

# Health Benefits of *Morinda citrifolia* (Noni): A Review

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## ABSTRACT

**Background:** *Morinda citrifolia* (Noni) has been used widely as a complementary and alternative therapy in many countries owing to its potent antioxidant activity and proven health benefits. Traditionally, it finds used as a therapeutic remedy to various diseases as an antibacterial, antitumor, anthelmintic, analgesic, anti-inflammatory, immunostimulant. Also it has proved beneficial in conditions like gastritis, skin diseases, respiratory infections, menstrual and urinary tract disorders, fever, diabetes and venereal diseases. **Objective:** This review emphasizes on the phytochemical and mineral profile of the different parts of Noni plant. In addition, this review corroborates the pharmacological basis for the various health benefits, traditional and medicinal applications of Noni. **Materials and Methods:** All the available information of Noni were collected from electronic databases such as Academic Journals, Ethnobotany, Ethnopharmacology, Springer, PubMed, Google Scholar, Science Direct and other primary and secondary sources. **Results:** According to our search results pertaining to scientific literature, *Morinda citrifolia* is used for more than 40 types of ailments worldwide. Crude extract of various parts of plant and fruit juice are reported

to contain amino acids, anthraquinones, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols, sugars, terpenoids etc. which are therapeutically useful for a broad range of pathological conditions. Fourteen human clinical trials have validated the remarkable health benefits of Noni.

**Conclusion:** Literatures prove that Noni is pharmacologically active and is used in different forms of cancer, viz. colon, esophageal, breast, colorectal cancers; cardiovascular diseases, diabetes, arthritis, hypertension. These properties are substantiated by the preclinical or/and clinical investigations.

**Key words:** *Morinda citrifolia*, Nutraceutical, Phyto-constituents, Antioxidant, Anticancer.

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## INTRODUCTION

*Morinda citrifolia* L. has been recognized as an important herb for treating various physiological disorders worldwide. *M. citrifolia* is commonly known as Indian mulberry or Noni in India.<sup>1</sup> Identifiable of this plant are its huge dark green and elliptical glossy leaves (Figure 1); white tubular flowers consisting of 75-90 ovoid to globose heads, 5-lobed white corolla (Figure 2). A yellowish-white ovoid lumpy bodied fruit approximately 12 cm in size composed of numerous, fused ripened ovaries each separate from white flower. The unripe fruit is dark green in color and the ripe fruit releases a strong butyric acid like decayed smell. The pulp is juicy and bitter, light dull yellowish white, gelatinous when the fruit is ripped; numerous hard triangular reddish brown pits are found (Figure 3).<sup>2</sup> The Noni juice is prepared from ripe Noni fruit which is having unpleasant odour and bitter taste. The fruit is covered with golden-brown pits containing four seeds. Each seed have an air sac at the end, which helps to drift in the water facilitating pollination (Figure 4).<sup>3,4</sup>

Noni plant exhibits a remarkably high therapeutic and safety profile that makes it popular as a health enhancer and food supplement worldwide.<sup>5</sup> The fruit contains hydrophilic compounds like carbohydrates, proteins, minerals, vitamins and small amount of fat (Table 1). The products obtained from the different parts of *M. citrifolia* plant viz. leaves, fruits, roots and barks are available in the market as Noni juice, capsule, powder, Noni concentrates, and also tea in the market. Among them Noni juice is most popular for its nutraceuticals and high therapeutic values around the globe. Noni juice has been recently established in European Union as a novel food.<sup>6</sup>

Though this review efforts have been made to provide ethnobotanical use, phytochemistry and scientific evidence for the therapeutic potential, discussing the pharmacology at a molecular level and the challenges confronted towards clinical validation of herbal medicines.

## Ethnobotanical use

It has been reported that *M. citrifolia* has wide range of therapeutic uses in ailments such as arthritis, burns, headache, wounds and skin infections.<sup>7</sup> Polynesian has been cultivated Noni more than 1000 years where it is used as a coloring agent, medicine and food. The root has been used for dyeing agents by the Australians and Indians for various gloom of red, purple and yellow.<sup>8</sup> Various parts of Noni plant such as stem, bark, root, leaf and fruits are used traditionally by Hawaiians and Tahitians as medicines for the treatment of ailments like cough, cold, pain and liver diseases, hypertension, blood pressure, tuberculosis, malaria, intestinal worms, diabetes, loss of appetite, hernias, urinary tract infection, menstrual disorder, cancer, cardiovascular diseases, arthritis etc. Seeds and its oil applied topically on the scalp as insecticide and used for the treatment of arthritis. Flowers find in application in case of insect stings. In Hawaii, Noni has been reported for topical use in conditions such as swellings, sprains, bruises and wounds.<sup>9,10</sup>

## Phytochemistry

It has been reported that different parts of Noni plant found to contain more than 160 phytoconstituents of which over 120 constituents have nutraceutical properties with proven biological activity.<sup>11</sup> The concise chemical nature of the plant is given in Table 2. Fermented fruit extract contain micronutrients, non-volatile and volatile components, ketones, lactones, beta-carotenoids, terpenoids, proxeronine.<sup>12</sup> Physicochemical, phytochemical and antimicrobial properties of Noni fruit collected at different maturity levels were investigated. The results showed the maximum antibacterial activity in ethanolic extract of mature Noni fruit against *K. Pneumonia* (21 mm) whereas in methanolic extract of mature Noni fruit showed maximum antifungal activity against *A. Flavous* (19 mm).<sup>13</sup>



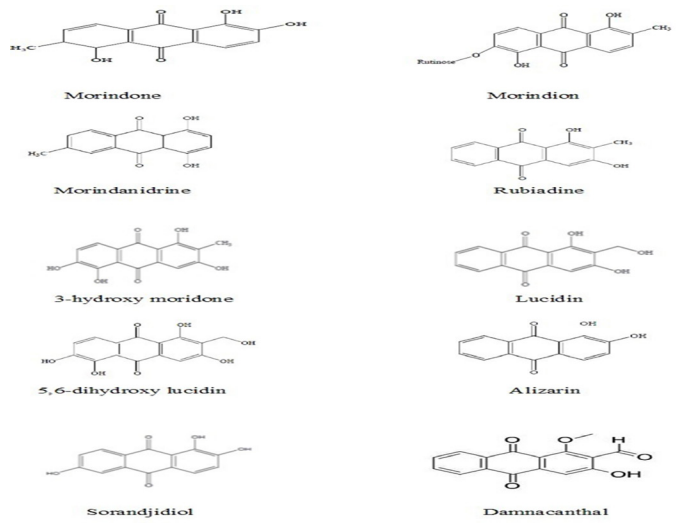
**Figure 1:** Noni plant.



**Figure 4:** Noni seeds.



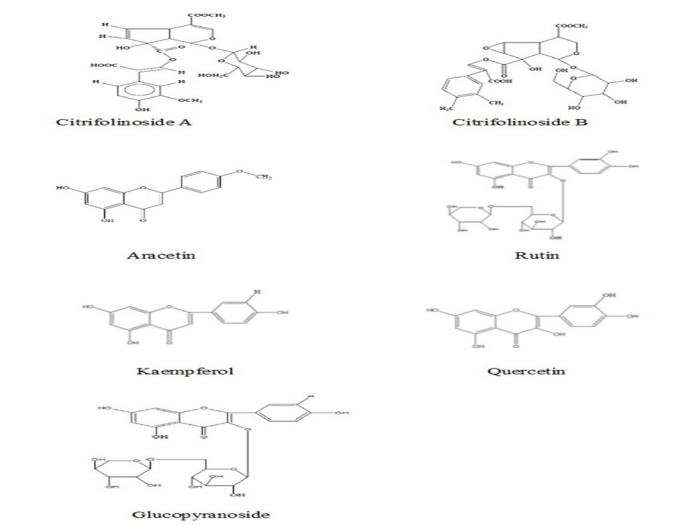
**Figure 2:** Noni flower.



**Figure 5:** Anthraquinone glycosides.<sup>14</sup>



**Figure 3:** Ripe and unripe fruits.



**Figure 6:** Miscellaneous glycosides.<sup>14</sup>

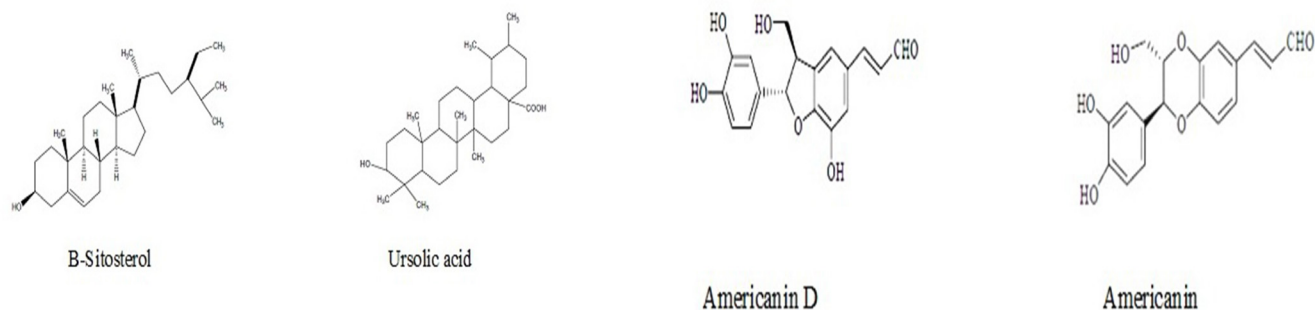


Figure 7: Sterol.<sup>14</sup>

Figure 10: Ligans.<sup>16</sup>

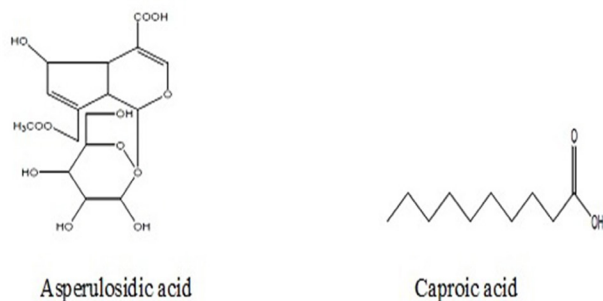


Figure 8: Asperulosidic acid, Caproic acid.<sup>14</sup>

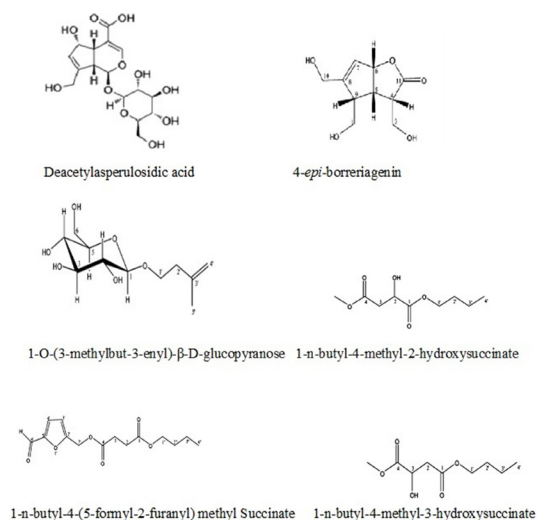


Figure 9: Deacetylasperulosidic acid, 4-epi-borriagenin, 1-O-(3-methylbut-3-enyl)-β-D-glucopyranose, 1-n-butyl-4-(5-formyl-2-furanyl) methyl Succinate, 1-n-butyl-4-methyl-2-hydroxysuccinate, 1-n-butyl-4-methyl-3-hydroxysuccinate glycosides.<sup>15</sup>

Table 1: Compositional profile of TNJ<sup>101</sup>

	Content	Unite
Proximate		
Moisture	89-90	g/100 g
Protein	0.2-0.5	g/100 g
Ash	0.2-0.3	g/100 g
Total fat	0.1-0.2	g/100 g
Total carbohydrate	9.0-11.0	g/100 g
Glucose	3.0-4.0	g/100g
Sucrose	<0.1	g/100 g
Energy	163-197	kJ/100 g
Dietary fiber	0.5 -1.0	g/100 g
<b>Vitamin</b>		
Vitamin C	3-25	mg/100 g
Vitamin B1	0.003-0.01	mg/100 g
Vitamin B2	0.003-0.01	mg/100 g
Vitamin B6	0.04-0.13	mg/100 g
Vitamin B12	0.1-0.3	mcg/100g
Folic acid	7.0-25.0	mcg/100 g
Biotin	1.5-5.0	mcg/100 g
Niacin	0.1-0.5	mg/100 g
Vitamin E	0.25-1.0	IU/100 g
Total carotene	18-22	IU/100 g
Pantothenic acid	0.15-0.5	mg/100 g
<b>Minerals</b>		
Calcium	20-25	mg/100 g
Iron	0.1-0.3	mg/100 g
Phosphorus	2.0-7.0	mg/100g
Magnesium	3.0-12	mg/100 g
Molybdenum	0.3-1.0	mg/100 g
Sodium	15.0-40.0	mg/100 g
Potassium	30.0-150	mg/100 g
Sodium chloride	0.09-0.12	%

**Table 2: Important chemical constituents of *Morinda citrifolia* along with their locations**

Chemical constituent	Part of Plant				Reference
	Frut	Leaf	Root	Plant	
Alizarin	+	-	+	-	[102][9] [103]
1,8-dihydroxy-2-methyl-3,7 Dimethoxyanthraquinone	-	-	-	+	[104]
Lusidin- $\omega$ -butyl ether	-	-	-	+	[104]
1,3-dihydroxy-2-Methylantraquinone	-	-	-	+	[104]
Trioxymethylantraquinone monoethyl ether	-	-	+	-	[38]
2-methyl-3,5,6-trihydroxyanthraquinone	-	-	-	+	[105]
Lusidin	-	-	-	+	[103]
5,6-dihydroxy lucidin	-	-	-	+	[9]
3-hydroxy morindone	-	-	-	+	[9]
Morindone	-	-	+	-	[4][103][105]
Damnacanthal	-	-	+	-	[75]
Rubiadinemonomethyl ether	-	-	+	-	[4]
Morindanidrine	-	-	+	-	[4]
Morindadiol	-	-	+	-	[4]
<b>Glycosides</b>					
$\beta$ -D-glucopyranoside	-	+	-	-	[75]
Citrofolinin-A	-	+	-	-	[102]
Asperulosidetetraacetate	+	-	-	-	[31][106]
$\beta$ -D-galactopyranoside	-	+	-	-	[75]
Kaempferol	-	+	-	-	[107]
Quercetin (Rutin)	-	+	-	-	[107]
Citrifolinoside-B	-	+	-	-	[75]
<b>Sterols</b>					
$\beta$ - sitosterol	-	+	-	-	[108]
<b>Acids</b>					
Caprylic acid	+	-	-	-	[4][109][102]
Caproic acid	+	-	-	-	[38]
Linoleic acid	-	-	-	+	[4]
Octanoic acid	+	-	-	-	[75][110]
Hexanoic acid	+	-	-	-	[38]
<b>Amino Acids</b>					
Alanine	-	+	-	-	[75][45]
Tryptophan	-	+	-	-	[102][4]
Threonine	-	+	-	-	[102][4]
Cysteine	-	+	-	-	[102]
Isolucine	-	+	-	-	[102] [4]
Lucine	-	+	-	-	[102][4]
Phenyl alanine	-	+	-	-	[102][4]
Arginine	-	+	-	-	[4]
Glutamic acid	-	+	-	-	[102][4]
Serine	-	+	-	-	[102][4]
Tyrosine	-	+	-	-	[102][4]
Valine	-	+	-	-	[102][4]
Histidine	-	+	-	-	[102][4]

Continued....

**Table 2: Contd.**

Methionine	-	+	-	-	[102][4]
Proline	-	+	-	-	[102][4]
Aspartic acid	-	+	-	-	[4]
<b>Sugars</b>					
Aarabinose	+	-	-	-	[29][111]
Galactose	+	-	-	-	[29][111]
Rhamnose	+	-	-	-	[29][111]
Glucuronic acid	+	-	-	-	[29][111]
Pentose	-	-	+	-	[4]
Hexose	-	-	+	-	[4]
<b>Esters</b>					
Ethyl caproate	+	-	-	-	[105]
Ethyl caprylate	+	-	-	-	[4]
Methyl octanoate	+	-	-	-	[110]
Methyl decanoate	+	-	-	-	[110]

\* Part of the plant is not reported

+ Present, - Absent.

**Table 3: Volatile components present in Noni juice<sup>19</sup>**

Volatile components	
Aldehydes and ketones	Acetaldehyde, 2-methylebutanol, 3-methylebutanal, 2-pentanone, 3-methyle-2-butanone, 2-hexanone, 2-Hexenal, Furfural, Benzaldehyde
Acids	Formic acid, Acetic acid, Butanoic acid, Hexanoic acid, Heptanoic acid, Octanoic acid, 2-octanoic acid, Nonanoic acid, Decanoic acid
Alcohols	Ethanol, 2-methyle-3-buten-1-ol, 1-butanol, 3-Methyl-3-buten-1-ol, 3-Methyl-2-buten-1-ol, Benzyl alcohol
Esters	Ethyl acetate, Butyl acetate, Methyl 2-methylepropanoate, Methyl butanoate, Ethyl butanoate, Butyl butanoate, Methyl 3-methylbutanoate, 4-Pentenyl butanoate, 3-Methyl-3-buten-1-yl 3-methylbutanoate, Methyl 2-methylbutanoate, Methyl hexanoate, Methyl 2-methylbutanoate, Methylehexanoate, Ethyl hexanoate, Butyl hexanoate, 4-pentanyl hexanoate, 3-Methyl-3-buten-1-yl hexanoate, Hexyl isovalerate, Methyl heptanoate, Methyl octanoate, Ethyl octanoate, Butyl octanoate, 3-Methyl-3-buten-1-yl octanoate, Methyl 2-octenoate, Methyl 3-octenoate, Methyl 3-octenoate, Methyl nonanate, Methyl 5-nonanate, Methyl decanoate, Ethyl decanoate, Methyl 4-decanoate, Ethyl 4-decanoate, Methyl salicylate, Methyl hexadecanoate
Terpenes	Linalool oxide, (Z)-3,7-Dimethyl-1,3,6-octatriene, (+)-4-Carene, D-Limonene, Ocimenol, Terpeneol
Sulfur Compounds	Methanethiol, S-Methyl thioacetate, Dimethyl disulfide, Methyl 3-methylthiopropoate, Ethyl 3-methylthiopropoate, 3-methylthiopropoic acid

### Phytoconstituents present in various parts of Noni plant represented with structure (Figure 5, 6, 7, 8, 9, 10)

Researchers isolated ninety six volatile components from Noni fruit at two different ripening stages (ripe and over ripe). Over ripened fruit showed significantly higher amounts of methyl hexanoate, methyl octanoate, ethyl octanoate and methyl 4 *E*-decanoate, while octanoic acid and decanoic acid concentrations were significantly low. These changes indicate that esterification occurs during maturation. Two unsaturated esters, 3-methyl-3-buten-1-yl hexanoate and 3-methyl-3-buten-1-yl octanoate significantly decreased in their concentrations in the ripe to over-ripe fruits.<sup>17</sup> Noni blossoms are found to contain iridoids and flavonoids as major phytochemicals.<sup>18</sup> It has also been reported that the volatile components viz. aldehydes, ketones, esters, alcohols, terpenes and sulphur compounds (Table 3) are present in ripe Noni fruit. This suggested that the presence of sulphur contributes to the flavour characteristics of Noni juice.<sup>19</sup> It was suggested that the production process (fermentation and juice vs drying or lyophilization) has no effect on the

anthraquinone content. In ripe fruit there is no as such influence on anthraquinone content. Also, suggested that commercial Noni products in the market whether fermented or unfermented juice or powder should be obtained from fully ripe Noni fruits and seed should be removed during drying process.<sup>20</sup>

Compared the Total Phenolic Content (TPC) of commercial Noni juice with blueberry and grape juice, reported that Noni juice contains 65.56% of total polyphenols against 27.90% and 6.54% which represent the 5% blueberry and grape juice, respectively. Blue berry and grape juice mask the unpleasant odour and bitter taste of Noni fruit juice and allows alteration in the organoleptic properties of commercialized Noni juice. Commercial Noni juice presented higher values of TPC (91.90 mg of gallic acid/100 ml juice) and antioxidant activity (5.85 mmol/L) when compared to its 5% diluted constituents.<sup>21</sup>

Identified polyphenols belonging to the coumarin, flavonoid and phenolic acid groups, and two iridoids in Noni juice by HPLC-DAD and Electro Spray Ionization Mass Spectrometric detection (HPLC-ESI-MS) method. Noni juice have free radical scavenging capacity. Furthermore, it also reduced carrageenan induced paw edema, directly inhibited COX-1

and COX-2 activities and inhibited the production of nitric oxide (NO) and prostaglandins E(2) in activated J774 cells, in a dose dependent manner.<sup>22</sup>

## Mechanism of action of phytoconstituents present in various parts of Noni plant

### Damnacanthal

Damnacanthal, an *anthraquinone* induced normal morphology and cytoskeletal structure in K-ras NRK cells at the tolerant temperature without changing the amount and localization of ras. The effect of damnacanthal was reversible and had not shown any effect on the morphology of RSVTs-NRK cells states the src oncogene. Hence, damnacanthal is a new inhibitor of ras function.<sup>23</sup> The MTT method confirmed that damnacanthal inhibitor the growth of MCF-7 cells at the concentration of 8.2 µg/ml for 72 h. Moreover, damnacanthal was found to induce cell cycle (CC) arrest at the G1 check point in MCF-7 cells by CC analysis. The result provided significant evidence in demonstrating that p53-mediated damnacanthal induced apoptosis through the activation of p21 and caspase-7.<sup>24</sup>

In another study, it was reported that damnacanthal acts against Hep G2 hepatocellular carcinoma cells by decreasing the phosphorylation level of Akt and targets matrix metalloproteinase-2 secretion in Hep G2 cells.<sup>25</sup> Reported that the damnacanthal possesses strong inhibitory activity towards tyrosine kinases i.e. Lck, Src, Lyn and EGF receptor.<sup>26</sup>

### Epigallocatechin gallate (EGCG)

EGCG present in Noni which is known for its potent antioxidant and antiangiogenesis activity also it inhibits the quinol oxidase (NOX) enzyme, which is responsible for tumor activity. Thus, Noni helps in antiangiogenesis by inhibiting NOX.<sup>27</sup>

### Alizarin and limonene

Found to inhibit the formation of blood vessels over the tumor by antiangiogenesis property. Thus Noni juice inhibit the growth and mutations of malignant cells and induce programmed cell death or apoptosis.<sup>28</sup>

### Polysaccharides

Glucuronic acid, galactose, arabinose, rhamnose, glycosides and trisaccharide fatty acid ester showed immuno-stimulatory, immune-modulatory, antibacterial, antitumor and anticancer activity.<sup>29</sup> 6-D-Glucopyranose pentaacetate is sulphated polysaccharides, which undermine the interaction between glucosaminoglycan and certain proteins. This helps to block the ability of mutated cells to adhere to new cells stopping metastasis.<sup>30</sup>

Compounds present in Noni fruit like iridoid glycosides, 6-alpha hydroxyadaxoside, 6 beta, 7-beta-epoxy-8-episplenoside as well as americanin, narcissoside, asperuloside, asperulosidic acid, citrifolin Bepimera, borrieriagenin, deacetylasperuloside, dehydromethoxy gaertneroside, cytidine, epi-dihydrocornin, d-glucose, d-mannitol, methyl alpha-d-fructofuranoside, methyl beta-d-fructofuranoside, nicotifloroside, and beta-sitosterol 3-O-beta-d-glucopyranoside showed antioxidant activity in both DPPH and NO<sub>2</sub> reducing activity bioassays.<sup>31</sup> Researcher's states that Noni has good antioxidant activity, having free radical scavenging activity and quenching lipid peroxides.<sup>32</sup>

### Quercetin

Reported decreased cell viability of both low metastatic cell line ACC-2 and high metastatic cell line ACC-M with quercetin treatment in a concentration and time dependent manner. Quercetin significantly decreases the apoptosis in ACC cells through a mitochondria dependent pathway which showed close correlation with down regulation of the PI3K/Akt/IKK-alpha/NF-kappaB pathway. Their result reveals that quercetin may be a hopeful chemotherapeutic agent against ACC

through its function of down regulating the PI3K/Akt/IKK-alpha/NF-kappaB signaling pathway.<sup>33</sup>

### Scopoletin

Scopoletin decreases carrageen induced iNOS and COX-2 expressions in the paw edema. These anti-inflammatory mechanisms of scopoletin may be related to the reduced in the level of MDA via increasing the activities of SOD, GPx and CAT in the paw edema.<sup>34</sup>

### Xeronine

Noni fruit contain proxeronine which combine with proxeroninase an enzyme present in the body to form xeronine which may help to enlarge the pore size of the tumor cells and allow anticancer drugs to enter the cells more easily. Also, xeronine increases the permeability of K<sup>+</sup> ions and prevent the formation of lactic acid from glucose.<sup>12</sup>

### Citrifolinoside

Citrifolinoside isolated from the leaves of *M. citrifolia* plant showed significant inhibition of UVB-induced Activator Protein-1 (AP-1) activity in cell cultures.<sup>35</sup>

### Monoterpene

A monoterpene, limonene present in Noni fruit has been shown to prevent mammary, liver, lung and other cancers. Limonene stimulate thymus gland to secrete more T cells which destroy the carcinoma cells.<sup>36</sup>

### Beta carotene

Suggested that beta carotene reduced the oxygen free radical and prevent oxidative damage. Also reported that long term use of moderate dose of β-carotene significantly reduced prostate cancer incidence in male smokers.<sup>37</sup>

### Ursolic acid

It possess anti-carcinogenic effect both externally and internally prevent growth of cancerous cells and induce apoptosis by modulating immune process of the body.<sup>38</sup>

### Gallic acid

Gallic acid reduced compound 48/80-or immunoglobulin E (IgE) which induced histamine release from mast cells. The inhibitory effect of gallic acid on the histamine release was mediated by the modulation of cAMP and intracellular calcium. Gallic acid decreased the phorbol 12-myristate 13-acetate and calcium ionophore A23187-stimulated pro-inflammatory cytokine gene expression and production such as TNF-α and IL-6 in human mast cells.<sup>39</sup>

## Preparation and standardization of Noni formulations

Reported there are two types of Noni juice on the basis of extraction like traditional and non-traditional; and other different formulations like Noni beverage, Noni squash, Noni syrup (Figure 11, 12, 13, 14, 15) analysed for pH, total soluble solids, acidity, reducing sugar, total phenol, ascorbic acid, tannins and pectin by standard methods.<sup>40</sup> The colour of Noni juice is measured by using Lovi bond tintometer.<sup>41</sup> As per the method of standardization reported, Quantity of sugar, citric acid, water, ginger extract including organoleptic characters can be used for the standardization of Noni juice.

Standardized Noni beverages like Ready to Services (RTS), Squash and Syrup which are prepared from Noni fruit juice. RTS was reported to contain 130 g sugar, 100 ml Noni fruit juice and 20 ml ginger extract in 770 ml water. Squash was found to add with 1500 g sugar, 7 g citric acid and 250 ml Noni fruit juice in 486 ml water. Noni syrup was found to be prepared by adding 680 g sugar, 10 g citric acid and 250 ml Noni juice in 310 ml of water.<sup>42</sup>

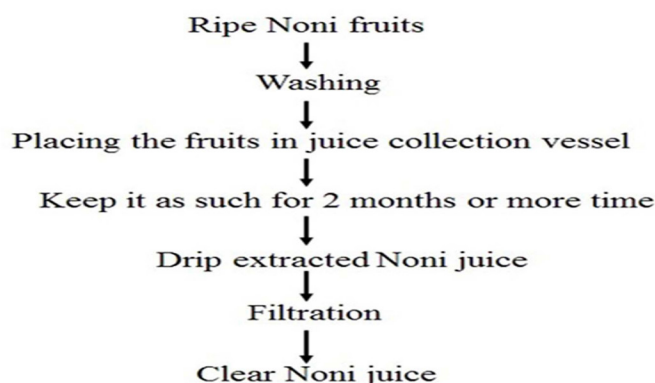


Figure 11: Flow sheet for production of traditional Noni juice.



Figure 12: Flow sheet for production of Non-traditional Noni juice.

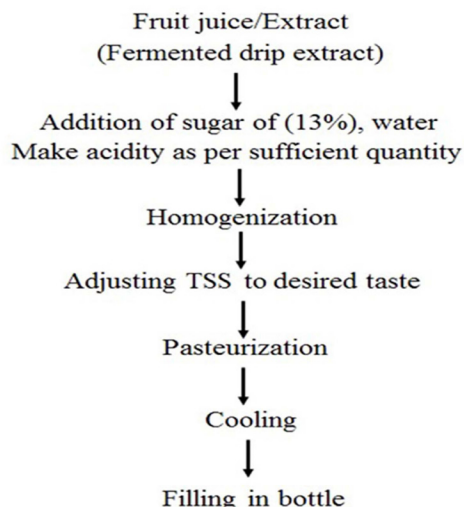


Figure 13: Noni.

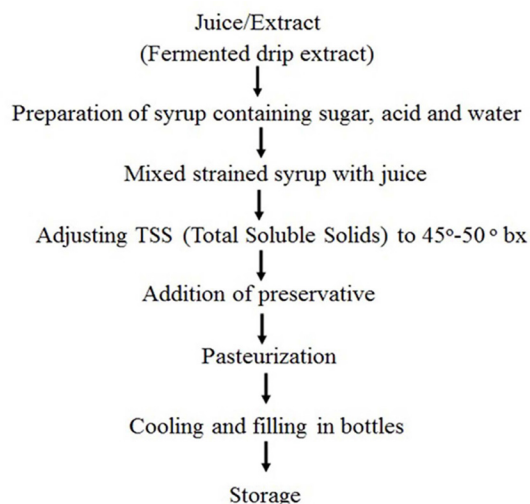


Figure 14: Preparation of Noni squash.

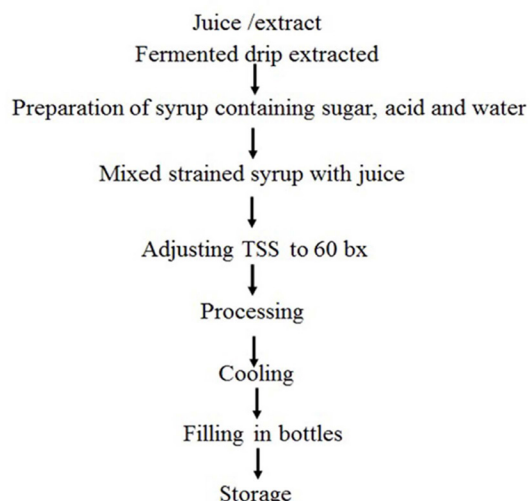


Figure 15: Preparation of Noni syrup.

### Proximate chemical composition of Noni fruit

The acidity of Noni juice extracted was reported to be 1.6%. The protein, ash and moisture content in Noni fruit reported as per (<http://www.healingnoni.com>) was 0.24%, 0.54% and 95.67% but the protein, ash and moisture content was 0.43%, 0.43% and 89.6% respectively also they carried out a study to improve the taste and flavour of the Noni fruits quash preparation. They diluted Noni juice with water at the ratio of 1:0.5, 1:1, 1:2 and 1:3 concentrations and converted into RTS containing 220 bx, 160 bx, 140 bx and 100 bx T.S.S., and evaluated for overall quality. It was found that the squash diluted in 1:3 proportion tasted better and having good flavour with consumer acceptance. Same authors carried out a study to improve the taste and flavour of the Noni syrup preparation. They diluted juice with water at the ration of 1:1, 1:2, 1:3 and 1:4 concentrations. It was found that the juice diluted with water in the ratio of 1:4 tasted better as compared to other concentrations. Finally they concluded that the squash and syrup with 1:3 and 1:4 dilutions respectively are more acceptable.<sup>42</sup>

Identified, developed and validated various constituents present in Noni juice by HPLC-MS method and quantitative data on the composition of Noni juice, including iridoid glucosides, scopoletin, rutin, fatty acid, sugar, and anthraquinones are reported.<sup>43</sup> Four characteristic analytes like scopoletin, rutin, quercetin, and 5, 15-DMM were detected in Noni fruits and commercial juices originating from different regions of the world, but in a significantly various ranges of concentration. Together, these characteristic components can be used as a reference for identification and authentication of Noni fruit raw materials and commercial Noni products.<sup>44</sup>

## Challenge in standardization of Noni preparations

The variation in phytochemical content in Noni fruits and juices may suggest different toxicological and pharmacological properties. While there are over 300 peer-reviewed scientific publications on Noni, data regarding efficacy and safety of one commercial Noni product may not be applicable to any others. So there is an urgent need for establishment of method of standardization of Noni preparations which is accepted worldwide and can be applicable to all Noni preparations.

## Pharmacological Activity of Noni

### Preclinical investigations

#### Effect on lung and colon cancer

In a recent study reported six known chemical compounds and two new compounds isolated from roots of the plant showed significant inhibitory effects on the proliferation of human lung and colon cancer cells.<sup>45</sup>

#### Effect on esophageal cancer

Reported in an *in-vivo* and *in-vitro* studies that black or red raspberries, strawberries, blueberries, Noni, wolfberry, inhibits the development of cancer by signifying that the all possesses both preventative and curative effects on rat esophageal cancer induced by N-nitrosomethylbenzylamine.<sup>46</sup>

#### Effect on breast cancer

The effects of Tahitian Noni Juice (TNJ) were tested on mammary carcinogenesis in MMTV-*neutransgenic* mice. Reported TNJ treatment did not affect mammary tumor latency, multiplicity and metastatic incidence. But TNJ showed significant diminution in tumor weight, size and longer tumor repetition times in mice. Overall, it was observed that, a mouse equivalent of dose for humans (<3 oz/day) remarkably inhibited the growth of mammary gland cancer.<sup>47</sup>

Investigated the effect of Noni juice on Ehrlich ascites tumors bearing Balb-c mice, concluded that Noni juice may be useful in the treatment of breast cancer either on its own or in combination with doxorubicin. This is because of the effect of Noni juice on Ehrlich ascites tumors bearing Balb-c mice, which produced significantly smaller, short and long diameters of the tumor tissues in each treated group compared to those in control group either alone or with doxorubicin.<sup>48</sup>

Reported the anti-growth effect of TNJ in one hundred and sixty female Sprague-Dawley rats. TNJ was found successful in reducing number of palpable tumors per group significantly in all the groups in which 3%, 5%, and 10% TNJ was administered. TNJ also found to significantly reduce the multiplicity and malignancy of lesions, and the survival rate of animals when compared with positive controls at different time points.<sup>49</sup>

#### Effect on colorectal cancer

Damnacanthal is able to suppress cancer in colorectal tumor genesis by the findings that damnacanthal exhibited cell growth arrest as well as caspase activity induction. Result suggests that damnacanthal having potent antitumorogenic activity in human colorectal cancer cells.<sup>50</sup>

### Effect on cervical cancer

Noni juice and cisplatin, either alone or in combination was able to induce apoptosis through the mitochondrial pathway on HeLa and SiHa cells. However, cisplatin showed slightly higher cell killing when compared to Noni juice while their combination showed additive effects. This result suggests that Noni juice can be used as a chemo adjuvant in the treatment of cervical cancer.<sup>51</sup>

### Antitumor activity

Noni juice has been found to improve survival time and produce curative effects when Noni-ppt (Noni-ppt obtained from Noni juice) was combined with sub-optimal doses of the standard chemotherapeutic agents like cisplatin, doxorubicin, 5-fluorouracil and vincristine. Their result suggests that Noni-ppt is a good supplemental agent in cancer treatment.<sup>29</sup> Reports of 10% concentration of Noni juice in growth media induce vessel degeneration and apoptosis within a few days. They also found that 10% Noni juice in media was an effective inhibitor of capillary initiation in explants from human breast tumors.<sup>28</sup>

### Chemoprotective effect

Evaluate the chemoprotective effect of ethanolic extract of *M. citrifolia* (EEMC) fruits by simultaneous administration orally at the dose of 100 and 200 mg/kg b.wt. in rats. Cisplatin 5.0 mg/kg was administered through i.p. route to induce nephrotoxicity. They determined serum biochemical parameters like serum creatinine, protein and urea as indicators of kidney damage. In result both doses has shown significant nephroprotective activity, which was confirmed by histopathological study.<sup>52</sup>

### Effect on cardiovascular system

Noni fruit has the ability to prevent arteriosclerosis related to the oxidation of low density lipoproteins (LDLs). They state that this beneficial effect could be due to presence of lignans.<sup>53</sup>

### Anti-psychotic activity

Acute treatment of *M. citrifolia* (1, 3, 5, 10 g/kg, p.o) significantly decreased apomorphine induced cage climbing behavior and climbing time in mice in a dose dependent manner. Similar significant inhibition of methamphetamine-induced stereotypy behavior and climbing time in mice was observed dose dependently. The 7 and 21 days treatment of TNJ in drinking water at 50 and 100% v/v significantly improved the apomorphine induced climbing behavior and climbing time in mice. These results suggest that TNJ has potential effect in the treatment of psychiatric disorders.<sup>54</sup>

### Anti-depressant activity

A number of scientists have investigated the potential action of some plants i.e. *Hypericum perforatum*, *Ginkgo biloba*, *Apocynum venetum*, *Valeriana officinalis*, *Melissa officinalis* and *M. citrifolia* for the treatment of depression and anxiety.<sup>55</sup> Additionally recent studies showed *M. citrifolia* as an inhibitor of MAO-A and MAO-B.<sup>56</sup>

### Effect on cognitive function

Another study investigated the effects of fruit juice on stress-induced impairment of cognitive function in mice using Morris water maze. They suggested that Noni juice protect brain from stress-induced impairment of cognitive function and reported this protective effect may be related to improvement in stress-induced decrease in blood vessel density in the hippocampal dentate gyrus.<sup>57</sup>

### Effect on nervous system

Researchers evaluated the protective effect of Noni juice on brain damage caused by ischemic stress in mice focused on the effect of fruit juice on the development of the post-ischemic glucose intolerance as a cerebral



protective mechanism. This mechanism may provide the neuronal protective effect of Oral Noni Juice (ONJ) against ischemic stress as derived from the above results.<sup>58</sup>

#### Effect on Alzheimer's disease

Evaluation of neuroprotective effect of Noni juice against scopolamine induced memory loss in mice indicated that oral administration of Noni juice developed reversible impairment of retention in step down latency inhibitory test. From the above result, authors assumed that Noni juice offers a protective effect against oxidative damage induced by scopolamine by maintaining the activities of superoxide dismutase (SOD) and concluded that Noni juice might be a potential therapeutic alternative in either the prevention or the treatment of Alzheimer's disease.<sup>59</sup>

#### Wound healing activity

*M. citrifolia* leaf extract was found to possess wound healing activity. Observations showed decrease in lipid peroxide level in *M. citrifolia* treated group which may be because of the presence of  $\beta$ -carotene, flavonol and iridoid glycosides that are antioxidant in nature is reported.<sup>60</sup>

#### Immunostimulant activity

Immune enhancing properties of *M. citrifolia* fruit enable the plant to exhibit immunostimulant activity on T and B lymphocytes as reported.<sup>61</sup>

#### Hepatoprotective activity

Acute liver injury induced by carbon tetrachloride (CCl<sub>4</sub>) in female Sprague-Dawley (SD) rats was found reversed by Noni juice. In the placebo group, administered CCl<sub>4</sub> with drinking water which was induced liver damage in rats. While in control group, pretreatment with 20% Noni juice in drinking water + CCl<sub>4</sub> markedly decreased hepatotoxic lesions. Concluded Noni juice have liver protective effect from extrinsic toxin exposure.<sup>62</sup>

#### Antioxidant activity

Evaluated the beneficial effects of Noni juice on antioxidant, haematological and biochemical changes caused by N-Methyl-N-Nitrosourea (NMU) induced mammary carcinogenesis in Sprague-Dawley rats. Results showed that Noni juice treatment significantly increased antioxidant enzymes level such as catalase, SOD and significantly decreased lipid peroxidation level in NMU challenged group when compared to NMU control group. Noni juice also showed a preventive effect against anemia, lymphocytosis and neutrophilia when compared to NMU control group. They concluded that Noni juice have liver and kidney protective effect in NMU induce carcinogenesis and could be useful to treat mammary gland in humans and animals.<sup>63</sup>

The antioxidant properties of ethanol and ethyl acetate extracts of root, fruit and leaf of *M. citrifolia* assessed by ferric thiocyanate method (FTC) and thiobarbituric acid methods (TBA) which indicated that the root extract showed higher activity than the fruit or leaf extracts.<sup>64</sup>

#### Anti-inflammatory activity

Bradykinin induced inflammatory response was inhibited and rapid collapse in rat paw edema were pretreated either by oral or i.p administration with Noni juice extract. This effect may be a result of interference with the B2 receptor mediated mechanism by which bradykinin induces rat paw edema.<sup>65</sup> Another study concludes that *M. citrifolia* juice selectively inhibits cyclo-oxygenase enzymes (COX-1 and COX-2) involved in breast, colon and lung cancer and shows anti-inflammatory activity.<sup>66</sup>

#### Antidyslipidemic activity

In an evaluation of antidyslipidemic effect of aqueous ethanolic extracts of different parts of *M. citrifolia* viz. fruits, leaves and roots, concludes the mechanism of antidyslipidemic effects of fruits, roots and leaves of

*M. citrifolia* through various pathways i.e. inhibition of biosynthesis, absorption and secretion of lipids. The results indicate that Noni can be used as a potential medicine for cardiovascular diseases.<sup>67</sup>

#### Antilipidemic activity

The effect of Noni seed oil on serum lipid levels in normal lipidemic and hyper lipidemic mice were evaluated and found a reduction in total cholesterol and triglyceride levels in both models are reported.<sup>68</sup>

#### Effect on GIT

Noni juice inhibits gastric emptying by stimulation of cholecystokinin (CCK) secretion which occurs simultaneously with an increase in plasma CCK cholecystokinin 1 (CCK1) receptors that are involved in the Noni induced inhibition of gastric emptying.<sup>69</sup> Scopoletin is a phytoconstituent present in Noni fruit found to be effective as a potential preventive and therapeutic agent for gastro-esophageal inflammatory diseases through its anti-secretory and prokinetic activities including an inhibitory activity on serotonin, free radicals, and cytokine-mediated inflammation.<sup>70</sup>

#### Antimicrobial activity

Powder form of various extracts of Noni leaves increases the growth inhibition activity of *E. coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger* in a dose dependent order. The overall result indicates the use of solvent extracts of Noni leaves is effective in the treatment of infectious disease.<sup>71</sup>

#### Antifungal activity

Methanolic extract of the dried Noni fruit exhibited maximum percentage of inhibition against *Trichophyton mentagrophytes* (79.3%), while approximately 50% activity was recorded against *Penicillium*, *Fusarium* and *Rhizopus* species.<sup>72</sup>

#### Antiviral activity

1-methoxy- 2-Formyl-3-hydroxyanthraquinone isolated from Noni roots suppressed the cytopathic effect of HIV infected MT-4 cells, without inhibiting cell growth and removal of endothelium.<sup>73</sup>

#### Hypoglycemic activity

Fermented Noni juice used to investigate the hypoglycemic activity in diabetes-induced rats. On the 20<sup>th</sup> day, after treatment in diabetic experimental animals, showed significant decrease in fasting glucose from an excess of 300 mg/dl (day 3) to 150 mg/dl (day 20). It can be assumed that *M. citrifolia* either potentiates the action of insulin directly or that it increases peripheral tissue sensitivity to the storage hormone.<sup>74</sup>

#### Smooth muscle stimulatory activity

Reported that the dried fruit has smooth muscle stimulatory activity and histaminergic effects based on tests conducted for biological activities in animal and anti-microbial studies.<sup>75</sup>

#### Spasmodic activity

Noni plant root extract possess antispasmodic, vasodilator and cardio depressant activities which are mediated through blockade of calcium channel as well as release of calcium from intracellular calcium which may make clear the use of *M. citrifolia* in diarrhea and hypertension.<sup>76</sup>

#### Anti-osteoporotic activity

Isolated seven anthraquinones from an ethanolic extract of the roots of *M. citrifolia*. Reported all the isolated components were found to inhibit osteoclast tartrate resistant acid phosphatase (TRAP) activity and bone resorption including the inhibitory effects on osteoclastic bone resorption in osteoporotic rats. Finally they suggested all the components have positive therapeutic effect against osteoporosis.<sup>77</sup>

### Immunomodulatory effect

In *in-vitro* study, TNJ and fruit juice concentrate potently activated the cannabinoid 2 (CB<sub>2</sub>), but inhibit the cannabinoid 1 (CB<sub>1</sub>) receptors in a concentration-dependent manner. But *in-vivo* studies reported decreased the production of IL-4 and increased the production of IFN- $\gamma$ . These results suggested that Noni juice modulates the immune system via activating of the CB<sub>2</sub> receptors and suppressing of the IL-4 but increasing the production of IFN- $\gamma$  cytokines.<sup>78</sup>

### Nephroprotective activity

Fruit juice can modify renal function and catecholamine contents in doxorubicin induced nephrosis, it was reported that Noni juice reduced plasma cholesterol; doxorubicin induced impaired renal function in rats along with compensatory increase in renal dopamine content. But no beneficial effects on renal function were observed when fruit juice was administered with doxorubicin.<sup>79</sup>

### Bone protective effect

Investigation on roots of *Morinda officinalis* reports its protective effect against bone loss in sciatic neurectomized and ovariectomized osteoporotic rats, which is due to the present of anthraquinone (1,3,8-trihydroxy-2-methoxy-anthraquinone 2-hydroxy-1-methoxyanthraquinone and rubiadin) in the plant.<sup>80</sup>

### Clinical investigations

#### Safety study

Some researchers conducted safety study of Noni fruit juice on ninety six healthy volunteers where different quantities of fruit juice were administered daily in the order 0 ml (placebo), 30 ml, 300 ml, or 750 ml. It was found that 300 ml significantly reduced the adverse events like headache, cough, nausea, menstrual cramp, nasal discharge and vomiting, upper respiratory and urinary tract infections.<sup>81</sup>

#### Anticancer activity

Consume 1 to 4 oz (1oz=30 ml) of TNJ daily may reduce the cancer risk in heavy cigarette smokers by blocking carcinogen DNA binding is suggested.<sup>82</sup> In another one month clinical trial on 68 current smokers, supplemented with two ounces of TNJ (n=38) or placebo (n=30) twice a day for 30 days which resulted in protection from oxidative damage induced by cigarette smoke and thereby reduced cancer risk related to smoking.<sup>83</sup>

#### Antioxidant activity in heavy smokers

Evaluated the antioxidant activity of TNJ in double-blind and placebo controlled clinical trial with 285 current heavy smokers for 30 days. Reported TNJ lowered free radicals viz. superoxide anion radicals (SAR) and lipid hydroperoxide (LOOH) levels significantly and observed no significant reductions in SAR or LOOH levels in the placebo group.<sup>84</sup>

#### Noni protect Malondialdehyde (MDA)-DNA adducts in heavy smokers

In one month clinical trial on 203 people, placebo-controlled trial, found TNJ reduced the amount of MDA caused DNA damage by 53%, and concluded TNJ is able to reduce the MDA-DNA adduct level at a tremendously significant level. The result suggests that it may reduce cancer risk in current smokers.<sup>85</sup>

#### Effect on cholesterol and triglyceride level in heavy smokers

Conducted one month clinical trial double-blind and placebo controlled in 132 heavy smokers with cholesterol level more than 190 mg/dl. Authors are reported TNJ decreases total cholesterol and triglyceride levels in current smokers. So they concluded that drinking TNJ may prevent heart disease.<sup>86</sup>

### Case studies

Reported on two case studies of gastric cancer patients being treated with Noni juice. Case 1: Doctor advice a male patient aged 69 years, to do surgery otherwise he would die within few months. But the patient ignored doctor's advice and he became incapacitated within two months as his body weight dropped from 165 to 79 pounds. He started to take homemade Noni juice and he is improved within a month and continued 6 months after that he stopped Noni juice. Seven years he has not got any gastric problem but in biopsy examination showed histology similar to his original cancer not increased so the patient again started Noni juice after that outcome was not reported. Case 2: A patient was 64 years old with gastric cancer, examined in gastrectomy, reported the cancer had spread to 17-28 lymph nodes and he was given 5 years to live. After that started to consume homemade Noni juice and he lived 16 years more, he died at age 80 of malnutrition due to gastric cancer.<sup>87</sup>

#### Effect in hypertension

One month open label clinical trial on 10 people by daily administrating of 4 oz. of TNJ, Reported Noni juice significantly decreased the high blood pressure, especially systolic high blood pressure.<sup>88</sup>

#### Effect on cholesterol in non-smokers

One month pilot study on 10 non-smoking hypercholesteromic subjects, who are not currently taking cholesterol medications, consuming 4 ounces of TNJ daily for 30 days; lowered the average pre-test total cholesterol from 184.4 to 182.4, at the end of the trial it increased the HDL/LDL from 0.36 to 0.37. Concluded that Noni juice has the potential to lower cholesterol through the mechanisms of inhibiting HMG-CoA reductase and hepatic/intestinal ACAT enzymes, acting as a dual inhibitor of both enzymes.<sup>89</sup>

#### Effect of leaf extract in skin protection

Noni leaf extract protected the skin against UV induced redness and swelling (erythema). Study suggests that leaves are safe for topical use and may be useful in mitigating UVB-induced injury to the skin.<sup>90</sup>

#### Effect on skin care regimen

Six week clinical trial of Noni based skin care regimen on 49 women, (age 38 to 55 years). Where in the subjects applied three formulations of Noni i.e. Noni juice, Noni seed oil and Noni leaf juice to the face and neck. Result shows significant reductions in lateral canthal fine lines and wrinkles and also stated that improved skin elasticity and firmness. There was no evidence of skin irritation was present in any participant at any time during the trial. Finally they concluded the trial results validate traditional uses of the Noni plant to improve skin health.<sup>91</sup>

#### Effects on serum lipid profile

A study reported that drinking 29.5 to 188 ml of Noni juice per day reduces cholesterol, triglycerides, and hs-CRP. Also a decrease in LDL and homocysteine, as well as increase in HDL, among the Noni juice drinkers were observed.<sup>92</sup>

#### Antidiabetic activity

Lowering glucose levels under fasting and postprandial conditions are reported when type-2 diabetes patients habitually consumed Noni juice as a combination therapy (Noni and oral hypoglycemic agents).<sup>93</sup>

#### Effect on osteoarthritis

In three month open level intervention trial (82 osteoarthritis patients) administered 3 oz of TNJ per day, reported significant improvements in symptoms such as pain and mobility.<sup>94</sup>

### Effect on menopause

A three-month intervention pilot study by administering two ounces of TNJ. Reported TNJ possess anti-osteoporosis effect and also improved mood, energy and attenuated hearing loss.<sup>95</sup>

### Immune boosting & antioxidant

In two month pilot study TNJ found to increase adaptive immune system activity by 32% and innate immune system activity by 30% while decreasing oxidative stress in the body 19%.<sup>96</sup>

### Effect in endurance

In a placebo-controlled, three week trial on 40 peoples, result revealed that TNJ increased the staying power by 21% and increased antioxidant activity by 25% when compared to placebo which showed no effect. Same researchers conducted drug screening test on six healthy adult volunteers (5 males and 1 female), consumed each volunteer 124 ml of TNJ. Reported no unlawful drugs or their metabolites of TNJ are present in the urine samples collected from both male and female volunteers.<sup>97</sup>

### Effect on gingivitis/periodontitis

Another study reports that the combination of good oral hygiene together with local and systemic treatment with Noni juice is a promising tool for the treatment of gingivitis and periodontitis.<sup>98</sup>

### Contraindication of Noni

Noni juice is rich in potassium, hence it is not recommended for patients who have liver and kidney dysfunctions. The consumption of Noni juice produces hyperkalemia in patients with potassium restricted diets which could lead to nausea, muscle weakness and irregular heart beat.<sup>99</sup> Another study reported the higher consumption of Noni juice during pregnancy delay ossification and skeleton alteration in the fetus.<sup>100</sup>

## CONCLUSION

*M. citrifolia* is an herbal remedy commonly known as Noni. Traditionally various parts of Noni plant were used in Polynesian island as an herbal medicine in various ailments. Many scientific literatures suggests that it contains many chemical components viz. amino acids, anthraquinones, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols etc. along with minerals, vitamins, micro and macro nutrients which are effective in many ailments. Researchers have proven in both preclinical and clinical models that Noni is pharmacologically active and can prevent cancer, heart disease, diabetes, cognitive dysfunction, hypertension etc., and maintain overall good health.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest. The authors themselves are responsible for the content and writing of the paper.

## ABBREVIATION USED

**TPC:** Total Phenolic Content; **NO:** Nitric oxide **CC:** Cell cycle; **EGCG:** Epigallocatechingallate; **NOX:** Quinol oxidase, **iNOS:** Inducible nitric oxide synthase; **MDA:** Malondialdehyde; **SOD:** Superoxide dismutase; **GPx:** Glutathione peroxidase; **CAT:** Catalase, **AP-1:** Activator Protein-1; **IgE:** immunoglobulin E **cAMP:** Cyclic adenosine monophosphate; **TNF-**

**a:** Tumor necrosis factor- $\alpha$ ; **IL-6:** Interlukine-6, **TSS:** Total soluble solids, **RTS:** Ready to Services; **bx:** Brix; **TNJ:** Tahitian Noni Juice; **EAC:** Ehrlich ascites carcinoma; **EEMC:** Ethanolic extract of *M. citrifolia*; **LDLs:** Low density lipoproteins, **MAO:** Monoamine oxidase, **ONJ:** Oral Noni Juice, **CCl<sub>4</sub>:** Carbon tetrachloride; **SD:** Sprague-Dawley; **NMU:** N-Methyl-N-Nitrosourea; **FTC:** Ferric thiocyanate, **TBA:** Thiobarbituric acid; **CCK:** Cholecystokinin, **TRAP:** Tartrate resistant acid phosphatase; **CB<sub>2</sub>:** Cannabinoid 2; **IFN- $\gamma$ :** Interferon-gamma, **oz:** Ounce; **DNA:** Deoxyribonucleic acid; **SAR:** Superoxide anion radicals; **LOOH:** Lipid hydroperoxide; **HDL/LDL:** High-density lipoprotein/low-density lipoprotein; **HMG-CoA:** 3-hydroxy-3-methylglutaryl-coenzyme A; **ACAT:** Acetyl-Coenzyme A acetyltransferase; **hs-CRP:** High-sensitivity C-reactive protein.

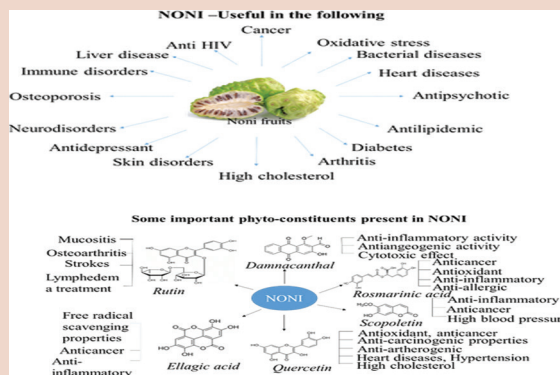
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### PICTORIAL ABSTRACT



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