

A comprehensive review on therapeutic perspectives of *Morinda citrifolia* (Indian Noni) to combat cancer

ABSTRACT

Back ground:

Indian Noni (*Morinda citrifolia* L.) is a large shrub or small evergreen tree, also known as Indian mulberry. It is a medicinal plant that has been used as conventional medicine and food additives for a long time. As a drug, plant bioactivity is attributed to its secondary metabolites. *M.citrifolia* has very rich nutrients and consists of over 100 varieties of chemical compounds which have been isolated so far from the plant. In disorders such as skin ailments, respiratory infections, gastritis, menstrual, abortion, diabetes, and venereal diseases, it also shows beneficial effects.

Materials and Methods:

The relation of noni juice or its extract (fruit, leaves or root) to anticancer and/or immunostimulant properties was investigated in this study. A Medline quest was performed along with cross-referencing using the main search terms '*Morinda citrifolia* and cancer'.

Results:

According to our search results for scientific study *M. citrifolia* is used in literature for more than 40 forms of ailments. Crude extract is recorded from various plant and fruit juice components. There are records of amino acids, anthraquinones, fatty acids, flavonoids, iridoids, lignans, polysaccharides, sterols, carbohydrates, terpenoids, etc. in the crude extract of different sections of plant and fruit juice that are therapeutically beneficial for a wide range of pathological conditions.

Conclusion:

Literature indicates that Nonii pharmacologically active and used in various cancer types (Colon, breast, esophageal, colorectal Cancers, cardiovascular disorders, diabetes, hypertension, arthritis). This plant's high potential classifies the compounds as the noteworthy medication of the future, and clinical trials are needed to demonstrate their effect on life-threatening diseases such as cancer. Further analysis warrants the isolation of the active components. These properties can be substantiated by the preclinical or/and clinical investigations.

Key words: *M.citrifolia*, Indian Noni, antioxidants, anticancer activity, therapeutic perspectives

1. INTRODUCTION

Modern principles of health assistance, such as dietary therapy and phytotherapy, have arisen as guidelines for the ingestion of nutraceuticals of plant origin. Nutraceutical provides the user

with prescription or nutritional benefits by supplying ways to preserve health and protect against illness [1]. A functional plant diet, on the other side, supplies the body with the essential quantities of vitamins, fats, proteins, carbohydrates and several other compounds necessary for its existence. Botanicals are however, commonly used as synonyms for herbal products. Then, a legal distinction between plant nutraceuticals and pharmacologically active herbals or botanicals is required [2]. In every community of the world, herbal and natural products of folk medicine have been used for centuries [3]. India is rich with herbs and medicinal plants and it has been documented that a significant number of plant extracts are of great value against various tropical diseases and physiological disorders such as cancers and tumours. Due to their low toxic effects and costs, usability and great utility as complementary therapies, natural medicines are gaining great popularity [4].

*M.citrifolia*L. (Rubiaceae)(MC), usually known to as noni [5] commonly referred to as famine fruit, plays an important role in everyday dietary intakes, as it contains a variety of vitamins, phytochemicals, and electrolytes. These constituents have many biological functions that perform a role in the immune system and are anti-tumor, antibacterial, antiviral, antifungal. In all seasons, this plant produces fruit [6]. With circular veins, these fruits are thick and ovoid in form. When unripe, they are green and when fully mature, yellowish-white. During the ripening process, the fruits have a tender, watery flesh, and a cheese scent that becomes more and more pronounced and pungent [7]. In treating parasitic, tumorous, anthelmintic, analgesic, microbial, fungal, coronary, hypotensive diseases, more than 160 phytochemicals have been isolated from the plant *M.citrifolia*, making it an herbal cure. In disorders such as skin diseases, respiratory infections, gastritis, menstrual diseases, diabetes and venereal diseases, it also shows beneficial effects. About 80 species are included in the genus *Morinda*, mainly of old-World origin *M.citrifolia*. In the Pacific and even in tropical America, *citrifolia* is spread [8]. Many portions of the *M.citrifolia*are attributed to their proposed cancer consequences [9], dyslipidemia[10] , inflammation [11] and immunostimulant properties [12]. In narcotics, including the stems, leaves, fruit, and seeds, *citrifolia* tree is used. The aim of this review is to analyze the anticancer property update associated with *M.citrifolia* L. (Noni Indian).

Scientific classification

Botanical name: *Morinda citrifolia*

Domain: Eukarya

Kingdom: Plantae

Phylum: Magnoliophyta

Class: Magnoliopsida (dicot)

Order: Rubiales

Family: Rubiaceae

Genus: *Morinda*

Species: *Morinda*



(coffee family)

citrifolia

Fig 1: *M.citrifolia* plant



Fig 3: *M.citrifolia* ripe and unripe fruits

Fig 2: *M.citrifolia* flower



Fig 4: *M.citrifolia* seed

Back ground of *M.citrifolia* L.

M.citrifolia is one of the most important fruits widely used for its restorative health properties, diminishing its popularity over the years due to the ripened fruit's unpleasant odour. *M.citrifolia* is also called as Indian Mulberry or Indian Noni [13]. *M.citrifolia* is often eaten in the form of juice. It is also often preferred for individuals to take *M.citrifolia* in the form of capsules containing dehydrated *M.citrifolia* berries. Throughout the year, the *M.citrifolia* plant blooms. The colour of the flower is white. *M.citrifolia* plant is evergreen plant[14].

Morphology and physiology

In South-East Asian countries, Australia and the Pacific Islands, there are 80 distinctive species of the genus *Morinda*. *M.citrifolia* is a small evergreen tree that grows to a height of up to 3-10 m before it matures. The arrangement of the leaves is pinnate, glossy, 5-17 cm long and 10-40 cm broad, opposite each other. It is distinguished by its straight trunk, bright green and elliptical leaves, its unusual ovoid, grenade like yellowish fruit-the development of the fruit seen is up to 12 cm consisting of a lumpy surface while the polygonal shaped parts are hidden. It gives a foul taste and odour to fruit when ripe [15]. In order to insert a peduncle, flowers are clustered together. The peduncles are 5 lobed corollas and the taunted rim calyx of up to 10-30 cm in length [14]. Root structures are a significant lateral compromise of a tap root. Yellowish wood and roots yielding yellow coloured dye are the species' most characteristic feature [16].

***M.citrifolia*L. phytochemistry**

M. citrifolia has very rich nutrients and consists of more than 100 chemical compound varieties that have been isolated from the plant so far. Based on the drying process, harvesting method and time, location of cultivation and development and climatic conditions, the variation in their chemistry [17]. Phenols, polysaccharides, anthraquinones, carotenes, flavonoids, steroids and lactone moieties are among other compounds identified from the fruit. Many volatile elements, such as terpenoid aldehydes and ketones [18], have also been isolated from the plant. Some experiments have also extracted fatty acids and esters from the fruit, containing sulphur compounds such as linalool and methanethiol etc. Hexanoic acid and octanoic acids, present in the mature fruits, were isolated from the plant [19]. While lipids are macronutrients, they are present in a much smaller quantity in the fruit. Eicosanoic acid has been isolated from caprylic acid. Higher seeds such as Nonioside A, B, C, D and E were successfully isolated from the plant's seeds. Saturated fatty acids have been identified from the seeds, such as palmitic acid, lauric acid, stearic acid and arachidic acid. Carotenoids and saponins are isolated from roots and fruits, primarily from beta carotene, present in higher concentrations in plant fruits and bark [20]. Flavonoids are primarily from roots derived from plants and tannins are also present along with flavonoids that belong to the polyphenols class. Fruits also contain flavonoids, although they are relatively smaller than the roots. The volume of the plant content ranges from 180-350 mg/100 g, and compounds such as kaempferol, quercetin, narcissoside, and rutin have been isolated. There is a community of tannins from the seeds and stems of the plant that are isolated. With the variance of the plant's growth stage, the phenolic content of the seeds was checked. The more mature and ripe the fruit, the lower the polyphenol level in the plant has been identified [21].

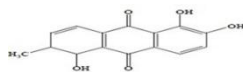
Table 1. Chemical composition of Noni [18].

Description	Content	Unit
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
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
Total carotene	18-22	IU/100 g

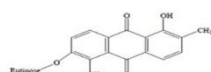
Pantothenic acid	0.15-0.5	mg/100 g
Calcium	20-25	mg/100 g
Iron	0.1-0.3	mg/100 g
Phosphorus	2.0-7.0	mg/100g
Magnesium	3.0-12	mg/100 g
Molybdenum	0.3-1.0	mg/100 g
Sodium	15.0-40.0	mg/100 g
Potassium	30.0-150	mg/100 g
Sodium chloride	0.09-0.12	%

Figure 5: Bioactive compounds of *M.citrifolia* [18]

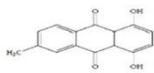
Anthraquinone glycosides



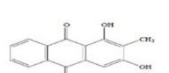
Morindone



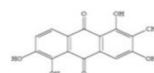
Morindion



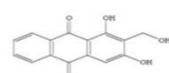
Morindandrine



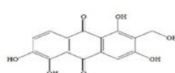
Rubiadine



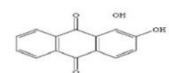
3-hydroxy morindone



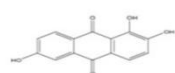
Lucidin



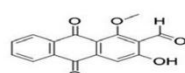
5,6-dihydroxy lucidin



Alizarin

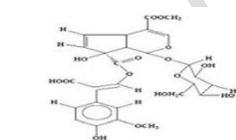


Sorandjidiol

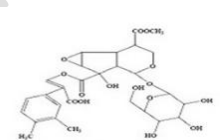


Damnacanthal

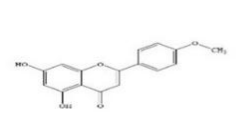
Other glycosides



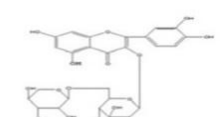
Citrifolinoside A



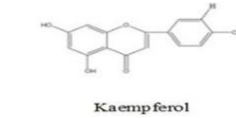
Citrifolinoside B



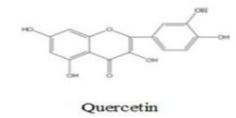
Aracetin



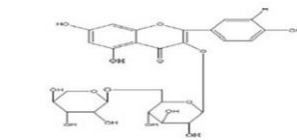
Rutin



Kaempferol



Quercetin



Glucopyranoside

Anti-cancer activity of *Morindacitrifolia*

As cancer cells have a lower growth factor than normal cells, cancer is a condition caused by abnormal cell division. Anti-cancer compounds are however, usually compounds that can prevent growth or kill cancer cells but do not damage normal cells. *M.citrifolia* fruit juice has long been used by people to cure cancer in the Hawaii and Tahiti islands [22]. Depending on the form, *M.citrifolia* fruit juice activates the immune system to help' the body against cancer, and destroys a small portion of cancer cells (0-36 percent). Components will activate the immune system in *M.citrifolia* juice [23]. In MMTc transgenic mice, which were models for mammary cancer, MC juice was examined for anti-tumour activity. There was no evidence of any activity or decline in breast cancer. It should also be advocated that fruit juice has little effects on the probability of occurrence of female breast cancer, but only has supplementation benefits [24]. A research to test the anti-cancer effect of fruit juice on the cell lines of Hela and Siha was performed and compared with the normal drug, Cisplatin. And a sample

was also tested with the combination of both, and the findings showed greater behaviour than individual groups in the combination [25].

Endophytic fungi are also associated with the capacity of *M. citrifolia* as an anti-cancer. As many as twelve distinct species of endophytic fungi isolated from leaves and three from *M. citrifolia* have been found by [26]. The development of human LU-1 (lung), PC-3 (prostate), and MCF-7 (breast) cell line carcinomas with IC₅₀ values of around 10µg/mL was inhibited by all (3) *M. citrifolia* leaf endophytic fungi [26]. The dichloromethane leaf extract was tested in cell lines for its anti-cancer efficacy. As responsible for the antineoplastic activity, chemical constituents such as damnacanthal, scopoletin and rutin were hypothesised. Epidermoid carcinoma, vaginal cancer cell lines, breast cell lines, and liver cells were tested. Compared to isolated lead molecules, the extract was powerful in inhibiting cell growth in a better efficacy. The potential of *M. citrifolia* as an anti-cancer is also attributed to the content of anthraquinone essential oil [27] and anthraquinone [28]. *M. citrifolia* fruit essential oil had an IC₅₀ value of 91.46 and 78.15µgm/L for human colorectal carcinoma line cells (HCT-116) and human breast carcinoma cells (MCF-7) respectively [27]. The plant's fermented exudate has been tested for its anti-cancer potency at a dose of 500 microlitres per day. The 180-ascites rat model of sarcoma was studied. It was observed that 80% of mice were less tumorous and 45 days after tumour induction, and those mice that were not treated were dead after 30 days of cancer induction [29]. There was also a research report that was performed on heavy tobacco smoking. After intake of the juice at 1 ounce, these subjects were assessed for the amount of DNA adducts relative to women who are higher in males. The method was proposed to stop the binding of DNA to the carcinogen [30]. An important inhibitory effect on the proliferation of human lung and colon cancer cells [28] is demonstrated by anthraquinone compounds isolated from *M. citrifolia* roots.

CONCLUSION

The plant of choice for food or medicine is *Morinda citrifolia*. It is well known that nearly all the disorders associated with all the body's organ systems are treated. Toxicity was still very low and mortality was seen at higher doses. Further research has been required to determine the plant's anti-cancer mechanisms. These properties can be substantiated by the preclinical or/and clinical investigations. In order to determine a potential role of *M. citrifolia*, further *in vitro* and *in vivo* animal studies are needed if any of the relevant bioactivities suggest the presence of unknown anticancer activity.

Reference

1. De Felice SL. FIM Rationale and Proposed Guidelines for the Nutraceutical Research & Education Act - NREA, November 10, 2002. Foundation for Innovation in Medicine.
2. Koch A, Brandenburger S, Turpe S, Birringer M. The need for a legal distinction of nutraceuticals. Food Nutr Sci. 2014; 5:905-13.
3. Acharya D, Shrivastava A. Indigenous Herbal Medicines: Tribal Formulations and Traditional Herbal Practices, Aavishkar Publishers Distributor, Jaipur- India, 2008;440.

4. Mahima A, Rahal R, Deb SK, Latheef, Samad HA. Immuno modulatory and therapeutic potentials of herbal, traditional /indigenous and ethno veterinary medicines. Pak. J Biol. Sci. 2012; 15:754-74.
5. Arunachalam V. *M.citrifolia*L. (Rubiaceae): a multi-purpose tree for coastal ecosystems and its variability in Konkan region of India. Genet Resour Crop Evol. 2018;65(6):1751–65.
6. Karuppaiah Jeyaprakash, Mohamad S. AlSalhi, SandhanasamyDevanesan, Anticancer and antioxidant efficacy of silver nanoparticles synthesized from fruit of *M.citrifolia*Linn on Ehrlich ascites carcinoma mice, Journal of King Saud University – Science. 2020; 32: 3181–86.
7. Heinicke RM. The pharmacologically active ingredient of Noni. Bulletin of the National Tropical Botanical Garden. 1985; 15:10-14.
8. Morton JF. The ocean-going noni, or Indian Mulberry (*Morinda citrifolia*, Rubiaceae) and some of its “colorful” relatives. Econ Bot. 1992;46(3): 241–56.
9. Sharma K, Pachauri SD, Khandelwal K, Ahmad H, Arya A, Biala P, Agrawal S, Pandey RR, Srivastava A, Srivastav A. Anticancer effects of extracts from the fruit of *M.citrifolia*(noni) in breast cancer cell lines. Drug Res. 2016;66(3):141–47.
10. Mandukhail SUR, Aziz N, Gilani AH. Studies on antidyslipidemic effects of *M.citrifolia*(noni) fruit, leaves and root extracts. Lipids Health Dis. 2010;9(1):88.
11. Mckoy MLG, Thomas EA, Simon OR. Preliminary investigation of the anti-inflammatory properties of an aqueous extract from *M.citrifolia*(noni). Proc West Pharmacol Soc. 2002;45:76–78.
12. Brown AC. Anticancer activity of *M.citrifolia*(noni) fruit: a review. Phytother Res. 2012; 26(10):1427–40.
13. Francis JK. Noni, *M.citrifolia*L. Rubiaceae U.S. URL: Department of Agriculture, Forest Service, International Institute of Tropical forestry, Rio Piedras Puerto Rico, 2003.
14. Elkins R. Hawaiian Noni (*Morindacitrifolia*) Prize Herb of Hawaii and the South Pacific. Woodland Publishing, Utah, 1998.
15. Swanholm CE, St John H, Scheuer PJ. A survey of alkaloids in Hawaiian plants. Pacific Science. 1959; 13:295-05.
16. Singh DR, Rai RB, *M.citrifolia*Linn. an important fruit tree of Andaman and Nicobar Islands, Nat. Prod. Radiance. 2007; 6(1):62
17. Deng S, West BJ, Jensen CJ. A quantitative comparison of phytochemical components in global noni fruits and their commercial products. Food Chemistry. 2010;122(1):267–70. Available from: 10.1016/j.foodchem.2010.01. 031.
18. Ali M, Kenganora M, Manjula SN. Health Benefits of *M.citrifolia*(Noni): A Review. Pharmacognosy Journal. 2016;8(4):321–34. Available from: 10.5530/pj.2016.4.4.
19. Wei G, Huang A, Ho C. Analysis of volatile compounds in noni fruit (*M.citrifolia*L.) juice by steam distillation-extraction and solid phase microextraction coupled with GC/AED and GC/MS. Journal of Food and Drug Analysis. 2011;19(1):33–39.

20. Aalbersberg WGL, Hussein S, Sotheeswaran S, Parkinson S. Carotenoids in the Leaves of *Morinda citrifolia*. Journal of Herbs, Spices & Medicinal Plants. 1993;2(1):51–54. Available from: 10.1300/j044v02n01_07.
21. Krishnaiah D, Bono A, Sarbatly R, Anisuzzaman SM. Antioxidant activity and total phenolic content of an isolated *M.citrifolia*L. methanolic extract from Poly-ethersulphone (PES) membrane separator. Journal of King Saud University - Engineering Sciences. 2015; 27(1):63–67. Available from: 10.1016/j.jksues.2013.01.002.
22. Liu, G., A. Bode, W.Y. Ma, S. Sang, C.T. Ho, and Z. Dong. Two novel glycosides from the fruits of *M.citrifolia*(noni) inhibit AP-1 transactivation and cell transformation in the mouse epidermal JB6 cell line1. Cancer Research. 2001; 61: 5749–56.
23. Brown AC. Anticancer activity of *M.citrifolia* (noni) fruit: a review. Phytother Res. 2012;26(10):1427–40.
24. Clafshenkel WP, King TL, Kotlarczyk MP, Cline JM, Foster WG, Davis VL.*Morindacitrifolia*(Noni) Juice Augments Mammary Gland Differentiation and Reduces Mammary Tumor Growth in Mice Expressing the Unactivated c-erbB2 Transgene. Evidence-Based Complementary and Alternative Medicine. 2012;2012:1–15. Available from: 10.1155/2012/487423.
25. Gupta RK, Banerjee A, Pathak S, Sharma C, Singh N. Induction of Mitochondrial- Mediated Apoptosis by *M.citrifolia*(Noni) in Human Cervical Cancer Cells. Asian Pacific Journal of Cancer Prevention. 2013;14(1):237–42. Available from:10.7314/apjcp.2013.14.1.237.
26. Wu, Y., S. Girmay, V.M. da Silva, B. Perry, X. Hu, and G.T. Tan. The role of endophytic fungi in the anticancer activity of *M.citrifolia* Linn. (noni). Hindawi Publishing Corporation. Evidence-Based Complementary and Alternative Medicine. 2015; 1-9. Article ID 393960, 8 pages. <http://dx.doi.org/10.1155/2015/393960>:
27. Piaru, S.P., R. Mahmud, A.M.S.A. Majid, S. Ismail and C.N. Man. Chemical composition, antioxidant and cytotoxicity activities of the essential oils of *Myristica fragrans* and *Morinda citrifolia*. J Sci Food Agric. 2012; 92: 593–97.
28. Lishuang, L.V., H. Chen, C.T. Ho, and S. Sang. Chemical components of the roots of Noni (*Morinda citrifolia*) and their cytotoxic effects. Fitoterapia. 2011; 82: 704–08.
29. Li J, Stickel SL, Bouton-Verville H, Burgin KE, Yu X, Wong DKW. Fermented noni exudate (fNE): A mediator between immune system and anti-tumor activity. Oncology Reports. 2008;20: 1505–09.
30. Wang MY, Su C. Cancer Preventive Effect of *Morinda citrifolia* (Noni). Annals of the New York Academy of Sciences. 2001; 952(1):161–68. Available from: 10.1111/j.1749-6632.2001.tb02737.x.