

A Review on the Ethnomedicinal, Therapeutic and Nutraceutical Importance of ‘Noni’ (*Morinda citrifolia* L.)

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Abstract: *Morinda citrifolia* L. commonly known as ‘Noni’ is native to south-east Asian countries and Australia. It is one of the most important traditional medicinal plants and has been heavily prompted for a wide range of uses. The plant has been used for over 2000 years in Polynesia and was formerly cultivated throughout the greater parts of India and now found only in the wild. All parts of the plant are reported to possess medicinal properties. Noni has attained significant economic importance worldwide in recent years because, a variety of health and cosmetic products are made from leaves and fruits. The market for the products is worldwide with the largest market in North America, Mexico, Asia and Australia. More than 200 entities sell Noni products, which are distributed across the globe and enjoy an enormous market share. The ethnomedicinal, therapeutic and nutraceutical potential of the plant is discussed in the present study.

Keywords: Ethnomedicinal, nutraceutical, anti-inflammatory, analgesic, immunomodulatory.

1. INTRODUCTION

Morinda citrifolia L. commonly known as ‘Noni’, which is the Hawaiian name is also called as ‘Indian Mulberry’ [1]. The plant is native to south-east Asian countries, Australia and Pacific islands. It is one of the most important traditional medicinal plants and has been heavily prompted for a wide range of uses. This plant has been used for over 2000 years in Polynesia. The Polynesians utilized the whole Noni plant in their medicinal remedies and also in the preparation of dye for some of their traditional clothes. The root, stem, bark, leaves, flowers and fruits of the Noni plant are all involved in various combinations in almost 40 known and recorded herbal remedies [2]. The plant was formerly cultivated throughout the greater parts of India and now found only in the wild. *M. citrifolia* fruit has a long history of use as a food in tropical regions throughout the world. Written documentation of the consumption of this fruit as a food source precedes the twentieth century. Captain James Cook of the British Navy noted in the late 1700S that the fruit was eaten in Tahiti [3]. An 1866 publication in London explained that *Morinda citrifolia* fruit was consumed as a food in the Fiji Islands [4]. Later publications describe the use of this fruit as a food throughout the Pacific Islands, South-east Asia, Australia, and India. The Noni plant is a small evergreen tree found growing in open coastal regions at sea level and in forest areas up to about 1300 feet above sea level. Noni is a small tree with straight trunk; leaves are broadly elliptic, acute, acuminate or obtuse and bright green. Flowers are white, in dense ovoid heads. Fruits are white when ripe, smooth and glossy, about the size of a small egg. The seeds, which are triangular shaped and reddish brown, have an air sac attached at one end, which makes the seeds buoyant. This could explain, in part, the wide distribution of the plant throughout the Polynesian islands.

Some recent studies are focused on the nutraceutical aspects of *M. citrifolia* fruits offering medical or health benefits to mankind. Most of the parts of the plant are reported to possess medicinal properties. The roots, stem, bark, leaves, flowers and fruits of the plant are used in various combinations in almost 40 known and recorded herbal remedies. Additionally, the roots of the plant yield dyeing principles used in textile and mat industry [5].

2. GENERAL DESCRIPTION

Noni (*Morinda citrifolia*) comes under the Family Rubiaceae, locally known as ‘Cheru-manjanaathi’. The Genus *Morinda* consists of 80 species distributed in south-east Asian countries, Australia and

Pacific islands. Noni is a small evergreen tree that grows to about 3-10 m in height at maturity, widely adapted to tropics. The leaves are opposite, pinnately veined, glossy, wide with 5-17 cm length and 10-40 cm width. Leaf blades are membranous, elliptic to elliptic ovate and glabrous. Petioles are stout and stipules are connate or distinct. The flowers are perfect, ovoid to globose heads, small, white, glossy, tubular and are grouped together to insert on a peduncle. The peduncles are 10-30 mm long, the calyx with a truncated rim and 5 lobed corolla [6]. The fruits are generally yellowish white and fleshy, about 5-10 cm long and with an embossed appearance. It is slightly wrinkling, semi-translucent and covered with small reddish brown buds containing the seeds. The fruit pulp is juicy, bitter, whitish in colour and ripe fruits exhale a strong butyric acid-like rancid smell. The seeds are brown and have distinct air chamber. They can retain the viability for months even after floating in water for months. It has an extensive lateral root system and a deep tap root is present. The yellowish wood and roots which yield yellow coloured dyeing principle are the main characteristic features of the species [7].

3. TRADITIONAL USES

Noni is an important fruit tree plant of Andaman and Nicobar islands and Nicobarese of Car Nicobar uses the leaf juice of the plant. It is applied on cuts and wounds for 3-4 days and is effective in promoting blood clotting [8]. In Lakshadweep, expressed juice of leaves is applied externally for traumatic affection. Islanders eat the seeds once a year with the belief that it promotes health [9]. The leaves of *Morinda citrifolia*, *Colubrina asiatica* and young plant of *Ficus ampelas* are boiled in pig fat and coconut oil and applied in the form of a bandage on fractured bone. In Philippines and Hawaii, Noni has been used as an effective insecticide [10].

4. MEDICINAL USES

The Polynesians utilized the whole plant for preparing herbal remedies. The root is used as a cathartic and febrifuge and applied externally to relieve pain and gout. Leaves are considered tonic and are used in wounds, ulcers and externally applied in gout. The charred leaves made in to a decoction with mustard are a favorite domestic remedy for infantile diarrhoea. Noni fruit juice is widely used for spongy gums, throat complaints, dysentery, leucorrhoea and sapraemia. The fruit juice is in high demand in medicine for different kinds of illnesses such as arthritis, diabetes, high blood pressure, muscle aches and pains, gastro ulcers, menstrual difficulties, head ache, heart diseases, mental depression, poor digestion, atherosclerosis, blood vessel problems, cancer, AIDS and drug addiction [11].

5. CHEMICAL CONSTITUENTS OF NONI

Approximately, 160 phytochemical compounds have been identified and isolated from different parts of *M. citrifolia*, and the chemical components differ largely according to the plant part. The major constituents are phenolic compounds, flavonoids, organic acids, alkaloids, alcohols and phenols, glycosides, carotenoids, esters, iridoids, ketones, lactones, lignans, nucleosides, triterpenoids, sterols and several minor compounds [12]. The major phenolic compounds that have been reported are anthraquinones, which include damnacanthal, morindone, morindine, rubiadin, 2-methoxy-1, 3, 6-trihydroxy anthraquinone, alizarin 1-O-methyl ether [13] 4-dihydroxy-2-methoxy-7-methyl anthraquinone [14], anthragallol 1, 3-di-O-methyl ether, anthragallol 2-O-methyl ether, austrocotin, 5, 15-dimethyl morindol, 6-hydroxyanthragallol-1, 3-di-O-methyl ether, morindone-5-O-methyl ether [15], 2-hydroxyanthraquinone and 2-methoxyanthraquinone [16]. The main organic acids include caproic acid, caprylic acid [17], lauric acid, linoleic acid, 2-methyl butanoic acid, 2-methylthiopropanoic acid, myristic acid, nonanoic acid, oleic acid, octanoic acid and palmitic acid [18]. Fatty acid glycosides and alcohols are one of the classes of compounds reported in the fruits [19]. They possess more or less pronounced amphiphilic properties and this is responsible for the soapy taste of ripe fruits. The leaves of the plant are substantial source of carotenoids [20]. The major alkaloid reported in the plant is xeronine and the other major compounds include scopoletin and β -sitosterol. Approximately 51 volatile compounds have been identified in the ripe fruit, which include organic acids such as octanoic acid and hexanoic acid, alcohols (3-methyl-3-buten-1-ol), esters (methyl octanoate and methyl decanoate), ketones (2-heptanone) and lactones [(E)-6-dodeceno- γ -lactone] [21].

6. NUTRACEUTICAL VALUE

Only partial information of the physico-chemical composition of Noni fruit juice is available. Noni fruit contains 90 % of water and the main components of the dry matter appear to be soluble solids, dietary fibers and proteins. The fruit protein content is very high (11.3 %) of the juice dry matter and the amino acids present are aspartic acid, glutamic acid and isoleucine. The main minerals reported in the fruit juice account for 8.4 % of dry matter such as potassium, sulfur, calcium, phosphorus and traces of selenium [22]. The studies showed that the leaf contain calcium (0.55 %), potassium (0.12 %), magnesium (0.06 %), manganese (4.47 ppm) and copper (2.23 ppm). Noni fruit contains calcium (0.0004 %), potassium (0.12 %), magnesium (0.01 %), manganese (1.557 ppm), copper (11.893 ppm) and iron (10.66 ppm). The vitamins reported in Noni fruit juice are mainly ascorbic acid (24-158 mg/100 g dry matter) and provitamin A [23]. The polysaccharide content of fruits has been studied using monosaccharide and glycosyl linkage analysis and the most abundant monosaccharides were arabinose, galactose, galacturonic acid and rhamnose [24]. According to Palu et al [25], Noni-based nutritional supplementation and exercise interventions positively affect body composition without side effects and are recommended to be used in combination for combating weight gain.

7. BIOLOGICAL ACTIVITIES OF NONI

The widespread claims on the therapeutic effectiveness of *M. citrifolia* have encouraged the researchers world-wide to study in detail about the biological effects and pharmacological actions of the plant.

7.1. Antimicrobial Activity

Some phenolic compounds in Noni exhibited antibacterial effects and they fight against bacterial strains such as *Pseudomonas aeruginosa*, *Proteus morgaii*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella* and *Shigella* [26]. In another study, the ripened fruits showed potent antibacterial effect and significantly inhibited *Salmonella typhosa*, *Salmonella Montevideo*, *Salmonella schottmuelleri* and *Shigella paradys* strains [27]. Dittmer (1993) also reported antimicrobial effect on different strains of *Salmonella*, *Shigella* and *E. coli*. The acetonitrile extract of the dried fruit inhibited the growth of *P. aeruginosa*, *B. subtilis*, *E. coli*, *Streptococcus pyrogene* [28]. Roots of the plant contain several anthraquinone compounds that have been shown to fight against infectious bacterial strains such as *Pseudomonas aeruginosa*, *Proteus morgaii*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella* sp. and *Shigella* species [29]. According to Duncan et al [30] scopoletin, a compound isolated from Noni inhibited the activity of *E. coli* and also helps in control of stomach ulcer through inhibition of *H. pylori*. The ethanol and hexane fruit extracts provide protection against *Mycobacterium tuberculosis* [31]. It has also been found that the methanol and aqueous crude extracts of the fruit was effective against *E. coli*, *Streptococcus* species, *Vibrio alginolyticus* and *V. harveyi*. According to Lee et al [32] the fruit methanolic extract demonstrated zones of inhibition in a range of 7.7-26 mm against *Vibrio cholerae*, *Klebsiella*, *B. subtilis*, *Lactobacillus lactis*, *P. aeruginosa*, *Salmonella typhi*, *E. coli*, *S. aureus*, *Streptococcus thermophiles*, *Shigella flexneri*, *V. harveyi* etc. According to Brett et al [33] iridoids from Noni fruits appear to be effective against yeast, Gram negative and Gram positive bacteria. The antibacterial compounds present in Noni are responsible for its use in the treatment of skin infections, cold, fevers and other bacterial health problems [34]. The ethanolic extract of tender Noni leaves exhibited anthelmintic effect and inhibited the human parasitic nematode worm *Ascaris lumbricoides* within a day [35]. Khuntia et al [36] reported similar results and the alcoholic extract produced more significant anthelmintic activity than petroleum ether extract and the activities were comparable to the reference drug piperazine citrate. The methanolic extract of the dried fruit exhibited maximum percentage (79.3 %) of inhibition against *Trichophyton mentagrophytes*, 50 % activity against *Penicillium*, *Fusarium* and *Rhizopus* species which explained the antifungal effect of Noni [37], [38]. The fruit ethanolic extract of *M. citrifolia* induced inhibition of cell growth on *Staphylococcus aureus* and *Escherichia coli* and cell growth inhibition on mouse melanoma B16-F10 cells [39].

7.2. Anti-Inflammatory Activity

Cyclooxygenase-2 (COX-2) inhibitors may be involved in breast, colon and lung cancer development. The over expression of COX-2 may lead to increased angiogenesis and inflammatory reaction, therefore the inhibition of COX-2 have a cancer preventive effect via anti-inflammatory activity and

decrease angiogenesis. The commercial Noni juice has a selective inhibition on cyclo-oxygenase enzymes (COX-1 and COX-2) involved in breast, colon and lung cancer, and also in anti-inflammatory activity. The inhibition of the activity of these enzymes by Noni juice was compared with that of commercial traditional non-steroidal inflammatory drugs such as aspirin, indomethacins and celebrex. Noni juice exhibited selective inhibition of COX enzyme activity *in vitro* and a strong anti-inflammatory activity comparable to that of celebrex without any side effects [40]. The anti-inflammatory activity was observed in an acute liver injury model in female rats induced by CCl₄. A decrease in inflammatory foci and lymphocyte surrounding central vein areas were observed at 6 h post CCl₄ administration in animals pre-treated with 10 % Noni fruit juice for twelve days in drinking water compared with CCl₄ without the fruit juice [41]. By inducing locally acute inflammatory response, with the help of a pro-inflammatory agent bradykinin, the activity of aqueous extract from Noni juice was assessed. The oral administration of Noni juice extract significantly inhibited the formation of rat paw edema. This may be due to the interference with B2 receptor mechanism by which bradykinin induced rat paw edema [42]. Another study showed that the higher dose of juice extract completely inhibited the inflammatory response to carrageenan. The bradykinin-induced inflammatory response was inhibited and subsided in rats pretreated with the fruit juice extract [43]. Rachel et al [44] reported that the ethanol extract of fruit powder has a selective inhibition on COX-1 and it did not exhibit nitric oxide scavenging activity both *in vitro* and *in vivo*. Several compounds from Noni juice also exhibited significant anti-inflammatory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice. A saccharide fatty acid ester, 2-O-(beta-D-glucopyranosyl)-1-O-octanoyl-beta-D-glucopyranose extracted from the fruits has got potent anti-inflammatory effect [45]. The flavonoids and phenolics, coumarin and two iridoids present in the fruit juice have reduced carrageenan-induced paw edema and directly inhibited cyclooxygenase COX-1 and COX-2 activities. It also inhibited the production of nitric oxide and prostaglandins in activated J744 cells [46]. The effect of freeze-dried juice extract squeezed from *M. citrifolia* leaves on TNF- α , IL-1 β and nitric oxide secretion by lipopolysaccharide-induced macrophage RAW 264.7 cells. The results were compared to rutin, dexamethasone and indomethacin standards. The results showed that the extract inhibited TNF- α secretion four times more than dexamethasone and indomethacin. The extract also suppressed IL-1 β secretion in a dose dependent manner. The extract also inhibited nitric oxide confirming its anti-inflammatory effect [47].

7.3. Anti-Viral Activity

A compound, 1-methoxy-2-formyl-3-hydroxyanthraquinone was isolated from the roots of Noni plant which suppressed the cytopathic effect of HIV infected MT-4 cells without inhibiting normal cell growth [48]. One of the human immunodeficiency virus type 1 (HIV-1) accessory protein is called viral protein R (Vpr) that contributes to multiple cytopathic effects, apoptosis and G2 cell cycle arrest. These proteins trigger HIV-1 pathogenesis. Kamata et al [49] reported that damnacanthal, a phytoconstituent of Noni fruit act as an inhibitor of Vpr induced cell death.

7.4. Analgesic Activity

Younos et al [50] reported the analgesic and sedative effects of Noni extract. It showed significant, dose related central analgesic activity in the treated mice. The analgesic efficacy of the extract was 75 % as strong as morphine, yet non-addictive and without any side effects. According to Wang et al [51] Tahitian Noni Juice (TNJ) exhibited analgesic effect by the "twisted method" animal model. For this, the pain-inducer used was a chemical named, antimony potassium tartarate which was administered intraperitoneally to produce twisting due to pain and the number of twists in the first 15 minutes after injection was recorded to indicate the degree of pain. The experiment showed a dose dependent effect of TNJ in mice. The analgesic efficacy of the lyophilized aqueous root extract was screened in mice through writhing and hot plate tests. The results showed that the extract exhibited 75 % analgesic efficacy [52]. Similar results were reported in the fruit alcoholic extract [53]. Basar et al [54] suggested that the Noni fruit preparations are effective in decreasing pain and joint destruction caused by arthritis. The effect was studied using the hot plate test. A 10 % solution of freeze concentrated Noni fruit puree in the drinking water ameliorated the pain sensitivity compared to analgesic drug tramadol in mice.

7.5. Anti-Oxidant Activity

Free radicals are generated in the biological system as a result of metabolic reactions and they are involved in the pathogenesis of human diseases particularly in degenerative diseases, cancer, ageing

etc. Free radicals cause lipid peroxidation and consequently oxidative damage to cell components and DNA which will finally result in cell damage. Fruits and vegetables are sources of natural antioxidants, which inhibit free radical-induced oxidative damage [55]. The antioxidant activity of TNJ was carried out by measuring the superoxide anion scavenging and lipid peroxide scavenging assays. The superoxide scavenging activity of TNJ was comparable to that of vitamin C [56]. The anti-oxidant effects of ethanol and ethyl acetate extracts of Noni fruit have been evaluated using ferric thiocyanate method (FTC) and thiobarbituric acid test (TBA). Results showed that ethyl acetate extracts exhibited potent inhibition of lipid peroxidation comparable to α -tocopherol and butylated hydroxyl toluene (BHT) [57]. Chang-hong et al [58] reported the isolation of three antioxidant phenolic compounds such as isoscopoletin, aesculetin and 3, 3', 4', 5, 7-pentahydroxy flavone from the ethyl acetate extract, which exhibited antioxidant property. The seed extract exhibited significant antioxidant activity in the oxygen radical absorbance capacity (ORAC) and ferric reducing antioxidant power (FRAP) assays [59]. Thani et al [60] reported that the leaves of the Thai Noni/Yor showed antioxidant effects and may have benefit as a food supplement for antioxidant activities in epidermoid and cervical cancers as compared to damnacanthal, rutin and scopoletin. Several polyphenols in Noni juice have demonstrated a mean range free radical scavenging effect. The Noni juice substantiated its antioxidant effect observed *in vitro* and *in vivo* and also the condition of oxidative stress produced by heavy smoking [61]. Several compounds of different polarity may contribute to the antioxidant effect of Noni fruit juice. Part of the antioxidant activity may be due to lipid soluble polyphenols, anthraquinones, α -tocopherol and β -carotene. These compounds promote the antioxidant activity in cancer cells [62]. It has also been reported that most of the natural antioxidant compounds work synergistically with each other to produce a broad spectrum of effects against free radical damage.

7.6. Anti-Tumour and Anti-Cancer Activities

Several studies reported that Noni has multiple cancer preventive effects. Hirazumi et al [63] reported that Noni precipitate significantly increased the life span of mice up to 75 % with implanted Lewis Lung Carcinoma (LLC) when compared to the control mice. The ethanol precipitated fraction of Noni juice composed of glucuronic acid, galactose, arabinose and rhamnose has been found to exhibit anti-tumour effects against Lewis Lung Carcinoma. According to Hirazumi et al [64] the Noni precipitate seems to suppress the tumour growth directly by stimulating the immune system. Noni precipitate can improve the survival time and curative effects when combined with suboptimal doses of standard chemotherapeutic drugs such as Adriamycin, cisplatin, 5-flourouracil and vincristine suggesting its importance in clinical application. Noni precipitate stimulates the release of several mediators such as cytokines from murine effector cells which slow down the cell cycle in tumours, increase the response of cells to other immunized cells that fight against tumour growth and have a potent macrophage activator capacity, which plays a crucial role in tumour inhibition [65]. Tahitian Noni Juice (TNJ) exhibited cytotoxic effect on cultured leukemia cell line at different concentrations. The synergistic effect was observed in TNJ with suboptimal dose of prednisolone, both of which induce apoptosis. ‘Ras’ oncogenes are associated with the signal transduction in several human cancers such as lung, colon, pancreas and leukemia. A compound called damnacanthal isolated from the roots of Noni plant act as an inhibitor of ‘Ras’ function [66]. The cell transformation induced by TPA or EGF in the mouse epidermal JB6 cell line was inhibited by two glycosides isolated from the Noni precipitate. The inhibitory effect was due to the AP1 activity of these compounds and they also blocked the phosphorylation of c-Jun [67]. The commercial Noni juice inhibited the formation of chemical carcinogenesis-DNA-adduct. When the tumour-induced rats were fed with 10 % Noni juice for one week, they showed reduced DNA-adduct formation. The intraperitoneal injection of the fermented Noni exudate significantly increased the percentage of natural killer cells and granulocytes in the peripheral blood, peritoneum and spleen. It also induced the complete tumour rejection in normal C57BL/6J mice and partial tumour inhibition in C57 nude mice lacking functional lymphocytes. From the study it can be concluded that fermented Noni exudate stimulates the innate and adaptive immune systems to reject tumour cells [68]. A polysaccharide rich substance from the fruit juice of *M. citrifolia* was found to possess both prophylactic and therapeutic potentials against immunomodulator sensitive Sarcoma 180 tumour system. The Noni precipitate produced 25-45 % cure in allogeneic mice [69]. It is reported that drinking 1-4 ounces of Tahitian Noni Juice (TNJ) daily may reduce the cancer risk in heavy cigarette smokers by blocking carcinogen-DNA binder or excising DNA adducts from genomic DNA. Noni fruit powder has both preventive and therapeutic

efficacy on rat esophageal cancer induced by N-nitrosomethyl benzylamine [70]. Another study showed that TNJ may inhibit mammary cancer at the initiation stage of chemical carcinogenesis [71]. Six known compounds together with two new compounds isolated from *M. citrifolia* exhibited significant inhibitory effects on the proliferation of human lung and colon cancer [72]. An anthraquinone compound isolated from the Noni roots, damnacanthal inhibited colorectal tumour-genesis and it was attained by cell growth arrest as well as Caspase activity induction [73]. According to Gupta et al [74] Noni can be used as a chemo-adjuvant for the treatment of cervical cancer. Noni/cisplatin by themselves and combination of Noni with cisplatin were able to induce apoptosis in both HeLa and SiHa cells through mitochondrial pathway, the up-regulation of pro-apoptotic members and down-regulation of anti-apoptotic members. This was accompanied by an increase in Caspase-9 and Caspase-3 activity. The rate of proliferation of mouse melanoma B16-F10 cells was significantly inhibited by different concentrations of fruit ethanolic extract of *M. citrifolia* (0-80 mg/ml). The time-dependent assay also confirmed the long-lasting suppressive effect on B16-F10 cells. Noni fruit methanolic extract exhibited cytotoxic activity against breast cancer (MCF7) and neuroblastoma (LAN5) cell lines in 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay [75].

7.7. Hepatoprotective Activity

Noni fruit juice has been examined on carbon tetrachloride (CCl₄)-induced hepatotoxicity in female Sprague-Dawley rats. Noni fruit juice was effective in protecting liver against acute CCl₄ toxicity [76]. An official European investigation confirmed that consumption of Noni juice is unlikely to induce adverse human liver effects [77]. It acts as an efficacious natural hepatoprotective nutritional supplement even at higher doses [78].

7.8. Hypotensive Activity

The total extract of Noni roots exhibited hypotensive effect [79]. The ethanolic and hot water extracts of roots were found to lower the blood pressure in anesthetized dog [80], [81]. It has been reported that Noni juice contains angiotensin-1 converting enzyme (ACE) [82]. Generally ACE is prescribed to treat high blood pressure and thus it can be recognized as a therapeutic intervention for the lowering of blood pressure.

7.9. Cardiovascular Effects

Recent research has proved the potential of Noni fruit on preventing arteriosclerosis, which is mainly related to the oxidation of low density lipoproteins (LDL). Methanol and ethyl acetate root extracts exhibited 88 and 96 % inhibition of copper-induced LDL oxidation with thiobarbituric acid reactive substance method. This effect may be due to the presence of lignans [83]. 5-lipoxygenase and 15-lipoxygenase play major role in cardiovascular illness [84]. Deng et al [85] isolated two new lignans and seven known compounds from the fruits which are responsible for the inhibition of 5- or 15-lipoxygenase [86]. The antispasmodic and vasodilatory effects of *M. citrifolia* root extract are mediated through blockage of voltage-dependent calcium channels and it also exhibited antidyslipidemic effect. Therefore this can be used as a potent cardiovascular medicine [87].

7.10. Anti-Hypercholesterolemic, Anti-Obesity and Anti-Hyperglycemic Activities

M. citrifolia fruit extract capsule (1g extract) significantly reduced total cholesterol and LDL-cholesterol levels in patients with hypercholesterolemia. The capsules when combined with control factors like age, body mass index, diet, exercise and smoking habit significantly reduced the cholesterol levels [88]. When Noni juice was taken for seven consecutive days, it reduced the rate at which food exited the stomach (gastric emptying) and it acts like an appetite suppressant, useful for weight loss [89]. According to Adrienne and Pratibha [90] Noni juice reduced body weight by 40 % in mice fed control diet and 25 % high-fat diet. It improved glucose tolerance in animals and also reduced adipose tissue weights and plasma glyceride levels. The hypoglycemic effects of the anthraquinone, damnacanthal-3-O-beta-D-primeveroside and lucidin 3-O-beta-D-primeveroside in Noni roots were studied in streptozotocin induced diabetic mice. The results showed that these two molecules are responsible for the glucose lowering effect and further work is required to elucidate cellular and molecular mechanisms [91]. The anti-diabetic effect of *M. citrifolia* fermented by fast fermented soya bean paste was evaluated using type-2 diabetes model in KK-Ay/TaJcl mice. The decrease in blood glucose level mediated by the fermented Noni extract was associated with a significant reduction in insulin resistance [92].

7.11. Immunomodulatory Activity

The mechanism of immunomodulatory activity of Tahitian Noni Juice (TNJ) and Noni fruit juice concentrate (NFJC) has been elucidated by Palu et al [93]. In the study, TNJ and NFJC modulate the immune system by the activation of CB2 receptors and production of IFN- γ cytokines but suppressing IL-4 cytokine. The ethanol precipitate of the fruit stimulates the release of several immune mediators such as TNF- α , IL-1 β , IL-10, IL-12p70, IFN- γ and nitric oxide but it suppressed IL-4. Thymus plays an important role in cellular immune function by generating T-cells and it is also involved in the ageing process. The animals administered with 10 % TNJ in drinking water showed 1.7 times weight gain of thymus compared to control group animals. Thus TNJ can enhance the immune response by stimulating thymus growth and thus it is involved in the anti-ageing and anti-cancer effects. Noni precipitate also demonstrated beneficial effects when combined with the Th1 cytokine, interferon gamma, but its activity was abolished when combined with Th2 cytokines, interleukin-4 or interleukin-10 suggesting that it induces a Th1 dominant immune status *in vivo*. The combination of Noni precipitate and imexon, a synthetic immunomodulator, also showed beneficial effects. The Noni precipitate suppresses tumour growth by the activation of host immune system. It contains a polysaccharide-rich substance that can inhibit the toxic effects in adapted cultures of lung cancer cells. It could activate peritoneal exudate cells to impart cytotoxicity when co-cultured with the tumour cells. The separated Noni fruit juice into 50 % aqueous alcohol and precipitated fractions can stimulate the BALB/c thymus cells in the thymidine (^3H) analysis and this may be due to the stimulation of T-cell immune response [94].

7.12. Wound Healing Activity

The wound healing activity of *M. citrifolia* was evaluated in rats by excision and dead space wound models. The extract administered animals showed 71 % reduction in the wound area compared to the control (57 %). In Noni-treated animals the mass and hydroxylproline content in the dead space wounds of granulation tissue were also increased significantly compared with controls [95]. In another study, wound healing potential of fruit juice was tested in streptozotocin-induced diabetic animals. The results indicated that the juice could significantly reduce the blood sugar level and hasten wound healing activity in diabetic rats [96]. 1, 4-dihydroxy-2-methoxy-7-methylanthraquinone from Noni fruit significantly increased elaboration of procollagen type 1C-terminal peptides and glycosaminoglycans and inhibited the expression of collagenase matrix metalloproteinase-1 in primary cultures of human fibroblasts. In a clinical trial, this molecule was found to elevate the dermal type 1 procollagen level in nude mouse skin. Thus the identified anthraquinone is a good candidate as anti-wrinkle agent due to its strong induction of biosynthesis of extracellular matrix compounds [97].

7.13. Estrogenic Activity

It has been reported that Noni has very weak estrogenic activity *in vivo*. The relative estrogenic potency of alcohol and water extracts of Noni was 1:1000 and 1:10000 respectively. Estrogenic activity is exhibited only at low doses and has very low potency compared to estradiol. *M. citrifolia* consists of a variety of phytoestrogens that bind to the estrogen receptors and exhibit protective effects on estrogen-related conditions such as menopausal symptoms and estrogen related diseases such as breast and prostate cancers and osteoporosis [98]. The estrogenic properties of Noni fruit *in vitro* were studied by estrogen receptor binding assay with both estrogen receptors, ER- α and ER- β and the estrogen-receptor dependent induction of alkaline phosphatase in Ishikawa cells. The fruit hexane extract exhibited significant activity in both the systems [99].

7.14. Effect on Mental Health and Ischemic Stress

Some reports showed that Tahitian Noni Juice (TNJ) provided a positive effect on mental health and it also improved the high frequency hearing. Noni fruit has preventing effect on anxiety disorders which is affected by 25 % of the adult population at some point during their life time [100]. The fruit crude methanolic extract showed significant affinity to the gamma-amino butyric acid A(GABA a), the common inhibitory neurotransmitter in the central nervous system and it exhibited 75 % binding inhibition as an agonist and induced anxiolytic and sedative effects. The ingestion of 10 % oral Noni juice by male ddY mice followed by 2h of middle cerebral artery occlusion (MCAO) suppressed the development of neuronal damage. Oral Noni Juice (ONJ) treatment significantly increased serum

insulin levels while serum adiponectin levels were not affected. This suggested that ONJ could facilitate insulin secretion after ischemic stress and may attenuate the development of glucose intolerance, which contribute to the neuronal protective effect. Noni fruit juice exhibited protection of brain against stress-induced impairment of cognitive function and this may be related to the improvement in stress-induced decrease in blood vessel density in the hippocampal dentate gyrus [101].

7.15. Nephro-Protective Activity

The chemoprotective effect of *M. citrifolia* fruit ethanolic extract was evaluated in cisplatin-induced nephrotoxicity in rats. Cisplatin (5 mg/kg) induces nephrotoxicity when intraperitoneally administered. The pathological signs such as glomerular atrophy, infiltration of cells and tubular congestion of the kidney cells were found in cisplatin induced nephrotoxic group. These symptoms were reduced or normalized in extract treated group. The biochemical estimation of serum parameters such as serum creatinine, serum urea and serum protein in extract treated group, which was elevated by cisplatin was found significantly reduced. Thus it proved to be a therapeutically useful nephroprotective agent [102]. Gentamycin induces loss in the re-absorptive capacity of renal proximal tubular cells which is caused as a result of decreased excretion of creatinine and urea with increased protein, calcium, magnesium, sodium, phosphorus and potassium. *M. citrifolia* extract administration to nephrotoxic rats, ameliorated the lipid ionic changes to near normal [103].

7.16. Allergenicity and Toxicity

The acute toxicity study of Tahitian Noni Juice (TNJ) has been carried out in rats and no adverse clinical symptoms were noted in experimental animals. 15,000 mg/kg dose was administered to the animals and they were observed for 14 days after the treatment. All the experimental animals survived and no sign of toxicity was observed in the organ necropsy [104]. To evaluate the systemic safety of TNJ, a 13 week oral toxicity study in Sprague-Dawley rats was carried out. The doses for administration were 0.4 ml/kg, 4 ml/kg and 8 ml/kg. All the animals were observed for adverse clinical signs, food and water consumption, weight gain and haematological, biochemical and histopathological evaluations were carried out. All the groups exhibited no treatment related differences in body and organ weight, food and water consumption, haematological, biochemical and histopathological examinations [105]. In a similar study, a 13-week oral toxicity study in rats indicated that the No-Observable-Adverse Effect Level (NOAEL) was above 20 ml of 4 times concentrated Noni juice extract/kg/day. This was equivalent to 80 ml Noni juice extract/ kg/day [106]. The different concentrations of various forms of TNJ were evaluated for allergenicity in guinea pigs. The test groups of animals were administered three times each week for two weeks. After 32 days, the experimental animals were challenged and observed for symptoms of allergic response. No positive allergic reactions were detected in any TNJ treated animals following the challenge. No upper limit for safe consumption of TNJ has yet been determined from the studies. It may be safely consumed in amounts that are typical for fruit juice beverages. Noni fruit, the main ingredient of TNJ has been safely consumed in other parts of the world for several hundred years [107], [108].

8. ECONOMIC IMPORTANCE

Noni root bark contains a colouring principle, Morindone and it is used for dyeing cotton, silk and wool in shades of red, chocolate or purple. The tender leaves are reported to be eaten as pot-herb in times of scarcity and fruits are also eaten. The tree is chopped for fodder. Leaves of the plant are used to rear silk worms and fruit pulp is used for cleansing hair. The fruits yield yellow essential oil consisting mainly of Hexoic acid and Octoic acid. The wood of the plant is used for making plates and toys [109]. The tropical climate is very much suitable for the cultivation of the plant which is gaining popularity due to its high medicinal and market value. The tree has attained significant economic importance worldwide in recent years. It is because a variety of health and cosmetic products are made from leaves and fruits. Commercial products such as beverages (fruit juice, fruit drinks), fruit powder (for manufacture of reconstituted juice or juice drink products made from dried ripe or unripe fruits), for manufacturing lotions, soaps etc., oil (from seeds), leaf powder (for encapsulation of pills) were also made from the plant. The market for products is worldwide with the largest market in North America, Mexico, Asia and Australia. The worldwide market for Noni products was estimated as 400 million US dollars in 2002. More than 200 entities sell Noni products, which are distributed across the globe and enjoy an enormous market share.

9. CONCLUSION

Natural products from traditional medicine have been used for centuries in every culture throughout the world and majority of local people in developing countries still depend on traditional medicine. The World Health Organization (WHO) has estimated that more than 80 % of the world population relies on traditional medical practices for primary health care needs [110]. This is because the traditional medicines are relatively accessible, inexpensive, locally available and devoid of any side effects compared to conventional medicines. Active phytochemicals with a wide range of therapeutic effects are required for the development of herbal drugs. Literature showed that *M. citrifolia* contains many phytochemicals and the researchers in this field should emphasize their research to maximum utilize the therapeutic potential of Noni.

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