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A Safety Review of Noni Fruit Juice

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ABSTRACT: ***Morinda citrifolia*** **L. (noni) fruit has been used in tropical regions as both food and folk medicine. The recent use of noni as a dietary supplement has increased greatly. To describe the safety of this fruit, a literature review and data from new studies are presented. Several preclinical safety tests and a human clinical safety study have revealed no adverse health effects, even at high doses. The available data substantiate its continued use as a safe food.**

Keywords: clinical study, dietary supplement, fruit juice, ***Morinda citrifolia*** **L. (noni), safety, toxicity**

Introduction

Morinda citrifolia L. (noni) is an evergreen or small tree that grows in many tropical regions of the world. Morton (1992) reports that the fruit of this tree has a history of use in the pharmacopoeias of Pacific Islanders and Southeast Asia. In the past decade, the global popularity of noni fruit juice has increased dramatically (Dixon and others 1999; McClatchey 2002). While there are several publications describing various potential health benefits of noni fruit (Wang and others 2002), journal publications regarding safety are limited.

A few case reports have been published in which a connection is attempted between an adverse event and noni fruit juice consumption (Mueller and others 2000; Carr and Bergeron 2004; Millonig and others 2005; Stadlbauer and others 2005). However, the sketchy details and limited number of cases reported are inadequate to draw any conclusion. On the other hand, the fruit has been subjected to an official safety evaluation within the European Union and found to be acceptable for human consumption (European Commission 2002).

This review article will compensate for the lack of information and context in the published literature, and will thus assist health professionals and scientists in assessing the wholesomeness of noni fruit juice.

Traditional Food Use

While noni fruit is most famous for its role in Polynesian, Melanesian, and Southeast Asian *materia medica*, there are also numerous ethnobotanical reports of its use as food (Rock 1913; Wilder 1934; Brown 1935; Yuncker 1943; Turbott 1949; Stone 1970; Degener 1973; Uhe 1974; Seemann 1977; Whistler 1992; Krauss 1993; Terra 1996). Some reports have indicated its use was limited to times of famine (Krauss 1993). This, however, is not correct. The fruit was reported to have been eaten often by Rarotongans (Cheeseman 1903), was a favorite ingredient in curries prepared by Burmese (Sturtevant 1919), and the Australian Aborigines were known to be very fond of the fruit (Maiden 1889). In 1769 Sydney Parkinson, one of Captain James Cook's crew on the *Endeavour*, recorded that Tahitians ate noni fruit (Parkinson 1773). This was likely the 1st written description of its use as a food. More than 2 centuries later, in 1943, the U.S. government recognized the fruit as edible (Merrill 1943). There has thus been ample human experience with eating noni fruit to validate its safety for human consumption.

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Safety Evaluations

Toxicity tests

Acute toxicity tests of noni fruit extracts have been performed in mice. The LD_{50} of the methanol extract of both the fruit and leaf was found to be greater than 1000 mg/kg when injected intraperitoneally in 4-wk-old male mice (Nakanishi and others 1965). Furthermore, administration of the extracts did not cause any noteworthy symptoms of toxicity, including convulsions, diarrhea, tail erection, or exophthalmos.

The LD_{50}cs of intraperitoneally injected aqueous and alcohol extracts of noni fruit were determined to be 7500 mg/kg and 3500 mg/kg body weight, respectively, in 3-wk-old female mice (Chearskul and others 2004). These values agree with and further define the acute intraperitoneal LD_{50} of crude noni fruit extracts.

Pureed noni fruit from Tahiti was administered by oral gavage at a dose of 15000 mg/kg to Sprague-Dawley rats. The animals were observed for 2 wk following administration. All animals survived and showed no signs of toxicity or behavioral changes. Conversely, all animals appeared healthy and gained weight. Gross necropsies of all animals at the end of 2 wk revealed no pathological effects. Consequently, the LD_{50} of noni fruit is greater than 15000 mg/kg (Product Safety Labs 2000). Compounds are considered nontoxic if the acute oral LD_{50} is greater than 5000 mg/kg, or if the acute intraperitoneal LD_{50} is greater than 2000 mg/kg. The LD_{50}cs of noni fruit and its crude extracts are all greater than the minimum criteria for nontoxic status.

A 28-d repeat dose oral toxicity test of the aqueous extract of noni fruit was conducted at a dose of 1000 mg/kg body weight (Mancebo and others 2002). There were no changes in clinical signs among the test animals. Also, no differences were noted between the test and control groups in weight gain, food consumption, hematological, or biochemical results; nor were any macroscopic or histopathological findings noted.

In another study, significant anxiolytic effects were noted in Wistar rats fed noni juice for 30 d. However, food consumption and weight gain were unaffected, nor was there any effect on clinical chemistry measurements, including SGPT, SGOT, alkaline

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phosphatase, blood urea nitrogen, creatinine, Na^+, K^+, and Cl (Kalandakanond and others 2004).

Several oral toxicity tests, with Sprague-Dawley rats, of a widely consumed commercial noni fruit juice, Tahitian Noni® Juice (TNJ; Provo, Utah, U.S.A.), have been completed (Wang and others 2002; West and others 2006). Acute and subchronic (13 wk) oral toxicity studies revealed no adverse effects from consuming doses equivalent to 80 mL/kg body weight/d. The parameters examined in these subchronic studies included histology, clinical chemistry, hematology, weight gain, and clinical observations. In addition, histological examinations were performed on the adrenals, aortic arch, brain, cecum, colon, duodenum, epididymides, eyes and optic nerves, femoral bone and marrow, heart, ileum, jejunum, kidneys, lacrimal gland, liver, lungs, caudal mammary gland, mandibular lymph node, mesenteric lymph node, esophagus, ovaries, pancreas, pituitary, prostate, rectum, submandibular salivary gland, sciatic nerve, seminal vesicles, skeletal muscle (right quadriceps femoris), skin, spinal cord (cervical, midthoracic and lumbar), spleen, sternum, stomach, trachea, testes, urinary bladder, thymus, uterus, and thyroids (including parathyroids).

The clinical chemistry examination in the subchronic studies included alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (GGT), glucose, cholesterol, triglycerides, carbamide, creatinine, total protein, protein electrophoresis (ALB, alpha 1 and 2, beta, and gamma), albumin/globulin ratio, sodium, potassium, calcium, magnesium, inorganic phosphorus, and chloride. Hematology parameters included hemoglobin, red blood cell count, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, white blood cell count, differential leucocyte count, platelet count, prothrombin time, and fibrinogen.

No pathological changes were observed at elevated doses in any of the 55 organs examined. There was no negative impact on blood cells, clotting factors, enzymes, electrolytes, or any of the measurements or observations made. The no observable adverse effect level (NOAEL) was subsequently determined to be > 80 mL/kg body weight.

Allergenicity tests

Assessing the risk for hypersensitivity to novel whole foods is difficult. The currently accepted standard methods for investigating the potential for Types I (immediate) and IV (delayed) hypersensitivity reactions are not designed for ingested and chemically complex substances, such as foods. There also seems to be no generally accepted standard methods for assessing Types II (cytotoxic) and III (immune complex) hypersensitivities. Furthermore, the effects of digestion are not accounted for in these models.

Current standard assays involve sensitization and challenge, either via the cutaneous and inhalation routes or by intravenous injection. Only very recently has there been some development using the brown Norway rat as a model for food allergy (Pilegaard and Madsen 2004).

With these issues in mind, 2 separate studies using guinea pigs were conducted to assess the allergenic potential of Tahitian Noni Juice. The 1st study involved 2 test groups of 6 animals each, a positive control group, and a negative control group (Kaaber 2000). The animals were induced via 4 subcutaneous injections, including the use of Freunds adjuvant, 1 wk apart then rested for 2 wk. The test and negative control groups were then challenged by oral gavage. The positive control group was challenged by intravenous injection. The test animals were observed for 24 h following each challenge. No allergic reactions to Tahitian Noni Juice were observed.

The 2nd study involved 45 guinea pigs in 6 groups. The study consisted of 3 test groups (1 group each for Tahitian Noni Juice, *M. citrifolia* fruit puree, and a concentrated *M. citrifolia* fruit juice), with accompanying naive control groups (Product Safety Labs 2000). The test groups were induced 3 times each wk for 2 wk via intraperitoneal injection. After 32 d of rest, all test animals were challenged orally and then observed for symptoms of an allergic response. No positive allergic reactions were noted in any of the animals following the challenge.

Previous research has demonstrated that the oral administration of allergens can cause an immunological response (sensitization). As stated in a joint FAO/WHO publication, "For oral sensitization studies to food proteins, guinea pigs have frequently been used and found to be very sensitive" (FAO/WHO 2001). Guinea pigs have been shown to exhibit an immunological response to cow's milk after ingestion (Devey and others 1976; Piacentini and others 1994). As such, the experimental conditions employed in the allergenicity studies of noni fruit juice were judged as sufficient to detect potential allergens.

The oral toxicity and allergenicity studies have been reviewed by the European Union's Scientific Committee on Foods. Their official opinion has led to the European Commission approval of *M. citrifolia* fruit juice as a safe food ingredient (European Commission 2002, 2003).

Genotoxicity tests

Relative to the study of the genotoxic potential of noni fruit is the analysis of its anthraquinone content. Anthraquinones occur in plants of the Rubiaceae family, such as *M. citrifolia*. However, these occur nearly exclusively in the roots (Thompson 1987). Additional analysis for the presence of anthraquinones in noni fruit was performed with particular attention given to the possible occurrence of lucidin and rubiadin, because of the noted genotoxicity of these 2 anthraquinones. Both compounds were undetectable in the juice at a detection limit of 10 ppb (European Commission 2002).

The common battery of tests used to evaluate the gentoxicity of a substance includes the bacterial reverse mutation test in *Salmonella typhimurium* (S. *typhimurium*) or Ames test (FDA 1997). However, this test has some severe limitations to its usefulness in evaluating plant foods, particularly fruits. Flavonoids are ubiquitous in fruits and thus have a long history of safe human consumption. But these compounds exhibit mutagenic activity in *S. typhimurium* (MacGregor and Jurd 1978). Despite their mutagencity in *S. typhimurium*, flavonoids are antimutagenic in mammalian systems (Ong and Khoo 1997; Okamoto 2005). This disparity of effect makes the Ames test of little usefulness in the evaluation of fruits, and a mammalian cell-line based assay must be used as a substitute.

To overcome the limitations of the Ames test, an *in vitro* primary gene mutation test of noni juice was performed in the Chinese hamster V79-cell line. The hypoxanthine phosphoribosyl transferase (HPRT) gene endpoint was examined in the presence and absence of S9 mix. The ethyl acetate extract of the juice (100-fold concentration) through a dose range of 0.003 to 3 μL/mL caused no gene mutations at the HPRT locus, indicating the absence of mutagenic activity in noni juice (Westendorf 2002a).

An unscheduled DNA synthesis (UDS) assay was performed *in vivo* and *in vitro* to determine the potential for noni juice to cause DNA damage such as the formation of DNA adducts. The detection of tritium labeled thymidine via autoradiography and silver grain counting in cell nuclei indicates repair of DNA damage. Tahitian Noni Juice was examined in 4 groups of 3 animals each (2 test groups and a positive and a negative control group). The net silver

grain count for Tahitian Noni Juice was similar to that of the negative control (saline) and substantially less than the positive controls (N, N-dimethylnitrosamine and 2-acetylaminoflourene). Therefore, no evidence of genotoxic action was observed in this test (Westendorf 2002b).

The clastogenic activity of noni juice was first evaluated in the mouse micronucleus test. A dose of 10 g of dehydrated noni juice/kg body weight was administered via gavage. The bone marrow of the animals was then examined microscopically and scored for the frequency of micronucleated polychromatic erythrocytes. The results showed no increase in micronuclei related to ingestion of noni juice, no clastogenic activity, nor any evidence of systemic toxicity (Edwards 2002).

A chromosomal aberration test was also performed with human lymphocytes following OECD guidelines (Edwards 2003). No significant increases were noted in the frequency of chromosome aberrations in 100 metaphases for each concentration of 625, 1250, 2500, and 5000 μg/mL (dry weight), both in the presence and absence of S-9 mix. These results corroborate those of the mouse micronucleus test.

The general complement of tests required to demonstrate the absence of genotoxic activity includes evaluation of gene mutations *in vitro*, DNA damage *in vitro*, and genetic damage *in vivo* (FDA 1997). Noni juice has been subjected to each of these requirements, with similar nontoxic results in each assay. A low risk for genetic toxicity to humans is clearly established.

Clinical safety studies

Noni fruit juice has been evaluated in clinical studies, 2 of which specifically addressed safety. The 1st was a single center, double-blind, 3-dose level, parallel group, placebo-controlled safety study of Tahitian Noni Juice in healthy subjects (Davies and Mugglestone 2003). Ninety-six subjects, 28 males and 68 females, ages 18 to 64 y, were randomly assigned to 4 groups. These groups included a placebo group and 3 test groups, each receiving a dose of 750 mL placebo or Tahitian Noni Juice per day. For 28 d, the test subjects consumed up to 750 mL of either the placebo or juice containing 1 of 3 doses of Tahitian Noni Juice. Two wk following the in-use phase (follow-up), subjects were again evaluated. Parameters investigated included hematological, biochemical, and urological measurements made at wk 0, 2, 4, and 6.

Hematological measurements included hemoglobin, hematocrit, mean cell volume, red cell count, prothrombin time, activated partial thrombinplastin time, total and differential white cell count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelet count. Biochemistry analysis included alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, lipids (LDL, HDL, cholesterol, triglycerides), creatine kinase, creatinine, gamma-glutamyl transferase, glucose, total protein, and uric acid. Urinalysis involved semiquantitative analysis for leucocytes, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose. Where necessary, a urine cytobacteriological examination was performed to characterize or count crystals, casts, epithelial cells, white blood cells, red blood cells, and bacteria. Measured vital signs included systolic and diastolic blood pressure, and heart rate. ECG measurements (12 leads) were also made for each subject at the prestudy screen and at wk 6. Any adverse events were recorded. Weight, vital signs, urinalaysis, and selected pathology results for wk 4 (the end of the in-use phase) and wk 6 (the 2 wk follow-up) are presented in Table 1 and 2. Values at these 2 time points are the best indicators for toxic effects that may have developed during the study, as well as recovery compared with possible residual effects. No clinically significant differences were noted in the parameters and measurements of this study between any of the groups. These data indicate that drinking up to 750 mL Tahitian Noni Juice per day is safe.

The 2nd clinical safety study was an NIH funded phase-I clinical study of noni fruit extract conducted at the Univ. of Hawaii. The major objective was the determination of toxicities and maximum tolerated dose. Twenty-nine patients were divided into 5 groups of at least 5 persons per group. Each subject received daily, for 28 d, orally administered capsules containing 500 mg ripe noni fruit extract. The initial dose group ingested 4 capsules (2000 mg). When no adverse effects were observed, the dose for the next group was increased by 2000 mg and so on, with the final group consuming 10 g daily. Ingestion of the noni capsules was well tolerated at all doses and did not result in any adverse events (Issell and others 2005). The maximum dose of the phase-I clinical study corresponds to approximately 200 mL (almost 1 cup) of noni fruit juice. As with the Tahitian Noni Juice study, there is an adequate margin of safety between the high dose and typical intake by consumers. The most commonly recommended serving size is 1 to 2 fluid ounces.

Noni juice and especially its ethanol insoluble precipitate (noni-ppt) have demonstrated some potential as immunomodulators, with activity against Lewis lung carcinoma (LLC) (Hirazumi and Furusawa 1999). Immunomodulating effects are also reported for some other safe foods and their components, such as kefir (Vinderola and others 2005); wakame, a seaweed widely consumed in Japan (Furusawa and Furusawa 1989); beta-glucan, a major component of oats and some edible fungi (Kobayashi and others 2005); and even chocolate (Sanbongi and others 1997). The activity of noni juice against LLC was not due to cytotoxicity, but may be partially due to dietary antioxidant compounds, as reported for other foods (Sazuka and others 1995; Chen and others 2005). Similar activity has also been reported for several other fruit juices, including cranberry and apple (Sun and others 2002). As these examples demonstrate, potential immunomodulation and antitumor effects do not necessarily equate to potential health risks.

The differential white blood cell (leukocyte) counts reveal much about the potential for any adverse effects from the possible immunomodulating properties of noni juice. Should indiscriminant stimulation of cytokine production occur, there would be changes in

Table 1—Weight and vital signs at wk 4 and 6 (follow-up) in clinical study

Measurement	Week	Placebo	30 mL TNJ	300 mL TNJ	750 mL TNJ
Weight (kg)	4	70.23	67.78	69.20	70.61
	6	70.22	67.67	69.11	69.57
Heart rate (bpm)	4	64.71	66.75	66.79	63.87
	6	67.88	64.58	65.88	63.67
Systolic blood pressure (mm Hg)	4	118.00	118.54	122.04	119.83
	6	119.21	121.50	119.13	117.04
Diastolic blood pressure (mm Hg)	4	69.33	69.92	70.79	71.09
	6	68.96	68.83	70.75	72.63

leukocyte populations, especially eosinophils (eosinophilia), since the cytokines induced *in vitro* by noni-ppt are pro-inflammatory, with the exception of interleukin-10 which is anti-inflammatory and actually regulates the others (Lucey and others 1996; Cundell and others 2003; Leng and others 2005). However, no such proliferation occurred, and there were no differences between the control groups and any dose group in the clinical safety study as well as in subchronic animal studies. Furthermore, no evidence of inflammatory conditions is revealed in any of the other study measurements. It seems apparent, therefore, that potential immunomodulating effects are kept under control through feedback mechanisms.

Case reports

A few case reports have discussed possible links between potential adverse events and noni juice. The reported effects are disparate and a role of direct toxicity is not established in any instance. Two case reports relate to nutritional content only and, as such, are of interest to those with special dietary restrictions. However, such restrictions apply to many foods and are not considered to be toxic actions.

The 1st case reported hyperkalemia in a patient consuming noni juice purchased from a health food store (Mueller and others 2000). The authors acquired a bottle of a noni juice through an Internet purchase and sent it to an outside laboratory for sodium and potassium analysis. There was no indication that the juice consumed by the patient was from the same manufacturer or included the same ingredients.

The label of the brand of noni juice analyzed listed grape juice, natural flowers, and Flower of Benjamin (an archaic term for benzoic acid) as additional ingredients. The laboratory test revealed a mean ± SD potassium content of 56.3 ± 2.5 meq/L. This is within the range observed for orange, tomato, and grapefruit juices. The authors pointed out that other fruit juices with similar potassium quantities should be restricted in the diets of patients with end-stage renal disease.

Commercial noni juices may include a wide variety of ingredients such as other fruit juices, botanicals, and organic acid salts used as preserving agents. Therefore, the mineral content may vary widely. It is, therefore, imperative that any health care professional ascertain the mineral content of the specific brand of noni juice before rendering an opinion on suitability for patients.

A case of acquired coumadin resistance was reported in a 41-y-old woman (Carr and others 2004). A decreased International Normalization Ratio (INR) had been unaffected by a steadily increased coumadin dose. It was later discovered that the patient had been drinking a specific brand of noni juice, which appeared to be fortified with vitamin K. The patient ceased drinking the juice and the INR increased, implicating the juice.

Table 2—Mean clinical pathology at wk 4 and 6 (follow-up) in clinical study

Measurement	Week	Placebo	30 mL TNJ	300 mL TNJ	750 mL TNJ
Hematocrit (%)	4	40.44	40.11	40.51	40.45
	6	40.05	39.83	40.25	40.25
Hemoglobin (g/dL)	4	13.43	13.40	13.53	13.38
	6	13.35	13.32	13.40	13.32
Mean cell volume (femtoliter)	4	91.99	90.50	90.82	89.73
	6	91.76	90.55	90.94	90.04
Platelets ($10^3/\mu$L)	4	259.13	242.88	243.38	239.91
	6	251.08	232.04	251.04	236.92
Red cell count ($10^6/\mu$L)	4	4.40	4.45	4.46	4.52
	6	4.37	4.42	4.43	4.48
White cell count ($10^3/\mu$L)	4	5.66	5.56	5.63	5.21
	6	5.53	5.56	5.37	4.94
Basophils ($10^3/\mu$L)	4	0.035	0.027	0.026	0.026
	6	0.030	0.030	0.026	0.026
Eosinophils ($10^3/\mu$L)	4	0.19	0.17	0.20	0.14
	6	0.16	0.17	0.23	0.15
Lymphocytes ($10^3/\mu$L)	4	1.79	1.69	1.73	1.73
	6	1.71	1.64	1.66	1.71
Monocytes ($10^3/\mu$L)	4	0.49	0.49	0.51	0.46
	6	0.50	0.51	0.51	0.45
Neutrophils ($10^3/\mu$L)	4	3.15	3.19	3.16	2.85
	6	3.14	3.20	2.95	2.61
Cholesterol (mmol/L)	4	5.04	4.99	4.68	4.97
	6	4.91	4.90	4.61	4.99
Creatine kinase (U/L)	4	102.06	109.84	105.28	102.70
	6	97.25	121.97	100.41	93.90
Creatinine (μmol/L)	4	73.43	73.47	75.52	74.12
	6	70.91	74.86	74.39	73.51
Glucose (mmol/L)	4	4.75	4.58	4.60	4.62
	6	4.76	4.64	4.71	4.68
HDL cholesterol (mmol/L)	4	1.70	1.70	1.59	1.68
	6	1.73	1.73	1.62	1.76
LDL cholesterol (mmol/L)	4	3.02	2.94	2.75	2.99
	6	2.97	2.95	2.75	3.04
Triglycerides (mmol/L)	4	0.81	1.03	1.00	0.89
	6	1.08	0.96	1.06	0.89
Uric acid (μmol/L)	4	265.90	284.91	265.89	298.11
	6	286.98	298.26	271.89	300.67
Activated partial thromboplastin time (s)	4	30.35	30.50	30.39	30.22
	6	30.40	30.81	31.24	30.58
Prothrombin time (s)	4	11.54	11.58	11.65	11.61
	6	11.83	11.76	11.81	11.75

The vitamin K content of noni fruit from Tahiti is negligibles or below limits of detection (Palu and others 2005). Therefore, the incident of coumadin resistance was not related to noni fruit itself, but to an added ingredient. As there are differences in ingredient compositions, coumadin resistance is not anticipated with every commercial noni juice product.

Four cases of hepatotoxicity, allegedly associated with drinking noni juice, have been reported in Austria and an adjoining area of southern Germany (Millonig and others 2005; Stadlbauer and others 2005; Yüce and others 2006). The 1st case involved a 45-y-old man with highly elevated alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma glutamyl transferase (GGT), and lactate dehydrogenase (LDH). He had been drinking 1 glass of noni juice per day for several weeks. Liver damage was confirmed by biopsy. Following cessation of noni juice, this man's transaminase levels were normalized in 1 mo. Anthraquinones were suggested as the possible cause of the dysfunction.

Two other cases were reported concurrently. These involved a 29-y-old man and a 62-y-old woman who had consumed noni juice at a rate of 71 and 16 mL/d, respectively. Both the man and the woman had elevated bilirubin, ALAT, ASAT, GGT, and alkaline phosphatase (ALKPH). Liver biopsies of both patients confirmed acute hepatitis and were attributed to idiosyncratic reactions. The man ultimately required a liver transplant, and the woman's laboratory values normalized 11 mo after cessation of the juice. As both patients had ingested noni juice, the investigators concluded that the liver dysfunction was due to herbal toxicity of noni juice. As in the previous report, anthraquinones were implicated as the causative agents.

The most recent case report describes a 24-y-old female with multiple sclerosis (MS). This woman was being treated with interferon-beta (IFNβ) when she developed elevated transaminase and bilirubin levels. She was removed from IFNβ, but transaminase and bilirubin measurements continued to increase throughout the following week, resulting in severe icterus. When questioned about dietary changes, she revealed that she had been drinking noni juice. She was counseled to immediately stop, which she did. Within the following month, her liver function tests normalized. Consequently, the authors of the case report suggest a causative role of noni juice.

There are limitations to all the case reports of hepatotoxicity. Liver toxicity from IFNβ is well known. One postmarketing survey revealed that as many as 67% of MS patients treated with this drug had elevated liver enzymes (Francis and others 2003). Furthermore, an analysis of all postmarketing surveys revealed that 1.4% of these patients experienced grade 3 or worse liver toxicity (Tremlett and others 2004). Liver toxicity from these IFNβ drugs has been known to continue and peak for up to 3 wk after cessation (Byrnes and others 2006). With such a striking history of known liver toxicity, it is unreasonable to point to noni juice as the source of liver damage in this patient.

In the Stadlbauer report, the authors admit problems with linking case 1 to noni juice consumption due to preexisting liver damage and the use of 7 g/d of a blend of Chinese herbs. Hepatotoxicity from this herbal blend has been reported previously (Kamiyama and others 1997; Matsuda and others 1997), with one of the ingredients, *Pinellia ternata*, banned in the United States due to health concerns (U.S. HHS 2004). There were approximately 2 mo between the latest ingestion of noni juice and the appearance of symptoms in case 2 of the Stadlbauer report. It is typical that symptoms begin to improve shortly following cessation of exposure. For example, significant improvement of liver function was seen in a patient within 1 wk after she stopped ingesting high doses of sennoside anthraquinones (Beuers and others 1991).

The subject of the 1st published case report did not initially admit any dietary changes. Only upon further questioning did he mention that he consumed noni juice. This raises suspicions that other contributing factors may not have been revealed or underreported during the interviewing process (Arber and others 2004; Klatsky and others 2006).

Early investigations failed to identify anthraquinones in noni fruits (Zenk and others 1975). Only recently with advances in analytical technology have any anthraquinones been successfully identified in noni fruit (Kamiya and others 2005; Pawlus and others 2005). However, the quantities (< 1 ppm) and chemical structures of these newly isolated anthraquinones cannot be reduced to anthrone radicals capable of causing tissue damage and are of no toxicological relevance (Westendorf 1993; West and others 2006).

The hepatotoxic effects of pyrlizidine alkaloids are an important food safety issue and need to be considered in any case of herbal hepatotoxicity (Pauwels and Mostefa-Kara 1993), but there is no previous evidence for the occurrence of alkaloids in *M. citrifolia* fruit (Nakanishi and others 1965; Paris and Jacquemin 1975; Barr and others 1988). Upon learning of 3 cases of liver dysfunction, the Austrian Agency for Health and Nutrition Safety (AGES) conducted its own investigation of Tahitian Noni Juice. Among other things, they tested the juice for the presence of anthraquinones, patulin, and pyrrolizidine alkaloids. These hepatotoxic substances could not be detected. The agency concluded in its report that noni fruit juice had no toxic effects on the liver (AGES 2005).

The suggested link between ingestion of noni juice and liver toxicity has been refuted on the basis that it is not consistent with histopathology and clinical chemistry results of subchronic oral toxicity tests in animals as well as observed laboratory values of clinical safety studies, and that no causal relationship can be proven, as explained by the investigator of the 1st case. Conversely, liver protective effects from noni juice have been demonstrated (Jensen and others 2006). Moreover, these case reports possibly reveal a regional bias in associating hepatotoxicity and noni juice ingestion.

No histological changes were attributed to ingesting noni juice quantities many times higher than consumed by the patients in these case reports. There was no significant or clinical difference in liver function tests between the placebo group and all treatment groups in the clinical safety study of TNJ (Table 3) as well as in the 2 subchronic (13 wk) oral toxicity studies in rats (Table 4).

In the most extreme case, there were significant confounding factors which investigators could not rule out, including concomitant use of several other herbal products, acetaminophen, and preexisting liver damage. According to the authors' admission, these can only be idiosyncratic reactions, if any causal relationship truly does exist. Idiosyncratic reactions are, by definition, rare occurrences and are not expected to be observed in significant numbers of the population. Even so, the circumstances of these cases do not support the existence of any causal relationship to noni juice (EFSA-X).

Conclusions

Since Parkinson's description of noni fruit as a food in 1769, others have observed this practice in other cultures. The increasing popularity of the juice today has necessitated this review. Data from clinical studies, toxicity tests, and chemical test have substantiated the use of this juice as a safe food. More detailed examination of the few recently reported cases of adverse health effects reveals that these were likely due to factors other than noni fruit. This review has drawn together, for the 1st time, documented food usages and formal safety studies. It appears from this review that noni juice is as safe as other common fruit juices.

Table 3—Laboratory values at wk 4 and 6 (follow-up) of clinical study

	Placebo		30 mL TNJ		300 mL TNJ		750 mL TNJ		
Measurement	Wk **4**	Wk **6**	Wk **4**	Wk **6**	Wk **4**	Wk **6**	Wk **4**	Wk **6**	**Normal Range**[a]
Alkaline phosphatase (U/L)	64	63	59	62	55	58	53	55	38 – 126
Alanine aminotransferase (U/L)	19	19	20	17	18	18	23	21	7 – 56
Aspartate aminotransferase (U/L)	19	18	20	19	19	19	21	20	5 – 35
γ-Glutamyl transferase (U/L)	22	21	27	24	21	20	21	21	8 – 78
Total bilirubin (mg/dL)	0.7	0.9	0.7	0.7	0.7	0.7	0.8	0.8	0.3 – 1.2
Total protein (g/dL)	6.9	6.9	7.0	6.9	7.0	6.9	7.1	7.0	6.3 – 8.2

[a]Kumar and Hagler (1999)

Table 4—Laboratory values in 13 wk studies of TNJ in SD rats

	Mean ALAT (μkat/L)		Mean ASAT (μkat/L)		Mean ALKPH (μkat/L)		Mean BILI (μmol/L)		Mean GGT (μkat/L)	
Dose	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
1st study										
Control	2.01	2	1.73	1.83	2.24	3.51	1.01	1.23	0.01	0
20 mL/kg	2.14	1.95	1.99	1.79	2.44	3.09	1.17	0.93	0.01	0
50 mL/kg	1.91	1.55	1.82	1.53	2.14	3.17	1.24	1.27	0.01	0
80 mL/kg	1.25	1.67	1.22	1.77	1.98	3.27	1.62	1.03	0.01	0
2nd study										
Control	2.01	2	1.73	1.83	2.24	3.51	1.01	1.23	0.01	0
20 mL/kg	2.14	1.95	1.99	1.79	2.44	3.09	1.17	0.93	0.01	0
50 mL/kg	1.91	1.55	1.82	1.53	2.14	3.17	1.24	1.27	0.01	0
80 mL/kg	1.25	1.67	1.22	1.77	1.98	3.27	1.62	1.03	0.01	0

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