



## A Review - Anticancer and Antidiabetic Activity of *Morinda citrifolia* (Noni) Fruit

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### Abstract

Traditional medicine has utilised *Morinda citrifolia*, often known as Noni or Indian mulberry, to cure variety of ailments. Noni is evergreen shrub with strong butyric acid odour and smell, as well as astringent taste, in its mature fruit and leaves. Crude extracts of *M. citrifolia* (Rubiaceae) produced from leaves and fruit using various solvents such as methanol, ethanol, and water and subjected to phytochemical analysis. *M. citrifolia* phytochemical investigations reveal wide range of secondary metabolites. Fruit and leaves of this traditional medicinal plant are used by many communities across world for their various therapeutic qualities. Individual components of *M. citrifolia*, including its fruits, seeds, barks, leaves, and flowers, are used for nutritional and medicinal purposes, but its fruit is thought to contain most important chemical compounds. Antiviral, antibacterial, antifungal, anticancer, anthelmintics, analgesic, hypotensive, anti-inflammatory, and immunological boosting properties have been discovered in *Morinda citrifolia*. Noni plant, in conclusion, has chemical components that are effective in treating variety of illnesses. As result, noni plant may be turned into phytopharmaca. We review noni's anti-diabetic properties, as well as distinctions between traditional and current noni use, as well as positive clinical trials of noni products and obstacles in clinical translation of noni's health advantages. First, freeze-dried noni fruit was tested, which decreased pain perception but did not reverse advanced cancer. In the second study, we looked at smokers who consumed unknown amount of noni juice and saw lower levels of aromatic DNA adducts and plasma superoxide anion radicals.

**Keywords:** *M. citrifolia*; Anti-Diabetic; Anti-Cancer; Phytochemical; Pharmacological Activity

### Introduction

*Citrifolia Morinda* Linn is common little evergreen tree or shrub in Rubiaceae family. *Morinda citrifolia* is Southeast Asian natural plant. It is grown in India, Malaysia, Caribbean, Polynesia, Central and North America, as well as Australia. Tree may reach height of 6 m and bears brilliant green oval-shaped leaves that are 10 to 30 cm in length. Fruits are ovoid in form and have terrible butyric acid odour and astringent taste when ripe. Seeds have air sac at one end that allows them to float, which helps to explain why Noni trees are so common in Indo-Pacific islands. Number of *in vitro* and *in vivo* investigations has previously been completed. Fruits, leaves, roots, and seeds of *Morinda citrifolia* are extensively employed in certain common medicine, including herbal and other

treatments, and variety of therapeutic benefits of *Morinda citrifolia* have previously been researched. *Morinda citrifolia* applications have been documented for all parts of plant, including fruit leaves and seeds, with most common and topically utilised being fruit leaves. Noni has been subject of large number of biological and chemical research dating back over 100 years in response to its ethnobotanical and popular usage [1].

The global prevalence of chronic inflammatory metabolic diseases such as type 2 diabetes (T2D) is rising. By 2030, prevalence of T2D is predicted to rise from 2.8 percent in 2000 to 4.4 percent. T2D-related fatalities are also predicted to increase globally between 2005 and 2030 [2]. T2D affects 25.8 million people in United

States, or 8.3% of population, including children and adolescents. T2D is frequently accompanied by metabolic problems such as dyslipidemia, hypertension, or vascular endothelial dysfunction, which can lead to micro- and macro vascular consequences [2]. Noni bark and roots were traditionally used to dye or clothe, but all plant components, including leaves and fruits, were primarily used medicinally to treat wounds, infections, menstrual cramps, bowel irregularity, diabetes, high blood pressure, or as purgative. Table 1 lists traditional and current applications of noni based on published literature, some of which have been thoroughly studied elsewhere. Goal of this study was to perform Medline search to find any studies that supported notion that noni juice or its extract had anticancer and/or immunostimulant effects. These Medline articles were utilised to provide evidence-based answer for physicians replying to patients who inquired about usefulness of noni juice in treatment of cancer. brief overview of plant, several varieties of noni juice, history of medicinal usage, review of research (*in vitro* studies, *in vivo* animal studies, *in vivo* human studies, case studies, safety), and suggested evidence-based response for customers are all included below [3].

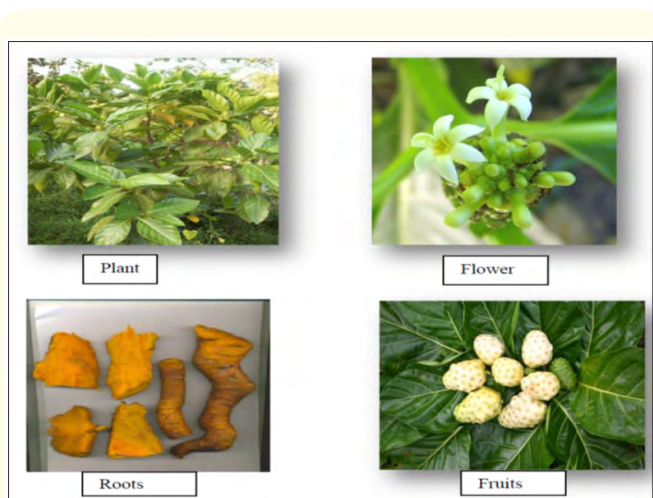
beta-carotenoids, ketones, lactones, terpenoids, proxeronine, and other constituents are found in *Morinda citrifolia* fruit extract. Fruit of *Morinda citrifolia* with physicochemical, phytochemical, and antibacterial characteristics was gathered at various maturity levels and studied. Phytochemical constituents of *Morinda citrifolia* have also been studied, including amino acids, fatty acids, lignin, anthraquinones, glycosides, sterols, alcohol and phenols, ester, and flavonoids. *M. citrifolia* fruit juice is healthy beverage that also has pharmacological effects. *Morinda citrifolia* juice can be utilised to establish brain protective mechanism known as post-ischemic glucose intolerance [4].

Plant parts	Types of compounds	Benefits
Fruit	Alkaloids (xeronin)	Increase enzyme activity and protein structure, activate immune Function.
	Polysaccharides (glucuronic acid, glycosides) Scopoletin	Immunostimulant, anticancer, antibacterial Dilates blood vessels, analgesic, antibacterial, antifungal, antiinflammatory, antihistamine
	Vitamin C	Antioxidants
	Dietary fiber	Lowering cholesterol, binding fat, regulating blood sugar levels
Leaf	Glycosides (flavonol glycosides)	Deworming, tuberculosis
Root	Anthraquinone (damnachantal)	Anticancer, antibacterial, antiseptic

**Table 1:** Shows findings of qualitative study of phytochemical substances found in noni, as well as advantages they provide.

**Anti-diabetic activity of *Morinda citrifolia* (NONI)**

Diabetes mellitus is type of hyperglycemia characterised by absolute insulin shortage or reduced insulin sensitivity in cells. Diabetes is metabolic disease caused by lack of insulin. The goal of this study was to see if *Morinda citrifolia* fruit juice had anti-diabetic effect. Wistar rats were used in the study, with 48 tails from four different groups being examined. Three groups of 36 mice were given single i/p 5 percent w/v alloxan monohydrate in normal saline to develop diabetes. One group was used as healthy control (Group-I), while other was used as diabetic control (Group-



**Figure 1:** Plant and Its Parts.

**Constituents of phytochemistry**

More than 160 phytoconstituents were found in *Morinda citrifolia* plant, with over 120 of them having nutraceutical characteristics and biological activity. Alcohols, phenols, micronutrients, acids, non-volatile and volatile components,

II). Effects of noni juice 2 mg/kg BW (Group-IV) were compared to typical standard medication, metformin 100 mg/kg (Group -III). Medication was taken orally. On days 1, 14, and 28 after commencing therapy, blood glucose levels, triglycerides, total cholesterol, HDL, LDL, and haemoglobin were measured. Following introduction of diabetes blood glucose and increased triglyceride and total cholesterol levels, HDL and LDL concentrations fell statistically substantially, but haemoglobin levels remained unchanged [5]. Although noni juice receiving group had better results, best results were achieved with conventional anti-diabetic medications. Noni juice was also given to Sprague-Dawley rats in studies done by other researchers. Study utilised twenty mature male Sprague-Dawley mice weighing between 145 and 230 g. They were separated into four groups, each of which had five mice. For course of research, first group (Group A) acted as control, receiving regular rat food and water [6]. Before introducing diabetes, four-week pre-treatment with noni juice was given to second group (Group B). Noni juice therapy was continued for remaining four weeks of diabetes induction in this group. After four weeks of diabetes induction, Group C got noni juice therapy. For four weeks before induction of diabetes with alloxan, Group D received distilled water at dose of 1 mL/150 mg body weight, distilled water at dose of 1 mL/150 mg body weight for four weeks after induction of diabetes with alloxan, and distilled water at dose of 1 mL/150 mg body weight for four weeks after induction of diabetes with alloxan. glycemia levels of animals in each of four groups were measured and compared. Glycemic control and treatment outcomes were greatest in mice given prophylactic noni juice (group B) before development of diabetes with alloxan. However, when noni juice therapy was stopped, hyperglycemia was reversed. Noni juice showed blood-glucose-lowering action in Sprague-Dawley rats following trial-induced diabetes, according to this study. Another study looked at effects of noni (*Morinda citrifolia* L.) fruit extract in diabetic rats and alloxan-induced diabetic mice utilising glucose tolerance technique. glucose tolerance test in mice revealed reduction in blood glucose levels of 37.0 percent, 27.4%, and 25.4 percent 30 minutes, 60 minutes, and 90 minutes after receiving extract at dosage of 500 mg/kg BW; and 28.8 percent, 19.6 percent, and 21.8 percent at dose of 1000 mg/kg. The results of this study showed that noni fruit extract decreased blood glucose levels in rats when measured using glucose tolerance technique, although difference was not statistically significant. Noni fruit extract

exhibited substantial antidiabetic efficacy in diabetic mice tested with alloxan at 500 and 1000 mg/kg BW. ethnobotanical study of traditional medical practitioners, herbalists, and herb merchants in Lagos State, Southwestern Nigeria, found that noni leaf juice, given twice daily for 12–16 weeks, was one of most common traditional herbal treatments for diabetes treatment. Another ethnopharmacological study found that majority of diabetics in Mauritius used NJ made from peeled and crushed fruits, and that it was either prescribed or recommended by majority of traditional healers [7]. According to respondents NJ was also professed to be used to treat diabetic neuropathy, diabetic dyslipidemia, and hypertension. When noni and Atrovastatin were used together to treat hypercholesterolemia, one adverse event occurred in form of diarrhoea. In each of these surveys, however, actual treatment results were not specified. Noni, on other hand, had no impact on decreasing blood glucose among two users in recent ethnopharmacological survey from Republic of Palau, but was beneficial for weight reduction across all 15 users and decreased high blood pressure in 42% of users. In 2002, first scientific trial investigating health effects of noni fruit began and ended in 2007. toxicity and effectiveness of freeze-dried ripe noni fruit extracts in cancer patients to regress advanced tumours was studied in phase-I clinical experiment, which was previously reviewed. For 28 days, patients were divided into five groups and given two, four, six, eight, or ten grammes of noni each day. While no adverse events were detected, all noni dosages showed substantial decrease in pain, as well as non-significant dose response for global health status [8]. Despite improvements in quality of life, noni did not show any therapeutic benefits on tumour regression, with exception of one patient with advanced stomach cancer who did not have any disease progression for 40 months while taking noni. Despite fact that there are numerous kinds of NJ on market, only Tahitian noni juice has been subjected to scientific trials. After oral treatment of *Morinda officinalis* root extracts to rats, pharmacokinetics of noni iridoid glycosides, monotropein, and deacetylasperulosidic acid were investigated. Monotropein had shorter half-life and was removed quicker than deacetylasperulosidic acid, according to plasma concentrations. Several additional bioactive components have been shown to be bioavailable in humans, including flavonoid quercetin (3, 30, 40, 5, 7-pentahydroxyflavone) and its glycoside, rutin (quercetin-3-O-b-rutinoside). The rising number of research have been prompted by growing number of diabetes patients

who embrace integrative or functional therapy. The anti-diabetic benefits of *M. citrifolia* in mice fed high-fat diet were studied by Nerurkar, *et al.* (2012). It was discovered that phosphorylation of transcription factor FOXO1 improved glucose metabolism. Similarly, it was discovered that using *M. citrifolia* juice to treat induced diabetes in mice resulted in lower blood glucose levels. When taken in conjunction with insulin, noni has synergistic effect. In study conducted by Kamiya, *et al.* (2008), hypoglycemic and hepatoprotective effects in diabetes-induced rats were investigated. Streptozotocin was used to cause diabetes. Diabetic experimental mice were assessed and treated for 20.0 days with *Morinda citrifolia* juice (02 ml/kg, twice day) and diabetic standard with glibenclamide, reference hypoglycemic medication. The blood glucose levels in both groups were significantly lower [9].

#### Anti-cancer activity of *Morinda citrifolia* (NONI)

*Morinda citrifolia* has been utilised for health issues and pharmacological actions such as anticancer, antiepileptic, antiinflammatory, antidiabetic, antioxidant, and other properties for numerous years. Polyphenols and flavonoids, which are found in noni, have been studied. Studies have shown that phytochemicals, particularly polyphenols, have antioxidant qualities and can assist to reduce risk of degenerative illnesses like cancer. Damnacanthol is medicinally useful component found in leaves and roots of Noni plant that has been used to treat variety of chronic illnesses including heart disease and cancer. Through cyclooxygenase2 (COX2) suppression, key inflammatory marker, and rise of tumour (cancer) suppressor gene, ethanolic extract of Noni fruit and leaves works on tumour cells and pathways involved in immune response [10]. In patients with various forms of cancer, *Morinda citrifolia* plant was utilised as medicinal or dietary supplement. Lim, *et al.* (2016) conducted study that demonstrated action of ethanolic extract of *M. citrifolia* fruit or leaves on tumour cells and pathways involved in immunological response via cyclooxygenase 2 (COX2) suppression, important inflammatory marker, and rise of tumor(cancer) suppressor gene and concentrated fruit on tumour cells and pathways involved in immunological response via cyclooxygenase 2 (COX2) suppression, important inflammatory marker, and Carcinogenic compounds tag covalently to DNA, forming structures known as diffract that, if not repaired, cause mutations. injection of 10% TNJ® in laboratory animals also prevents gene mutations: carcinogenic compounds tag covalently

to DNA, forming structures known as diffracts that, if not repaired, cause mutations [11]. *Morinda citrifolia* can be utilised to prevent these formations from forming. notion that *Morinda citrifolia*, L has cancer-preventive action during beginning stage of carcinogenesis was investigated by Liu, *et al.* According to early findings, soaking 10 percent Noni Juice produced from *Morinda citrifolia* fruit in drinking water for one week prevented development of DMBA-DNA adducts. Female SD rats had 30 percent less DMBA-DNA adducts in their hearts, 41 percent fewer in their lungs, 42 percent fewer in their livers, and 80 percent fewer in their kidneys. Male C57 BL-6 mice showed even more significant results: 10% noni reduced DMBA-DNA adduct formation by 60% in heart, 50% in lung, 70% in liver, and 90% in kidney. antioxidant activity of Noni was tested *in vitro* using lipid hydro peroxide (LPO) and Tetrazolium nitroblue (TNB) tests to investigate mechanism of this protective action. Findings imply that noni's antioxidant activity and inhibition of carcinogen-DNA adduct formation may contribute to *Morinda citrifolia's* cancer-preventive action [12]. Majority of breast cancer treatment, according to Rangadhar, is surgery when tumour is confined, with potential adjuvant chemotherapy and/or radiation. Patients are broadly classified into high risk and low risk cases based on clinical criteria (age, kind of cancer, size, metastasis), with each risk group following distinct treatment protocols. Radiation therapy, chemotherapy, hormone therapy, and immune therapy are all options for treatment. Nothing can ensure you won't have breast cancer. Chemotherapy and radiation have several side effects that make patient's condition worse than disease itself. Due to its immunological boosting and nutritive complementing properties, Indian Noni helps to overcome majority of adverse effects of all cancer cases, including breast cancer. It also includes number of bio anti-carcinogenic substances that aid in improving efficacy of cancer treatment [13]. It can be used as primary preventive strategy, secondary prevention tool, or adjuvant immune boosting supplement in conjunction with standard cancer treatment. cytotoxic effects of water and ethanol extracts of whole noni fruit, pulp, peel, and seed were examined on HMEC (Clonetics Human Mammary Epithelial Cells), MCF-7 breast cancer, and invasive version of MCF-7 (MCF-7i), which was created in our lab, by Johnson, *et al.* cytotoxicity of noni extracts on all three cell lines was determined using XTT procedure from Boehringer Mannheim and ToxiLight and ViaLight HS methods from Bio Whittaker. Noni has general cytotoxic impact on normal breast epithelial HMEC



cells, non-invasive and invasive breast cancer cells MCF-7 and MCF-7i, according to preliminary findings. Takashima, *et al.* (2007) revealed that novel compounds derived from leaves (not fruit) of *Morinda citrifolia* did not demonstrate cytotoxic action by themselves, but only when combined with tumour necrosis factor-related apoptosis-inducing ligand (TRAIL). This research is similar to Liu and colleagues' previous findings, which found that TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) can cause apoptosis in some tumour cells [14]. Furthermore, TRAIL and chemotherapy can work together, presumably due to chemotherapy-induced increases in expression of TRAIL receptor called DR5. Hornick, *et al.* (2003) observed that noni juice with 5 percent vol/vol or above prevents start of new vascular sprouts from placental vein explants in another research associating noni juice indirectly to anticancer action. 10% noni growth medium caused apoptosis in wells of human breast tumour explants, with vasculature quickly degenerating within 2–3 days. Hornick concluded that action of noni juice was not mediated by immune system since no leukocytes were found in culture. Punjanon (2006) investigated effects of crude extract of noni fruit (0.1 mg/mL) on cancer cell lines. percent cytotoxicity ranged from 0 to 36 percent, and degree of efficacy, like with many possible anticancer drugs, was dependent on kind of malignancy. In this example, noni extract suppressed neuroblastoma (36 percent) and breast cancer (29 percent) cell lines more efficiently than hamster (6 percent) or green monkey (0 percent) kidney cells, with just little effect on human laryngeal cells (13 percent) [15]. However, kidney cancer is tough malignancy to cure in general, and any reduction of cancer cell growth implies that noni extract contains anticancer ingredient or combination of substances. Rats were given Tahitian noniW juice in study done by Wang and Su (2001) and financed by noni juice firm (concentration not reported). Three rats from each group were administered 25 mg/kg DMBA intragastrically and then killed after 24 hours. Tahitian noniW juice group was shown to have lower levels of DMBA-DBA adduct production in their organs, which is precursor to chemical carcinogenesis. Rat survival rates were not provided. Adriamycin, bleomycin, camptothecin, cisplatin, etoposide, 5-fluorouracil, imexon, interferon, mitomycin-C, and vincristine were all shown to have synergistic or additive positive effects with noniprecipitate, according to Furusawa, *et al.* (2003). When coupled with paclitaxel, cytosine arabinoside, or immunosuppressive anticancer medicines such cyclophosphamide,

methotrexate, or 6-thioguanine, it was not effective. Noniprecipitate exhibited greater immunomodulatory impact when coupled with imexon, but not with MVE-2 (maleic anhydride divinylether) copolymer. Mice administered noni-precipitate and exposed to sarcoma tumour cells (S180) exhibited cure rate of 25% to 45 percent. Macrophage inhibitors (2-chloroadenosine), T cells (cyclosporine), and natural killer (NK) cells (anti-asialo GM1 antibody) all reduced cure rate. Interferon improved chance of survival from 71% to 100%. In another study, mice (five in treatment group and five in water control) were given Tahitian noniW juice (1 percent or 1 mg/mL, concentration of noni juice in commercial product not specified) orally and ad libitum for 16 days, resulting in decreased IL-4 but increased interferon gamma production. They also performed *in vitro* test using splenocytes and peritoneal exudate cells from animals. immune system was shown to be modulated by Tahitian noniW juice and noni fruit juice concentrates (NFJC, 5 percent or 5 mg/mL from noni fruit puree) via activating CB2 (cannabinoid) receptors while inhibiting CB1 receptors. noni precipitate was injected into animals rather than given to them orally in majority of noni experiments mentioned above. Li and colleagues used intraperitoneal injection in 2008 study looking at anticancer effects of noni exudate in sarcoma 180 ascites animal model. findings of numerous mini-experiments were presented in this paper; however graphics rendered results difficult to understand. To discover active components, they did CD marker profile research, preventive study, treatment study, and lastly fractionation and tumour analysis. In preventive and therapy experiments, they utilised four nude mice per group and four beige mice per group. Noni juice was used to treat stomach cancer patients in two case studies, according to Wong. first case was 69-year-old man who was told by four doctors that if he didn't have surgery, he would die in few months. When refusing surgery, patient became bedridden after his weight plummeted from 165 to 79 pounds in just two months. He began consuming homemade noni juice, and after month, his health improved, and he stopped self-treating after six months. He had no stomach symptoms seven years later, but biopsy revealed histology that was identical to that of his first malignancy, so he self-treated with noni juice again, with no reported results. antiproliferative activity of methanolic extract of *M. citrifolia* fruit has been demonstrated in variety of cell lines, including human breast cancer and neuroblastoma, green monkey kidney (Vero) cells, baby hamster kidney (BHK) cells, and African

human epithelial type 2 cells (Hep2). When ethanolic extract of *Morinda citrifolia* was evaluated in B16-F10 melanoma cells, it showed antiproliferative activity (LAN5). According to Hirazumi, *et al.* (1994), ethanolic extract of Noni leaves reduces expression of epidermal growth factor receptor (EGFR), lung adenocarcinoma biomarker, in albino mice while acting on Lewis lung cancer in synergetic animals [16].

## Conclusion

According to findings, *Morinda citrifolia* has many phytochemical components, has been studied *in vitro* and *in vivo*, and has strong action with favourable safety profile for treating patients with various diseases or illnesses. Finally, we discovered that taking *Morinda citrifolia* fruit and leaf extract and understanding its processes may help to avoid diabetes and cancer. According to findings, *Morinda citrifolia* has many phytochemical components, has been studied *in vitro* and *in vivo*, and has strong action with favourable safety profile for treating patients with various diseases or illnesses. Finally, we discovered that taking *Morinda citrifolia* fruit and leaf extract and understanding its processes may help to avoid diabetes and cancer.

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