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PHARMACOLOGICAL OVERVIEW OF FREEZE DRIED ANDAMAN NONI (*MORINDA CITRIFOLIA*.L) AGAINST CANCER AND NEUROLOGICAL DISORDER

Hariom Singh, Saswata Banerjee, Saumen Karan, Biswajit Das, Debjyoti Naskar and Tapan Kumar Chatterjee*

Division of Pharmacology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, West Bangal, India

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Correspondence to Author:
Dr. Tapan Kumar Chatterjee

Associate Professor, Division of Pharmacology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata - 700032, West Bangal, India

E-mail: crctkc@gmail.com

ABSTRACT: Noni (*Morinda citrifolia*) is one of the important traditional medicinal plants have been used by Polynesia over a period of 2000 years. *Morinda citrifolia* belongs to family Rubiaceae (Coffee family) which is an evergreen small sized tree, with glossy and deeply veined leaves found in tropical regions and islands of South Pacific, West Indies, India, Africa, and Australia. Noni fruit juice traditionally has been used in different disorders such as abnormal menstruation, acne/ boils, constipation, diarrhea, arthritis, diabetes, fever, high blood pressure, gastric ulcers, sprains, mental depression, senility, poor digestion, atherosclerosis, blood vessel problems, and drug addiction. Noni consist of major chief chemical constituents such as alkaloid xeronine, scopoletin and dammacanthol, besides this it also contains Vitamin A and C and minerals like magnesium, potassium, iron, aminoacids, alizarin, ursolic acids. The review summarizes the pharmacological action and traditional uses of Noni along with the scientific researches and novel pathways to treat cancers and various neurological disorders. Noni can inhibit cancer via inhibition of ras a GTP binding protein and by modification of misfolded protein by one of its component named Xeronine. It also possesses antiangiogenic property approach via COX-2 inhibition, which is a promising approach in the treatment of cancer now a day. Taking into account its biological and pharmacological activity Noni proves itself a plant of high therapeutic potential against many diseases and has the potential to become a promising agent in the treatment of cancer.

INTRODUCTION: *Morinda citrifolia* L. (Noni) is a small evergreen tree found in many tropical regions of the world and has established its presence in the pharmacopoeias of Pacific Islanders and Southeast Asia [1]. Medicinal properties of Noni fruit as folklore medicine have been found in ancient literatrure [2, 3]. Traditionally it was found to be effective in high blood pressure, arthritis, burns, tumor, gastric ulcers, sprains, mental depression. Scientifically proven studies showed the use of Noni in diabetes, pain, cancer, wounds, hypertension, menstrual cramps, inflammation and immune-compromised diseases [4].

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It was also used as food and had been reportedly found that people of Rarotongans [5] preferred it as a favorite ingredient for curry preparation [6]. Noni has been used by Polynesians for over 2000 years as traditional medicine [7]. While they migrated to different parts of the world they brought Noni plant with them which found its vast importance as herbal remedies for various diseases and in maintaining good health [8]. Andaman freeze dried noni is a superior form of noni with potent pharmacological effects.

Botanical Classification: [9]

Domain: Eukarya
Kingdom: Planteae
Phylum: Magnoliophyta
Class: Magnoliopsida
Order: Rubiales
Family: Rubiaceae
Genus: Morinda
Species: Citrifolia

Description:

Noni (*Morinda citrifolia* linn) also known as Indian Mulberry, Nuna, Cheese fruit, Tookunja, Great morinda, Mouses'pineapple, Yellow root, belonging to family Rubiaceae. It is an evergreen tree having stem diameter of 13 cm [6]. Sapwood is yellowish-brown soft in nature and the bark is of gray or brown color smoothish to slightly rough in nature. Twigs are light green and four-angled [10, 11, 12].

Noni is found to grow in open coastal regions of 1300 ft from sea level [13] predominantly in tropical countries such as Africa, Australia, Barbados, Cambodia, Caribbean, Cayman Islands, Cuba, Dominican Republic, El Salvador, Fiji, Florida, French West Indies, Guadeloupe, Guam, Haiti, Hawaii, India, Jamaica, Java, Laos, Malaysia, Marquesas Islands, Philippines, Polynesia, Puerto Rico, Raratonga, Samoa, Seychelles, Solomon Islands, Southeast Asia, St. Croix, Surinam, Tahiti, Thailand, Tonga, Trinida and Tobago and Vietnam [14].

FIG. 1: NONI FRUIT

Cultivation of Noni:

Noni grows relatively in moderate dry and wet environment, 1500 feet above sea level. Propagation of Noni is mainly done by seed or stem cuttings which is more preferred technique [15, 16]. Noni thrives with moderate irrigation and can survive extended drought once established and mature Noni plants can begin to bear fruit about 9 months after planting depending on the altitude, mean annual temperature of 20-35 ^{0}C, annual rainfall of 250-4000 mm [17].

Morphology:

The leaves are opposite or whorled with long or short petiolate, dark green in color, glossy appearance, prominently veined, and having epiliptic to oblong shape (10-30×5-15cm), flowers were bisexual, protandrous, five lobed white tubular 1.25 cm long, fruit is syncarp, ovoid, ellipsoid or roundish (3-10×3-6cm), the pulp is fleshy and juicy, dull yellow or yellowish white in color and gelatinous when the fruit is ripe [1,18]. Seeds were fleshy, medium-sized, ovoid to obvoid or reniform in shape. Seed remain viable for several months by floating on water [19].

Microscopy:

Microscopic evaluation of the freeze dried powdered Noni powder showed the presence of single acicular calcium oxalate crystals, lignified cells, starch cells and oil globules. It shows the presence of thin walled parenchymal cells with spira vessels [20, 21]. Microscopy of leaves reveals presence of Paracytic stomata consisting of a guard cell and a subsidiary cell which is the unique characteristic of the family Rubiaceae, [22] raphides of calcium oxalate crystal, palisade cells and spongy cells were also found [23].

Chemical composition:

The anthraquinones, flavonoids and phenolics are the major groups of secondary metabolites responsible for the therapeutic actitvities of the plant Indian Mulberry [24]. Oligo- and polysaccharides, glycosides, alkaloids components, octoanoic acid, potassium, vitamin C, terpenoids, anthraquinones (nordamnacanthal, morindone, rubiadin, and rubiadin, methyl ether, anthraquinone glycoside), carotene, vitamin A, flavones glycosides, linoleic acid, alizarin, amino acids, acubin, L-asperuloside, caproic acid, caprylic acid, ursolic acid, rutin, and a putative proxeronine are mainly present in Noni [25].

About 51 volatile compounds have been identified in the ripe fruit [26], including organic acids (mainly octanoic and hexanoic acids), alcohols (3-methyl-3-buten-1-ol), esters, ketones (2-heptanone), and lactones [27]. The most important alkaloid reported is Xeronine [28]. The fruit contains 90% of water and the main components of the dry matter appear to be soluble solids, dietary fibers and proteins. Amino

acids present inside fruits are aspartic acid, glutamic acid and isoleucine [29].

Phytochemistry:

Phytochemical screening of aqueous, ethanolic and methanolic extracts of *Morinda citrifolia* showed the presence of secondary metabolites such as steroids, flavanoids, terprnoids, cardiac glycosides, protein, saponins, amino acids, fats and oils, reducing sugars and carbohydrates using various reagents and chemicals [30,31]. Retired biochemist, Ralph Heinicke, claimed the presence of natural precursor for xeronine named Proxeronine which is converted to the alkaloid, xeronine, in the body by an enzyme proxeronase [28].

He stated that Xeronine is responsible for modification of the molecular structure of proteins and interacts with proteins such as enzymes, receptors and changes them into their original or proper conformation leading to proper functioning of receptor or enzyme [32]. Xeronine, is active in very small quantities and is one of the most important enzymes of human body produced in the large intestine. It can further change the membrane permeability of cell and leads to the absorption of larger molecules facilitating the digestion process.

Thus, xeronine deficiency leads to improper absorption of many nutrients molecule. Novel thing about noni fruit is that it contains xeronine like other plants along with proxeronine and proxeronase in much greater quantities than other plants. Proxeronine is the precursor of xeronine, and in presence of proxeronase, proxeronine is converted to xeronine [33].

Traditional uses of *Morinda citrifolia:*

Juice of unripened fruits of Noni is used for the treatment of sore found inside the mouth. Leaves of Noni were applied in burn injury. Noni leaves were rubbed on the umbilical cord to promote breathing process in neonates during apnoea like problems. Boiled combination of Noni leaves and coconut oil with *Curcuma longa* was used for the good health of postparturition mother. Noni fruit juice was also used in intoxication state, used as insecticide to wash hair, in high blood pressure and diabetes. Fruit was also used as purgative, laxative, blood purification [34].

Pharmacological uses of Noni:

Analgesic and anti-inflammatory effect:

Chronic inflammatory diseases and pain are one of the world's major health related problems. Antinociceptive effect of Noni fruit in Swiss albino mice has been reported through various *in vivo* models such as acetic acid induced writhing test, radiant heat model, tail immersion model and formalin induced pain model [35, 36].

The anti-inflammatory activity was found by the down-regulation of lipopolysaccharide-induced nuclear factor-κB (NF-κB) activity which in turn results in the reduced expression of pro-cytokines, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). COX 2 inhibitors were somewhat found effective in colon, lung and breast cancer. Studies reveled that use of NSAIDS like aspirin and others decreases the incidence of lung and breast cancer [37, 38]. As the main target of NSAID is COX 2 enzyme [39], COX 2 over expression lead to inflammatory reaction and angiogenesis[40].

Anti hypertensive activity:

Moorthy and coworkers found that an ethanol extract of the Noni roots lowered the blood pressure in an anesthetized dog[41]. A Hawaiian physician reported that Noni fruit juice had a diuretic effect [42].

Anticancer activity:

Noni has potent anticancer activity against EAC induced solid tumor as well as liquid tumor. Staining with trypan blue also reveals that Noni has cytotoxic action [43]. The most reliable parameter for conferring the anticancer activity of any drug is the increase in the life span of animals. Cancer chemotherapy leads to the major problems such as myelosuppression and anemia [44, 45].

Anaemia in EAC cell bearing mice is just because of the decrease in Hb content and RBC count and this occur because of iron deficiency or because of myelopathic condition [46]. Morever, administration of freeze dried Noni restores the haemoglobin level, RBC, and WBC count more or less to normal levels and this confers that the freeze dried Noni possess protective action on the haematopoietic system. Alcoholic ppt of Noni prolongs the mean

survival time upto 75% in lewis lung carcinoma induced mice and it was found that Noni inhibits tumor growth by stimulation of immune system[47, 48]. Several researches showed that dammacanthol isolated from Noni root inhibit the Ras function, as Ras gene is responsible for signal transduction in various type of human cancers such as pancreas, lung, colon, and leukemia [49]

Immune booster activity of Noni:

Tumor necrosis factor alpha is responsible for the inhibition of tumorogeneis and also play role in the regulation of immune cells as well as in apoptosis induction. Dysregulation of this factor leads to the various diseases such as cancer, alzheimer, major depression and inflammatory bowl diseases [50]. Tumor necrosis factor is also known to be endogenous tumor promoter, alcoholic ppt of Noni was found to be effective in inhibition of TNF alpha and controlling the over-regulation of tumor necrosis alpha factor [51].

Extracts and fractions of *M citrifolia* fruits showed the stimulatory effect on important components of the adaptive immune system such as T lymphocytes and B lymphocytes. The effects of the plant extracts on lymphocytes were assessed by in vitro (MTT assay) and in vivo (cell mediated immune response) techniques [52].

Psoriasis

Psoriasis is a chronic, relapsing, cutaneous condition with 1-2% prevalence in the general population. Psoriatic arthritis is a chronic inflammatory arthropathy present in 30% of patients with psoriasis. Noni juice concentrate has been reported to stimulate the cannabinoid receptors, decrease in interleukin (IL)-4 levels and increase interferon levels indicate the immunostimulant potential of this plant.

In addition, a polysaccharide-rich substance was reported to stimulate the release of tumor necrosis factor, IL-1, IL-10, IL-12 and nitric oxide. Recently, the hydroalcoholic extract and one of the fractions of Noni fruits was found to significantly enhance the antibody titer in immuno compromised animals [52]. Anthraquinone isolated from Noni significantly increased elaboration of Procollagen type I C terminal peptide and glycosaminoglycans as well as reduced expression of the collagenase matrix metalloproteinase-1 in study of human fibroblast. Together these observations suggest that extract from Noni might be a strong inducer of the biosynthetic activity of extracellular matrix components. Therefore, extracts from Noni might contribute to the treatment of not only tumors but also immunological and skin disorders [53].

Wound healing:

Wounds are common clinical entities in day-to-day life, which may be major or minor. The process of wound healing can be classified into five phases - cellular phase (granulation), narrowing of wound area (wound contraction), collagen deposition (collagenation), epithelial covering (epithelialisation) and scar remodeling (cicatrisation).

These phases are concurrent but independent of each other. Any agent who accelerates the process is a promoter of wound healing [54]. Changes in blood malondialdehyde (MDA) levels and histopathological studies were also carried out. From the results, it may be concluded that the *M. citrifolia* aqueous leaves enhances the wound healing and possess antioxidant activity [55].

Antispasmodic activity of Noni:

The spasmolytic effect of medicinal plants is usually mediated through calcium channel blockade[56]. The 70% aqueous-ethanolic extract of the *Morinda citrifolia* roots caused a concentration-dependent inhibition of spontaneous contractions in isolated rabbit jejunum preparations, thus showing antispasmodic action [56]. To assess whether the spasmolytic activity of this plant was also mediated through Ca^{++} channel blockade (CCB), high K^{+} (80 mM), as KCl, was used to depolarize the preparations.

High K^{+} (> 30 mM) is known to cause smooth muscle contractions through opening of voltage-dependent L-type Ca^{++} channels, thus allowing influx of extracellular Ca^{++} causing a contractile effect [57] and a substance causing inhibition of high K^{+}-induced contraction is considered as a blocker of Ca^{++} influx. Noni root relaxed the high K^{+} (80 mM)-induced contractions, similar to that caused by Verapamil, a standard Ca^{++} antagonist [58].

Antiviral activity of Noni:
Umezawa and coworkers found a compound isolated from Noni roots named 1-methoxy-2-formyl-3-hydroxyanthraquinone suppressed the cytopathic effect of HIV infected MT-4 cells, without inhibiting cell growth [59].

Antibacterial and antifungal activity of Noni:
Antimicrobial assay of solvent extracts were performed by Disc diffusion method [60]. Antibacterial and antifungal activity was determined by measuring the diameter of the zone of inhibition, surrounding microbial growth [61]. *Morinda citrifolia* extracts showed maximum inhibition against E. coli with the extract of petroleum ether. The gram positive *S.aureus* was susceptible in water extract. The maximum inhibition was observed against *C. albicans* with the chloroform extract.

The water extract showed significant effect against *A.niger* [62]. Extracts from the ripe Noni fruit exhibited moderate antibacterial properties against *Ps aeruginosa*, *M pyrogenes* and *E coli*, and were also shown to have moderate antibacterial properties against *Salmonella typhosa*, *Salmonella montevideo*, *Salmonella schottmuelleri* and *Shigella paradys* [63]. Duncan demonstrated that scopoletin, a health promotor in Noni, inhibits the activity of E coli, commonly associated with recent outbreaks resulting in hundreds of serious infections and even death. Noni also helps stomach ulcer through inhibition of the bacteria H pylori [64].

Antihelmentic activity:
It was found that the ethanol extract of the tender Noni leaves because paralysis and death of the human parasitic nematode worm, *Ascaris Lumbricoides*, within a day [65, 66].

Antidyslipidemic action:
Dyslipidemia is an independent and modifiable risk factor for cardiovascular diseases. Its prevalence is growing not only in developed countries but also in developing countries. Tyloxapol is a non-ionic surfactant causes drastic increase in serum triglycerides and cholesterol levels due to increase in hepatic cholesterol synthesis particularly by the increase in HMG Co-A (3-hydroxy-3-methyl-glutaryl Co-A) activity and by the inhibition of lipoprotein lipase responsible for hydrolysis of plasma lipids [67]. Significant inhibition of rise in lipid levels by extracts of various parts of *Morinda citrifolia* in this model is indicative of inhibition of cholesterol biosynthesis by inhibition of HMG Co-A. This enzyme plays a key role in controlling lipid levels in plasma and other tissue. However, failure of the Noni extracts to cause complete inhibition indicates the involvement of additional mechanisms [68].

Antioxidant properties:
The antioxidant properties of ethanol and ethyl acetate extracts of *M. citrifolia* L. fruit have been assessed using the ferric thiocyanate method (FTC) and thiobarbituric acid test (TBA). The authors found that ethyl acetate extract strong inhibited lipid oxidation, comparably to the same weight of pure α-tocopherol and butylated hydroxyl toluene (BHT). Radical scavenging activity was also measured in vitro by the Tetrazolium nitroblue (TNB) assay in commercial juice by assessing the capacity of the juice to protect cells and lipids from oxidative alteration promoted by superoxide anion radicals (SARs) [69].

FIG 2: PHARMACOLOGICAL ACTIVITIES OF NONI

Newer Approaches:
Cancer therapy by inhibiting the *ras* a GTP binding protein: Dammacanthol is present in Noni root, and which inhibits the *ras* [49]. Ras is GTP

binding protein and belongs to large family of monomeric GTPases. Ras is responsible for cellular proliferation through a series of enzyme cascade events. Activation of members of the *ras* family by guanine nucleotide exchange factors (GEFs) leads in turn to activation of a protein kinase cascade termed the mitogen-activated protein kinase (MAP kinase or MAPK) pathway. Activation of the MAPK pathway is one of the major routes used by growth factor receptors to signal to the nucleus and stimulate cell growth [70].

Ras, which is a proto-oncogene product, functions like a G-protein, and conveys the signal (by GDP/GTP exchange) by the receptor tyrosine kinase (RTK). Activation of Ras in turn activates transcription factors that initiate gene expression, resulting in a variety of cellular responses, including cell division like in case of malignancy [71]. In normal conditions signaling regulated cell growth and proliferation, but in case of cancer, such growth is no longer regulated and results in formation of tumor. Thus, utilizing this novel property of Noni, it can be used in the treatment of cancers, like leukemia.

Therapeutic utilization of Xeronine in neurological disorders and cancer via modification of misfolded proteins:

Proteins are essential element for every organism because they participate in every process occurring inside the cell. Therefore, if their function is impaired, the consequences can be devastating. As we grow older, mutations and thermodynamics (as well as some external factors) conspire against us, resulting in the misfolding of proteins [72]. A common feature of almost all protein conformational diseases is the formation of an aggregate caused by destabilization of the alpha-helical structure and the simultaneous formation of a beta-sheet, for various diseases associated with protein misfolding, one or more proteins are converted from the native structure to an aggregated mass, which is commonly called an 'amyloid'.

The most common feature of all the neurodegenerative disorders is the occurrence of brain lesions, formed by the intra- or extracellular accumulation of misfolded, aggregated or ubiquitinated proteins misfolding of proteins is associated with some neurodegenerative diseases like alzheimers disease and parkinson disease respectively[73].

Retired biochemist, Ralph Heinicke, claimed that xeronine is able to modify the molecular structure of proteins. He stated that xeronine will interact with the protein change them into their original or proper conformation and results in proper functioning of proteins [28].

Taking into account of this activity of xeronine which is found in noni in sufficient quantity it can be used as useful tool in treating neurological disorders like Alzhemier and Parkinson disease. A protein named p53 is a tumor suppressor protein, that stops the cell cycle if there is DNA damage until and unless DNA is repair [72] structural changes in the above protein may cause cancer, thus xeronine may be useful keeping its potential of modification of protein to its original form.

Cancer treatment via anti-angiogenic approach by COX-2 inhibition:

In vitro studies have also revealed the potential of noni juice to inhibit Cyclooxygenase-2 (COX-2) activity, as well as that of 5-lipoxygenase [74, 75]. COX 2 inhibitors were somewhat found effective in colon, lung and breast cancer, studies reveled that use of NSAIDS like aspirin and others decreases the incidence of lung and breast cancer [37,38] and the main target of NSAID is COX 2 enzyme [39], Cyclooxygenase (COX) is the rate-limiting enzyme in the biosynthesis of prostaglandins. COX-2 is induced by many pro-inflammatory cytokines, including IL-1β, VEGF [76].

COX-2 over expression lead to inflammatory reaction and angiogenesis [40]. Some studies showed production of pro-steroids by COX-2 promotes the expression of pro-angiogenic factors [77]. Inhibition of COX-2 by non-steroidal anti-inflammatory drugs leads to restricted angiogenesis and down-regulates production of pro-angiogenic factors, such as VEGF, basic fibroblast growth factor and mitogen activated protein[78]. Like that of NSAID noni also restrict angiogenesis by inhibition of COX-2 and this lead to inhibition of VEGF which is an important pro-angiogenic factor.

CONCLUSION: *Morinda citrifolia* commonly known as Noni, used as a food in tropical regions from Indonesia to the Hawaiian Islands, and it is used as an herbal remedy for multiple diseases. Its fruit, leaves, seeds, bark and roots have been traditionally used for the prevention or improvement of various diseases, including arthritis, infections, colds, cancer, and diabetes. It has been found that *Morinda citrifolia* L. has antioxidant potential equivalent or similar to that of synthetic antioxidants, such as BHT and BHA, which are currently used as food additives. Scientific studies proved the therapeutic use of Noni as anticancer, antiviral, antifungal, antibacterial, antifungal, antibacterial, antihelmitic, antinociceptive, wound healing, immunostimulant, in psoriasis, hypertension making the Noni as a promising potential agent for various disorders.

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