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REVIEW

Anticancer Activity of *Morinda citrifolia* (Noni) Fruit: A Review

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This review investigated the relationship of noni juice, or its extract (fruit, leaves or root), to anticancer and/or immunostimulant properties. A Medline search was conducted using the key search words '*Morinda citrifolia*' and '*Morinda citrifolia* and cancer' (1964 to October, 2011) along with cross-referencing. Botanical and chemical indexes were not included. A total of 304 and 29 (10%) articles, respectively, were found under these key terms. Of the 19 studies actually related to cancer, seven publications were *in vitro* cancer studies, nine were *in vivo* animal cancer studies, and three were *in vivo* human cancer studies. Among the *in vitro* studies, a 'concentrated component' in noni juice and not pure noni juice may (1) stimulate the immune system to 'possibly' assist the body fight the cancer, and (2) kill a small percentage (0–36%) of cancer cells depending on the type. The nine animal studies suggest that a concentrated component in noni juice may stimulate the immune system; but only slightly increases the number (about 1/3; 25–45%) of surviving mice. Other than two case studies, only two human clinical studies existed. The first consisted of testing freeze-dried noni fruit, which reduced pain perception, but did not reverse advanced cancer. The second was on smokers ingesting an unknown concentration of noni juice who experienced decreased aromatic DNA adducts, and decreased levels of plasma superoxide anion radicals and lipid hydroperoxide.

Factors to consider in the future are clearly defining the substance being tested, and whether or not the juice is pasteurized. Some reports of hepatotoxicity exist, although there were confounding factors in most of the case reports. More importantly, noni juice is high in potassium and needs to be monitored by patients with kidney, liver or heart problems. In conclusion, a few *in vitro* and *in vivo* animal studies suggest a possible unidentified substance in unpasteurized noni fruit juice that may have a small degree of anticancer activity. The isolation of the active component warrants further research. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Noni (*Morinda citrifolia*).

INTRODUCTION

Noni juice, obtained from the Pacific Basin *Morinda citrifolia* tree's fruit, is promoted in the popular press as a complementary treatment for a variety of medical conditions, including cancer (Anonymous, 2011a, 2011b; Solomon, 2003). The purpose of this review was to conduct a literature search using Medline to decipher any research related to the claim that noni juice, or its extract, has anticancer and/or immunostimulant properties. These Medline articles were used to create an evidenced-based response for clinicians responding to patients asking questions about noni juice's effectiveness against cancer. What follows is a brief description of the plant, types of noni juice, a history of medicinal uses, a review of the literature (*in vitro* studies, *in vivo* animal studies, *in vivo* human studies, case studies, safety), and a suggested evidence-based response for clients.

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DESCRIPTION OF NONI DIETARY SUPPLEMENT

Morinda citrifolia L. is a small evergreen tree believed to have originated in Southeast Asia that spread across the tropics to Australia, the Pacific Basin and the Caribbean (Kinghorn *et al.*, 2011). The tree belongs to the family Rubiaceae and its genus consists of 80 species that grow primarily in coastal tropical regions up to 1300 feet above sea level (Nelson and Elevitch, 2006). The plant is very hardy and can even grow out of hardened lava cracks.

The lumpy-surfaced fruit is produced year round and looks like a 'grenade'. Initially, the unripe fruit is green, turns yellow as it ripens, and softens into translucent sheen as it becomes overly ripe. The odor and taste of the translucent fruit is not pleasant, and the Hawaiians do not routinely eat the fruit. As a result of growing in different geographical locations, it has various names that include, but are not limited to, noni in Hawaii, nono in Tahiti, Indian Mulberry in India, Ba ji tian in China and cheesefruit in Australia (Wang and Su, 2001).

Types of noni juice products

Noni juice can be created through either homemade or commercial methods. The homemade method provides

100% noni juice and was speculated to have been introduced by Chinese immigrants to Hawaii. Based on personal observations, fully ripened fruits are placed into a glass (or earthen) jar, and then it is tightly sealed so the contents naturally decompose over 3 weeks (approximately 1 month, but possibly up to 3 months), where it is kept at room temperature or in the refrigerator until it is decanted or strained through a filter (cheesecloth).

Commercially, noni juice is manufactured in large vats and then sold as juice (pasteurization usually required). The concentration can also be 100%, but varies as some manufacturers incorporate other juices which simultaneously reduces the cost and/or covers unpalatable flavors (Nelson and Elevitch, 2006). Noni juice can also be used to create freeze-dried pills, concentrated extracts, powders, tinctures, and even fruit leather similar to dried fruit strips.

BRIEF BACKGROUND OF NONI MEDICINAL USES IN HAWAII

Based on existing Bishop Museum records, Handy, Pukui and Livermore (1934) stated that, 'The juice of the ripe fruit boiled is used as a remedy for diabetes, and fermented, as a tonic for heart trouble and high blood pressure'. Another use was reported by McClatchey (2002) who indicated that the leaf was held briefly over fire to release the contents within the membranes before being used as a poultice over wounds. It appears that unripe green fruit was used primarily for external remedies, specifically for mouth sores, gingivitis, toothache and abscesses. Interviews with Hawaiian healers do not support the use of ripe fruit for any medical condition. In fact, Etkin and McMillen reported that the Hawaiians used few internal medicines, other than cathartics and emetics, prior to mid-19th century (Etkin and McMillen, 2003).

More recent uses of noni for medical conditions appear to have followed the research and publications of a Dole scientist, Ralph M. Heinicke (McClatchey, 2002; Heinicke, 1985, 2001; Wang *et al.*, 2002). He received a patent in which he claimed xeronine could be used for 'complete cures of hard core drug addicts with no withdrawal symptoms' (Heinicke, 1985). Although it is not evidenced-based, he also suggested that noni could be used for 'arthritis, atherosclerosis, blood vessel problems, drug addiction, gastric ulcers, high blood pressure, injuries, menstrual cramps, mental depression, poor digestion, relief of pain, senility, sprains, and many others' (Heinicke, 1985).

Heinicke proposed that the active substance in noni was similar to the unknown ingredient in bromelain (pineapple enzyme) that he called 'xeronine'. He suggested that the precursor was proxeronine that was only active if taken on an empty stomach. This was the origin of the popular method in the lay literature to consume noni on an empty stomach in order for it to be 'effective'. However, no chemical structure was ever provided. Since that time, various chemical constituents in noni juice have been reported by a number of researchers, and the process of deciphering the bioactive components in noni fruit continues (Akihisa *et al.*, 2010, 2007; Bui *et al.*, 2006; Chan-Blanco *et al.*, 2006; Cimanga *et al.*, 2003; Chunhieng *et al.*, 2005; Deng *et al.*, 2011; Dussosoy *et al.*, 2011; Hemwimol *et al.*, 2006; Kamiya *et al.*, 2005;

Kinghorn *et al.*, 2011; Lv *et al.*, 2011; Nandhasri *et al.*, 2005; Pawlus *et al.*, 2005; Pawlus and Kinghorn, 2007; Samoylenko *et al.*, 2006; Sang *et al.*, 2003; Shotipruk *et al.*, 2004; Siddiqui *et al.*, 2006; Stalman *et al.*, 2003; Su *et al.*, 2005; Vickers, 2002; Wang *et al.*, 2011, 2002, 2000, 1999; Westendorf *et al.*, 2007).

REVIEW OF THE LITERATURE

To determine if any anticancer activity related to noni was reported in the scientific literature, a Medline search was conducted using the key search words '*Morinda citrifolia*' and '*Morinda citrifolia* and cancer' (1964 to October 2011) along with cross-referencing. Botanical and chemical indexes possibly containing noni articles were not included. A total of 304 and 29 (10%) articles, respectively, were found under these key terms. Among the 304 Medline articles (1964 to March 2011) citing medical conditions associated with *Morinda citrifolia* not related to cancer, were those related to hypertension (Dang-Van-Ho, 1954, 1955; Gilani *et al.*, 2010; La Barre *et al.*, 1961); tuberculosis (Anonymous, 2001; Saludes *et al.*, 2002); antiinflammatory and/or antioxidant (Akihisa *et al.*, 2007; Basar *et al.*, 2010; Basu and Hazra, 2006; Berg and Furusawa, 2007; Calzuola *et al.*, 2006; Dussosoy *et al.*, 2011; McKoy *et al.*, 2002; Okusada *et al.*, 2011; Serafini *et al.*, 2011; Song *et al.*, 2010; Wang *et al.*, 2009a, 2009b); osteoporosis and auditory improvement (Bao *et al.*, 2011; Langford *et al.*, 2004; Li *et al.*, 2008a, 2008b); wound healing (Mathivanan *et al.*, 2006; Nayak *et al.*, 2007, 2009; Palu *et al.*, 2010; Su *et al.*, 2005); AIDS (Kamata *et al.*, 2006); diabetes (Nayak *et al.*, 2007, 2011; Nerurkar *et al.*, 2011; Horsfall *et al.*, 2008; Kamiya *et al.*, 2008; Owen *et al.*, 2008); cataracts related to diabetes (Gacche and Dhole, 2011), sickle cell disease (Mpiana *et al.*, 2007); antifungal (Jainkittivong *et al.*, 2009); gout (Palu *et al.*, 2009); immunostimulant (Alitheen *et al.*, 2010; Nayak and Mengi, 2010; Zhang *et al.*, 2009); hypercholesterolemia (Mandukhail *et al.*, 2010); neuronal protective effect (Harada *et al.*, 2010); postoperative nausea and vomiting (Prapaitrakool and Itharat, 2010) and gastric ulcer and reflux esophagitis (Mahattanadul *et al.*, 2010).

Of the 19 studies related to cancer seven publications were specifically related to *in vitro* cancer studies, nine to *in vivo* animal cancer studies (some data overlapped with *in vitro* studies), and three to *in vivo* human cancer studies. It is important to note that noni juice not only varied in concentration, but was also tested in various forms (extract, powder or precipitate). These limited number of studies are now briefly detailed to summarize the science of noni's relationship, if any, to *in vitro* or *in vivo* anticancer activity.

IN VITRO STUDIES (7 STUDIES)

The anticancer effect of noni extract, and/or a polysaccharide found in the ethanol-precipitate, has been tested against various cancer cell lines *in vitro* in seven studies (Table 1). Hirazumi first reported noni fruit juice contains a polysaccharide with antitumor activity that enhances the release of cytokine (IFN-gamma) from thymocytes (Hirazumi and Furusawa, 1999). This

Table 1. *In vitro* research related to noni precipitate, juice extract and leaves

Author, year	Study design	Treatment	Measurable outcomes
Hirazumi and Furusawa, 1999	Lewis lung peritoneal cells (LLC)	Noni ppt from juice of ripe 3-day noni fruits Crude juice flash evaporated to concentrate juice. 95% ethanol to soluble and ppt fraction. PPT collected by centrifugation and dried	Lewis lung peritoneal cells (LLC) (noni at 6.25 mg/mL) 22% Increased cytokine production from cells
Liu <i>et al.</i> , 2001	Mouse epidermal cells (JB6)	Two glycosides extracted from noni juice: (1) 6- <i>o</i> -(beta-D-glucopyranosyl)-1- <i>o</i> -octanoyl-beta-D-glucopyranose (2) Asperulosidic acid	Both compounds suppressed induced growth in mouse epidermal cells (JB6)
Hornick <i>et al.</i> , 2003	Human breast tumor explants	Commercial noni juice centrifuged and filtered Noni 5% (vol/vol)	Inhibits the proliferation of angiogenic initiation. Capillary vessels from cancer cells rapidly degenerated (2–3 days) in media supplemented with 10% noni % cytotoxic (antiproliferative) of cancer cell lines (noni at 0.1 mg/mL (1.5 mg/mL): Hamster kidney cells (BHK) 6% African green monkey kidney (Vero) 0% Laryngeal carcinoma (Hep2) 13% Breast cancer (MCF7) 29% (50%) Neuroblastoma (LAN5) 36% (50%)
Arpornsuwan and Punjanon, 2006	Hamster kidney cells (BHK) African green monkey kidney (Vero) Laryngeal carcinoma (Hep2) Breast cancer (MCF7) Neuroblastoma (LAN5)	50 g of dried fruit powder dissolved in 500 mL methanol for 2 days 40 mg dried filtered material dissolved in 1 mL of DMSO Crude extract at 0.1, 1 mg/mL, 1.5 mg/mL	
Zhang <i>et al.</i> , 2009	Dendritic cells (immune cells)	Dendritic cells were treated with fermented noni exudate (from fruit grown in Kawaihae on Hawaii's South Kohala coast) Fresh leaf extract (using dichloromethane)	Stimulated proliferation of splenocytes Stimulated B cells to produce IgG and IgM Did not directly stimulate B cell proliferation Inhibitory effect against KB and HeLa cells with IC ₅₀ values of 21.67 and 68.50 µg/mL, respectively Other extracts reduced antiproliferative effects on all cancer lines (IC ₅₀ 103 to 600 + µg/mL)
Thani <i>et al.</i> , 2010	Human epidermoid carcinoma (KB) Human cervical carcinoma (HeLa) Human breast carcinoma (MCF-7) Human hepatocellular carcinoma (HepG2) African green monkey kidney (Vero)		
Nuansanit <i>et al.</i> , 2011	Human colorectal cancer cell lines (HCT-116, SW480, and LoVo)	Damnacanthal, an anthraquinone compound, isolated from the roots	Inhibited cell proliferation and induced caspase activity in human colorectal cells

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water-soluble, ethanol precipitate was a polysaccharide-rich substance described as 'a gum Arabic heteropolysaccharide, composed of the sugars glucuronic acid, galactose, arabines and rhamnose, by phenol-sulphuric acid staining and TLC'. No antitumor activity was detected in the ethanol-soluble fraction. They reported that *M. citrifolia* fruit juice in the Lewis lung peritoneal carcinomatosis model enhancing the immune system through the release of tumor necrosis factor-alpha (TNF), interleukin-1beta, interleukin-10, interleukin-12, interferon-gamma, nitric oxide (Hirazumi and Furusawa, 1999).

Soon after, Liu *et al.* (2001) studied two unidentified glycosides (NB10 and NB11 extracted from the *n*-butyl alcohol soluble fraction of noni fruit extract) in the mouse epidermal JB6 cell line and reported suppressed TPA-(12-O-tetradecanoylphorbol-13-acetate) and EGF-(epidermal growth factor) induced cell transformation and associated AP-1 activities.

It is interesting to note that Takashima *et al.* (2007) reported that new compounds from the leaves (not fruit) of *Morinda citrifolia* did not show cytotoxic activity alone, but in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). This parallels Liu and associates earlier work where they reported that 'tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) can induce apoptosis in certain tumor cells. In addition, TRAIL and chemotherapy can act cooperatively, possibly as a result of chemotherapy-induced increases in expression of a TRAIL receptor, DR5 (Liu *et al.*, 2001)'.

Another study linking noni juice indirectly to anticancer activity was conducted by Hornick *et al.* (2003) who reported that a 5% vol/vol or greater noni juice inhibits the initiation of new vessel sprouts from placental vein explants. In human breast tumor explants, a 10% noni growth medium resulted in apoptosis in wells with vessels rapidly degenerated within 2–3 days. As a result, Hornick postulated that the effect of noni juice was not mediated by the immune system as they did not observe leukocytes in the culture (Hornick *et al.*, 2003).

In 2006, Arpornsuwan and Punjanon (2006) tested a crude extract of noni (0.1 mg/mL) fruit against various cancer cell lines. The percent cytotoxicity ranged from 0 to 36% and as with many potential anticancer substances, the degree of effectiveness depends on the type of cancer. In this particular case, neuroblastoma (36%) and breast cancer (29%) cell lines were more effectively inhibited by the noni extract than hamster (6%) or green monkey (0%) kidney cells, with a slight affect on human laryngeal cells (13%). However, kidney cancer is a difficult cancer to treat overall, and observing any inhibition of cancer cell proliferation suggests that some substance, and or a combination, in noni extract is having an anticancer effect.

Wong published two case studies involving cancer patients consuming homemade, unpasteurized, fermented noni juice (Wong, 2004). Interested in the mechanism, he collaborated with Zhang *et al.* (2009) to study the effect of fermented noni exudate (juice) on dendritic cells. They reported stimulated proliferation of splenocytes, stimulated B cells to produce IgG and IgM, but did not directly stimulate B cell proliferation. In a personal communication (2007), Wong mentioned that not all varieties of noni produce sufficient juice, but one that did grew in Kawaihae on Hawaii's South Kohala Coast.

Unlike the research with noni fruit precipitate and extracts reported above, Thani *et al.* (2010) investigated the anticancer activity of fresh noni leaf extracts. They reported an inhibitory effect against human epidermoid carcinoma (KB) and human cervical carcinoma (HeLa) cells. Another research group, Nualsanit *et al.* (2011) isolated damnacanthal, an anthraquinone compound, from the roots of *Morinda citrifolia* L. and reported that it increased apoptosis in human colorectal cancer cell lines (HCT-116, SW480 and LoVo). They suggested that damnacanthal activates the retinoic acid receptor (ERK) pathway and enhanced expression of transcription factor CCAAT/enhancer binding protein beta (C/EBPbeta), in addition to being previously known as being a potent inhibitor of p56^{lck} tyrosine kinase activity.

Summary of *in vitro* studies

Most of the preliminary studies conducted by Hirazumi and Furusawa utilized a polysaccharide ethanol-precipitate and not pure noni juice. They suggested this substance stimulated the immune system through macrophages reported to release cytokines, nitric oxide (NO), interleukin-1 and interleukin 12 (IL-1, IL-12) and tumor necrosis factor (TNF). Other immune related factors increased were natural killer (NK) cells and cytotoxic T cells. Researchers from two separate studies found antiproliferative compounds in the leaves and roots of *Morinda citrifolia* L. Unrelated to the immune system was a study by Hornick *et al.* (2003) showing that noni juice (5% vol/vol) inhibited initiation of new vessel sprouts, but other ingredients of greater concentration may have been responsible. Only a few antiproliferation studies have been reported and these report some moderate, but not complete, inhibition on selected cancer cell lines.

IN VIVO STUDIES – ANIMAL (9 STUDIES)

While conducting *in vitro* studies with noni and cancer, Hirazumi and Furusawa also tested noni juice in animals inoculated with cancer. As a result, many of their *in vitro* studies published in Medline overlap with concurrent *in vivo* animal studies (Table 2). In 1994, Hirazumi and associates reported that 4 out of 13 mice treated with the ethanol extract of noni juice survived resulting in an increased life span of 119% (Hirazumi *et al.*, 1994). In 1996, she reported that all 5/5 untreated mice developed ascites, while none (0 out of 5) of the noni-precipitate treated mice experienced ascites (Hirazumi *et al.*, 1996).

A study conducted by Wang and Su (2001) and funded by a noni juice company, provided rats with Tahitian noni[®] juice (concentration not reported). Three rats from each group were given 25 mg/kg DMBA intragastrically and killed 24 h later. The Tahitian noni[®] juice group was reported to experience reduced DMBA-DBA adduct formation in organs which is an initiation step to chemical carcinogenesis. Survival rates of rats were not reported.

Furusawa *et al.* (2003) further reported that the noni-precipitate showed synergistic or additive beneficial effects with some chemotherapy drugs, specifically, adriamycin, bleomycin, camptothecin, cisplatin, etoposide, 5-fluorouracil, imexon, interferon, mitomycin-C and vincristine. It was not beneficial when combined with

Table 2. In vivo animal research related to noni fruit precipitate, extract or juice

Author, year	Subjects – type and number	Treatment	Measurable outcomes
Hirazumi <i>et al.</i> , 1994	Not provided	Mice inoculated IP with Lewis lung peritoneal carcinoma (LLC) (1) Control (2) Original noni juice of 6–15 mg sold per 0.2 mL volume	Control – 15 days mean survival time Noni – about 35 days mean survival time 9/22 mice survived 50 + days (41%)
Hirazumi <i>et al.</i> , 1996	Control – 5 mice Treatment – 5 mice	Sarcoma 180 ascites tumor Noni ppt (500 µg/mouse administered QOD for five days. Body weight to detect ascites measured for 2 weeks Control: Lewis lung peritoneal carcinoma (LLC) 3 Treatment Groups	Control – Ascites in 5/5 mice Noni ppt - Suppressed ascites in 5/5 mice
Hirazumi and Furusawa, 1999	55–58 mice Inconsistent number of mice per treatment group	1) Noni crude juice inoculations (3, 6, 12, 15, 20 mg/mouse) 2) Noni ppt fractions (insoluble) 3) Noni soluble	Antitumor activity effects from 6–15 mg crude noni juice per mouse. Prolonged lifespan by more than 75% Group mg/mouse # survivors Control 0/55 0% 1) Crude Juice 3 1/10 10% 6 4/18 ^b 22% 12 4/17 ^b 24% 15 9/22 ^a 41% 20 2/11 18% 2) Noni ppt 0.8 15/39 ^a 38% 1.6 5/22 ^b 23% 5.2 0/12 0% 3) Noni soluble 5.2 0/12 0% 10.4 0/19 0% ^a <i>p</i> < 0.001; ^b <i>p</i> < 0.01
Wang and Su, 2001 (corporate funding)	Rats (# not provided)	Cancer (DMBA – 7,12-dimethylbenz(a)anthracene) was given intragastrically on day 8. Three rats from each group killed after 24 h Control: Water for 1 week Treatment group: 10% Tahitian noni [®] juice (TNJ) replaced drinking water for 1 week 8 small experiments with Ascites tumor cells (S180) Control: Treatment: (0.5 mg in 0.1 mL water; 4.0 – 6.5 mg per mouse) 1) Noni ppt from ripe fruit juice (Hawaii) 2) Noni ppt from Tahitian noni [®] juice (TNJ)	DMBA adducts measured in various organs. TNJ reduced DMBA adducts 30% (60% in heart, 41% (50% in lung, 42% (70% in liver, and 80% (90% in kidneys of female (and male) rats, respectively
Furusawa <i>et al.</i> , 2003	Mice		Noni-ppt produced a survival rate of 25–45% Interferon worked better than noni by increasing survival rate even more (71–100%) Cure rate abolished with macrophage inhibitors (2-chloroadenosine), T cells (cyclosporine, or natural killer (NK) cell (anti-asialo GM1 antibody)

(Continues)

Table 2. (Continued)

Author, year	Subjects – type and number	Treatment	Measurable outcomes
Palu <i>et al.</i> , 2008	Control-5 mice Treatment-5 mice	Control: Water for 16 days Treatment groups: Tahitian noni [®] juice (TNJ) (1% or 1 mg/mL of commercial product; -unknown noni concentration) for 16 days Noni fruit juice concentrates (NFJC) (5% or 5 mg/mL from noni fruit puree)	Decreased IL-4, but increased interferon gamma in mice study Splenocyte and peritoneal exudate cells treated with TNJ or NFJC resulted in activation of CB ₂ (cannabinoid) receptors, while inhibiting CB ₁ receptors
Li <i>et al.</i> , 2008	CD marker profile study Prevention study 4 nude mice/group 4 beige mice/group Treatment study 4 nude mice/group 4 beige mice/group Fractionation study 4 nude mice/group 4 beige mice/group	Mice were intraperitoneally injected with fermented noni exudate (500 µL fNE/mouse/day) (from fruit grown in Kawaihae on Hawaii's South Kohala coast) injected with carcinogen after fNE injection (prevention study) or before fNE injection (treatment study): S180 tumor cells/Lewis lung carcinoma(LL/2) cells	CD marker profile study Increased peripheral blood granulocytes and natural killer (NK) cells Increased peritoneal total leukocyte counts Prevention study > 85% of nude mice were tumor free 1.5 month after tumor inoculation vs 100% death of control mice. Beige mice have no functional NK cells and all died within 20 days Treatment study Prolonged survival of the nude mice, but they eventually all died Fractionation study
Taskin <i>et al.</i> , 2009	31 Mice (Balb-c) 8 mice/treatment group 7 mice/control	Four groups of mice induced with Ehrlich ascites tumor Oral noni (Alnoni [®] Hanoju Europe Ltd, Dinxperlo, The Netherlands) Doxorubicin (potent anticancer agent) Oral noni + doxorubicin Control (Oral 0.9% NaCl)	The supernatant contains the antitumor substance Tumor diameters about 40–50% smaller than those in control group Due to induction of apoptosis Noni may be useful in the treatment of breast cancer Percent noni in Alnoni [®] not specified, so conclusion suspect
Stoner <i>et al.</i> , 2010	10 groups of 15 rats each	Rat esophagus induced with carcinogen N-nitrosomethylbenzylamine (NMBA) for 5 weeks, then placed on diets containing 5% of either black or red raspberries, strawberries, blueberries, noni, açai or wolfberry	All seven berry types were equally capable of inhibiting tumor progression in the rat esophagus Tumor incidence: 60–75% in berry groups 60% in noni group 95% in carcinogen 0% in control group

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paclitaxel, cytosine arabinoside, or immunosuppressive anticancer drugs such as cyclophosphamide, methotrexate or 6-thioguanine. In terms of immunomodulators, noni-precipitate had a stronger effect when combined with imexon, but not with MVE-2 (maleic anhydride divinylether) copolymer. Mice subjected to sarcoma tumor cells (S180) and given the noni-precipitate had a cure rate of 25% to 45%. This cure rate was abolished with macrophage inhibitors (2-chloroadenosine), T cells (cyclosporine, or natural killer (NK) cells (anti-asialo GM1 antibody). Interferon increased the survival rate by 71% to 100%.

In another study, Tahitian noni[®] juice (1% or 1 mg/mL, concentration of noni juice in commercial product not specified) was provided orally and *ad libitum* to mice (five in treatment group and five in water control) for 16 days resulting in decreased IL-4, but increased production of interferon gamma (Palu *et al.*, 2008). They also conducted an *in vitro* test with the animal splenocytes and peritoneal exudate cells. Both Tahitian noni[®] juice and noni fruit juice concentrates (NFJC, 5% or 5 mg/mL from noni fruit puree) were found to modulate the immune system by activating CB₂ (cannabinoid) receptors, while suppressing CB₁ receptors.

In most of the above noni studies, the noni precipitate was injected into the animals rather than being administered orally. Intraperitoneal injection was also utilized by Li and associates in a 2008 study investigating the possible antitumor effect of noni exudate in a sarcoma 180 ascites mouse model (Li *et al.*, 2008a, 2008b). This publication reported on several mini-experiments, however, the figures made the results difficult to decipher. In summary, they conducted a CD marker profile study, a preventative study, a treatment study, and finally a fractionation and tumor study to determine the active components. They used four nude/group and four beige mice/group in the prevention and treatment studies.

CD marker profile study: Increased peripheral blood granulocytes and natural killer (NK) cells occurred, along with increased peritoneal total leukocyte counts.

Prevention study: Mice were injected with carcinogen (S180 tumor cells, or Lewis lung carcinoma) following intraperitoneally injected fermented noni exudate (500 µL fNE/mouse/day). Greater than 85% of nude mice were tumor free 1.5 months after tumor inoculation, versus 100% of the control mice dying. The beige mice all died within 20 days because they have no functional NK cells.

Treatment study: The carcinogen was injected followed by administration of fNE. Although the nude mice experienced prolonged survival, they eventually all died.

Fractionation study: This study revealed that it is the supernatant containing the antitumor activity substance.

Another antitumor study with mice was conducted a year later in 2009 (Taşkin *et al.*, 2009). Three groups of eight mice each induced with Ehrlich ascites tumor were provided with (1) oral noni, a commercial product from the Netherlands (Alnoni[®] Hanoju Europe Ltd, percent noni juice unclear), (2) doxorubicin, a potent anticarcinogen, and (3) oral noni and doxorubicin. The control of seven mice consumed oral 0.9% NaCl. The tumor diameters in all treated groups were approximately 40–50% smaller than those in control group. When noni

was combined with the anticancer drug, doxorubicin, the effect was greater than either noni or doxorubicin alone. Although noni juice concentrations were not reported, they suggested that oral noni juice may be useful in the treatment of breast cancer either on its own or in combination with doxorubicin.

In 2010, Stoner and associates conducted a study determining the ability of different freeze-dried berry types to prevent chemically induced tumorigenesis in the rat esophagus. This is a model for human esophageal squamous cell carcinoma as the berry material comes in direct contact with the esophagus. The berries tested were the four commonly consumed berries in the USA – strawberry, blueberry, red raspberry and black raspberry – and three other berry types – noni, goji and açai. All seven berry types were equally capable of inhibiting tumor progression in the rat esophagus. Tumor incidence was 60–75% in berry groups, specifically 60% in the noni group, versus 95% in the carcinogen group, and 0% in the control group.

Summary of *in vivo* animal studies

Only nine studies utilizing animals have been conducted testing noni extract. The results suggest a bioactive in noni juice extract (not leaves, roots or other plant parts) may be effective against cancer up to approximately 30% of the time in laboratory rodents. However, the noni precipitate or extract was injected rather than orally consumed by these animals with the exception of the Stoner study. It should also be noted that noni juice extract was provided early in the cancer process. As with other cancers, early treatment is imperative, especially if the substance's effectiveness works through immune enhancement.

IN VIVO STUDIES – HUMAN (3 STUDIES)

Only two case studies and an NIH clinical trial report the use of noni as a complementary treatment for cancer in humans (Table 3).

Case studies

Wong reported two case studies of gastric cancer patients being treated with noni juice (Wong, 2004). Case 1 was a 69 year old male informed by four doctors that he would die within a few months without surgery. The patient refused surgery and became bedridden within 2 months as his weight dropped from 165 to 79 pounds. He started taking homemade noni juice and his condition improved within a month and after 6 months he ceased the self-treatment. Seven years later he did not have any gastric symptoms, however, a biopsy showed a histology similar to his original cancer so he self-treated himself again with noni juice and the outcome was not reported.

Case 2 was of a 64 year old man with gastric cancer that underwent a gastrectomy. The cancer had spread to 17 of 28 examined lymph nodes, and he was given 5 years to live. The patient consumed homemade noni juice and lived 16 more years until he died at age 80 of malnutrition due gastric cancer (Wong, 2004).

Table 3. *In vivo* human research related to noni

Author, year	Subjects – type and number	Study design	Treatment	Dosage/Duration	Measurable outcomes
Wong, 2004 Issell <i>et al.</i> , 2005 (Abstract only)	2 case studies 29 advanced cancer patients	Case study by MD Phase I NIH study	Observation 500 mg freeze dried noni fruit extract	Not clear 4 capsules (2 g) daily up to 20 capsules (10 g) daily Duration not stated	Not clear No adverse events Decrease in pain interference with activities ($p < 0.006$) No measured tumor regressions No significant difference for fatigue or depression Decreasing aromatic DNA adducts in peripheral blood lymphocytes (PBLs)
Wang <i>et al.</i> , 2009; Wang <i>et al.</i> , 2009 (1 study, 2 articles)	203 smokers 285 smokers	Double blind, placebo controlled	1–4 ounces of Tahitian noni [®] juice (TNJ) (concentration not provided) 1) 118 mL TNJ 2) 29.5 mL TNJ 3) 118 mL placebo	1 month	Decreasing levels of plasma superoxide anion radicals (SAR) and lipid hydroperoxide (LOOH)

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Clinical studies

A year later in 2005, Issell *et al.* conducted a NIH Phase I human clinical trial (dose finding study) to investigate the effect of ripe noni fruit extract given to 29 advanced cancer patients in the form of a dietary supplement (freeze-dried pills) (Issell *et al.*, 2005). The researchers from the University of Hawaii's Cancer Research Center started 29 advanced cancer patients on a daily dosage of four capsules (500 mg each; 2 g). Subsequent dose levels increased to 10 g (20 capsules) daily. They reported no measured tumor regression, decrease in Brief Fatigue Inventory (BFI) or Center for Epidemiologic Studies Depression Scale (CES-D). However, there was a significant decrease in pain interference. In addition, no adverse events using CTCAE (Common Terminology Criteria for Adverse Events) criteria were attributable to noni.

Although not directly related to cancer patients, two reports on smokers ingesting Tahitian noni[®] juice were published in 2009 by Wang and associates. They found decreasing aromatic DNA adducts in peripheral blood lymphocytes (PBLs) after 1 month of drinking 1–4 ounces of Tahitian noni[®] juice (concentration not provided) (Wang *et al.*, 2009a, 2009b). They also revealed increasing levels of plasma superoxide anion radicals (SAR) and lipid hydroperoxide (LOOH) levels in the smokers ingesting Tahitian noni[®] juice compared with controls (Wang *et al.*, 2009a, 2009b).

Summary of *in vitro* human clinical studies

Despite the numerous claims to consumers about noni products being 'effective' against cancer (Anonymous, 2011a, 2011b; Solomon, 2003), no human clinical trials in Medline exist to support this claim. Only two case studies of limited data and one NIH study exist to date. Clinical data are currently lacking to either support or refute the use of noni juice and or its extract as a complementary cancer treatment. The paucity of research on noni as a possible complementary cancer treatment suggests the need for further clinical trials.

As with many cancers, the dietary or herbal treatment may be most effective in the early stages. Few drugs work in advanced cancer patients. The other aspect to question is the form of the noni juice. If indeed, 100% pure noni juice that is not pasteurized, dried, or processed in any other way is the form reported in common practice to have an 'effect', then perhaps therein lies the bioactive ingredient. The yet to be identified substance with anticancer activity might be a mold, a component of the mold growing in the noni juice, or some other unknown substance. While it is problematic to provide an unpasteurized, fermented product to cancer patients with compromised immune systems, the noni extract does appear to enhance the survival rate of rats and so the key question becomes, 'What is this substance in noni having a positive effect in rats, and can be safely provided to humans in a clinical trial?' If such a research protocol could pass an Institutional Review Board, then testing pure fermented noni juice in cancer patients would be the next step. The issues of uniform dose and safety remain.

SAFETY OF NONI JUICE (8 CASE STUDIES)

A common concern with many herbal and/or dietary supplements is potential toxicity. Often these reports appear in the literature as case studies reported by physicians. To date, eight such cases have been reported and are summarized in Table 4.

Feedback on noni juice safety

West, Jenson and Westendorf (2006a), who work in the Research and Development Department of Tahitian noni[®] juice (Provo, UT), indicated that causality for each toxicity case cannot be established, and is only by association. Confounding these case studies are pre-existing medical conditions in the patients: renal insufficiency (Mueller *et al.*, 2000), toxic hepatitis, chronic B-cell leukemia and glioblastoma (Stadlbauer *et al.*, 2005, 2008) and multiple sclerosis (Yuce *et al.*, 2006). The only patient without a preexisting condition was Millonig's 45 year old male with acute hepatitis (Millonig *et al.*, 2005). This case occurred in Austria as did the other two reported by Stadlbauer, while Yuce's study originated in Germany. These European reports appeared around the time that noni fruit juice was approved as a Novel Food by the European Commission in 2003 (European Commission, 2003).

West, Jensen and Westendorf (2006a) initially reported preliminary results of 96 human subjects consuming up to 750 mL of Tahitian noni[®] juice (% not specified) per day for 28 days showed no effect on liver enzyme tests. These data were officially published in a 2009 study showing that the group consuming noni had fewer adverse events than the control group. Measurable outcomes included hematology, biochemistry, urinalysis, vital signs and electrocardiogram (ECG) measurements (West *et al.*, 2009a, 2009b). The percent noni juice in this study was not provided, and the latest version of 'Tahitian noni[®]' key ingredients (not all listed) are described as a 'puree' combined with grape and blueberry juice concentrate (Anonymous, 2011a, 2011b).

An animal safety study by West, Su and Jensen (2009a) revealed that two 13 week oral toxicity studies of rats consuming Tahitian noni[®] juice (% not specified) did not show any significant change in liver enzyme tests. The No Observable Adverse Effect Level (NOAEL) in these rats was determined to be approximately 90 mL of Tahitian noni[®] juice per kg per day. West *et al.* (2006a, 2006b) published a safety review on noni juice citing various unpublished LD₅₀ studies with mice and rats testing extracts (aqueous, alcohol and methanol) of noni fruit. He also suggested that the anthraquinones in noni fruit that occur are unlikely to contribute to toxicity because their quantities are too small to be of any toxicological significance (Westendorf *et al.*, 2007). However, amounts are higher in the stem and root of the *Morinda citrifolia* so the potential for toxicity exists if manufacturers utilized either of these plant portions. One study by Carr *et al.* (2004) did suggest that noni juice interferes with the coumadin or warfarin drug, but upon further investigation by West *et al.* (2006b), it appeared that this particular brand of noni juice had added vitamin K at the time.

Further safety data are available from Potterat and Hamburger (2007), who authored a review article on the phytochemistry, pharmacology and safety of *Morinda citrifolia* (Noni). Ultimately, all patients on dietary supplements should be monitored for side-effects and/or drug-supplement interactions. Women who are pregnant or breast-feeding should avoid all dietary supplements except prenatal vitamins and minerals, or others recommended by their physicians.

LIMITATIONS OF REVIEW

This review was strictly Medline-based with associated articles, and while comprehensive with regard to this resource, is not entirely inclusive of all the literature, nor should it be viewed as such. While limiting the literature review to this source ensures some degree of standardization, it also did not broaden the search to other valuable indexes such as those in botany, agriculture, anthropology and other fields such as NapAlert and/or FDA Poison control reports.

EVIDENCED-BASED CLINICAL RESPONSE FOR CLIENTS

Healthcare providers may now answer their client's questions about noni fruit juice and its relationship to cancer based on a limited 19 Medline articles (as of October 2011) serving as the foundation for the above literature review. The take-home message to clients is to first maintain cancer medical treatment under the care of a physician (oncologist), to inform the health practitioner of any herbal and/or dietary supplement consumption, and that complementary medicine is 'complementary' and preferably for adults that are not pregnant or lactating. Patients needing to avoid noni juice include those that have to watch their potassium intake because of pre-existing kidney (Burrowes and Van Houten, 2005), liver or heart problems.

Questions regarding noni juice and cancer can be answered by saying that only 19 studies exist on the subject of which the seven were 'in-the-test-tube' studies. These studies also suggest that it was the 'concentrated component' in noni juice and not pure noni juice that may: (i) Stimulate the immune system to 'possibly' assist the body fight the cancer from within; (ii) Kill a small percentage (0–36%) of cancer cells depending on the type; (iii) Approximately 9 of the 19 studies were 'animal studies' suggesting that a concentrated component in noni juice (not pure noni juice); (iv) Boosts the animals immune systems; but only slightly increases the number (about 1/3; 25–45%) of mice surviving.

Only three human clinical studies exist to date. A NIH study determined that freeze-dried noni (not noni juice) may have reduced pain perception, but that it did not reverse cancer in patients with advanced cancer. However, very few conventional treatments can reverse advanced cancer either so the real question is whether or not noni juice, or its concentrated component, can influence cancer in its early stages when it might be influenced by the immune system. In addition, two

Table 4. Human toxicity case study reports related to oral ingestion of noni juice products

Author, year	Subject	Concomitant Factors	Dosage/Duration	Measurable outcomes
Mueller <i>et al.</i> , 2000	45 year old male	Chronic renal insufficiency patient compliant with low potassium diet	Patient consuming a 'shot' of noni juice before each meal (% unknown, but drink also contained white grape juice, natural flavors, and Flower of Benjamin) Noni juice = 56 mEq/L (similar to orange or tomato juice)	Hyperkalemia (elevated serum potassium concentration (5.8 mEq/L) Elevated blood urea nitrogen (50 mg/dL) Elevated serum creatinine (4.0 mg/dL)
Millonig <i>et al.</i> , 2005	45 year old male	Unremarkable medical history No signs of heart, lung or liver diseases Ultrasound showed normal liver without signs of fatty liver, fibrosis, or liver cirrhosis	Drinking a 'glass' (not quantified) of noni juice every day for 3 weeks	Acute hepatitis Elevated liver enzymes (transaminases, LDH, direct bilirubin) Physical symptoms of malaise, thoracic discomfort, nausea, appetite loss, shortness of breath during exercise, and fatigue Cessation of noni juice paralleled normalization of liver enzyme tests after 2 days (started to fall), 10 days (considerably decreased) and within one month (completely normalized) Acute hepatitis and liver failure. Treated with liver transplant
Stadlbauer <i>et al.</i> , 2005	Case 1: 29 year old man	Previous toxic hepatitis, Gilberts syndrome, upper respiratory tract medications (paracetamol), and asthma medications (beta2-agonists, glucocorticoids, eosinophilia) Ingesting 7 g/day of a Chinese herbal mix 9 days prior to admission	1.5 L Tahitian noni® juice (unknown %) over 3 weeks	
	Case 2: 62 year old woman	No previous evidence of liver disease Four years prior diagnosed with chronic B-cell leukemia and treated with fludarabine	2 L Noni juice over 3 months	Acute hepatitis diagnosed based on elevated liver enzymes and liver biopsy. Vomiting and diarrhea Condition improved over 1 month and normalized within 9 months
Yuce <i>et al.</i> , 2006	24 year old female	Multiple sclerosis treated with interferon beta-1a for previous 6 weeks	Drinking noni juice (amount not clear) for the past 4 weeks	Fulminant hepatitis and beginning of acute liver failure. Liver biopsy indicated drug-induced toxicity. Interferon beta previously reported with hepatotoxicity (Wallack and Callon, 2004) Cessation of noni juice coincided with normalization of liver enzyme tests within 1 month Hepatotoxicity Spontaneous recovery
López-Cepero Andrada <i>et al.</i> , 2007	33 year old female	Abdominal pain	Unknown	

(Continues)

Table 4. (Continued)

Author, year	Subject	Concomitant Factors	Dosage/Duration	Measurable outcomes
Stadlbauer <i>et al.</i> , 2008	43 year old male	Diagnosed with glioblastoma Levetiracetam (500 mg twice daily) for tumor-related seizures	Drinking Tahitian noni [®] juice (unknown %) 20 mL twice a day for two weeks	High liver enzymes (AST 192 U/L; ALT 516 U/L). Bilirubin normal Levetiracetam known to induce abnormal liver function tests, hepatitis, and hepatic failure Jaundice and acute hepatotoxicity
Yu <i>et al.</i> , 2011	14 year old male	Concurrently taking ibuprofen twice weekly for headaches	Consuming 20 oz (10 two-ounce bottles of an antioxidant drink or 2.5 cups) over 2 months. Brand not specified Other ingredients included, aloe vera, acai berry, muscadine grape, mangooseen, noni berry, gogi berry, pomegranate, blueberry, green tea extract, and plant-derived vitamins and minerals	Questionable to suggest that noni is a causative factor considering subjects ibuprofen usage, risk of such usage to acute hepatitis (Lee, 2010), other ingredients, and that only 2 ½ cups of the diluted 'noni drink' was consumed over two months

¹Chinese Herbal Mixture – bupleuri, pinellia, scutellaria, codonopsis, glycyrrhizae, schizonepeta and paeonia.

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reports from one study were obtained on smokers ingesting an unknown concentration of noni juice who experienced decreased aromatic DNA adducts, and decreased levels of plasma superoxide anion radicals and lipid hydroperoxide.

Commercial noni juice concentrations vary, and perhaps the bioactive plant component exists predominately in the fermented product. Another question needing answers is whether or not pasteurization, common to most commercialized fruit juices, destroys the bioactive(s)? Most of the studies reported in this review appear to have researched the precipitate, extract or juice from fermented noni juice that has not been pasteurized. In addition, most of the animal studies were conducted with the precipitate being injected into the animal, rather than being orally consumed.

It is important that all future noni research specify whether or not the noni juice source was, (1) fermented and for how long, and (2) pasteurized or unpasteurized. There appears to be some unidentified chemical substance in unpasteurized, fermented noni juice executing a stimulatory effect on the immune system biomarkers. The extent of influence on inhibiting cancer cell lines currently remains to be identified in humans.

More studies are necessary to determine the potential, if any, of the specific bioactives in fermented, non-pasteurized noni juice to affect early stage cancer in humans. Although a few *in vitro* and *in vivo* animal studies suggest an unidentified anticancer activity present to a small degree, the active component warrants further research.

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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