

MINI-REVIEW

Do the Health Claims Made for *Morinda citrifolia* (Noni) Harmonize with Current Scientific Knowledge and Evaluation of its Biological Effects

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Abstract

Morinda citrifolia, also known as Great Morinda, Indian Mulberry, or Noni, is a plant belonging to the family Rubiaceae. A number of major chemical compounds have been identified in the leaves, roots, and fruits of the Noni plant. The fruit juice is in high demand in alternative medicine for different kinds of illnesses such as arthritis, diabetes, high blood pressure, muscle aches and pains, menstrual difficulties, headache, heart diseases, AIDS, gastric ulcer, sprains, mental depression, senility, poor digestion, arteriosclerosis, blood vessel problems, and drug addiction. Several studies have also demonstrated anti-inflammatory, antioxidant and apoptosis-inducing effects of Noni in various cancers. Based on a toxicological assessment, Noni juice was considered as safe. Though a large number of *in vitro*, and, to a certain extent, *in vivo* studies demonstrated a range of potentially beneficial effects, clinical data are essentially lacking. To what extent the findings from experimental pharmacological studies are of potential clinical relevance is not clear at present and this question needs to be explored in detail before any recommendations can be made.

Keywords: *Morinda citrifolia* (Noni) inflammation - antioxidant - cancer - DNA repair

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Introduction

Among the medicinal plants discovered by the ancestors of Polynesians, *Morinda citrifolia* (Noni) is one of the important traditional folk medicinal plants that have been used for over 2000 years in Polynesia (Morton, 1992; Serafini et al., 2011). Noni is commonly referred to the species *M. citrifolia*. It is also known by various local names such as Nona, Nono, Nuna, Pain Bush, Pain Killer Tree, Cheese Fruit, Forbidden Fruit, Headache Tree, Nino, Pinuela, Hog Apple, Mona, Mora de la India, and Wild Pine in various parts of the world. Noni is an evergreen tree found growing in open coastal regions at sea level and in forest areas up to about 1300 feet above sea level. It is often found growing along lava flows. Noni is identifiable by its straight trunk, large, bright green and elliptical leaves, white tubular flowers, and its distinctive, ovoid, "grenade-like" yellow fruit. The fruit can grow in size up to 12 cm or more, and has a lumpy surface covered by polygonal-shaped sections. The seeds, which are triangular shaped and reddish brown, have an air sac attached at one end, which makes the seeds buoyant. The mature Noni fruit has a foul taste and odor (Morton, 1992).

Morinda citrifolia and its Chemical Composition

Various compounds identified in the leaves, fruits,

and roots of Noni plant are scopoletin, octoanoic acid, potassium, Vitamin C, terpenoids, alkaloids, anthraquinones (such as nordamnacanthal, morindone, rubiadin, and rubiadin-1-methyl ether, anthraquinone glycoside), linoleic acid, alizarin, amino acids, acubin, L-asperuloside, caproic acid, Caprylic acid, ursolic acid, rutin, carotene, Vitamin A, flavones, glycosides, iridoid glycosides, and a putative prexeronine (Pawlus et al., 2005; Akihisa et al., 2007; Alitheen et al., 2010; Gupta et al., 2013). Predominantly, fruit contains fatty acids; while the roots and bark contain anthraquinones (Alitheen et al., 2010).

Noni-Based Nutritional Supplementation for Weight Gain

Noni-based nutritional supplementation and exercise interventions positively affect body composition without side effects and are recommended to be used in combination for combating weight gain (Palu et al., 2011).

Probiotic Potential of Noni Juice

One study assessed the feasibility of Noni as a raw substrate for the production of probiotic Noni juice by lactic acid bacteria (*Lactobacillus casei* and *Lactobacillus plantarum*) and bifidobacteria (*Bifidobacterium longum*). Changes in pH, acidity, sugar content, cell survival

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and antioxidant properties during fermentation were monitored. All tested strains grew well on Noni juice. *L. casei* produced less lactic acid than *B. longum* and *L. plantarum*. Moreover, Noni juice fermented with *B. longum* had a high antioxidant capacity that did not differ significantly ($p < 0.05$) from that of lactic acid bacteria. Finally, they suggested that *B. longum* and *L. plantarum* are optimal probiotics for fermentation with Noni juice (Wang et al., 2009).

Medicinal use of *M. citrifolia*

The Polynesians utilized the whole Noni plant for herbal remedies. The fruit juice of Noni has been in great use in alternative medicine for various illnesses such as arthritis, diabetes, high blood pressure, muscle aches and pains, menstrual difficulties, headache, heart diseases, AIDS, gastric ulcer, sprains, mental depression, senility, poor digestion, arteriosclerosis, blood vessel problems, drug addiction, and various cancers. Scientific evidence of the benefits of the Noni fruit juice is limited but there is some anecdotal evidence for successful treatment of colds and influenza (Basar et al., 2010; Gilani et al., 2010).

Anti-inflammatory Activity of Noni

Several polyphenols belonging to the coumarin, flavonoids and phenolic acid groups, and two iridoid present in Noni juice have demonstrated reduced carrageenan-induced paw edema, directly inhibited cyclooxygenase COX-1 and COX-2 activities and inhibited the production of nitric oxide (NO) and prostaglandins E(2) (PGE(2)) in activated J774 cells, in a dose dependent manner. This study showed that Noni's biological effects include anti-inflammatory action through NO and PGE (2) pathways that might also be strengthened by anti-oxidant effects (Dussosoy et al., 2011). Together, the results suggested that properties of *M. citrifolia* extract should be explored further in order to achieve newer tools for managing painful and inflammation conditions, including those related to oxidant states. Several compounds of Noni juice have also been found to exhibit potent anti-inflammatory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation (1 microg/ear) in mice (Akihisa et al., 2007).

Noni and Stress-induced Impairment of Cognitive Function

Another finding suggested that the administration of Noni fruit juice protects brains from stress-induced impairment of cognitive function and that this protective effect may be related to improvement in stress-induced decreases in blood vessel density in the hippocampal dentate gyrus (Muto et al., 2010).

Antioxidant Properties of *Morinda citrifolia*

Previous research has established that fruits and vegetables are major sources of dietary antioxidants.

Epidemiological studies have demonstrated that consumption of fruits and vegetables may reduce free-radical-induced oxidative damage and lipid peroxidation in cigarette smokers (Wang et al., 2009; Bullo' M et al., 2011).

Mature Noni fruit had been shown to have antioxidant capacity similar to that of navel oranges and tangerines; Noni leaves similar to that of green tea. Maturation increased antioxidant capacity, total phenols, and ascorbic acid content of Noni fruits, and ripening beyond maturity decreased all three, suggesting that mature Noni fruits are good sources of dietary antioxidants and thus supports the practices by Pacific traditional healers of using fruits as internal remedies and of Noni manufacturers of processing Noni products as dietary supplements (Jian et al., 2011).

In one study, the leaves of the Thai Noni/Yor, (*Morinda citrifolia* Linn) showed antioxidant properties, giving IC_{50} values of 0.20-0.35 mg/ml, thus concluding the leaves of *M. citrifolia* may have benefit as a food supplement for antioxidative activities in epidermoid and cervical cancers as compared to Damnacanthal, rutin, and scopoletin (Thani et al., 2010).

Several polyphenols belonging to the coumarin, flavonoid, and phenolic acid groups, and two iridoids in Noni juice have demonstrated a mean range free radical scavenging capacity, thus showing antioxidant properties (Dussosoy et al., 2011).

As noted earlier, molecular epidemiologic studies have demonstrated that SAR and LOOH levels in smokers are significantly higher than in nonsmokers (van et al., 2004). The results of one trial substantiate the antioxidant properties of Noni juice observed *in vitro* and *in vivo*, as well as demonstrate an effect under conditions of oxidative stress produced by heavy smoking (Wang et al., 2009).

It is highly possible that several compounds of different polarity may contribute to the antioxidant activity of *M. citrifolia* fruit juice (Noni). Part of the antioxidant activity may be due to lipid soluble polyphenols, anthraquinones, α -tocopherol, and β -carotene present in Noni as many natural phytochemicals have been demonstrated to promote antioxidant in cancer cells, including phenolics, alkaloids, damnacanthal, and flavonoids (Alshawti et al., 2011; Serafini et al., 2011). It has also been reported that most natural antioxidant compounds often work synergistically with each other to produce a broad spectrum of effects against free radical attack.

Noni and Ischemic stress

Fruit juice of *Morinda citrifolia* (Noni juice) is a well-known health drink and has various pharmacological properties including antioxidant and anti-inflammatory effects. One study showed that ingestion of 10% Oral Noni juice (ONJ) by Male ddY mice followed by 2 h of middle cerebral artery occlusion (MCAO) suppressed the development of neuronal damage; glucose intolerance observed on the 1st day after MCAO completely disappeared after 10% ONJ administration; and ONJ treatment significantly increased serum insulin levels much further than the control group on the 1st day, while serum adiponectin levels were not affected at all. These

results suggested that ONJ could facilitate insulin secretion after ischemic stress and may attenuate the development of glucose intolerance, suggesting that these mechanisms may contribute to the neuronal protective effect of ONJ against ischemic stress (Harada et al., 2010).

Noni and Xanthine Oxidase (XO) Enzyme

It was elucidated that inhibitory effect of XO enzymes by Noni is the mechanism by which Noni ameliorates gout and gout-like diseases. Further, the results also support the traditional usage of Noni in the treatment of gout (Palu et al., 2009).

Noni Rejects Tumor Cells

The mechanism of tumor rejection by *Morinda citrifolia* remains unknown though the anti-tumor activity of *Morinda citrifolia* fruit juice (Noni) has been previously reported. In another study, they demonstrated that intraperitoneal injection of fermented Noni exudate (fNE) significantly increased the percentages of granulocytes and NK cells in the peripheral blood, peritoneum, and spleen, induced complete tumor rejection in normal C57BL/6J mice, partial tumor rejection in C57 nude mice lacking functional lymphocytes, and no tumor rejection in NK cell deficient beige mice. Over 85% of the C57BL/6J mice that received fNE survived the first tumor injection and rejected up to 5×10^6 tumor cells when re-challenged. These data demonstrated that fNE appears to be able to stimulate the innate immune system and the adaptive immune system to reject tumor cells. NK cells respond quickly and appear to be among the major players of the innate immune system, while the adaptive immune system reacts later with a retained memory (Li et al., 2008).

Anticancer Properties of Noni

Complementary and alternative medicine use is common among cancer patients. In many surveys, herbal medicines are among the most commonly used group of treatments. Herbal remedies are believed by the general public to be safe, cause less side effects, and less likely to cause dependency (Okalu and White, 2011). Search for new chemopreventive and antitumor agents that are more effective but less toxic has kindled great interest in phytochemicals.

An immunomodulatory polysaccharide-rich substance (Noni-precipitate) from the fruit juice of *Morinda citrifolia* has been found to possess both prophylactic and therapeutic potentials against the immunomodulator sensitive Sarcoma 180 tumor system. The antitumor activity of Noni-ppt produced a cure rate of 25-45% in allogeneic mice and its activity was completely abolished by the concomitant administration of specific inhibitors of macrophages (2-chloroadenosine), T cells (cyclosporine) or natural killer (NK) cells (anti-asialo GM1 antibody) (Furusawa et al., 2003).

Noni-ppt showed synergistic or additive beneficial effects when combined with a broad spectrum of chemotherapeutic drugs, including cisplatin, adriamycin,

mitomycin-C, bleomycin, etoposide, 5-fluorouracil, vincristine or camptothecin. It was not beneficial when combined with paclitaxel, cytosine arabinoside, or immunosuppressive anticancer drugs such as cyclophosphamide, methotrexate or 6-thioguanine. Noni-ppt also demonstrated beneficial effects when combined with the Th1 cytokine, interferon gamma, but its activity was abolished when combined with Th2 cytokines, interleukin-4 or interleukin-10, thereby suggesting that Noni-ppt induces a Th1 dominant immune status *in vivo*. The combination of Noni-ppt with imexon, a synthetic immunomodulator, also demonstrated beneficial effects (Furusawa et al., 2003).

Several studies reported that Noni has multiple cancer protective properties. Oncostatic activities related to cancer prevention include reductions in TPA- or EGF-induced cell transformation, reduction in DMBA-induced DNA damage and lesion formation (Wang and Su, 2001; Wang et al., 2002), and concentration-dependent free-radical scavenging effects (Wang and Su, 2001; Pawlus et al., 2005; Su et al., 2005). Similarly, additional anticancer activities, including antiangiogenic (Hornick et al., 2003) and cancer cell-selective cytotoxic properties (Hirazumi et al., 1994; Arpornsuwan and Punjanon, 2006), suggest its potential as a treatment to inhibit tumor growth and progression.

Also, a few *in vitro* and *in vivo* animal studies suggest a possible unidentified substance in un-pasteurized Noni fruit juice that may have a small degree of anticancer activity. The isolation of the active component warrants further research (Brown, 2012).

Another result suggested that drinking 1-4 oz of TNJ daily may reduce the cancer risk in heavy cigarette smokers by blocking carcinogen-DNA binding or excising DNA adducts from genomic DNA (Wang et al., 2009).

Noni and Esophageal Cancer

Although only a few studies have tested the cancer inhibitory actions of Noni *in vivo*, one recent study demonstrated that Noni fruit powder had both preventative and treatment efficacy on rat esophageal cancer induced by N-nitrosomethylbenzylamine (Stoner et al., 2010).

Noni and Breast Cancer

Morinda citrifolia L. (Noni) is an herbal remedy with promising anti-cancer properties. Approximately 41% of women are utilizing complementary and alternative medicine (CAM) forms of medicine to manage their breast cancer (Ernst, 2000; Wanchai et al., 2010), including products from the *Morinda citrifolia* (Noni) plant.

One study showed that TNJ may prevent mammary breast cancer at the initiation stage of chemical carcinogenesis (Clafshenkel et al., 2012). Another study demonstrated the anti-growth effect resulting from the induction of apoptosis, the active caspase-3 cells in tissues; and decreased proliferation on Ehrlich ascites tumor grown in female Balb-c mice; thus concluding that Noni may be useful in the treatment of breast cancer either on its own or in combination with doxorubicin (Taskin et al.,

2009). However, further studies are warranted to assess the dosage and safety of using Noni fruit juice in combination with anti-cancer drugs against breast cancer; and needs to make a firm conclusion before implementing it into the clinical practice.

Noni and Lung & Colon Cancer

Roots of *Morinda citrifolia* (Noni or Yor in Thai) have been used traditionally for thousands of years to treat chronic diseases such as cancer and heart disease. In one study, six known compounds, together with two new compounds (2 and 3) isolated from *Morinda citrifolia* (Noni) showed significant inhibitory effects on the proliferation of human lung and colon cancer cells (Lv et al., 2011).

Noni and Colorectal Cancer

Damnacanthal, an anthraquinone compound, isolated from the roots of *Morinda citrifolia* L. (Noni), has been used for traditional therapy in several chronic diseases including cancer. One study examined systematic approaches on the cancer-suppressing capability of Damnacanthal in colorectal tumorigenesis; and found that Damnacanthal exhibited cell growth arrest as well as Caspase activity induction; and the pro-apoptotic protein & non-steroidal anti-inflammatory activated gene-1 (NAG-1) highly induced in colorectal cancer. They also found that Damnacanthal enhanced transcription factor CCAAT/enhancer binding protein β (C/EBP β), which controls NAG-1 transcriptional activity. Taken together, these results indicated that Damnacanthal increased anti-tumorigenic activity in human colorectal cancer cells and that C/EBP β plays a role in Damnacanthal-induced NAG-1 expression (Nualsanit et al., 2011).

Noni and Cervical Cancer

Gupta et al. (2013) demonstrated that Noni/Cisplatin by themselves and combination of Noni with Cisplatin were able to induce apoptosis through the mitochondrial pathway, in both HeLa and SiHa cells, particularly through the up-regulation of pro-apoptotic members and down-regulation of the anti-apoptotic members. This was accompanied by an increase in activity of caspases-9 and -3, thus primarily activating intrinsic pathway of apoptosis. Hence, Noni offers potential to be used as a chemo adjuvant, especially for treatment of cervical cancer (Gupta et al., 2013).

Noni and DNA Repair

Rats treated with a Noni juice concentrate did not show DNA repair synthesis (UDS) in primary rat hepatocytes, nor could DNA adducts or DNA strand breaks be observed. In summary, chemical analysis and genotoxicity tests revealed that Noni juice does not have a genotoxic potential and that genotoxic anthraquinones do not exist in Noni juice (Westendorf et al., 2007).

Flavonoids in citrus have been found to stimulate

DNA repair in prostate cancer cell lines (Alshawti et al., 2011; Wong and Abdul, 2012); whereas, Vitamin A has been found to enhance DNA-repair activities and the subsequent removal of DNA adducts may be one of the mechanisms involved in vitamin A-mediated protection against cancer (Wolterbeek et al., 1995). However, the effects of Flavonoids and Vitamin A, present in Noni juice, needs to be explored on DNA repair genes.

Morinda citrifolia (Noni) Fruit-- Photochemistry, Pharmacology, and Safety

Products derived from Noni fruit (*Morinda citrifolia*) have been commercialized in the USA since the 1990s and are increasingly distributed all over the world. A large number of beneficial effects have been claimed for Noni. Fruit juice of Noni has been approved as a Novel Food by the European Commission in 2003. One article reviewed current knowledge on the phytochemistry, pharmacology, safety aspects of Noni fruit and Noni-derived products, and health-related claims and benefits (Potterat and Hamburger, 2007). The knowledge on the chemical composition of Noni fruit has considerably increased over recent years. A number of *in vitro* and, to a certain extent, *in vivo* studies demonstrated a range of potentially beneficial effects. However, clinical data are essentially lacking. To what extent the findings from experimental pharmacological studies are of potential clinical relevance is not clear at present. Based on a toxicological assessment, Noni juice was considered as safe. Due to recent reports of cases of hepatotoxicity, the safety issue has been re-examined in Europe. While the European Food Safety Authority sees no link between adverse effects on liver and consumption of Noni juice, a continuing monitoring of the situation is desirable and some vigilance advised (Potterat and Hamburger, 2007).

Conclusion

Though a large number of *in vitro*, and, to a certain extent, *in vivo* studies demonstrated a range of potentially beneficial effects; clinical data are essentially lacking. To what extent the findings from experimental pharmacological studies are of potential clinical relevance is not clear at present; and needs to be explored yet.

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