WY, et al. Flavokawain A induces apoptosis in MCF-7 and MDA-MB231 and inhibits the metastatic process in vitro. *PLoS One* 2014, 9:e105244

Abu N, Mohamed NE, Yeap SK, Lim KL, Akhtar MN, et al. In vivo anti-tumor effects of flavokawain A in 4T1 breast cancer cell-challenged mice. *Anticancer Agents Med Chem* 2015a, 15:905-915

Abu N, Mohamed NE, Yeap SK, Lim KL, Akhtar MN, et al. In vivo antitumor and antimetastatic effects of flavokawain B in 4T1 breast cancer cell-challenged mice. *Drug Des Devel Ther* 2015b, 9:1401-1417

Abu N, Mohameda NE, Tangarajoo N, Yeap SK, Akhtar MN, et al. In vitro Toxicity and in vivo Immunomodulatory Effects of Flavokawain A and Flavokawain B in Balb/C Mice. *Nat Prod Commun* 2015c, 10:1199-1202

Anke J, Ramzan I. Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.) *J Ethnopharmacol* 2004, 93:153-160

Anke J, Fu S, Ramzan I. Kavalactones fail to inhibit alcohol dehydrogenase in vitro. *Phytomed* 2006, 13**:**192-195

Backhauß C, Krieglstein J. Extract of kava (Piper methysticum) and its methysticin constituents protect brain tissue against ischemic damage in rodents. *Eur J Pharmacol* 1992, 215:265–269

Barnes J, Anderson LA and Phillipson JD. Herbal Medicines Third edition, Pharmaceutical Press, 2007, 389-403

Baum SS, Hill R, Rommelspacher H. Effect of kava extract and individual kavapyrones on neurotransmitter levels in the nucleus accumbens of rats. *Progress Neuropsychopharmacol Biol Psychiat* 1998, 22:1105-1120

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Behl M, Nyska A, Chhabra RS, Travlos GS, Fomby LM, Sparrow BR et al. Liver toxicity and carcinogenicity in F344/N rats and B6C3F1 mice exposed to Kava Kava. *Food Chem Toxicol* 2011, 49:2820–2829

Bhate H, Gerster G, Gracza E. Orale Prämedikation mit Zubereitungen aus Piper methysticum bei operativen Eingriffen in Epiduralanästhesie. *Erfahrungsheilkunde* 1989, 339-345

Bhate H, Gerster G. Behandlung mit Phytotranquilizern vor der Narkose. *Therapeutikon* 1992, 6:214-222

Biber A, Noldner M, Schlegelmilch R. Development of a formulation of kava-kava extract through pharmacokinetic experiments in animals. *Naunyn Schmiedebergs Arch Pharmacol* 1992, R24 (Abstract 93)

Bilia AR, Gallon S, Vincieri FF. Kava-kava and anxiety: growing knowledge about the efficacy and safety. *Life Sci* 2002, 70:2581–2597

Blaszcyk T, Kryzanowska J, Lamer-Zarawaska E. Kawa-Kawa als Antimykotikum. *Pharm Ztg* 1997, 142:1734-1736

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, et al., editors. The Complete German Commission E Monographs. American Botanical Council, Austin Texas 1998, 156–157

Bodkin R, Schneider S, Rekkerth D, Spillane L, Kamali M. Case Report Rhabdomyolysis associated with kava ingestion *Am J Emerg Med* 2012, 30:635.e1–635.e3

Boerner RJ. Kava kava in the treatment of generalized anxiety disorder, simple phobia and specific social phobia. *Phytother Res* 2001, 15:646-647

Boonen G, Ferger B, Kuschinsky K, Häberlein H. In vivo Effects of the Kavapyrones (+)-Dihydromethysticin and(±)-Kavain on Dopamine, 3,4-Dihydroxyphenylacetic Acid, Serotonin and 5-Hydroxyindoleacetic Acid Levels in Striatal and Cortical Brain Regions. *Planta Med* 1998a, 64:507—510

Boonen G. Hberlein H. Influence of Genuine Kavapyrone Enantiomers on the GABA A Binding Site. *Planta Med* 1998b, 64:504-506

British Herbal Pharmacopoeia, 1983, 1:162-163

British Pharmaceutical Codex, The Pharmaceutical Press, 1911, 557-558

Brown AC, Onopa J, Holck P, Kaufusi P, Kabasawa D, Craig WJ, et al. Traditional kava beverage consumption and liver function tests in a predominantly Tongan population in Hawaii. *Clin Toxicol* 2007, 45:549-556

Bruneton J. Pharmacognosie, Phytochimie, Plantes medicinales, 3rd ed. 2005, 443-446

Bujanda L, Palacios A, Silvarino R, Sanchez A, Munoz C. Kava-induced acute icteric hepatitis. *Gastroenterol Hepatol* 2002, 25:434-435

Cagnacci A, Arangino S, Renzi A, Zanni AL, Malmusi S, Volpe A. Kava-kava administration reduces anxiety in perimenopasal women. *Maturitas* 2003, 44:103-109

Cairney S, Maruff P, Clough AR. The neurobehavioural effects of kava. Australian and New Zealand *J Psychiat* 2002, 36:657-662

Cairney S, Clough AR, Maruff P, Collie A, Currie BJ, Currie J. Saccade and cognitive function in chronic kava users. *Neuropsychopharmacol* 2003, 28:389-396

Campo JV, McNabb J, Perel JM, Mazariegos GV, Hasegawa SL, Reyes J. Kava-induced fulminant hepatic failure. *J Am Acad Child Adolesc Psychiatry* 2002, 41:631-632

Capasso A, Sorrentino L. Pharmacological studies on the sedative and hypnotic effect of Kava kava and Passiflora extracts combination. *Phytomed* 2005, 12:39–45

Christl SU, Seifert A, Seeler D. Toxic hepatitis after consumption of traditional kava preparation. *J Travel Med* 2009, 16:55–56

Clayton NP, Yoshizawa K, Kissling GE, Burka LT, Chan P-C, Nyska A. Immunohistochemical analysis of expressions of hepatic cytochrome P450 in F344 rats following oral treatment with kava extract. *Exp Toxicol Pathol* 2007, 58:223–236

Clough AR, Bailie RS, Currie B. Liver function test abnormalities in users of aqueous kava extracts. *J Toxicol Clin Toxicol* 2003, 41:821-829

Connor KM, Davidson JR. A placebo-controlled study of Kava kava in generalized anxiety disorder. *Int Clin Psychopharmacol* 2002, 17:185-188

Connor KM, Payne V, Davidson JR. Kava in generalized anxiety disorder: three placebo-controlled trials. *Int Clin Psychopharmacol* 2006, 21:249-253

Côté CS, Kor C, Cohen J, Auclair K. Composition and biological activity of traditional and commercial kava extracts. *Biochem Biophys Res Commun* 2004, 322:147-152

Cropley M, Cave Z, Ellis J and Middleton RW. Effect of kava and valerian on human phisiological and psychological responses to mental stress assessed unedr laboratpry conditions. *Phytother Res* 2002, 16:23-27

DAC 1998:Kava-Kava-Wurzelstock: K155-1-K155-6

Davies LP, Drew CA, Duffield P, Johnston GAR, Jamieson DD. Kava pyrone and resin: Studies on GABAA, GABAB and benzodiazepine binding sites in rodent brain. *Pharmacol Toxicol* 1992, 71:120–126

De Leo V, Marca Al, Morgante G, Lanzetta D, Florio P, Petraglia F. Valutazione dell'associazione di estratto di Kava-Kava e terapia ormonale sostitutiva nel trattamento d'ansia in post menopausa. *Minerva Ginecol* 2000, 52:263-267

Di Silvestro RA, Zhang W, Di Silvestro DJ. Kava feeding in rats does not cause liver injury nor enhance galactosamine-induced hepatitis. *Food Chem Toxicol* 2007, 45:1293–1300

Dinh LD, Simmen U, Bueter BK, Bueter B, Lundstrom K, Schaffner W. Interaction of Various Piper methysticum Cultivars with CNS Receptors in vitro. *Planta Med*, 2001, 67:306-31

Duffield AM, Jamieson DD, Lidgard RO, Duffield PH, Bourne DJ. Identification of some human urinary metabolites of the intoxicating beverage kava. *J Chromatogr A* 1989a, 475:273–281

Duffield PH, Jamieson DD, Duffield AM. Effect of aqueous and lipid-soluble extracts of kava on the conditioned avoidance response in rats. *Arch Int Pharmacodyn* 1989b, 301:81–90

Duffield PH, Jamieson DD. Development of tolerance to kava in mice. *Clin Exp Pharmacol Physiol* 1991, 18:571–578

Duke JA et al. Handbook of Medicinal Herbs 2nd ed., 2002:438

Emser W, Bartylla K. Verbesserung der Schlafqualität. Zur Wirkung von Kava-Extrakt WS 1490 auf das Schlafmuster bei Gesunden TW. *Neurol Psychiatr* 1991, 5:636–642

Eskander RN, Randall LM, Sakai T, Guo Y, Hoang B, Zi X. Flavokawain B, a novel, naturally occurring chalcone, exhibits robust apoptotic effects and induces G2/M arrest of a uterine leiomyosarcoma cell line. *J Obstet Gynaecol Res* 2012, 38:1086-1094

ESCOP Monographs. 2nd ed. Piperis methystici rhizoma (kava-kava), European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2003, 365-382

FDA. Consumer advisory: kava-containing dietary supplements may be associated with severe liver injury. US Food and Drug Administration. 2002. Available at: http://www.fda.gov/Food/ResourcesForyou/Consumers/ucm085482.html. Accessed June 2016

Feltenstein MW, Lambdin C, Ganzera M, Dharmaratne RW, Nanayakkara D, Khan IA, Sufk K. Anxiolytic Properties of Piper methysticum extract samples and fractions in the chick social–separation–stress procedure. *Phytother Res* 2003, 17:210–216

Fischer B, Hartwich C, editors. Hagers Handbuch der Pharmazeutischen Praxis. Vol 4. 5th ed. Springer-Verlag, Berlin 1919, 639

Foo H, Lemon J. Acute effects of kava, alone or in combination with alcohol, on subjective measures of impairment and intoxication and on cognitive performance. *Drug Alcohol Rev* 1997,16:147-55

Foster BC, Vandenhoek S, Hana J, Krantis A, Akhtar MH, et al. In vitro inhibition of human cytochrome P450-mediated metabolism of marker substrates by natural products. *Phytomed* 2003, 10:334-342

Frenzel C, Teschke R. Herbal Hepatotoxicity: Clinical Characteristics and Listing Compilation *Int J Mol Sci* 2016, 17:588; doi 10.3390/ijms17050588

Friese J, Gleitz J. Kavain, dihydrokavain, and dihydromethysticin non-competitively inhibit the specific binding of [3H]-batrachotoxinin-A 20-alpha-benzoate to receptor site 2 of voltage-gated Na^+ channels. *Planta Med* 1998, 64:458-459

Fu S, Korkmaz E, Braet F, Ngo Q, Ramzan I. Influence of kavain on hepatic ultrastructure. *World J Gastroenterol* 2008, 14:541–546

Fu S, Tattam BN, Duke CC, Ramzan I. High-performance liquid chromatography assays for desmethoxyyangonin, methysticin, kavain and their microsomal metabolites. *Biomed Chromatogr* 2009, 23:81–91

Fu S, Rowe A, Ramzan I. Kavalactone metabolism in the isolated perfused rat liver. *Phytother Res* 2012a, 26:1813–1816

Fu S, Rowe A, Ramzan I. Kavalactone metabolism in rat liver microsomes. *Phytother Res* 2012b, 26:1057–1061

Furgiuele A, Kinnard W, Aceto M, Buckley J. Central activity of aqueous extracts of Piper methysticum(Kava). *J Pharm Sci* 1965, 54:247-252

Garner L, Klinger J. Some visual effects caused by the beverage kava. *J Ethnopharmacol* 1985, 13:307-311

Garrett K, Basmadjian G, Khan I, Schaneberg B, Seale TW. Extracts of kava (Piper methysticum) induce acute anxiolytic-like behavioral changes in mice. *Psychopharmacol* 2003, 170:33–41

Gastpar M, Klimm HD. Treatment of anxiety, tension and restlessness states with Kava special extract WS 1490 in general practice: a randomized placebo-controlled double-blind multicenter trial. *Phytomed* 2003, 10:631-639

Geier FP, Konstantinowicz T. Kava treatment in patients with anxiety. *Phytother Res* 2004, 18:297-300

Gessner B, Cnota P. Untersuchung der Vigilanz nach Applikation von Kava-Kava-Extrakt, Diazepam oder Plazebo. *Z Phytother* 1994, 15:30–37

Gleitz J, Beile A, Peters T. (±)–Kavaine inhibits veratridine-activated votalage-dependent Na^+-channels in synaptosomes prepared from rat cerebral cortex. *Neuropharmacol* 1995, 34:1133–1138

Gleitz J, Friese J, Beile A, Ameri A, Peters T. Anticonvulsive action of (±)–kavaine estimated from its properties on stimulated synaptosomes and Na^+ channel receptor sites. *Eur J Pharmacol* 1996, 315:89–97

Gleitz J, Beile A, Wilkens P, Ameri A, Peters T. Antithrombotic action of the kava pyrone (+)–kavaine prepared from Piper methysticum on human platelets. *Planta Med* 1997, 63:27–30

Gow PJ, Connelly NJ, Hill RL, Crowley P, Angus PW. Fatal fulminant hepatic failure induced by a natural therapy containing kava. *Med J Aust* 2003; 178:442-3

Gruenwald J, Brendler T, Jaenike C, editors. PDR for Herbal Medicines. 3nd ed. Montvale 2004, 482-489

Guo L, Li Q, Xia Q, Dial S, Chan PC, Fu P. Analysis of gene expression changes of drug metabolizing enzymes in the livers of F344 rats following oral treatment with kava extract. *Food Chem Toxicol* 2009, 47:433-442

Guo L, Shi Q, Dial S, Xia Q, Mei N, et al. Gene expression profiling in male B6C3F1 mouse livers exposed to kava identifies-changes in drug metabolizing genes and potential mechanisms linked to kava toxicity. *Food Chem Toxicol* 2010, 48:686-696

Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Khan IA, Shah A. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clin Pharmacol Ther* 2005a, 77:415-426

Gurley BJ, Gardner SF, Williams DK., Gentry WB, Hubbard MA, et al. Effect of goldenseal. black cohosh, kava kava, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4 phenotypes. *Clin Pharmacol Ther* 2005b, 77:P36

Gurley BJ, Swain A, Barone GW, Williams DK, Breen P, et al. Effect of goldenseal (Hydrastis canadensis) and kava kava (Piper methysticum) supplementation on digoxin pharmacokinetics in humans. *Drug Metab Dispos* 2007, 35:240-245

Gurley BJ, Swain A, Hubbard MA, Hartsfield F, Thaden J, et al. Supplementation with goldenseal (Hydrastis canadensis), but not kava kava (Piper methysticum), inhibits human CYP3A activity in vivo. *Clin Pharmacol Ther* 2008a, 83:61-69

Gurley BJ, Swain A, Hubbard MA, Williams DK, Barone G, et al. Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea. *Mol Nutr Food Res* 2008b, 52:755-763

Hänsel R, Keller K, Rimpler H, Schneider G, editors. Hagers Handbuch der Pharmazeutischen Praxis. Vol 6. 5th ed. Springer-Verlag, Berlin 1994, 201-212

Hansel R, Woelk H, editors. Unerwunschte Wirkungen des Kavatrinkens/Toxicologie. In: Spektrum Kava-Kava, 2nd ed Basel: Aesopus Verlag 1995:19-20

Hänsel R. Kava-Kava (Piper methysticum G. FORSTER) in der modernen Arzneimittelforschung. *Z Phytother* 1996, 17:180–194

Hänsel R. Characterization and physiological activity of some kawa constituents. *Pacific Science* 1968, Vol.XXII:293-313

Herberg KW. Zum Einfluß von Kava-Spezialextrakt WS 1490 in Kombination mit Ethylalkohol auf sicherheitsrelevante Leistungen. Bericht zu einer doppelblinden, randomisierten, placebokontrollierten Studie. TÜV-Projekt 954-411001, 1992:1-24

Herberg KW. Zum Einfluß von Kava-Spezialextrakt WS1490 in Kombination mit Ethylaklohol auf sicherheitsrelevante Leistungsparameter. *Blutalkohol* 1993, 30:96-105

Herberg KW. Beeinflusst Kava-Extrakt in Kombination mit Ethylalkohol die Fahrsicherheit? *Natura Med* 1997, 12:28-36

Holm E, Staedt U, Heep J, Kortsik C, Behne F, Kaske A, Mennicke I. Untersuchungen zum Wirkprofil von D,L-Kavaine*. Arzneim-Forsch/Drug Res* 1991, 41:673–683

Hseu YC, Lee MS, Wu CR, Cho HJ, Lin KY, et al. The Chalcone Flavokawain B Induces G2/M Cell-cycle Arrest and Apoptosis in Human Oral Carcinoma HSC-3 Cells through the Intracellular ROS Generation and Down-regulation of the Akt/p38 MAPK Signaling Pathway. *J Agric Food Chem* 2012, 60:2385-2397

Hsu SY, Lin MH, Lin LC, Chou CJ. Toxicologic studies of dihydro-5,6-dehydrokawain and 5,6-dehydrokawain. *Planta Med*, 1994, 60:88-90

Humberston CL, Akhtar J, Krenzelok EP. Acute hepatitis induced by Kava Kava. *J Toxicol* 2003, 41:109-113

Hüttemann D. Kava-Kava. Comeback unter strengen Auflagen. *Pharm Zt* 2015, 160:1172-1174

IARC monographs on the evaluation of carcinogenic risks to humans, 2015, volume 108:117-141

Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR. An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine (Baltimore)* 2005, 84:197-207

Jaggy H, Achenbach H. Cepharadione A from Piper methysticum. *Planta Med* 1992,58:111

Jamieson DD, Duffield PH. The antinociceptive actions of kava components in mice. *Clin Exp Pharmacol Physiol* 1990a, 17:495–507

Jamieson DD, Duffield PH. Positive interaction of ethanol and kava resin in mice. *Clin Exp Pharmacol Physiol* 1990b, 17:509-514

Jeong HJ, Lee CS, Choi J, Hong YD, Shin SS, et al. Flavokawains B and C, melanogenesis inhibitors, isolated from the root of Piper methysticum and synthesis of analogs. *Bioorg Med Chem Lett* 2015, 25:799-802

Jhoo JW, Ang CY, Heinze TM, Deck J, Schnackenberg LK, Beger R D et al. Identification of C-glycoside flavonoids as potential mutagenic compounds in kava. *J Food Sci* 2007, 72:C120–125

Johnson BM, Qiu SX, Zhang S, Zhang F, Burdette JE, Yu L et al. Identification of novel electrophilic metabolites of Piper methysticum Forst (kava). *Chem Res Toxicol* 2003, 16(6):733–740

Johnson TE, Hermanson D, Wang L, Kassie F, Upadhyaya P, et al. Lung tumorigenesis suppressing effects of a commercial kava extract and its selected compounds in A/J mice. *Am J Chin Med* 2011, 39:727-742

Johnson D, Frauendorf A, Stecker K, Stein U. Neurophysiologisches Wirkprofil und Verträglichkeit von Kava-Extrakt WS 1490: eine Pilotstudie mit randomisierter Auswertung. *TW Neurologie Psychiatrie* 1991, 5:349-354

Jussofie A, Schmitz A, Hiemke C. Kavapyrone enriched extract from Piper methysticum as a modulator of the GABA binding site in different regions of rat brain. *Psychopharmacol* 1994, 116:469–474

Keledjian J, Duffield PH, Jamieson DD, Lidgard RO, Duffield AM. Uptake into mouse brain of four compounds present in the psychoactive beverage kava. *J Pharm Sci* 1988, 77:1003–1006

Kinzler E, Krömer J, Lehmann E. Wirksamkeit eines Kava-Spezial-Extraktes bei Patienten mit Angst-, Spannungs-, und Erregungszuständen nicht-psychotischer Genese. Doppelblind-Studie gegen Plazebo über 4 Wochen. *Arzneimittelforsch/ Drug Res* 1991, 41:584-588

Klohs MW, Keller F, Williams RE, Toekes MI, Cronheim GE. A chemical and pharmacological investigation of Piper methysticum FORST. *J Med Pharmaceut Chem* 1959, 1:95–103

Köppel C, Tenczer J. Mass spectral characterization of urinary metabolites of D, L-kawain. *J Chromatogr A* 1991, 562:207–211

Kretzschmar R, Meyer H. Uber die antikonvulsive Wirksamkeit von Methysticin, einem Wirkstoff aus Piper methysticum Forst, in Kombination mit gebriuchlichen Antikonvulsiva. *Arch Int Pharmacodyn* 1965, 177:267–268

Kretzschmar R, Teschendorf HJ, Ladous A, Ettehadieh D. On the sedative action of the kava rhizome. *Acta Pharmacol Toxicol* 1971; 29:26

Kretzschmar R, Meyer HJ Vergleichende Untersuchung über die antikonvulsive Wirksamkeit der Pyronverbindungen aus Piper methysticum FORST. *Arch Int Pharmacodyn* 1969, 177:261–277

Kretzschmar R, Meyer HJ, Teschendorf HJ. Strychnine antagonistic potency of pyrone compounds of the kavaroot (Piper methysticum Forst.). *Experientia* 1970, 26:283-284

Kuo YF, Su YZ, Tseng YH, Wang SY, Wang HM, Chueh PJ. Flavokawain B, a novel chalcone from Alpinia pricei Hayata with potent apoptotic activity: Involvement of ROS and GADD153 upstream of mitochondria-dependent apoptosis in HCT116 cells. *Free Radic Biol Med* 2010, 49:214-226

Lebot V, Merlin M, Lindstrom L. Kava the Pacific Elixir: The Definitive Guide to its Ethnobotany, History and Chemistry. New Haven: Yale University Press; 1992. pp.68–69

Lebot V, Levesque J. Genetic control of kavalactone chemotypes in Piper methysticum cultivars. *Phytochem*, 1996, 43:397-403

Lebot V, Legendre L. Comparison of kava (Piper methysticum Forst.) varieties by UV absorbance of acetonic extracts and high-performance thin-layer chromatography. *J Food Compos Anal* 2016, 48:25–33

Lehmann E. Wirkung von Kava-Kava bei akuter Angst. *Psychoonkologie* 1988, 59-64

Lechtenberg M, Quandt B, Schmidt M, Nahrstedt A. Is the alkaloid pipermethystine connected with the claimed liver toxicity of Kava products? *Pharmazie* 2008, 63:71-74

Lehmann E, Klieser E, Klimke A, Krach H, Spatz R. The efficacy of kavain in patients suffering from anxiety. *Pharmacopsychiatry* 1989, 22:258-262

Lehmann E, Kinzler E, Friedemann J. Efficacy of a special Kava extract (Piper methysticum) in patients with states of anxiety, tension and excitedness of non-mental origin - A double-blind placebo-controlled study of four weeks treatment. *Phytomed* 1996, 113-119

Lehrl S. Clinical efficacy of kava extract WS 1490 in sleep disturbances associated with anxiety disorders. Results of a multicenter, randomized, placebo-controlled, double-blind clinical trial. *J Affect Disord* 2004, 78:101-110

Leitzman P, Narayanapillai SC, Balbo S, Zhou B, Upadhyaya P, et al. Kava blocks 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in association with reducing O6-methylguanine DNA adduct in A/J mice. *Cancer Prev Res* 2014, 7:86-96

Leulier A, Manceau P. Precis de Matiere Medicale, Tome Premier, 5th ed., Librairie Maloine 1946, 615-616

Li X, Xu X, Ji T, Liu Z, Gu M, Hoang BH, Zi X. Dietary feeding of Flavokawain A, a Kava chalcone, exhibits a satisfactory safety profile and its association with enhancement of phase II enzymes in mice. *Toxicol Rep* 2014, 1:2-11

Ligresti A, Villano R, Allarà M, Ujváry I, Di Marzo V. Kavalactones and the endocannabinoid system: The plant-derived yangonin is a novel CB1 receptor ligand, *Pharmacol Res* 2012, 66:163–169

Lim ST, Dragull K, Tang CS, Bittenbender HC, Efird JT, Nerurka PV. Effects of kava alkaloid, pipermethystine, and kavalactones on oxidative stress and cytochrome P450 in F-344 rats. *Toxicol Sci* 2007, 97:214–221

Lin E, Lin WH, Wang SY, Chen CS, Liao JW, et al. Flavokawain B inhibits growth of human squamous carcinoma cells: Involvement of apoptosis and cell cycle dysregulation in vitro and in vivo. *J Nutr Biochem* 2012, 23:368-378

Lindenberg D, Pitule-Schödel H. D,L-kavain in comparison with oxazepam in anxiety disorders. A double-blind study of clinical effectiveness [D,L–Kavain im Vergleich zu Oxazepam bei Angstzuständen. Doppelblindstudie aur Wirksamkeit]. *Fortschritte der Medizin* 1990, 108:49-54

Liu Z, Xu X, Li X, Liu S, Simoneau, AR, et al. Kava chalcone, flavokawain A, inhibits urothelial tumorigenesis in the UPII-SV40T transgenic mouse model. *Cancer Prev Res* 2013, 6:1365-1375

Lüde S, Török M, Dieterle S, Jäggi R, Büter KB, Krähenbühl S. Hepatocellular toxicity of kava leaf and root extracts. *Phytomed* 2008, 15:120–131

Ma Y, Sachdeva K, Liu J, Ford M, Yang D, Khan IA, Chichester CO, Yan, B. Desmethoxyyangonin and dihydromethysticin are two major pharmacological kavalactones with marked activity on the induction of cytochrome P4503A23. *Drug Metab Dispos* 2004, 32:1317-1324

Madaus G. Lehrbuch der biologischen Heilmittel. Vol 1. Georg Thieme Verlag, Leipzig 1938, 2142-2146

Magura EI, Kopanitsa MV, Gleitz J, Peters T, Krishtal OA. Kava extract ingredients, (+)-Methysticin and (±)-Kavain inhibit voltage-operated Na^+ channels in rat CA1 hippocampal neurons. *Neuroscience* 1997, 81:345–351

Malsch U, Kieser M. Efficacy of kava-kava in the treatment of non-psychotic anxiety, following pretreatment with benzodiazepines. *Psychopharmacol* 2001, 157:277-283

Martin AC, Johnston E, Xing C, Hegeman AD. Measuring the chemical and cytotoxic variability of commercially available kava (Piper methysticum G. Forster). *PLoS One* 2014, 9:e111572

Martindale. The Extra Pharmacopoeia. The Pharmaceutical Press, London 2009, CD accesed

Mathews JD, Riley MD, Fejo L, Munoz E, Milns NR, Gardner ID, Powers JR, Ganygulpa E, Gununuwawuy BJ. Effects of the heavy usage of kava on physical health: summary of a pilot survey in an aboriginal community. Med J Aust 1988 148:548-555

Mathews JM, Etheridge AS, Black SR. Inhibition of human cytochrome P450 activities by kava extract and kavalactones. *Drug Metab Dispos* 2002, 30:1153–1157

Mathews JM, Etheridge AS, Valentine JL, Black SR, Coleman DP, Patel P et al. Pharmacokinetics and disposition of the kavalactone kawain: interaction with kava extract and kavalactones in vivo and in vitro. *Drug Metab Dispos* 2005, 33:1555–1563

Matthias A, Blanchfield JT, Penman KG, Bone KM, Toth I, Lehmann RP. Permeability studies of Kavalactones using a Caco-2 cell monolayer model. *J Clin Pharm Ther* 2007, 32:233–239

Meissner O, Häberlein H. HPLC analysis of flavokavins and kavapyrones from Piper methysticum Forst. *J Chromatogr B Analyt Technol Biomed Life Sci* 2005, 826:46-49

Meyer HJ. Pharmakologie der wirksamen Prinzipien des Kava-Rhizoms (Piper methysticum Forst.). *Arch. Int Pharmacodyn Ther* 1962, 138:505-536

Meyer HJ, Meyer-Burg J. Hemmung des Elektrokrampfes durch die Kawa-Pyrone Dihydromethysticin und Dihydrokavaine *Arch Int Pharmacodyn* 1964, 148: 97–110

MHRA. Report of the Committee on Safety of Medicines Expert Working Group on the safety of Kava. 2006. Available from: http://www.mhra.gov.uk [Accessed on March 2016]

Mittmann U, Schmidt M, Vrastyakova J. Akut-anxiolytische Wirksamkeit von Kava-Spissum-Spezialextrakt und Benzodiazepinen als Prämedikation bei chirurgischen Eingriffen - Ergebnisse einer randomisierten, referenzkontrollierten Studie. *J Pharmakol Ther* 2000, 9:99-108

Möller HJ, Heuberger L. Anxiolytic potency of D,L kavain. Results of a placebo-controlled, double-blindstudy [Anxiolytische Potenz von D,L–Kavain]. *Munchener Medizinische Wochenschrift* 1989, 131:656–659

Möller HJ, Ulm K, Glöggler A. Kavain as an aid in the withdrawal of benzodiazepines (Therapy study) [Kavainals Hilfe beim Benzodiazepin–Entzug]. *Munchener Medizinische Wochenschrift* 1992,134:41–44

Moller HJ Volz HP, Reimann IW, Stoll KD., Opipramol for the treatment of generalized anxiety disorder: a placebo-controlled trial including an alprazolam-treated group. *J Clin Psychopharmacol* 2001, 21:59-65

Musch E, Chrissafidou A, Malek M. Akute Hepatitis durch Kava-Kava und Johanniskraut: immun-vermittelter Mechanismus? *Dtsch Med Wochenschr,* 2006, 131**:**1214-1217

Münte TF, Heinze HJ, Matzke M, Steitz J. Effects of oxazepam and an extract of kava roots (Piper methysticum) on event related potentials in a word recognition task. *Neuropsychobiol* 1993, 27:46–53

Narayanapillai S, Leitzman P, O'Sullivan G, Xing C. Flavokawains A and B in Kava, Not Dihydromethysticin, Potentiate Acetaminophen-Induced Hepatotoxicity in C57BL/6 Mice. *Chem Res Toxicol* 2014a, 27:1871−1876

Narayanapillai SC, Balbo S, Leitzman P, Grill AE, Upadhyaya P, et al. Dihydromethysticin from kava blocks tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis and differentially reduces DNA damage in A/J mice. *Carcinogenesis* 2014b, 35:2365-2372

Nerurkar PV, Dragull K, Tang C-S. In vitro toxicity of kava alkaloid, pipermethystine, in HepG2 cells compared to kavalactones. *Toxicol Sci* 2004, 79:106–111

Neto JT. Eficácia e tolerabilidade do extrato de kava-kava WS 1490 em estados de ansiedade. Estudo multocêntrico brasileiro. *Rev Bras Med* 1999, 56:280-284

Norton SA and Ruze P. Kava dermopathy. *J Am Acad Dermatol* 1994, 31:89-97

NTP. Summary of data for Chemical Selection: Kava-Kava. November 1998 (available on http://ntp-server.niehs.nih.gov; accessed on January 2016)

NTP. Toxicology and carcinogenesis studies of kava kava extract (CAS No. 9000–38–8) in F344/N rats and B6C3F1 mice (gavage studies). *Natl Toxicol Program Tech Rep Ser*, 2012, 571:1–186.

Otoguro K, Iwatsuki M, Ishiyama A, Namatame M, Nishihara-Tsukashima A, et al. In vitro antitrypanosomal activity of some phenolic compounds from propolis and lactones from Fijian Kawa (Piper methysticum). *J Nat Med* 2012, 66:558-561

Parmar VS, Jain S C, Bisht K, Jain R, Taneja P, Jha A, Tyagi OD, Prasad A K, Wengel J, Olsen CE, Boll PM. Phytochemistry of the genus *Piper*. *Phytochem* 1997, 46:597–673

Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. *J Clin Psychopharmacol* 2000; 20:84-89

Pittler MH, Ernst E. Kava extract versus placebo for treating anxiety. Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD003383. DOI: 10.1002/14651858.CD003383

Pittler MH, Ernst E. Kava extract versus placebo for treating anxiety (Review) In: The Cochrane Library, Issue 6, 2010. Oxford: Update Software

Rasmussen AK, Scheline RR, Solheim E, Hänsel R. Metabolism of some kava pyrones in the rat. *Xenobiotica* 1979, 9:1–16

Robinson V, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG Jr, Shank RC et al. Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of Piper methysticum leaf/root/stem extract and Piper methysticumroot extract. *Int J Toxicol* 2009, 28:175S–188S

Rowe A, Narlawar R, Groundwater PW, Ramzan I. Kavalactone pharmacophores for major cellular drug targets. *Mini Rev Med Chem* 2011, 11:79 –83

Ruze P. Kava-induced dermopathy: A niacin deficiency? *Lancet* 1990, 335:1442 –1445

Russell PN, Bakker D, Singh NN. The effects of kava on alerting and speed of access of information from long-term memory. *Bull Psychonomic Soc* 1987,25:236-237

Russmann S, Lauterburg B H, Helbling, A. Kava hepatotoxicity. *Ann Int Med* 2001, 135:68-69

Russmann S, Barguil Y, Cabalion P, Kritsanida M, Duhet D, Lauterburg BH. Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia. *Eur J Gastroenterol Hepatol* 2003, 15:1033-1036

Russmann S, Lauterburg BH, Barguil Y, Choblet E, Cabalion P, Rentsch K, Wenk M. Traditional aqueous kava extracts inhibit cytochrome P450 1A2 in humans: Protective effect against environmental carcinogens? *Clin Pharmacol Ther* 2005, 77:453-454

Sakai T, Eskander RN, Guo Y, Kim KJ, Mefford J, Hopkins J, Bhatia NN, Zi X, Hoang BH. Flavokawain B, a kava chalcone, induces apoptosis in synovial sarcoma cell lines. *J Orthop Res* 2012, 30:1045-1050

Saletu B, Grünberger J, Linzmayer L, Anderer P. EEG-brain mapping, psychometric and psychophysiological studies on central effects of kavain – a kava plant derivative. *Hum Pharmacol* 1989, 4:169–190

Sallström B, Hill R, Rommelspacher H. Effect of kava extract and individual kavapyrones on neurotransmitter levels in the accumbens of rats. *Prog Neuro-Psychopharmacol & Biol Psychiat* 1998, 22:1105-1120

Sarris J, Teschke R, Stough C, Scholey A & Schweitzer I. Re-introduction of kava (Piper methysticum) to the EU: is there a way forward? *Planta Med* 2011, 77:107-10

Sarris J, Kavanagh DJ, Adams J, Bone K, Byrne G. Kava Anxiety Depression Spectrum Study (KADSS): a mixed methods RCT using an aqueous extract of Piper methysticum. *Complement Ther Med* 2009a, 17:176-178

Sarris J, Kavanagh DJ, Byrne G, Bone KM, Adams J, Deed G. The Kava Anxiety Depression Spectrum Study (KADSS): a randomized, placebo-controlled crossover trial using an aqueous extract of Piper methysticum. *Psychopharmacol* 2009b, 205:399-407

Sarris J, Kavanagh DJ, Deed G, Bone KM. St. John's wort and Kava in treating major depressive disorder with comorbid anxiety: a randomised double-blind placebo-controlled pilot trial. *Hum Psychopharmacol,* 2009c 24:41-48

Sarris J, Scholey A, Schweitzer I, Bousman C, Laporte E, et al. The acute effects of kava and oxazepam on anxiety, mood, neurocognition; and genetic correlates: a randomized, placebo-controlled, double-blind study. *Hum Psychopharmacol* 2012, 27:262-269

Sarris J, Stough C, Bousman CA, Wahid ZT, Murray G, et al. Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychopharmacol* 2013a. 33:643-648

Sarris J, Stough C, Teschke R, Wahid ZT, Bousman CA, et al. Kava for the treatment of generalized anxiety disorder RCT: analysis of adverse reactions, liver function, addiction, and sexual effects. *Phytother Res* 2013b, 27: 1723-1728.

Sarris J, Laporte E, Scholey A, King R, Pipingas A, Schweitzer I, Stough C. Does a medicinal dose of kava impair driving? A randomized, placebo-controlled, double-blind study. *Traffic Inj Prev* 2013 c, 14: 13-17.

Schmidt M.-Is kava really hepatotoxic? An analysis of the known data on adverse effects of kava preparations on the liver. 2003. Article extracted from http://www.uni-muenster.de/Chemie/PB/Kava/kavaframe.html

Scherer MD. Kava-Kava extract in Anxiety Disorders: An Outpatient Observational Study. *Adv Ther* 1998, 4:261-269

Schmitz D, Zhang CL, Chatterjee SS, Heinemann U. Effects of methysticin on three different models of seizure like events studied in rat hippocampal and entorhinal cortex slices. *Naunyn Schmiedebeberg's Arch Pharmacol* 1995; 351:348–355

Schulz H, Jobert M, Hübner WD. The quantitative EEG as a screening instrument to identify sedative effects of single doses of plant extracts in comparison with diazepam. *Phytomed* 1998, 5:449-458

Schulz V, Hansel R, Tyler VE. Rational phytotherapy: A physicians' guide to herbal medicine. (3rd ed.) Springer Verlag, New York, 1999:71-79

Seitz U, Ameri A, Pelzer H, Gleitz J, Peters T. Relaxation of evoked contractile activity of isolated guinea-pig ileum by (±)-kavaine. *Planta Med* 1997, 63:303–306

Siegers CP, Honold E, Krall B, Meng G, Habs M. Ergebnisse der Anwendugsbeobachtung L 1090 mit Laitan Kapseln, *Ärztl. Forschung* 1992, 39:7-11

Simeoni P, Lebot V. Identification of factors determining kavalactone content and chemotype in Kava (Piper methysticum Forst. f.) *Biochem System Ecol* 2002, 30:413–424

Siméoni P, Lebot V. *Buveurs de Kava,* Port Vila, Vanuatu, Géo-Consulte, 2014

Singh YN, Devkota A. Aqueous kava extracts do not affect liver function tests in rats. *Planta Med* 2003, 69:496–499

Singh YN. Kava: an overview. *J Ethnopharmacol* 1992, 37:13–45

Singh YN. Kava. From Ethnology to Pharmacology*,* Boca Raton, London, New York, Washington, CRC Press, 2004

Singh NN, Ellis CR, Singh YN. A double-blind, placebo-controlled study of the effects of kava (kavatrol) on daily stress and anxiety in adults. *Alt Ther Health Med* 1998, 4:97-98

Sorrentino L., Capasso A., Schmidt M. Safety of ethanolic kava extract: Results of a study of chronic toxicity in rats, *Phytomede* 2006, 13:542–54

Spree MH, Croy HH. Antares - ein standardisiertes Kava-Kava-Praparat mit dem Spezialextrakt KW 1491 *Kassenarzt* 1992, 17:44-51

Staedt U, Holm E, Heep J, Riesmüller S, Kortsik C, Steiner G. Studies on effects of D,L-Kawain-psychometry, EEG and Hamilton scale [Zum Wirkungsprofil von D,L–Kavain]. *Medizinische Welt* 1991, 42:881–891

Strahl S, Ehret V, Dahm H H, Maier K P.Nekrotisierende Hepatitis nach Einnahme pflanzlicher Heilmittel. *Dtsch Med Wschr* 1998, 123:1410-1414

Stickel F, Baumuller H-M, Seitz K, Vasilakis D, Seitz G, Seitz HK. et al. Hepatitis induced by Kava (Piper methysticum rhizoma) *J Hepatol* 2003, 39:62–67

Tang J, Dunlop RA, Rowe A, Rodgers KJ, Ramzan I. Kavalactones yangonin and methysticin induce apoptosis in human hepatocytes (HepG2) in vitro. *Phytother Res* 2010a, 25:417–423

Tang Y, Li X, Liu Z, Simoneau A R, Xie J, Zi X. Flavokawain B, a kava chalcone, induces apoptosis via up-regulation of death-receptor 5 and Bim expression in androgen receptor negative, hormonal refractory prostate cancer cell lines and reduces tumor growth. *Int J Cancer* 2010b, 127:1758-1768 (only Abstract available)

Tarbah F, Mahler H, Kardel B, Weinmann W, Hafner D, Daldrup T. Kinetics of kavain and its metabolites after oral application, *J Chromatogr B Analyt Technol Biomed Life Sci* 2003, 789:115–130

Teschke R, Lebot V. Proposal for a kava quality standardization code. *Food Chem Toxicol* 2011, 49:2503–2516

Teschke R, Fuchs J, Bahre R, Genthner A, Wolff A. Kava hepatotoxicity: comparative study of two structured quantitative methods for causality assessment. *J Clin Pharm Ther* 2010, 35:545-563

Teschke R, Gaus W, Loew D. Kava extracts: safety and risks including rare hepatotoxicity. *Phytomede* 2003, 10:440-446

Teschke R, Schwarzenboeck A and Hennermann KH. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. *Eur J Gastroenterol Hepatol* 2008, 20:1182–1193

Teschke R, Genthner A, Wolff A. Kava hepatotoxicity: comparison of aqueous, ethanolic, acetonic kava extracts and kava-herbs mixtures. *J Ethnopharmacol* 2009a, 123:378-384

Teschke R, Wolff A. Kava hepatotoxicity: regulatory data selection and causality assessment. *Digest Liver Dis* 2009b, 41:891-901

Teschke R, Qiu SX, Lebot V. Herbal hepatotoxicity by kava: update on pipermethystine, flavokavain B, and mould hepatotoxins as primarily assumed culprits. *Dig Liver Dis* 2011, 43:676–681

Teschke R, Wolff A. Regulatory causality evaluation methods applied in kava hepatotoxicity: are they appropriate? *Regul Toxicol Pharmacol* 2011, 59:1-7

Thomsen M, Vitetta L, Schmidt M, Sali A. Fatal fulminant hepatic failure induced by a natural therapy containing kava. *Med J Aust* 2004, 180:198-199

Thompson R, Ruch W, Hasenhrl RU. Enhanced cognitive performance and cheerful mood by standardized extracts of Piper methysticum (kava-kava). *Hum Psychopharmacol* 2004, 19:243–250

Triolet J, Shaik A A, Gallaher D D, O'Sullivan M G, Xing C. Reduction in colon cancer risk by consumption of kava or kava fractions in carcinogen-treated rats. *Nutr Cancer* 2012, 64:838-846

Trucksess M, Weaver C, Oles C, D'Ovidio K, Rader J. Determination of aflatoxins and ochratoxin A in ginseng and other botanical roots by immunoaffinity column cleanup and liquid chromatography with fluorescence detection. *J AOAC Int* 2006, 89:624–630

Tzeng Y-M, Lee M-J. Neuroprotective properties of kavalactones. *Neural Regener Res*2015, 10:875-877

Uebelhack R, Franke L, Schewe H-J. Inhibition of platelet MAO-B by kava pyrone-enriched extract from Piper methysticum FORTSER (Kava-Kava). *Pharmacopsychiat* 1998, 31:187–192

Unger M, Holzgrabe U, Jacobsen, W, Cummins C, Benet LZ. Inhibition of cytochrome P450 3A4 by extracts and kavalactones of *Piper methysticum* (Kava-kava). *Planta Med* 2002, 68:1055–1058

Volz HP, Kieser M. Kava-kava extract WS 1490 versus placebo in anxiety disorders - a randomized placebo-controlled 25-week outpatient trial. *Pharmacopsychiatry* 1997, 30:1-5

Walden J, Von Wegerer J, Winterz U, Berger M, Grunze H. Effects of Kawain and dihydromethysticin on field potential changes in the hippocampus. *Prog Neuro-Psychopharmacol. & Biol Psychiat* 1997, 21:697-706

Wang J, Qu W, Bittenbender H C., Li QX. Kavalactone content and chemotype of kava beverages prepared from roots and rhizomes of Isa and Mahakea varieties and extraction efficiency of kavalactones using different solvents. *J Food Sci Technol* 2015, 52:1164-1169

Warnecke G. Psychosomatische Dysfunktionen im weiblichen Klimakterium. Klinische Wirksamkeit und Verträglichkeit von Kava-Extrakt WS 1490. *Fortschr Med* 1991, 109:119-122

Warnecke G, Pfaender H, Gerster G, Gracza E. Wirksamkeit von Kawa-Kawa-Extrakt beim klimakterischen Syndrom. Eine Doppelblindstudie mit einem neuen Monopräparat. *Z Phytother* 1990, 11:81-86

Weaver CM, Trucksess MW. Determination of aflatoxins in botanical roots by a modification of AOAC Official Method 991.31: single-laboratory validation. *J AOAC Int* 2010, 93(1):184–189

Witte S, Loew D Gaus W. Meta-Analysis of the Efficacy of the Acetonic Kava-Kava Extract WS®1490 in Patients with Non-Psychotic Anxiety Disorders *Phytother Res* 2005, 19:183–188

Whittaker P, Clarke JJ, San RH, Betz JM, Seifried HE, de Jager LS et al. Evaluation of commercial kava extracts and kavalactone standards for mutagenicity and toxicity using the mammalian cell gene mutation assay in L5178Y mouse lymphoma cells. *Food Chem Toxicol* 2008, 46:168–174

Williamson E.M. Potter's Herbal Cyclopaedia. Saffron Walden, Essex 2003, 101-102

Weiss J, Sauer A, Frank A, Unger M. Extracts and kavalactones of Piper methysticum G. Forst (kava-kava) inhibit P-glycoprotein in vitro. *Drug Metab Dispos* 2005, 33:1580-1583

Whitton PA, Lau A, Salisbury A, Whitehouse J, Evans CS. Kava lactones and the kava-kava controversy *Phytochem* 2003, 64:673-679

WHO Assessment of the risk of hepatotoxicity with kava products. World Health Organization Geneva, 2007

WHO monographs on selected medicinal plants. Vol. 2. Rhizoma Piperis Methystici. World Health Organisation. Geneva 2004, 231-245

Woelk H, Kapoula O, Lehrl S, Schröter K, Weinholz P. Behandlung von Angst-Patienten. Doppelblindstudie: Kava-Spezialextrakt WS 1490 versus Benzodiazepine. *Z Allg Med* 1993, 69:271-277

Wu D, Yu L, Nair MG, DeWitt DL, Ramsewak RS. Cyclooxygenase enzyme inhibitory compounds with antioxidant activities from Piper methysticum (kava kava) roots. *Phytomed* 2002, 9:41-47

Xuan TD, Elzaawely A A, Fukuta M, Tawata S. Herbicidal and Fungicidal Activities of Lactones in Kava (Piper methysticum). *J Agric Food Chem,* 2006, 54:720-725

Yamazaki Y, Hashida H, Arita A, Hamaguchi K, Shimur F. High dose of commercial products of kava (Piper methysticum) markedly enhanced hepatic cytochrome P450 1A1 mRNA expression with liver enlargement in rats *Food Chem Toxicol* 2008, 46:3732–3738

Zenger K, Agnolet S, Schneider B, Kraus B. Biotransformation of Flavokawains A, B, and C, Chalcones from Kava (Piper methysticum), by Human Liver Microsomes. *J Agric Food Chem* 2015, 63:6376-6385

Zhang L, Rowe A, Braet F, Ramzan I. Macrophage depletion ameliorates kavalactone damage in the isolated perfused rat liver. *J Toxicol Sci* 2012, 37:447–453

Zhao X, Chao Y L, Wan Q B, Chen X M, Su P, Sun J, Tang Y. Flavokawain B induces apoptosis of human oral adenoid cystic cancer ACC-2 cells via up-regulation of Bim and down-regulation of Bcl-2 expression. *Can J Physiol Pharmacol* 2011, 89:875-883

Zhou P, Gross S, Liu J-H, Yu B-Y, Feng L-L, Nolta J, Sharma V, Worms D, Qiu S.X. Flavokawain B, the hepatotoxic constituent from kava root, induces GSH sensitive oxidative stress through modulation of IKK/NF-kappaB and MAPK signaling pathways. *FASEB J* 2010, 24:4722–4732

Zou L, Harkey MR, Henderson GL. Effects of herbal components on cDNA-expressed cytochrome P450 enzyme catalytic activity. *Life Sci* 2002, 71:1579–1589

Zou L, Harkey MR, Henderson GL. Synthesis, in vitro, reactivity, and identification of 6-phenyl-3-hexen-2-one in human urine after kava-kava (*Piper methysticum*) ingestion. *Planta Med* 2005, 71:142–146

Zou L, Henderson GL, Harkey MR, Sakai Y, Li A. Effects of kava (kava-kava, 'awa, yaqona, Piper methysticum) on c-DNA-expressed cytochrome P450 enzymes and human cryopreserved hepatocytes, *Phytomedi* 2004, 11:285–294

References consulted but not included in the AR:

Anonymous 2002. Kava-Kava: Eine Lücke, die keiner wollte. Interview mit Prof. Volker Faust. *Natura Med,* 17, 14

Anonymous. Hepatic toxicity possibly associated with kava-containing products - United States, Germany, and Switzerland, 1992-2002. *MMWR Weekly* 2002, 51:1065-1067

Anonymous. Toxicological Evaluation of Kava drink, Lucknow, India, National Botanical Research Institute, 2008

Boerner RJ, Klement S. Attenuation of neuroleptic-induced extrapyramidal side effects by kava special extract WS 1490. *Wiener Med Wschr* 2004, 154:508-510

Brauer RB, Stangl M, Stewart JR, Pfab R, Becker K. Acute liver failure after administration of herbal tranquilizer kava-kava (Piper methysticum). *J Clin Psychiatry* 2003, 64:216-218

Clough AR, Currie BJ, Yunupingu MW, Conigrave KM. Action is required to reduce kava supply in Arnhem Land . . . again! *Med J Aust* 2006, 184:91-92

Dona G, Cuzzoni G, Pecorini M. Die Wirkung von Kavain bei älteren Patienten mit neurovegetativen und psychischen Symptomen. *Therapiewoche* 1986, 36:2836-2844

Ernst E. A re-evaluation of kava (*Piper methysticum*). *Br J Clin Pharmacol* 2007, 64:415-417

Fu PP, Xia Q, Guo L, Yu H, Chan PC. Toxicity of kava kava. *J Environ Sci Health C* 2008, 26:89-112

Gerber B. Erfahrungen mit Kavapyronen bei vegetativen und psychosomatischen Beschwerden sowie Einsatz beim Sport. *Erfahrungsheilkunde* 1988, 3:170-174

Gerber B. Neuronika - Eine echte Alternative zur herkömmlichen Tranquilizer-Therapie. *Naturheilpraxis* 1986, 39:89-94

Grunze H, Langosch J, Schirrmacher K, Bingmann D, Von Wegerer J, Walden J. Kava pyrones exert effects on neuronal transmission and transmembraneous cation currents similar to established mood stabilizers--a review. *Prog Neuropsychopharmacol Biol Psychiatry* 2001, 25:1555-1570

Hapke HJ, Sterner W, Heisler E, Bräuer H. Toxicological studies with Kavaform. *Farmaco* 1971, 26:692-720

Hashimoto T, Suganuma M, Fujiki H, Yamada M, Kohno T, Asakawa X. Isolation and synthesis of TNF-a release inhibitors from Fijian kawa (*Piper methysticum*). *Phytomed* 2003, 10:309-317

Hofmann R, Winter U. Anwendungsbeobachtung zur Wirksamkeit und Verträglichkeit eines Kava-Kava-Extrakt-Präpartes (Antares 120). *Abstract band 5. Phytotherapiekongress, 5.-6. November.* Bonn, 1993.:Gesellschaft für Phytotherapie

Hoover JM, Kaye AD, Ibrahim I N, Fields AM, Richards TA. Analysis of responses to kava kava in the feline pulmonary vascular bed. *J Med Food* 2006, 9:62-71

Jans W, Krall B. Kava special extract WS 1490 Laitan(R) in clinical research. Abstract Volume: 5th Congress on Phytotherapy, 5-6 November 1993. Bonn: Society for Phytotherapy

Kohlenberg FJ, Butterweck V, Verspohl EJ, Winterhoff H. Piper methysticum (Kava-Kava): Pharmacological investigations on the central activity. *Naunyn Schmiedebergs Arch Pharmacol* 1999, R93:359

Kraft K. Verwaltungsgericht Köln kippt das Kava-Verbot. *Z Phytother* 2014, 35:186-189

Krach H. Wirksamkeit und Verträglichkeit eines Phytotranquilizers. *Z Allg Med* 1986, 62:1028-1031

Kretschmer W. Kavain als Psychopharmakon. *Münch Med Wschr* 1970, 112: 154-158

Kretschmer W. Psychische Wirkungen von Kavain. *Münch Med Wschr* 1974, 116:741-742

Krypsin-Exner K. Wirkung von Kavain bei Alkoholkranken in der Entziehungsphase. *Münch Med Wschr* 1974, 116:1557-1560

Kuchta K, Schmidt M, Nahrstedt A. German Kava Ban Lifted by Court: The Alleged Hepatotoxicity of Kava (Piper methysticum) as a Case of Ill-Defined Herbal Drug Identity, Lacking Quality Control, and Misguided Regulatory Politics. *Planta Med* 2015, 81:1647-1653

Lebot V. What went wrong in the South Pacific? A few practical solutions *Kava 2015: International Conference on Kava. Speaker abstracts.* Honolulu, Hawai'i: Chaminade University, Honolulu, 2015

Martin HB, McCallum M, Stofer WD, Eichinger MR. Kavain attenuates vascular contractility through inhibition of calcium channels. *Planta Med* 2002, 68:784-789

Matsuda H, Hirata N, Kawaguchi Y, Naruto S, Takata T, Oyama M, Iinuma M, Kubo M. Melanogenesis stimulation in murine B16 melanoma cells by Kava (Piper methysticum) rhizome extract and kavalactones. *Biol Pharm Bull* 2006, 29:834-837

Mohamad AS, Akhtar MN, Zakaria ZA, Perimal EK, Khalid S, et al. Antinociceptive activity of a synthetic chalcone, flavokawin B on chemical and thermal models of nociception in mice. *Eur J Pharmacol* 2010, 647:103-109

Prokop L. Untersuchungen zum vegetativen Wirkungsmechanismus von Kavain und Magnesium-Orotat. *Wien Med Wschr* 1971, 121:399-402

Sarris J, Teschke R, Stough C, Scholey A, Schweitzer I. Re-introduction of kava (Piper methysticum) to the EU: is there a way forward? *Planta Med* 2011, 77:107-10

Schmidt N, Ferger B. Neuroprotective effects of (+/-)-kavain in the MPTP mouse model of Parkinson's disease. *Synapse* 2001, 40:47-54

Schmidt M. Draft Monograph: Rhizoma Kava Kava (Noble Kava). Piperis methystici rhizoma et radix. 2016. Submitted to BfArM

Schmidt M. Randomized, placebo-controlled double-blind trial: Efficacy of a kava ethanol extract in the treatment of elderly patients with anxiety. 2017 (*Unpublished Article* provided by Schmidt M during public consultation)

Schmidt M, Carreno I, Vergano P. Technical assistance to the integration to the multilateral trading system and support to the integrated framework. Ref: 9 ACP RPR 140-039/11: Establishment of health and safety standards for the production and export of kava-based products, Brussels, 2012, ACP-EU-TBT

Schmidt M, Gebhardt R. Impact of kava cultivar, plant part and extraction medium on in-vitro cytotoxicity of kava (*Piper methysticum*) in HepG2 and Hep3B cells. *Planta Med* 2006, 72:P346

Schmidt M, Carreno I, Vergano P. *African, Caribbean and Pacific Group of States. Scientific and legal assistance for the development of a quality and safety standard for Kava productiona and trade in the Pacific region, ACP-EU TBT Programme (REG/FED/022-667),* Brussels, 2015, ACP-EU-TBT

Schmidt M, Nahrstedt A. Ist Kava lebertoxisch? Eine Analyse der bekannten Daten zum Leberrisiko von Kava-Präparaten. *Dtsch Apoth Ztg* 2002, 142:1006-1011.

Schmidt M, Nahrstedt A, Lüpke NP. *Piper methysticum* (Kava) in der Diskussion: Betrachtungen zu Qualität, Wirksamkeit und Unbedenklichkeit. *Wien Med Wschr* 2002, 152: 382-388

Solomon S. Counting on the trendy to revive kava, a traditional drink. *New York Times* 2017.

Steiner GG, The Correlation between Cancer Incidence and Kava Consumption. *Hawaii Med J* 2000, 59:420-422

Sträter B. Kava-Kava-Revival? VG Köln: Risiko-Nutzenbewertung im Vergleich zu Benzodiazepinen positiv. *Pharm Ind* 2014, 76:1161-1162

Sträter B. Kava-Kava Revival: Zur Revision einer Risikoentscheidung. *Pharm Ind* 2015, 77:294-295

Stopper J. 2013. *RE: Kaviar 30*

Tsutsui R, Shinomiya K, Takeda Y, Obara Y, Kitamura Y, Kamei C. Hypnotic and sleep quality–enhancing properties of kavain in sleep-disturbed rats. *J Pharmacol Sci* 2009, 111:293–298

Unger L. Veränderung psychovegetativer Beschwerden unter Therapie mit Kavain. Erfahrungen mit Neuronika© in der Praxis. *Therapiewoche* 1988, 38:3171-3174

Volz HP. Kava-Kava und Kavain. Pflanzliches Anxiolytikum - Eine kritische Analyse der klinischen Studien. *Münchn Med Wschr* 1997, 139:42-46

Volz HP, Hänsel R. Kava-Kava und Kavain in der Psychopharmakotherapie. *Psychopharmakother* 1994, 1:33-39

Waller DP. Report on Kava and liver damage. Toxicological expertise for the American Herbal Producs Association, 2002. February 15

Warnecke G, Gerster G, Jäger H. Anxiolyse mit einem Phyto-Tranquilizer in der Frauenheilkunde. *Med Welt* 1986, 37:1379-1383

Warnecke G. Langzeittherapie psychischer und vegetativer Dysregulationen mit Zubereitungen aus Piper methysticum. *Erfahrungsheilkunde* 1989, 6:333-338

Wruck CJ, Gotz ME, Herdegen T, Varoga D, Brandenburg LO, Pufe T. Kavalactones protect neural cells against amyloid beta peptide-induced neurotoxicity via extracellular signal-regulated kinase 1/2-dependent nuclear factor erythroid 2-related factor 2 activation. *Mol. Pharmacol* 2008, 73: 1785-1795

Zi X, Simoneau AR. Flavokawain A, a novel chalcone from kava extract, induces apoptosis in bladder cancer cells by involvement of Bax protein-dependent and mitochondria-dependent apoptotic pathway and suppresses tumor growth in mice. *Cancer Res* 2005 65:3479-3486