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LETTERS TO THE EDITOR

Noni juice is not hepatotoxic

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Abstract

Noni juice (*Morinda citrifolia*) has been approved for use as a safe food within the European Union, following a review of safety. Since approval, three cases of acute hepatitis in Austrian noni juice consumers have been published, where a causal link is suggested between the liver dysfunction and ingestion of anthraquinones from the plant. Measurements of liver function in a human clinical safety study of TAHITIAN NONI® Juice, as well as subacute and subchronic animal toxicity tests revealed no evidence of adverse liver effects at doses many times higher than those reported in the case studies. Additionally, *M. citrifolia* anthraquinones occur in the fruit in quantities too small to be of any toxicological significance. Further, these do not have chemical structures capable of being reduced to reactive anthrone radicals, which were implicated in previous cases of herbal hepototoxicity. The available data reveals no evidence of liver toxicity.

Key words: Noni juice; *Morinda citrifolia*; Novel food; Human clinical safety study

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TO THE EDITOR

Morinda citrifolia (noni) fruit juice was approved as a novel food ingredient in pasteurized fruit drinks by the European Commission Decision of 05-06-2003. This approval was based on the opinion of the EU Scientific Committee on Food (SCF) of Tahitian Noni® Juice, following a safety review of this product[1].

During 2004, an Austrian case report was published in which it is suggested that noni fruit juice may be responsible for acute hepatitis[2]. A second report was published in the August 2005 issue of this journal in which noni juice was again suggested to be the cause of two other cases of acute hepatitis in Austria[3]. In both publications, the authors suggest the presence of anthraquinones in the juice may be responsible for the liver dysfunction observed in their patients. However, experimental data fails to reveal any direct liver toxicity from noni juice.

TAHITIAN NONI® Juice, the brand associated with the latest case reports, was investigated in a human clinical study (unpublished data. Mugglestone C *et al*. A single centre, double-blind, three dose level, parallel group, placebo controlled safety study with TAHITIAN NONI® Juice in healthy subjects, BIBRA International Ltd. UK, 2003). Ninety-six subjects were randomly assigned to four groups. These groups included a placebo group and three test groups, receiving up to a dose of 750 mL TAHITIAN NONI Juice per day. For 28 d, subjects drank 750 mL of either the placebo or juice containing one of three doses of TAHITIAN NONI Juice.

Several parameters were investigated with measurements being made at study screening, d 0 (baseline), wk 2, wk 4, and wk 6. The measurements most applicable to the evaluation of liver function and hepatocellular disease were alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (BIL), gamma-glutamyl transferase (GGT), total protein, and prothrombin time (which is useful for determining the extent of hepatocellular disease).

Other study measurements included hemoglobin, hematocrit, mean cell volume, red cell count, activated partial thrombin time, total and differential white cell count, platelet count, lipids (LDL, HDL, cholesterol, triglycerides), creatine kinase, creatinine, gamma-glutamyl transferase, glucose, total protein, and uric acid. Additionally, urinalysis involved semi-quantitative ("dipstick") analysis for leucocytes, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin and glucose. Where necessary, a urine cyto-bacteriological examination was performed to characterize or count crystals, casts, epithelial cells, white blood cells, red blood cells and bacteria. Vital signs were measured, including systolic and diastolic blood pressure and heart rate. ECG measurements (12 lead) were also made for each subject. All adverse events were recorded. Selected mean laboratory values for the various groups are presented in Table 1.

Differences between mean values were clinically insignificant and well within the range of normal values. Furthermore, there was no evidence of any dose-related adverse events. The study results indicate that TAHITIAN

Table 1 Mean clinical laboratory values by week and dose groups

Parameter	Value	Placebo	30 mLTNJ	30 mL TNJ	750 mLTNJ
ALP (U/L)	Mean wk 0	61.67	58.65	54.00	54.44
	Mean wk 2	55.80	57.83	51.16	54.47
	Mean wk 4	63.56	59.48	54.99	53.07
	Mean wk 6	62.69	61.50	58.22	55.04
ALT (U/L)	Mean wk 0	17.80	18.00	17.88	21.98
	Mean wk 2	18.53	19.53	17.80	24.11
	Mean wk 4	18.99	20.10	17.75	22.71
	Mean wk 6	19.21	16.90	17.63	20.92
AST (U/L)	Mean wk 0	18.30	18.55	18.27	20.71
	Mean wk 2	18.04	19.67	19.18	22.32
	Mean wk 4	18.93	19.55	19.19	20.90
	Mean wk 6	18.42	18.95	18.64	19.87
Total bilirubin	Mean wk 0	12.12	10.55	10.93	11.30
(μmol/L)	Mean wk 2	13.19	11.31	11.47	14.20
	Mean wk 4	12.23	11.63	12.07	14.03
	Mean wk 6	14.77	11.99	11.44	13.98
GGT (U/L)	Mean wk 0	20.31	24.74	22.51	21.36
	Mean wk 2	21.19	26.74	23.03	20.99
	Mean wk 4	21.87	26.54	21.14	21.21
	Mean wk 6	21.11	24.22	20.00	21.07

Table 2 Serum values in female Sprague Dawley rats in 1st 13-wk study (Mean ± SD)

Females					
Dose	ALT (μkat/L)	AST (μkat/L)	ALP (μkat/L)	BIL (μmol/L)	GGT (μkat/L)
Control	2.1 ± 0.5	2.26 ± 0.46	2.07 ± 0.27	1.21 ± 0.61	0.02 ± 0.01
0.4 mL/kg	1.89 ± 0.62	2.15 ± 0.81	2.22 ± 0.29	1.43 ± 0.52	0.01 ± 0.01
4 mL/kg	1.98 ± 0.34	1.99 ± 0.39	2.08 ± 0.41	1.36 ± 0.54	0.01 ± 0
8 mL/kg	1.94 ± 0.33	1.74 ± 0.18	2.3 ± 0.45	1.22 ± 0.63	0.01 ± 0

Table 3 Serum values in male Sprague Dawley rats in 1st 13-wk study (Mean ± SD)

Males					
Dose	ALT (μkat/L)	AST (μkat/L)	ALP (μkat/L)	BIL (μmol/L)	GGT (μkat/L)
Control	2.47 ± 0.42	2.11 ± 0.58	2.97 ± 0.33	1.59 ± 0.32	0.01 ± 0.01
04 mL/kg	2.27 ± 0.52	1.8 ± 0.56	2.82 ± 0.39	1.5 ± 0.41	0 ± 0
4 mL/kg	2.35 ± 0.44	1.86 ± 0.32	2.77 ± 0.36	1.5 ± 0.36	0 ± 0
8 mL/kg	2.4 ± 0.61	2.06 ± 0.76	3.18 ± 0.44	1.6 ± 0.49	0.01 ± 0

Table 4 Serum values in female Sprague Dawley rats in 2nd 13-wk study (Mean ± SD)

Females					
Dose	ALT (μkat/L)	AST (μkat/L)	ALP (μkat/L)	BIL (μmol/L)	GGT (μkat/L)
Control	2.01 ± 0.3	1.73 ± 0.43	2.24 ± 0.36	1.01 ± 0.77	0.01 ± 0.01
20 mL/kg	2.14 ± 0.52	1.99 ± 0.71	2.44 ± 0.47	1.17 ± 0.72	0.01 ± 0.01
50 mL/kg	1.91 ± 0.53	1.82 ± 0.43	2.14 ± 0.43	1.24 ± 0.58	0.01 ± 0.01
80 mL/kg	1.25 ± 0.25	1.22 ± 0.12	1.98 ± 0.22	1.62 ± 0.77	0.01 ± 0.01

Table 5 Serum values in male Sprague Dawley rats in 2nd 13-wk study (Mean ± SD)

Males					
Dose	ALT (μkat/L)	AST (μkat/L)	ALP (μkat/L)	BIL (μmol/L)	GGT (μkat/L)
Control	2 ± 0.26	1.83 ± 0.21	3.51 ± 0.42	1.23 ± 0.25	0 ± 0
20 mL/kg	1.95 ± 0.3	1.79 ± 0.31	3.09 ± 0.47	0.93 ± 0.56	0 ± 0
50 mL/kg	1.55 ± 0.2	1.53 ± 0.28	3.17 ± 0.38	1.27 ± 0.45	0 ± 0
80 mL/kg	1.67 ± 0.4	1.77 ± 0.47	3.27 ± 0.29	1.03 ± 0.45	0 ± 0

NONI® Juice is safe to consume, in quantities up to 750 mL/d, confirming the EU SCF opinion that high consumption quantities are appropriate.

The aqueous extract of *M. citrifolia* fruit was evaluated in a repeat dose oral toxicity assay in rats[4]. For 28 d, Sprague Dawley rats received 1000 mg/kg body weight. Animals were observed for clinical symptoms, body weight was recorded, and hematology and serum chemistry parameters were measured.

Among the serum chemistry measurements were AST, ALT, and GGT. There were no significant differences between the males and females of the test and control groups, with the exception of a lower AST value observed in the females of the treatment group, and an exceptionally low ALT value for the males of the control group that resulted in a statistical difference for treated males. In either instance, however, the values observed in the treatment groups were within the normal range for these animals and did not correspond to a dose-response relationship. These results did not reveal any adverse liver effects.

Two 13-wk oral toxicity studies of TAHITIAN NONI® Juice in rats were performed (unpublished data, Glerup P. TAHITIAN NONI® Juice-A 13-wk oral (gavage) toxicity study in rats. Scantox Biologisk Laboratorium, Lille Skensved, Denmark, Lab no. 35 207, March 2000; and Glerup P. TAHITIAN NONI® Juice-A 13-wk oral (gavage) toxicity study in rats. Scantox Biologisk Laboratorium, Lille Skensved, Denmark, Lab no. 39 978, May 2001). In each study, 80 Sprague Dawley rats (40 males and 40 females) were included. Six consecutively higher doses were examined in each study, with a high dose equivalent to 80 mL TAHITIAN NONI® Juice/kg per day (20 mL/kg of 4-fold concentrated juice).

Study measurements indicative of liver effects were ALT, AST, ALP, GGT, total bilirubin, total protein, protein by electrophoresis, globulins, albumin/globulin ratio, and prothrombin time. Additionally, clinical observations included liver weights, and macroscopic and microscopic (histological) examination of the livers. Laboratory data for liver function for each dose group in each study are mentioned in Tables 2, 3, 4, and 5.

No treatment-related changes were observed in any of the dose groups for any of these measurements, including histological examinations, demonstrating a lack of toxicity to the liver. Consequently, the No Observable Adverse Effect Level (NOAEL) was determined to be greater than 80 mL TAHITIAN NONI Juice/kg per day.

The NOAEL is much higher than the amounts ingested

by the patients described in the case studies. In the most recent publication, the first patient consumed a daily dose of 71.4 mL (1.5 L consumed over 3 wk). The second case reported in this publication describes a daily consumption rate of 23.8 mL (2 L consumed over 3 mo). The weight of each patient is not given, but assuming an average weight of 70 kg, the doses consumed would be 1.02 mL/kg per day and 0.34 mL/kg per day. The NOAEL of the animal studies is almost 80 times greater than these two doses. The high dose in the clinical study was approximately 10 times higher.

The first published case report claims that the patient drank a glass of noni juice every day for a few weeks. No exact quantity is specified; no indication is given as to how large the glass was or how much of it was filled. However, assuming a full cup volume of 250 mL and a patient weight of 70 kg, the dose would be 3.6 mL/kg. The NOAEL of the animal studies is 22 times greater than the ingestion rate of this patient, and the clinical study high dose is three times more. Not only are all reported doses in these cases well within the highest doses of the controlled studies, where no liver effects were observed, but were also sufficiently low to assume a large margin of safety. If there is any true causal link, it is likely to be only idiosyncratic in nature.

As a pretext for implicating noni juice in liver toxicity, the authors of both reports cite publications containing only limited information, including similar case reports for the herbal laxative drugs Senna (*Cassia augustifolia*)[5] and Cascara sagrada (*Rhamnus purshianus*)[6]. The laxative effects of these herbal preparations are due to large quantities of a specific class of anthraquinones[7] (different than those in the noni plant).

In these cases, the patients had ingested large quantities of the herbs for an extensive time. Consequently, the investigators propose a potential involvement of anthraquinones. A similar assumption is made in the few case reports of other herbs cited by the authors of these two publications[8-10]. In these instances, however, the role of the anthraquinones directly isolated from these herbs, and linked to the patients' liver dysfunction was not supported by any additional experimental evidence. In fact, support for these assumptions is based on limited information from experimental studies of sennosides[11] and luteoskyrin[12], which do not occur in the noni plant.

The suggestion of an anthraquinone involvement in the three Austrian cases is not based on solid data. The first argument against such a causal link is a quantitative one. Until very recently, investigators had been unable to identify or isolate anthraquinones from noni fruit[13]. However, two recent publications have reported the presence of anthraquinones in noni fruit, at very low concentrations. The first report describes 48.3 mg of isolated material, distributed amongst six anthraquinones, from 1.3 kg of dried noni fruit from Indonesia[14]. On a dry weight basis, the total concentration is 37×10^{-6}. In the juice form, the concentration would be approximately 3×10^{-6}. The second publication describes isolating a few micrograms of anthraquinones from 9 kg of dried fruit[15]. The anthraquinone concentration in this study was less than 1×10^{-6}. Such low yields and concentrations are responsible for the inability of earlier researchers to identify anthraquinones in the fruit.

In comparison to Senna and Cascara sagrada, the total anthraquinone content of noni fruit is insignificant. The European Pharmacopoeia describes Senna leaf as containing no less than 2.5% (25×10^{-3}) anthraquinones; the standardized extract is to contain no less than 5.5%. Cascara sagrada is described as having a minimum anthraquinone content of 8% (80×10^{-3}). These concentrations are many thousands of times higher than that in noni juice. Where a large quantity of Senna and Cascara is required to induce liver toxicity, it is unreasonable to assume a barely detectable quantity of anthraquinones in noni juice can have the same effect.

Beyond the minute quantity of anthraquinones in noni fruit juice is a second issue of chemical structure. Anthraquinones do not have the same universal biological effects. Differences in bioactivities, toxic or otherwise, are seen amongst variants of other types of compounds as well. Thus, it is not reasonable to assume that one category of anthraquinones will have the same exact toxic action as another. The anthraquinones present in the laxative herbs, linked to the previous cases of hepatotoxicity, are 1, 8-di hydroxyanthraquinones (1, 8-DHA's). On the other hand, those that occur in *M. citrifolia* are substituted 9, 10-anthraq uinones[16,17]. These structural differences result in different modes of action. The 9, 10-anthraquinones can not be reduced in biological systems to form anthrone radicals, while 1, 8-DHA's can[18]. It is the formation of anthrone radicals that is required to produce tissue damage[19].

In summary, human and animal studies of high doses of TAHITIAN NONI® Juice reveal no adverse liver effects. Further, anthraquinones in noni fruit are of insufficient quantities and fail to possess the necessary chemical structures to cause liver tissue damage. The available data demonstrates that noni juice is not directly toxic to the liver

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