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Effects and Molecular Mode of Action of Noni (*Morindacitrifolia*) Juice And Its Active Components.

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ABSTRACT

Morindacitrifolia, also known as noni belongs to the family Rubiaceae has been in high demand in ayurvedic medicine. It has been used long since in various cultures as a medicine for cure of various ailments. This review attempts to analyze the evidence for the claim as a therapeutic cure for many diseases. This review article is presented to compile all the updated information on its phytochemical and pharmacological activities. Studies indicate fruit juice possesses antioxidant, anti-inflammatory, apoptotic and anticancer, properties. Various effects like antibacterial, anti-fungal, anti HIV, antiboneresorption, antispasmodic, antipyretic, anti-diarrheal, anti-allergic, immunomodulation, cardiogenic, hypo-lipidemic, anti-microbial, gastro-protective have been studied. Clinical trials using this fruit juice for a variety of conditions should also be conducted. Currently the market is flooded with products with claim cure for all ailments. This review analyzes the beneficial effects of the use of Morinda Citrofolia. Evidence based result shows that consumption of noni could be beneficial both protective and curative

Keywords: Ayurvedic drugs, alternative therapy, chronic ailments, molecular mechanism.

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INTRODUCTION

Morindacitrifolia also called noni or Indian mulberry has been used from ancient past as food and medicine. The Polynesians used it widely as a medicine and claimed it having healing properties. Currently with the shortage of effective allopathic cure, there is trend towards usage of ayurvedic and traditional medicinal practices for use in chronic diseases. In these diseases, modern medicines could not be taken for a prolonged period of time due to the adverse effects of the drugs and thus as a result more and more people are looking for alternative therapy. In this context Morindacitrifolia has gained popularity both due to/for its traditional usage and its ability to maintain general health [1]. It is commonly marked as Tahiti noni juice (TNJ) with fruit extract of Hawaii origin.

A number of major essential therapeutic constituents have been identified in the noni plant: namely, scopoletin, octoanoic acid, potassium, vitamin C, terpenoids, alkaloids, anthraquinones, β -sitosterol, carotene, vitamin A, flavone glycosides, linoleic acid, amino acids, calcium, and phosphorus [2-6]. The therapeutic uses of Morindacitrifolia are wide and varied including anti-bacterial, antiviral, antifungal, antitumor, antihelminthic, analgesic, hypotensive, anti-inflammatory, and immune enhancing effects [7].

A few of the medicinal uses are for digestive problems such as diarrhea, intestinal worms, nausea, food poisoning; respiratory illness such as congestive cough, dry cough, tuberculosis, cholera, infant chest colds and sore throat; cardiovascular disorder like hypertension; inflammatory conditions such as arthritis, asthma, abscesses, mastitis, gout and other bone joint problems. Other common uses of noni has been in the area of skin conditions where it is being utilized for treating wounds, ulcers, abscesses, menstrual cramps, gastric ulcers, ring worm, boils, cellulitis, swellings, scalp conditions and sores. It has been used in the treatment of tumors and broken bones, jaundice and other forms of liver disease. It has been used to treat dysentery, hypercholesterolemia, and diabetes [8, 3]. Other than the medical roles; it is also a noted analgesic or pain reliever. With these documented traditional knowledge on health benefits, Morindacitrifolia has been marketed as noni juice and has been widely consumed worldwide. This review is to analyze the current status of benefits of using noni and documented mechanistic evidence regarding the same.

MATERIALS AND METHODS

A detailed search was conducted using PUBMED (<http://www.pubmed.com/>) to find the current trends regarding therapeutic benefits. Search results were refined using key words like clinical trial, patient's interview and toxic effects documented during the consumption period. Total of 40 articles were found to be relevant to the search and the information was documented.

Phytochemistry:

It is proven that the biological properties of Noni have been attributed to its active components. These active components in noni are classified under the molecular groups including flavonoids, glycosides, vitamins, anthraquinones and polyunsaturated fatty acids [9, 3]. Other than these groups, studies in in-vitro and in-vivo animal models suggest that the presence of active components such as polysaccharide rich substances which have antitumor effects [10]. In clinical trials utilizing the extracts, however, noni has yet to be substantiated to have anticancer activity. However, with their diverse nutrient range and multiple clinical roles against various disorders, noni juice has been recommended as food supplement and allowed for use in the United States since 1996 and by the European Commission in 2003.

Specifically, the molecules, their associated cellular therapeutic actions and related clinical study carried out using Morindacitrifolia are listed in (Table I)

The table I shows the components and their biological action. Some components have not been proved to be beneficial clinically. Long term clinical studies were not found, however prolonged use as native medicine justifies its potential. Toxicity mostly liver dysfunction has been reported.

Active component	Action	Benefit	Clinical/ Animal Study	Results/ongoing
Precursor of Xeronine[11]	Modify the molecular of structure of protein	Reduces blood pressure, menstrual cramps, arthritis, sprain, injuries, mental depression, senility	10 subjects, one month open trial. Brigham Young university Hawaii [3]	Reduced systolic blood pressure.
Scopoletin[12]	Provides immune resistance.	Found in most organs after continuous consumption.	Study in mice shows increased weight of thymus [2, 3]	Can be used in cancer prevention.
TNJ	Reduces free radical injury. Prevents apoptosis. COX2 and COX1 inhibitor	Prevents ageing Reduces inflammation and cancer prevention [13-15]. Joint health of the neck (cervical spondylitis)	285 people, double-blind, placebo-control, one month trial. The University of Illinois College of Medicine and TNI R&D. 203 people, double-blind, placebo-controlled, one month trial. The University of Illinois College of Medicine 90 people, therapeutic control groups, one month trial. Nigerian Journal of Health and Biomedical Sciences	As little as 1 serving TNJ per day (30 mL or 1 oz) lowered free radicals significantly. As little as 1 serving TNJ per day (30 mL or 1 oz) lowered amount of DNA damage by approximately half Serving of TNJ alone improved range of movement & pain; combination therapy had benefits
Damnacanthal Anthroquinone	Prevents natural killer cells from multiplication in malignant tumors. Prevents ras oncogene [14]. Anti-fungal action improves immunity.	Preventive in dermoid and cervical cancer [13]. Anti-inflammatory, Anti-bacterial, parasite infection, reduces thrombosis.	Treatment of cervical cancer. . Ras oncogene associated with lung, colon, pancreas cancers and leukemia's [14, 15]. <i>In vitro</i> inhibition of staphylococcus aureus and E.coli.used an animal model to demonstrate that noni leaf extract had therapeutic benefits in wound healing [16].	Can be used as adjuvant therapy. Prevents infection
Glycosides betasterol.	Anti-diuretic, improves immunity, lowers cholesterol.	Reduces risk of thrombosis.	132 people , double-blind, placebo-control, one month trial [43]	Cholesterol lowered by as much as 22%, triglycerides by as much as 54%, HDL increased by as much as 16%
Alcohol extract of noni.	Stimulates release of TNF- α , Interleukin -1 β , IL-10, IL-12, IFN - γ and nitric oxide.	Immunologic benefit. Improves thymus function and T cell immunity.	Animal study on mice shows inhibition of tumors [17].	Prevent towards tumors caused by T cell immunity.
Acetone, chloroform, methanol, ethanol extract of noni.	Known to inhibit 87% of tubercle bacilli [2]	Anti-tubercular activity [18]	No documented long term study.	Could be used along with anti-tubercular drugs.

Phenolic compounds-Anti microbial activity	Inhibitory effect on common pathogens	Prevents infection and improves immunity.	<i>In vitro</i> study for anti-bacterial action on cell lines B16-F10 cells [19].	Inhibition of growth of <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> .
Noni seed extract	Prevents free radical injury and anti-ageing effect	Prevention of skin cancer	The study was to examine whether a 50% ethanolic extract of the seeds of <i>Morinda citrifolia</i> and its constituents have matrix metalloproteinase-1 (MMP-1) inhibitory activity in UVA-irradiated normal human dermal fibroblasts (NHDFs)[20].	The extracted <i>Morinda citrifolia</i> (10µg/mL) inhibited MMP-1 secretion from UVA-irradiated NHDFs, without cytotoxic effects, at 48h after UV exposure. These results suggested that 1 suppresses intracellular MMP-1 expression, and consequent secretion from UVA-irradiated NHDFs, by down-regulation of MAPKs phosphorylation [20].
Eugenol	Analgesic ,counter irritant	Dental pain relieving[21]n Can be used in root canal irrigant[22]	Long term clinical studies to be done.	.
Serotonin	It is well established that serotonin is an important brain neurotransmitter, and plays a significant role in temperature regulation, sleep, hunger and sexual behavior.	Serotonin deficiency has been implicated in a number of pathological conditions including migraine headaches, obesity, depression and Alzheimer's disease	Research at the University of Hawaii's Biomedical Sciences Department	Could be used as substitute for drug like Prozac as it does not have adverse effect.
Analgesic effect of TNJ, thus providing scope for the potential, natural analgesic compounds [1].	The data from this experiment also indicated that noni juice was able to make the animals tolerate more pain		Wang and Fu examined the analgesic properties of TNJ "twisted method" animal model	
Toxicity studies	No adverse effect on long term intake		Study done on rat model for subacute toxicity by giving 500mg /day for 13 weeks [22]. R Study on guinea pigs for toxicity[23,24]	It was concluded that the no-observed-adverse-effect level (NOAEL) for <i>Morinda citrifolia</i> was 5000 mg/kg body weight/day No allergic reaction noted

Pharmacology:

Only a few pharmacological investigations have been carried out based on the ingredients present but thus the molecular mechanism of action is yet to be explored in complete detail. A summary of the mechanistic findings of the pharmacological studies is presented below.

Anti-bacterial:

In Polynesian culture noni has been used as native medicine to treat infection [25, 26]. Studies have shown that the fruit extract of *Morindacitrifolia* have anti-bacterial action against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella* and *Shigella* [27, 28]. Not only the aqueous fruit extract, and even the ethanolic extract of the fruit has shown potent anti-bacterial activity [19, 16]. Thus the therapeutic applications include treatment of infections in the skin, cold and fever [25, 27].

The added clinical benefit of anti-bacterial activity is that it could promote better wound healing. Likewise the action against *Helicobacter pylori* can be used to treat peptic ulcer [28, 29]. Bushnell and Leach demonstrated that acetone extracts obtained from *Morindacitrifolia*, showed antibacterial activity. In an in vitro anti-fungal assay *M. citrifolia* fruit extract showed activity against *Trichophytonmentagrophytes*, *Penicillium sp.*, *Fusarium sp.* *Rhizopus* [29] and *C. albicans*

These widespread medicinal uses of this plant would suggest that the pharmacologically active substances and alternative methods of extraction and screening should be utilized in obtaining the major bioactive component in the plants for the purpose of new drug development [30]. In an in vitro anti-fungal assay *M. citrifolia* fruit extract showed activity against *Trichophytonmentagrophytes*, *Penicillium sp.*, *Fusarium sp.* *Rhizopus* [29] and *C. albicans*.

Some of the specific components in noni which contribute to this bactericidal property are acubin, L-asperloside, alizarin and anthraquinone. Though bacterial infection could be treated allopathically with already existing drugs, still current treatment especially of nosocomial origin is difficult to treat due to emergence of drug resistant bacterial species.

Antioxidant Activities:

Most chronic diseases are common in aged individuals as they are more susceptible to increased oxidative damage of tissues. Most debilitating diseases like osteoarthritis, cervical spondylitis and osteoporosis repair can be better managed if the therapy could limit disease. The array of anti-oxidant mix in noni could help not only in reducing the progress of disease but also in preventing further damage to the tissues. Currently some of the active component of noni has been characterized for its anti-oxidant effect. The American and African origin fruits seem to show potent antioxidant activity [31]. For instance, deacetylasperulosidic acid (DAA) is a major phytochemical constituent of *Morindacitrifolia* (noni) fruit and supportively noni juice has demonstrated to have very high antioxidant activity in in vivo and in human trials. In these studies, serum malondialdehyde concentration, superoxide dismutase and glutathione peroxidase activities were measured and compared among groups. A dose-dependent reduction in malondialdehyde was evident as well as a dose-dependent increase in superoxide dismutase activity, and clearly these results suggest that DAA contributes to the antioxidant activity of noni juice by increasing superoxide dismutase activity. These active components may explain the mechanism of action for the antioxidant properties in human clinical trial [32].

Anti-Diabetic role:

Methanolic extract from fruits of *M. citrifolia* showed potential stimulatory effects on glucose uptake in 3T3-L1 adipocyte cells, indicating the potential role of lignans as lead molecules for antidiabetic agents [33]. Also in in vitro alloxan induced diabetic animals, noni juice augments insulin action [34]. The effect Tahitian Noni juice (TNJ) on blood glucose level in streptozotocin (STZ) induced diabetic rats has been assessed, by reducing the intestinal absorption of glucose TNJ possess hypoglycaemic activity [35]. Results from this research suggest that TNJ can possibly help in the treatment of diabetes. Noni fruit juice inhibited weight gain, and improved glucose level maintenance insulin tolerance and fasting glucose in high fat diet-fed mice. During glucose metabolism regulation noni fruit inhibits hepatic FoxO1 mRNA expression, with a concomitant increase in FoxO1 phosphorylation and nuclear expulsion of the proteins. In addition noni juice significantly inhibits gluconeogenic genes, phosphoenolpyruvate C kinase (PEPCK) and glucose-6-phosphatase (G6Pase) in mice fed with high fat diet (Fig 1) [36].

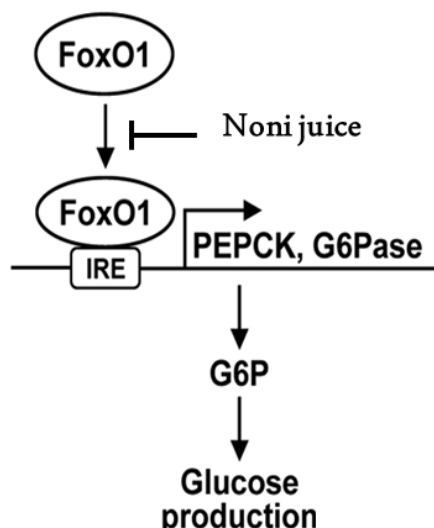


Fig 1: Glucose metabolism regulation by noni fruit

Noni fruit inhibits hepatic FoxO1 mRNA expression. Increase in FoxO1 phosphorylation and nuclear expulsion of the proteins significantly inhibits gluconeogenic genes, phosphoenol pyruvate C kinase (PEPCK) and glucose-6-phosphatase (G6Pase) in mice fed with high fat diet

Anti-inflammatory Activities:

In an in vitro study, the anti-inflammatory activity of *M. citrifolia* fruit juice was detected by measuring its direct inhibitory activities on cyclooxygenase (COX)-1 and -2 [37, 38]. The in vivo study on Tahitian *M. citrifolia* fruit juice comparing to the existing anti-inflammatory drugs, showed a significant reduction in the induced carrageenan paw edema in rats, revealing a strong anti-inflammatory effect comparable to that of non-steroidal inflammatory drugs, such as acetylsalicylic acid, indomethacin and celecoxib, without side effects [33]. Mechanistically, noni at 6% concentration increased the expression of Toll like receptor -4 (TLR-4) and TLR-5, chemokines, interleukin-8 (IL-8), interleukin-12 (IL-12), and decreased the expression of IL-6 and TLR-7, 4% Noni stimulated the expression of TLR-3 in blood and gut tissue of chickens. Over expression of IL-12 and IL-8, TLR-3, TLR-4 and TLR-5 indicate antiviral and antibacterial properties and decreased expression of IL-6 indicates the anti-inflammatory property of noni fruit extract. However, Noni had no effects on immunoglobulins or α 1-acid glycoprotein concentration. Further investigations have to be done to find the active ingredients present in Noni and their effects on viral and bacterial infections which could help commercializing the molecules [39].

Bone regeneration:

The effect of noni on inducing osteogenesis in bone mesenchymal stem cells was studied in vitro and in vivo. Results showed that at a concentration of 200 μ M it induced osteogenic changes and more bone regeneration was noted in the animal model [40].

Anti-cancer activities:

Currently there is growing interest on anticancer drugs or remedies with minimal or no side effects. Most chemo therapeutic drugs presently available are highly toxic. Studies on noni have shown to have anti-cancerous effect also. This may be of particular advantage when used along with stem cell therapy, which have been implemented to have undergone mitotic change. Mesenchymal stem cells when clinically applied can support tumors through increased growth and/or protect the tumor by suppressing the immune response. Currently there are no evidence for direct causation however if used along with noni the potential for change could be limited [34-44].

Wang and coworkers demonstrate that a cytotoxic effect of TNJ on cultured leukemia cell line at various concentrations. TNJ on cultured cancer cells showed a dose-dependent cytotoxicity by inducing cancer cell necrosis at high doses and apoptotic at lower doses. Also a 50% ethanolic extract of the seeds of noni and its constituents have matrix metalloproteinase-1 (MMP-1) inhibitory activity in UVA – irradiated normal human dermal fibroblasts (NHDFs). The noni fruit extract (10µg/ml) inhibited MMP-1 secretion from UVA-irradiated NHDFs, without cytotoxic effects, at 48h after UV exposure. This is probably by suppression of intracellular MMP-1 expression, and consequent secretion from UVA-irradiated NHDFs through down-regulation of MAPK phosphorylation [20]. Noni fruit juice inhibited proliferative signalling like manganese induced expression of HIF-1 α (a tumorangiogenic transcription factor), extracellular-regulated protein kinase-1/2 (ERK-1/2), c-Jun N-terminal kinase-1 (JNK-1), protein kinase B (PKB), S6 and eukaryotic translation initiation factor-2 α (eIF-2 α) in A549 cells. Further studying individual isolated molecules and on more cancer cell lines could provide further information on cancer controlling mechanism (Fig 2) [45].

In this direction, Damnacanthal originated from *Morindacitrifolia* mediated apoptosis in SKHep 1 cells by sustained activation of the p38 MAPK pathway, leading to the transcription of the death receptor family genes encoding DR5/TRAIL and TNF-R1/TNF- α genes as well as the p53-regulated Bax gene. The damnacanthal-mediated expression of DR5/TRAIL and TNF-R1/TNF- α results in caspase 8 activation, leading to Bid cleavage. In turn, activated Bid, acting with p53-regulated Bax, leads to cytochrome c released from mitochondria into the cytoplasm. Combined activation of the death receptors and mitochondrial pathways results in activation of the downstream effector caspase 3, leading to cleavage of PARP and apoptosis (Fig.3A) [46]. Damnacanthal was shown to inhibit the oncogene Ras, p56lck tyrosine kinase, NF-KB pathway and induce apoptosis in vitro (14).

In addition, two novel glycosides 6-O-(β -D-glucopyranosyl)-1-O-octanoyl- β -D-glucopyranose and asperulosidic acid from noni juice, suppressed 12-O-tetradecanoylphorbol-13-acetate (TPA)- and epidermal growth factor (EGF)-induced AP-1 transactivation and cell transformation in mouse epidermal JB6 cells. TPA- or EGF-induced phosphorylation of c-Jun was also blocked by these compounds, indicating that c-Jun N-terminal kinases were critical in mediating AP-1 activity but not extracellular signal-regulated kinases or p38 kinases in cell transformation in JB6 cells (Fig.3B) [15].

The effect of TNJ on tumor growth suppression was studied in HERS/nue- over expression breast cancer. TNJ was found to reduce the tumor growth. This could be used as an adjuvant in cancer patients to reduce tumor size before surgery. Although further studies will be required to determine if TNJ has analogous actions in women as those discovered in this mouse model, tumorigenesis in MMTV-neu mice has many similarities to human HER2⁺ breast cancer [47].

Adverse reaction Noni has claim of being without adverse reaction when taken for a prolonged period. The use of noni for medicine dates as far as 2000 years ago. However currently studies are being done for clinical application and adverse effects have been a concern for most researchers. Most of the results point to noni being safe and without adverse defect on prolonged intake.

Two studies using guinea pigs were performed to assess the allergenic risk of TNJ. Both study designs included an induction phase and a rest period, followed by a challenge with Noni juice. Following the challenge, the animals were observed for 24 h. No allergic reactions to Noni juice were seen in this study [23, 5]. The second study involved forty-five guinea pigs. The study consisted of several test groups using various forms concentrations of noni juice with accompanying negative control groups. No positive allergic reactions were seen in any Noni group of the animals following the challenge [47]

No upper limit for safe consumption has yet been determined from these studies. The data indicates that TNJ may be safely consumed in amounts that are typical for fruit juice beverages, though the results of these studies only apply directly to *Morinda* TNJ [24, 25].

CONCLUSION

On the evidenced based data on the biological properties and clinical trials done now internationally on Noni it seems that it can be used for its beneficial effects on wound healing. However there are no direct

studies on its bone regenerative capacity, this study could an insight into its regenerative potential. The data also shows that it is relatively a safe agent to be used for therapeutic purposes.

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