

REVIEWS

Morinda Citrifolia – Noni: A brief review of its anti cancer activity

Niveditha Baiju, Pramod.P.Mathews, Skariah.K.S, Ambika K

Department of Oral Pathology, Indira Gandhi Institute of Dental Sciences Kothamangalam,
Kerala, India.

Correspondence to : **Dr. Niveditha Baiju**, Head of the Department of Oral Pathology, Indira
Gandhi Institute of Dental Sciences, Kothamangalam, Kerala, India.

E-mail : neenadoc@gmail.com

Abstract

Noni, with the botanical name *Morinda Citrifolia* is a medicinal plant which is used as a natural nutritional food supplement world wide for centuries. It has been reported to have broad therapeutic effects including anticancer activity. Noni's effect to cure cancer is at the cellular level. This article reviews the composition and the mechanism of the anticancer activity of Noni.

Introduction

Noni, with the botanical name *Morinda citrifolia* is a medicinal plant that has been used world wide for centuries. Its various vernacular names are: Indian mulberry, nuna or Mannanatti on the Indian subcontinent. Noni is native to south east

Asia and Australia and is cultivated in Polynesia, India, the Caribbean, Central and northern South America.¹ Ancient Aayurvedic texts cite Noni as Ashyuka, which in Sanskrit means 'longevity'.

It is primarily used to stimulate the immune system and thus to fight bacterial, viral,

parasitic and fungal infections. It is also used to prevent the formation and proliferation of tumours including malignant neoplasm.²

Plant Description

The genus *Morinda* (Rubiaceae), including the species *Morinda citrifolia*, is made up of around 80 species. *Morinda citrifolia* is a bush or small tree, 3-10 m tall with abundant wide elliptical leaves (5-17 cm length, 10-40cm width)^{2,3} (Figure 1).

Figure 1



The noni fruit (3-10cm length, 3-6cm width) is oval and fleshy with an embossed appearance (Figure 2). It is slightly wrinkled, semi translucent and ranges in colour from green to yellow to almost white at the time of picking. The ripe fruit exhales

a strong butyric acid like rancid smell. The pulp is juicy and bitter, light dull yellow or whitish gelatinous, when the fruit is ripe, numerous hard triangular reddish-brown pits are found, each containing four seeds.⁴

Figure 2



Noni is consumed as juice, although leaves, flower bark and roots can also be used.²

Most commercially available forms are juice, powder and pills (Figure 3).

Figure 3



Composition

Noni, has 160 phytochemical compounds. The major micronutrients are phenolic compounds, organic acids, alkaloids, proteins, minerals and vitamins.⁴

Anti cancer agents in Noni

1. Polysaccharides

6-D-Glucopyranose pentaacetate

A sulphated polysaccharide, destabilize the interaction between glucosaminoglycan and certain proteins. This helps block the

mutated cells ability to adhere to new cells, stopping metastasis.⁵

Noni precipitate

Ethanol precipitable fraction is a unique polysaccharide, This polysaccharide is made up of 4 sugars(glucuronic acid, galactose, arabinose and rhamnose). It has immunomodulatory effects⁶

2. Anthraquinones

The known biological activity of the anthraquinones found in Noni includes fighting inflammation, bacteria, parasites and tumors. Anthraquinones are also used to boost the body's immune system.

Damnacanthal an anthraquinone found in Noni inhibits the formation of tumours by interfering with the growth of *ras* gene activation.⁷

Alizarin is another anthraquinone that has found to have an antiangiogenic effect. It blocks blood circulation to malignant tumors.

Researchers found that quinines significantly inhibited or stopped the growth of malignant cells from human colon carcinoma.⁸

Quinones reduced the effect of cancer causing agent Cytochrome C without causing the formation of any free radicals.⁹

Epigallocatechin gallate (EGCg)

EGCg is a polyphenolic flavonoids antioxidant that is found in abundance in Noni. EGCg in Noni inhibits the quinol oxidase (NOX) enzyme tumor activity property thus helps in antiangiogenesis. NOX enzyme are found in a variety of cell types and tissues where they react with oxygen to generate reactive oxygen species (ROS), the free radical form of oxygen that damage to the DNA of cell. NOX is activated in normal cell during cell division process in response to growth hormone signal, but active in all the time in cancerous cell and responsible for the cancerous cell proliferation, cell motility, invasion and angiogenesis process, all of them prerequisites for tumor metastasis.¹⁰

3. Monoterpenes

One of the most common monoterpenes scientist have examined is limonene (found in lemons and in noni juice). The monoterpene limonene has been shown to prevent mammary, liver, lung and other cancers. Limonene stimulate thymus gland to secrete more T cells that destroy the carcinoma cells. In vitro data suggest it may be effective in treating some forms of leukaemia.¹¹

4. Terpenoid compounds

Related to monoterpenes, terpenoid compounds or terpenes are also found in noni. The specific terpenes in noni are eugenol, beta carotene and urosolic acid.

Beta carotene is associated with reducing cancers of the lung, skin, cervix, prostate and respiratory and gastrointestinal tracts. Beta carotene is believed to function by quenching the singlet oxygen free radical and prevent oxidative damage. And also helps in boosting the thymus gland. Long term use of moderate dose of beta carotene substantially reduced prostate cancer incidence and deaths from it in male smokers.¹²

Urosolic acid a penta cyclic terpenoid has anti carcinogenic effect both externally and internally prevent growth of cancerous cells and induce apoptosis by modulating immune process of the body.¹³

5. Proxeronine

Proxeronine is the critical element of the xeronine system, a system in the body that consists of proxeronine, proxeroninase, and xeronine. Proxeronine combines with proxeroninase to form xeronine, which is used by the body to rebuild the damaged cells. The primary function of xeronine is to regulate the rigidity and shape of specific proteins. Xeronine declines with age, stress and poor diet.¹⁴

Mechanism of cancer prevention

Cytotoxicity

Cytotoxicity involves attacking the cancer cells directly by changing the cell biology so that the cells are either killed or prevented from dividing. Damnacanthol isolated from Noni roots is an inhibitor of *ras* function in K-Ras NRK cells.⁷

In vitro studies on leukaemia cell has showed that Noni extracts affect several genes of the apoptotic pathway and cell cycle, by dose dependent manner and as a result causes inhibition of cell growth.

Immunomodulation

Noni is found to inhibit the existence or growth of cancer cells by manipulating the immune system. Noni precipitate was found to stimulate several mediators from murine effector cells including TNF alpha, IL-1 beta, IL-10, IL-12, IFN-gamma and Nitric

oxide. Thus it was later concluded that the Noni juice seems to suppress tumor growth indirectly by stimulating the immune system.¹⁵ Mechanism by which noni can do these function is called 'adoptogenesis'.

Nitric oxide (NO) ,produced by activated macrophages plays a role in the host protection against pathogen as well as malignant tumors. Noni increases the body's biosynthesis of NO

Interleukin

Noni modulates production activity and effectiveness of IL-2 and enhances the production of B cell antibodies and also the cytotoxicity of natural killer cells.

Interferons

Noni modulates the production and activity of IFN gamma and helps in activation of macrophages and the over all process of cell mediated immunity.

Anti angiogenesis

Angiogenesis is the creation of new tiny blood vessels. New blood vessels develop for instance to help cuts and other wounds .But during cancer the same process create new, very small blood vessels that provide a tumor with its own blood supply.

Noni has been shown to exhibit anti angiogenesis in cancers *i.e.*, to stop tumors from developing new blood vessels. *In vitro* studies reveal that Noni induces vessel degeneration and apoptosis of cells.¹⁶

Prevention of formation of DNA adducts

Most chemical carcinogens need activation by our body enzymes to be transformed to an ultimate form that readily binds to genetic DNA to form DNA adducts. Carcinogen DNA adducts formation causes DNA damage. Carcinogen DNA adducts can be repaired by body enzymes. The unrepaired DNA damage will be responsible for mutation and the consequent cancer development. Therefore preventing carcinogen DNA adduct formation is a key step for cancer prevention at the initiation step of carcinogenesis .There are studies on animal models to prove that Noni has got the ability to prevent or block the carcinogen induced DNA adduct formation.¹⁷

Antioxidant activity

Oxidative damage induced by reactive free radicals is involved in the development of cancer. Antioxidants are known to reduce free radical induced oxidative damage, therefore reducing cancer risk. Antioxidants in Noni help in scavenging reactive oxygen free radicals and quenching lipid peroxides.¹⁷

Toxicity

High dosage of noni has been found to raise the serum transaminase and lactic dehydrogenase levels (LDH). Due to high potassium concentration (56.3mEq/L) in Noni, there are reports of renal toxicity^{18,19}

Conclusions

Noni is a natural fruit that has enormous uses especially in the treatment and prevention of cancer. Most of the

experiments thus far carried out have been preclinical (animal or *in vitro* studies). Scientific studies have opened some interesting avenues, but have not conclusively demonstrated the medicinal value of this plant. Randomized clinical trials have to be carried out to know the exact effect in human diseases. If, in the future, medicinal values of Noni can be adequately assessed, especially of its anticancer activity, this fruit could have significant medicinal value.

References

1. Nelson,SC. Noni cultivation in Hawaii. *Fruit and Nuts* 2001;4:1-4.
2. Dixon, AR, McMillen H, Etkin NL. Ferment this: the transformation of noni, a traditional Polynesian medicine (*Morinda Citrifolia*, Rubiaceae). *Ecological Botany* 1993;53:51-68.
3. Mortan JF. The ocean going Noni, or Indian mulberry (*Morinda Citrifolia*, Rubiaceae) and some of its 'colourful relatives'. *Ecological Botany* 1992;46:241-256.
4. Dittnar A. *Morinda Citrifolia* L – Use in indigenous Samoan medicine. *Journal of Herbs, Spices and Medicinal Plant* 1993;1:77-92.
5. Liu JM. *et al.* Analysis of the in vitro inhibition of mammary adenocarcinoma cell adhesion by sulphated polysaccharides. *Anticancer Research* 2000; 20 (5A):3265-71.
6. Hirazumi A, Furusawa E. An immunomodulatory polysaccharide rich substance from the fruit juice of *Morinda Citrifolia* (Noni) with antitumor activity. *Phytotherapeutic Research* 1999;13:380-387.

7. Hirmatsu T, Imoto M, Koyano T, Umezawa K. Induction of normal phenotypes in *ras* transformed cells by damnacanthal for *Morinda Citrifolia*. *Cancer Lett* 1993;73:161-166.
8. Kamei H, *et al.* Inhibition of cell growth in culture by quinines. *Cancer Biother Radiophar* 1998;3:185-188.
9. Tarasiuk J, Stefanska B and Borowski E. The direct reduction of cytochrome *c* by some anthraquinone anti tumor compounds. *Anticancer Drug Design* 1996;11:Issue3.
10. EGCg in Green Tea Found to Limit Activity of Breast Cancer Cells. *Asia Pacific Bio Tech News* 1998; 2:p.562.
11. Hohl RJ. Monoterpenes as regulators of malignant cell proliferation. *Adv Exp Med Biol* 1996;401:137-46.
12. Heinonen OP, Albanes D, Virtamo J, Taylor PR, *et al.* Prostate cancer and supplementation with alpha – tocopherol and beta – carotene: incidence and mortality in a controlled trial. *Journal of the National Cancer Institute* 1998;90:440-446.
13. Wang MY, West BJ, Jensen CJ, Nowicki D. *Morinda Citrifolia* (Noni): A literature review and recent advances in Noni research. *Acta Pharmacol Sin.*2002;23:1127-41.
14. Heinicke, Ralph. The Xeronine system: a new cellular mechanism that explains the health promotion action of Noni and Bromelain. *Direct source publishing: Orem, Utah* 2001.
15. Hirazumi A, Furusawa E, Chou SC, Hokama Y. Immunomodulation contributes to the anticancer activity of *Morinda Citrifolia* (Noni) fruit juice. *Proc West Pharmacol Soc* 1996;39:7-9.
16. Hornick CA, Myers A, Sadowska-Krowicka H, Anthony CT, Woltering EA. Inhibition of angiogenic initiation and disruption of newly established human vascular networks by juice from *Morinda Citrifolia* (Noni). *Angiogenesis* 2003;6:143-9.
17. Wang MY, Su C, Cancer preventive effect of *Morinda Citrifolia* (Noni). *Annals of the New York Academy of sciences* 2001;952:161-168.

18. Stadbaver V, Fickert P, Lackner, *et al.* Hepatotoxicity of Noni Juice: Report of 2 cases. *World J Gastroenterol* 2005;11:4958-60.
19. Mueller BA, Scott MK, *et al.* Noni juice (*Morinda Citrifolia*) - hidden potential for hyperkalemia. *Am J Kidney Dis* 2000;3:10-12.