

Morinda citrifolia L.: Phyto-pharmacological perspective review

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ABSTRACT

Morinda citrifolia is a tree in the coffee family, Rubiaceae. Its native range extends through Southeast Asia, Central America, and Australasia, and the species is now cultivated throughout the tropics and widely naturalised. *M. citrifolia* L. also called as Noni or Indian mulberry is a small evergreen tree. It is one of the most important traditional Polynesian medicinal plants. The present study was undertaken to review of *M. citrifolia* for its effects on antioxidant, anti-epileptic, breast cancer prevention, antibacterial effect, liver protective effects, antifungal activity, anti-helminthic activity, anxiolytic activity, estrogenic activity, immunological activity, analgesic activity, hypotensive activity, insecticidal activity, and cancer preventive effect. This plant has also been popular as a source of red, yellow, and purple dyes.

KEY WORDS: Anti-bacterial, *Morinda citrifolia*, immunological activity, hypotensive

INTRODUCTION

Scientific Classification

Kingdom: Plantae
Order: Gentianales
Family: Rubiaceae
Genus: *Morinda*
Species: *Morinda citrifolia*

Botanical Description

Morinda citrifolia is an evergreen shrub or small crooked tree with a conical crown, 3-8(-10) m tall, with a deep taproot; bark grayish or yellowish-brown, shallowly fissured, glabrous; branchlets quadrangular. Leaves opposite and simple, elliptic-lanceolate, (10-)15-50 cm × 5-17 cm, entire, acute to shortly acuminate at apex, cuneate at base, pinnately nerved, glabrous; petioles 0.5-2.5 cm long; stipules variable in size and shape, broadly triangular. Inflorescences globose heads, 1-4 cm long-peduncled, in axils of stipules opposite normally developed leaves; flowers bisexual, fragrant; corolla funnel-shaped, up to 1.5 cm long, white; stamens inserted on the mouth of the corolla; stigma bilobed. Fruit an ovoid syncarp of red-brown, pyramidal, 2-seeded drupes, 3-10 cm × 2-3 cm, yellow-white. *M. citrifolia* is sometimes subdivided into

two varieties: var. *citrifolia* and var. *bracteata* (Roxb.) Hook.f. The latter has calyx-limbs with 12 leaf-like, linear-lanceolate lobes ca. 1-1.5 cm long; the stem is straighter, and the leaves are smaller than var. *citrifolia*.

The Noni fruit begins green, turns a waxy yellow, and as mentioned, has an unpleasant, insipid, foul or fetid odor, especially as it ripens to whiteness and falls from the tree. One of Noni's special interests is its specialized seeds. Although they cannot travel long distances at sea, they do possess a woody watertight air sac that enables them to float between closely spaced islands. Noni's seeds can survive over a year in salt water and still germinate.

Uses of *M. citrifolia*

M. citrifolia (Noni) juice can increase mental clarity and attention span, as well as allow greater physical performance levels. It also benefits the following systems of the body.

- Immune system: Supports the immune system's natural ability to fight disease and infection
- Circulatory system, tissues, and cells: *M. citrifolia* (Noni) juice is a superior antioxidant that helps rid the body of harmful free radicals. It also increases energy levels
- Digestive system: *M. citrifolia* (Noni) juice supports

proper digestion and helps you absorb more nutrients at the cellular level

- Skin and hair: *M. citrifolia* (Noni) Juice contains components that are specifically important to the skin and hair. It also helps carry beneficial substances to the skin
- Most commonly used to improve mental alertness, and enhance learning and academic performance.

Phyto Constituents of *M. citrifolia*

M. citrifolia fruit powder contains carbohydrates and dietary fiber in moderate amounts. These macronutrients evidently reside in the fruit pulp, as *M. citrifolia* juice has sparse nutrient content. The main micronutrients of *M. citrifolia* pulp powder include vitamin C, niacin (vitamin B₃), iron and potassium. Vitamin A, calcium, and sodium are present in moderate amounts. When *M. citrifolia* juice alone is analyzed and compared to pulp powder, only vitamin C is retained in an amount that is about half the content of a raw navel orange. Sodium levels in *M. citrifolia* juice (about 3% of dietary reference intake) are high compared to an orange, and potassium content is moderate. The juice is otherwise similar in micronutrient content to a raw orange. *M. citrifolia* fruit contains a number of phyto chemicals, including lignans, polysaccharides, flavonoids, iridoids, fattyacids, scopoletin, catechin, beta-sitosterol, damnacanthal, and alkaloids.

Antioxidant Activity

Antioxidant activity and total phenolic content of an isolated *M. citrifolia* L. Methanolic extract by using membrane separator were investigated. The extract of *M. citrifolia* L. Fruit by methanol was separated into permeate and retentate by poly-ethersulphone (PES). The effect of temperature in the range of 30-70°C, and pressure in the range of 0.5-1.5 bar on the antioxidant activity and total phenolic content was studied. The 2, 2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity exhibited a gradual increase in permeates collection from membrane separation. The total phenolic content was also found to follow the same trend. The optimum magnitudes of DPPH radical scavenging activity and total phenolic content were found to be 55.60% and 43.18 mg GAE/10 g of the sample respectively (Duduku Krishnaiah *et al.*, 2015).

Anti-epileptic Activity

Fruit extract of *M. citrifolia* (Noni), a medicinal plant used in many neuro protective ayurvedic preparations was evaluated for its protective effect against seizures

induced by maximal electroshock (MES) method in rats. A daily dose of 200 and 400 mg/kg of the extract was administered to the animals for 15 days, after which seizures were induced by MES method and the duration of various phases of epileptic attacks were recorded and compared with the control animals. A significant ($P < 0.01$ and $P < 0.001$) reduction in the time taken for righting reflex (recovery) was noted in the experimental animals. The levels of biogenic amines such as dopamine, serotonin and nor-adrenaline in the forebrain region were also estimated, and a significant level of restoration was observed in the extract treated animals. Significant results were observed in the estimated parameters thereby justifying the use of this medicinal plant in the treatment of epilepsy (Muralidharan and Srikanth 2010).

Breast Cancer Prevention

The tumor latency in Tahitian Noni juice (TNJ) groups was delayed about 60-90 days when compared with positive controls. The number of palpable tumors per group was significantly reduced by 73%, 72% and 80% in 3%, 5%, and 10% TNJ groups respectively when compared with positive controls at the end of 330 days after DMBA administration. The number of palpable tumors in the placebo groups was slightly reduced in the early stage, but much less than that in the TNJ groups. The multiplicity and malignancy of lesions were significantly reduced and the survival rate of animals in the TNJ groups was significantly increased compared with positive controls at different time points. Histological examination showed that the malignancy of lesions in TNJ groups did not show a significant change when compared with that in positive and placebo groups (Wang *et al.*, 2013).

Antibacterial Effect

Mycoplasmas possess remarkable immunoregulatory properties and can potentially establish chronic latent infections with little signs of disease. *M. citrifolia* (Noni) is largely used in traditional medicine. It was also reported that NJ is typically applied for the treatment of cutaneous infections. In recent years, multiple resistances in human pathogenic microorganism have developed due to the indiscriminate used of antibiotic drugs commonly employed in the treatment of infectious diseases. The objective of the study was to evaluated the antibacterial activity of the fruit juice of *M. citrifolia* against medically important mycoplasma. *M. citrifolia* fruit juice was subjected to screening against *Mycoplasma pneumoniae*, *Mycoplasma penetrans*, and *Mycoplasma fermentans*. The antibacterial activity was assessed by the presence or absence of growth. *M. citrifolia* fruit juice produced the

highest antibacterial activity against mycoplasmas tested. The activity of 100% fruit juice indicates that the active components are concentrated in this fraction. This is the first report of antibacterial activity of *M. citrifolia* fruit juice against medically important mycoplasmas in comparison with other microorganisms (Rivera *et al.*, 2011).

Liver Protective Effects

This study evaluated the protective effects of Noni fruit juice on acute liver injury induced by carbon tetrachloride (CCl₄) in female Sprague–Dawley (SD) rats. Liver damage (micro-centrilobular necrosis) was observed in animals pretreated with 20% placebo (drinking water) + CCl₄. However, pretreatment with 20% NJ in drinking water + CCl₄ resulted in markedly decreased hepatotoxic lesions. Furthermore, serum alanine aminotransferase and aspartate aminotransferase levels were significantly lower in the Noni group than the placebo group. In a correlative time-dependent study, one dose of CCl₄ (0.25 mL/kg in corn oil, p.o.) in female SD rats, pretreated with 10% placebo for 12 days, caused sequential progressive hepatotoxic lesions over a 24 h period, while a protective effect from 10% NJ pretreatment was observed. These results suggest that NJ is effective in protecting the liver from extrinsic toxin exposure (Wang *et al.*, 2008).

Antifungal Activity

Candida albicans live in 80% of the human population with no harmful effects, although overgrowth from cellular yeast to a filamentous form results in candidiasis, which was often observed in immunocompromised individuals such as AIDS, cancer chemotherapy, and organ or bone marrow transplantation. Recent research has demonstrated that it contains a water-soluble component or components that interfere with the morphological conversion of *C. albicans* and may have potential therapeutic value with regard to candidiasis (Banerjee *et al.*, 2006; Usha *et al.*, 2010). Other studies showed that methanol extract of the dried fruit exhibited maximum percentage of inhibition against *Trichophyton mentagrophytes* (79.3%), while approximately 50% activity was recorded against *Penicillium*, *Fusarium* and *Rhizopus* species (Jayaraman *et al.*, 2008; Jainkittivong *et al.*, 2009).

Anti-helminthic Activity

Alcoholic extracts of tender leaves showed good *in vitro* anthelmintic activity against human *Ascaris lumbricoides* (Raj, 1975). Similar findings were also reported (Khuntia *et al.*, 2010) and they showed that the alcoholic extract produced more significant anthelmintic activity than

petroleum ether extract and the activities are comparable with the reference drug piperazine citrate. Traditionally, it has been used in the Philippines and Hawaii as an effective insecticide (Morton, 1992).

Anxiolytic Activity

Recent research has demonstrated the effects of fruit on preventing anxiety disorders, affecting an estimated 25% of the adult population at some point during their lifetime (Kjernisted and Bleau 2004). Methanol crude extract of fruit showed significant affinity to the gamma-amino butyric acid A, the commonest inhibitory neurotransmitter in the central nervous system and displayed 75% binding inhibition as an agonist and thus induce its anxiolytic and sedative effects. Further work is required to identify compounds, which are responsible for the activities measured (Deng *et al.*, 2007).

Estrogenic Activity

M. citrifolia has been reported to have very weak estrogenic activity *in vivo*. According to (Chearskul *et al.*, 2004) the relative estrogenic potency of alcohol and water extracts of *M. citrifolia* was 1:1,000 and 1:10,000 respectively, indicating that the estrogenic activity is only seen at low doses, and even then it has very low potency in comparison to estradiol, suggesting that the beneficial effects of Noni are not closely linked to estrogen-mediated action. A variety of phytoestrogens have been identified, which bind to the estrogen receptor (ER) and comprises protective effects on estrogen-related conditions, such as menopausal symptoms and estrogen-related diseases, namely prostate and breast cancers, osteoporosis and cardiovascular diseases. A German research team has also studied the estrogenic properties of the fruit in two *in vitro* assays, the ER binding assay with both ER, ER- α and ER- β , and the ER dependent induction of alkaline phosphatase in Ishikawa cells. Hexane extracts prepared from the fruit exhibited high activity in both systems (Basar *et al.*, 2006). Besides the aforementioned investigations, the chemical nature of phytoestrogen in Noni is still mysterious and needs further investigations.

Immunological Activity

Recent research examined the mechanisms involved in immunological properties of TNJ and Noni fruit juice concentrates in mice. The result showed that both modulate the immune system via the activation of the CB2 receptors and suppression of the interleukin (IL-4), but increasing the production of interferon- γ (IFN- γ) cytokines (Palu *et al.*, 2008). In a related report, it has

been found that ethanol precipitation of the fruit contains a polysaccharide-rich fraction that showed antitumor activity in the Lewis lung carcinoma model in mice. It also stimulates the release of several potential mediators, including tumor necrosis factor- α (TNF- α), IL-1 β , IL-10, IL-12 p70, IFN- γ and nitric oxide (NO), but had no effect on IL-2 and suppressed IL-4 (Hirazumi and Furusawa 1999).

Analgesic Activity

The lyophilized aqueous extract of the roots was screened for analgesic activities in mice through writhing and hot plate tests. The data from this experiment showed that analgesic efficacy of the extract is 75% as strong as morphine, yet non-addictive and also proved to be non-toxic (Younos *et al.*, 1990). Similar findings were also reported by (Punjanon *et al.*, 2005) the alcoholic extract of fruits. The analgesic activity of Noni fruit puree on mice was investigated using the hot plate test. A 10% solution of freeze concentrated Noni fruit puree in the drinking water of mice reduced the pain sensitivity comparable to the central analgesic drug tramadol. This effect was only partly reversed by the application of the morphine antagonist naloxone. An alcohol extract of Noni fruit puree also caused an inhibition of matrix metalloproteinase-9 release from human monocytes after stimulation with lipopolysaccharide. This effect was comparable to hydrocortisone (10-5 M). The findings of (Basar *et al.* 2006) suggest that the preparations of Noni fruits are effective in decreasing pain and joint destruction caused by arthritis. Further studies are necessary for the identification of the active compounds and mechanism of action.

Hypotensive Activity

Youngken *et al.*, 1960 found that the total extract of the roots has a hypotensive effect. Later on, found that the ethanol extract of the roots lowered the blood pressure in an anesthetized dog. Recently, it has been reported that NJ contains an angiotensin-I-converting enzyme (ACE). Since ACE is commonly prescribed to treat high blood pressure, therefore this can be recognized as a therapeutically intervention for lowering blood pressure.

Anti-inflammatory Activity

The aqueous extract of the fruit was investigated for anti-inflammatory activity against bradykinin and carrageenan-induced edema in the rat paw. The results showed that the bradykinin-induced inflammatory response was inhibited and subsided rapidly in rats that were pretreated either orally or intraperitoneally with fruit juice extract,

whereas a higher dose of extract was required to inhibit completely the inflammatory response to carrageenan (McKoy *et al.*, 2002). Another study showed that ethanol extract of fruit powder has a selective inhibition effect on cyclooxygenase-1 (COX-1). Its IC₅₀ value (163 μ g/ml) was lower than those produced by aspirin (241 μ g/ml), whereas much higher than indomethacin (1.2 μ g/ml) used as the reference COX-1 inhibitors in this study. By contrast, It should be noted that it did not exhibit (*in vitro* and *in vivo*) NO* scavenging activity, a key mediator in the phenomenon of inflammation (Li *et al.*, 2003). Akihisa *et al.*, 2007 reported that new saccharide fatty acid ester 2-O-(beta-D-glucopyranosyl)-1-O-octanoyl-beta-D-glucopyranose extracted from the fruits has got a highly promising anti-inflammatory candidate.

Nutraceutical Studies

Morinda citrifolia L. also known as Noni or Indian mulberry is a small evergreen tree. It is one of the most important traditional Polynesian medicinal plants. This study is focused on nutraceutical studies in *M. citrifolia*-fruit. The mineral analysis of macro nutrients and micronutrients were founded in *M. citrifolia*. The proximate analysis of ash content and crude fiber content was estimated by AOAC method and thereby the total carbohydrates, and total proteins were estimated by Anthrone method and Lowry's method. Moreover the vitamin C content of the fruit extract estimated by Titration method. Finally, the determination of amino acids by OPA deviation using HPLC technique was performed in the fruit. The fundamental knowledge of nutrient profile will enable further investigation in *M. citrifolia* (Anbazahan *et al.*, 2014).

Renoprotective Effects

Gentamicin treatment caused nephrotoxicity as evidenced by a marked elevation in blood urea and serum creatinine. Serum urea, serum uric acid, serum creatinine and blood urea nitrogen were increased with gentamicin compared to saline-treated animals (162.33 \pm 9.92 mg/dl, 3.13 \pm 0.12 mg/dl, 6.85 \pm 0.35 mg/dl and 75.86 \pm 4.64 mg/dl respectively). Co-administration of Noni fruit juice with gentamicin decreased the rise in these parameters in a dose-dependent manner. Study of renal morphology by light microscope showed epithelial loss with intense granular degeneration involving >50% renal cortex in gentamicin treated rats, whereas in Noni fruit juice plus gentamicin treated rat revealed insignificant changes in tubular epithelium. Our data suggest that supplementation of Noni fruit juice may be useful in reducing gentamicin nephrotoxicity in rats (Pai *et al.*, 2013).

M. citrifolia is one of the important medicinal plants having a lot of phytochemicals, which plays very important role in medicines. In this present investigation, the animals are induced to kidney stone by giving ethylene glycol mixed with water and given orally, and 0.5% ammonium chloride are mixed with water and given orally for 28 days. The induced rats are treated with Noni (1 in 10 ml) mixed with H₂O and given to the rats for 28 days and induced to kidney stone + ammonium chloride is treated with Noni extract mixed with water and given to the rats for 28 days. After the treatment the urinary parameters like creatinine, protein, calcium, oxalate, phosphate are decreased except magnesium, its level is increased and serum creatinine level is decreased. The results are showing the good medicinal properties of Noni extract of *M. citrifolia* (Bhavani *et al.*, 2014).

Antitumor Activity

The fruit juice of *M. citrifolia* (Noni) contains a polysaccharide-rich substance (Noni-ppt) with antitumor activity in the Lewis lung (LLC) peritoneal carcinomatosis model. Therapeutic administration of Noni-ppt significantly enhanced the duration of survival of inbred syngeneic LLC tumor bearing mice. It did not exert significant cytotoxic effects in an adapted culture of LLC cells, LLC1, but could activate peritoneal exudate cells to impart profound toxicity when co-cultured with the tumor cells. This suggested the possibility that Noni-ppt may suppress tumor growth through activation of the host immune system. Concomitant treatment with the immunosuppressive agent, 2-chloroadenosine (C1-Ade) or cyclosporin (cys-A) diminished its activity, thereby substantiating an immunomodulatory mechanism. Noni-ppt was also capable of stimulating the release of several mediators from murine effector cells, including TNF- α , IL-1b, IL-10, IL-12 p70, IFN-g and NO, but had no effect on IL-2 and suppressed IL-4 release. Improved survival time and curative effects occurred when Noni-ppt was combined with sub-optimal doses of the standard chemotherapeutic agents, adriamycin, cisplatin, 5-fluorouracil, and vincristine, suggesting important clinical applications of Noni-ppt as a supplemental agent in cancer treatment (Anne Hirazumi and Furusawa 1999).

Insecticidal Activity

An ethanol extract of the tender Noni leaves induced paralysis and death of the human parasitic nematode worm, *A. lumbricoides* within a day (Raj, 1975). Noni has been used in the Philippines and Hawaii as an effective insecticide (Murdiatia *et al.*, 2000).

Antibacterial Activity

During this study, the antibacterial activity of *M. citrifolia* leaf, fruit and seed extract was assessed *in-vitro* by using disc diffusion method. A total of five different accessions of *M. citrifolia* plants were randomly selected and screened for antibacterial activity against five different bacterial pathogens. Overall analysis of the antibacterial activity of various extracts revealed that the best inhibitory activity was produced by the seed extract (12.23 mm) compared to the leaf and fruit extract. *Escherichia coli* and the *Pseudomonas* spp. were inhibited by all the extracts; however, *Salmonella* spp., *Staphylococcus aureus*, and *Klebsiella* spp. were not inhibited by all the extracts. The analysis of the antibacterial activity of all the accessions revealed that the best antibacterial activity was produced by accession 5 followed by accession 1, 2, 3 and 4 respectively (Sunder *et al.*, 2011).

Treatment of Psoriasis

M. citrifolia (Noni) fruits have been used traditionally to treat diabetes, high blood pressure, cancer, mechanical injury, and arthritis. However, its mechanism of action have not yet been fully elucidated. Herein, I describe an important case in which psoriasis was treated with *M. citrifolia* in combination with conventional anti-rheumatism therapy. This is the first report showing the effect of *M. citrifolia* on skin lesions associated with psoriasis. This case sheds light on the pathological difference between skin lesions and arthropathy associated with psoriasis (Okamoto, 2012).

Cancer Preventive Effect

M. citrifolia (Noni) has been used in folk medicine by Polynesians for over 2,000 years and is reported to have a broad range of therapeutic effects, including anticancer activity. The exact mechanism of action is unknown. The hypothesis is generated from the experiment that *M. citrifolia* possesses a cancer preventive effect at the initiative stage of carcinogenesis. The antigenotoxic potential of NJ was demonstrated on the aflatoxin B1 induced genotoxicity. *In vitro* studies were carried on human lymphocyte culture. We have used chromosomal aberration (CA), sister chromatid exchange (SCE) and cell cycle kinetics (CCK) with and without S9 mix. As markers in this experiments. Four doses *viz.*, 200, 250, 300, 350 μ l/ml per culture were selected and found that NJ significantly reduces the frequencies of CA, SCE and enhances RI *in vitro*. It was also noticed that the anti-genotoxic potential of NJ shows dose - response relationship. The results suggest that NJ was a potent

anti-carcinogen may contribute to the cancer prevention (Ahmad *et al.*, 2012).

CONCLUSION

To conclude, this review provides scientific evidence of the antioxidant, anti-epileptic, breast cancer prevention, antibacterial effect, liver protective effects, antifungal activity, anti-helminthic activity, anxiolytic activity, estrogenic activity, immunological activity, analgesic activity, hypotensive activity, insecticidal activity, and cancer preventive effect. In future investigation about the isolation of the biomarker components in *M. citrifolia* it will be separable for particular active constituents based on the pharmacological activity.

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