



Immunomodulatory actions of a Polynesian herb Noni (*Morinda citrifolia*) and its clinical applications

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ABSTRACT

Morinda citrifolia (Noni) is a popular traditional medicinal plant consumed in various forms in several countries around the world as a complementary and alternative treatment due to its established health benefits. Noni is rich in bioactive substances and has significantly exhibited pro-oxidant and immunomodulatory effects. In this review, we highlight the pharmacological basis related to the phytochemicals and polysaccharides present in Noni and its potential therapeutic effects. We screened electronic databases such as PubMed, Google Scholar, Scopus for scientific literature. Our results indicate that Noni is beneficial for various diseases with its crude extracts showing therapeutic benefit for a wide range of pathological diseases. We believe that further pharmacological and toxicological studies in addition to well-designed controlled clinical trials can validate Noni to be an effective and novel natural product for prophylactic and therapeutic use of several diseases.

1. Introduction

Noni; also known as Indian Mulberry, Hog apple, Canary wood Ba Ji Tian and Cheese Fruit, is a green shrub or small tree that grows in Southeast Asia, USA (Hawaii) and Australia.^{1,2} Nearly all the parts obtained from Noni, including the roots, stem, bark, fruits and leaves have been useful as a curative or a preventive measure in managing various acute and chronic diseases in the Polynesian culture for the past 2000 years.³ Noni is considered as the original “canoe plant” brought by Polynesian colonists in their voyaging canoes to Hawaii. This herb has become a part of modern-day civilization and is one of the popular dietary supplements in Asia, Europe, United States of America and other Polynesian countries.^{4,5} Various preparations of Noni’s fruit and leaves are available as capsule, tablet, liquid and powder formulations. Traditionally, Noni has been known to be used in the treatment of various diseases including: cancer, infections, cold, flu, diabetes mellitus, hypertension, arthritis, gastric ulcers, sprains, depression, senility, muscle ache and pain.^{6–8} The anecdotal evidence indicates that Noni prevents or treats various infections by stimulating the immune system.⁹ Considering the health benefits of Noni, the European Commission of Health and Consumer Protection accepted it as a novel

natural product. Due to the exclusion of antibiotic prophylaxis in the animal food industry by several countries, and the possibility of a ban subject in other countries, there is increasing demand for natural products with health benefits.¹⁰

The bioactive substances of the natural products can be generally classified into “phytochemicals and polysaccharides”. Phytochemicals are low molecular weight chemicals present in plants which are known to support human wellbeing and are mainly classified based on their chemical structures.¹¹ The major chemical classes isolated from Noni are betalains, indoles, glucosinolates, organosulfides, sulfides, mono or polyphenolic compounds, terpenes (isoprenoids, terpenoids) and organic acids (Fig. 1). Phytochemicals exhibit their activities by rendering antioxidant action (scavenging free radicals), modulating endocrine functions (hormonal properties), regulating exocrine effects (potentiate or inhibit enzyme activity or protein expression), inducing immune responses (immunomodulatory effects, anti-complementary), affecting nucleic acid (prevent the replication of DNA & affect RNA), and exhibiting antibacterial functions (preventing the adhesion of pathogens to mammalian cells, target the cell wall, affect the nutrients for the pathogen). Polysaccharides are polymeric carbohydrate structures of simple sugars attached by glycosidic bonds and can be classified as

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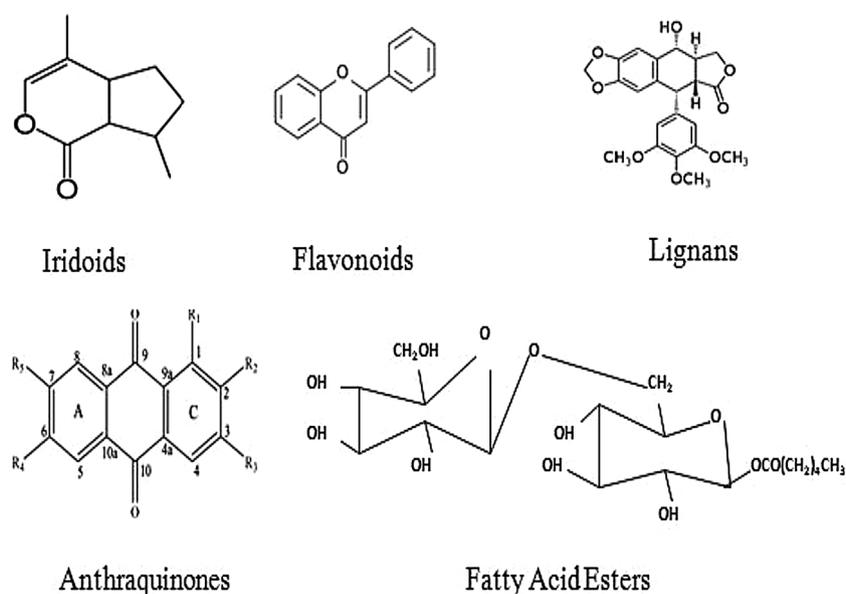


Fig. 1. Major classes of phytochemicals present in Noni fruit.

Table 1
Comparison between Polysaccharides and Phytochemicals.

Bioactive Substances of Noni		
	Polysaccharides	Phytochemicals
Molecular weight	High	Low
Chemical classes	Homopolysaccharides, Heteropolysaccharides, Complex heteropolysaccharides Homogalacturonan, Rhamnogalacturonan, Arabinan, Type I arabinogalactan. Pectic polysaccharides (Arabinogalactan-protein Xyloglucan, Heteroxytan and Heteromannan)	Betalains, Indoles, Glucosinolates, Organosulfides, Sulfides, Mono or Polyphenolic compounds Terpenes (Isoprenoids, Terpenoids) and Organic Acids, Iridoids, Flavonoids (Quercetin, kaempferol and catechin), Lignans (Matairesinol and Secoisolariciresinol, 3,3'-Bisdemethylpinoresinol, Americanol A, Americanin A, Americanoic acid A, Morindolin and Isoprincepin), Anthraquinones (Nordamnacanthal, Morindone, Rubiadin, and Rubiadin- 1-methyl ether, Anthraquinone glycoside)
Functions	Alters the mechanical properties, Reserves energy, Immunomodulation, Modulates multiple regulatory processes of the cells, Enhances texture and flavor of food products and beverages	Renders anti-oxidant action, Modulates endocrine and Regulates exocrine effects, Induces immune responses, Affects nucleic acid, Exhibits antibacterial functions.

homopolysaccharides (homoglycans-one sugar or one sugar derivative), heteropolysaccharides (heteroglycans-two different units associated with proteins/glycoproteins and lipids) and complex heteropolysaccharides (plant gums). The major functions of polysaccharides are their ability to alter the mechanical properties (gelling and thickening), energy reservation, immunomodulation and modulation of the multiple regulatory processes of the cells. Furthermore, homopolysaccharides are used to treat shock and are added in gels to enhance the texture and flavor of food products and beverages (Table 1). Nutrient composition and chemical analyses of Noni fruit suggest that its polysaccharides and phytochemicals have immunomodulatory effects, as supported by *in vitro* and *in vivo* results.^{2,12–18} The traditional botanicals have been used for many generations and their consumption is conventional and generally recognized to be safe and effective.¹⁹ The current literature highlighted the following actions of Noni (*Morinda citrifolia*): Immunostimulatory effects, antitumor, anti-inflammatory, antidiabetic, anti-obesity, antibacterial / anti-septic, antifungal, antiviral, antinociceptive / analgesic, antioxidant, neuroprotective, anti-angiogenic, antiemetic and anti-nausea, anti-gastric ulcer / esophagitis, antimutagenic, antipsychotic, and anxiolytic effects. Hence, in this scientific review article, we focus on the immunomodulatory activities of the bioactive substances (polysaccharides and phytochemicals) present in Noni.

2. Phytochemicals in noni fruit exert immunomodulatory effects

Phytochemicals present in the Noni enhance the immune response and suppress inflammation therefore, they can prevent a wide range of disease states or symptoms.^{20–22} Noni has shown to reduce the inflammation and tissue damage in ulcerative colitis with minimal side effects.^{1,22} Noni augmented the anti-inflammatory mediators and significantly suppressed the pro-inflammatory cytokines in mouse models.^{23–25} Low molecular weight anti-inflammatory phytochemicals of Noni could cross the blood brain barrier and prove effective against neurodegenerative diseases.^{26–28} Several *in vitro* and *in vivo* studies have shown that Noni fruits have antioxidant, anti-inflammatory, anti-dementia, liver-protective, anticancer, analgesic, and immunomodulatory effects^{6,29} (Table 1).

2.1. Mechanisms of immunomodulatory effects of Noni

Noni has shown to exert its immunomodulatory effect by influencing the various components of the immune system.³⁰ Supplementation of Noni in drinking water to broiler chickens significantly increased the total antibody titers and reduced (75%) the mortality of broilers challenged with the infectious bursal disease virus (IBDV).¹⁸ The feeding of Noni to newborn calves enhanced the antibacterial properties against

Escherichia coli.³¹ Another study indicated a positive correlation between CD25+ expression and protection against infection by Noni.³² Furthermore, Noni supplementation during gestation increased gene expression of toll-like receptors (TLR-1, TLR-2, TLR-4, TLR-5, and TLR-10), interleukins (IL-4, IL-17) & their receptors (IL-4R, IL-17RA, IL17RB), chemokine (CXCL11) and co-stimulators (CD27, TNF- α , and Foxp3). Moreover, administration of Noni to the mouse resulted in an increased percentage of NK cells and decreased CD19+ B-cells in the spleen, and blood.^{23, 33} These changes in immune response were positively correlated with the survival of C57BL/7 J mice challenged with S180 tumor cells. Noni has shown to diminish intracellular reactive oxygen species, significantly attenuate COX-2, IL-8, prostaglandin E2 production and neutrophil chemotaxis in colon epithelial cells by suppressing the translocation of the p65 subunit. Noni exhibited protective effect in the spleen of old F344 rats, which resulted in the reversal of the age-related decline in neural-immune interactions.³⁴ Noni induced immunostimulatory activity by increasing nitric oxide (NO) production and the expression of IL-1 β , IL-6, IL-12, TNF- α , IFN- γ .³⁵ Similarly, immunostimulatory properties of Noni have been attributed to facilitatory action on intracellular signaling pathways involving ERK1/2, Akt and NF- κ B.³⁴ In conclusion, phytochemical substances of Noni have significant immunomodulatory ability to alter cell-mediated and humoral immunity.

2.2. Major phytochemicals present in Noni

Phytochemicals isolated from the Noni belong to five major classes - iridoids, flavonoids, lignans, anthraquinones and fatty acid esters.^{3,12,30,33,36-43}

2.2.1. Iridoids

Iridoids and polyphenols present in Noni has the capacity to scavenge free radicals, subdue COX-1 /COX-2 activities, inhibit the production of nitric oxide (NO), PGE2 and decrease carrageenan-induced paw edema.^{29,44} Gaertneroside, which structurally resembles the citrifolinolide of Noni, inhibited the classical pathway of the complement system.⁴⁵ Remarkably, iridoids (deacetyl asperulosidic acid) from *Oldenlandia diffusa* inhibited the oxidation of low-density lipoproteins. This may be a possible mechanisms to reduce atherosclerosis due to the oxidation of lipids by macrophages.⁴⁶ Asperuloside and deacetylasperulosidic acids have shown to inhibit the secretion of TNF- α . These reports on iridoids propose that the prophylactic and therapeutic properties such as the antioxidant, anti-inflammatory and the effect on complement system are attributed to the phenolic compounds and iridoids.^{33,45,47-49}

2.2.2. Flavonoids

Flavonoids are known to be natural antioxidants exhibiting inhibition of various enzymes associated with production of radical oxygen species.⁵⁰ Quercetin, kaempferol and catechin isolated from Noni or in a chemically pure form have been investigated for their possible immunological properties in an *in vitro* and *in vivo* model. Quercetin inhibited antigen-stimulated histamine release by human basophils/ mast cells, inhibited leukocyte migration, leukotriene-B4 (LTB-4) and PGE2 concentrations in carrageenan-induced pleural exudates.⁵¹ Flavonoids exhibit anti-complementary activity on the classical and alternative pathways in isolated rat mast cells and RAW 264.7 mouse macrophage.^{52,53} Quercetin and catechins decreased COX-2 expression,^{1,54} reduced nitrous oxide secretion by stimulated macrophages,^{53,55} decreased T-cell proliferation and IL-2 secretion by inhibiting the MAPK and phospholipase-C pathways, via high affinity binding to ZAP-70 kinase.⁵³⁻⁵⁷ Noni also protected SH-SY5Y cells against tert-butyl-hydroperoxide-induced oxidative stress and apoptosis by upregulation of Nrf2 along with endogenous antioxidants and affecting mitochondrial pathway.⁵⁸ Thus, flavonoids present in Noni and other botanicals can significantly exert protective effects by affecting the immune system.

2.2.3. Lignans

Lignans are an important class of phytoestrogens found in plants. These are polyphenolic chemicals which are derived from phenylalanine and monolignols. Lignans play a role in the anti-inflammatory and antioxidant activity and can reduce the risk of breast, ovarian and prostate cancers in humans.⁵⁹⁻⁶² Lignans in Noni actively played a role in the reduction of LDL-oxidation in a dose-dependent manner, which may be due to its free radical scavenging effect and thereby helped in the prevention of arteriosclerosis.⁶³

2.2.4. Anthraquinones

Anthraquinones such as nordamnacanthal, morindone, rubiadin, rubiadin-1-methyl ether and anthraquinone glycoside are found in Noni.^{64,65} Anthraquinones isolated from Noni exhibit chemopreventive properties.¹² 2-methoxy-1,3,6 trihydroxyanthraquinone, extracted from Noni, increased the activity of quinone reductase as compared to the positive control L-sulforaphane and these results indicate that the anthraquinones found in Noni fruit have extremely low toxic potential and high therapeutic index.⁶³

2.2.5. Fatty acid esters

The fatty acid esters found in Noni are primarily short chain fatty acids with a glucopyranose ring (Fig. 1). Fatty acid esters isolated from Noni fruits namely 2-O-(β -D-glucopyranosyl)-1-O-octanoyl- β -D-glucopyranose, 2-O-(β -D-glucopyranosyl)-1-O-hexanoyl- β -D-glucopyranose, 6-O-(β -D-glucopyranosyl)-1-O-octanoyl- β -D-glucopyranose, 2,6-di-O-(β -D-glucopyranosyl)-1-O-octanoyl- β -D-glucopyranose inhibited the 12-O-tetradecanoylphorbol-13-acetate (TPA) induced ear inflammation in mice.^{12,39}

2.2.6. Miscellaneous phytochemicals

In addition to the 5 classes of phytochemicals, Noni also contains various other phytochemicals with immunomodulatory activities. The glycosidic form of β -sitosterol palmitate showed strong anti-complementary activity against the classical pathway^{3,66} and inhibited the release of IL-10 secretions from peripheral blood mononuclear cells isolated from patients suffering from multiple sclerosis.^{3,66} In addition, vanillin (4-hydroxy-3-methoxybenzaldehyde) detected in Noni inhibited carrageenan-induced paw edema of rats in a dose dependent manner^{3,67,68} and potentially inhibited LPS-stimulated COX-2 expression in macrophages.^{66,67}

3. Polysaccharides in the Noni fruit

Generally, the alcoholic fraction of Noni fruit contains 80% pectins and 5% protein-bound arabinogalactans.³ Noni mainly contains pectic polysaccharides (homogalacturonan, rhamnogalacturonan, arabinan, and type I arabinogalactan), along with arabinogalactan-protein and low amounts of xyloglucan, heteroxyylan and heteromannan.⁶⁹ Polysaccharides are immunomodulators based on their capacity to regulate the immune response during the etiology and progression of infectious and inflammatory diseases.⁷⁰ Polysaccharides impact both innate and cell-mediated immunity via interactions with macrophages, monocytes, neutrophils and T-cells. Similar purified polysaccharide fractions, isolated from *Echinacea purpurea* and *Tinospora cordifolia* exhibited immunological activities.^{30,31,71} Noni extract enhanced nitrite production and had substantial bactericidal activity.^{20,21} Polysaccharides of Noni were also able to stimulate the release of various mediators (TNF- α , IL-1 β , IL-10, IL-12, IFN- γ and NO) from murine effector cells.⁴⁹ Furthermore; Noni, when combined with IFN- γ , exhibited a synergistic effect on nitrite production.²² Polysaccharides present in Noni enhanced the phagocytic activity of neutrophils. Oral dosing of these fractions also increased serum IL-6 in vaccine challenged mice.³¹ IL-6 plays an important role in stimulating immunoglobulin production, in turn enhancing vaccine induced protection. Polysaccharides of Noni also exhibited antitumor activity by modulating the immune system.

Treatment of Noni against aggressive murine lung carcinoma (LLC1) or sarcoma (S180) cell challenged mice increased the rodent's survivability and life span. The antitumor activity of Noni was abolished with simultaneous treatment of macrophage, NK cell or T-cell inhibitors.^{16,72} Peritoneal exudate cells, obtained from mice treated with polysaccharide rich Noni, were cultured with concanavalin A in the presence of LPS and this decreased the secretion of IL-4 from peritoneal exudate cells.⁷² In conclusion, Noni fruit polysaccharides enhance cytokine and chemokine release from immune cells, therefore modulating an immune response. Noni conceivably suppressed cancer growth in human cancer patients due to the presence of polysaccharides,^{6,16,21–23,25,29,30,73,74,75}

4. Potential therapeutic effects of Noni

Noni juice has been designated for wide range of chronic pathological conditions such as cancer, diabetes mellitus, cardiovascular diseases, inflammatory disorders and obesity.⁵ It also possesses wound healing activity, gout and hyperuricemia healing activity and immunity enhancing properties.^{76,77} Current research on Noni and its constituents have focused on these main areas: cancer, inflammatory disorders, menstrual disorders, gastrointestinal disorders, metabolic diseases and CNS disorders (Fig. 2).

4.1. Anticancer effect

Cancer is the leading cause of death and source of morbidity in adults.^{78,79} The pathogenesis of cancer starts from the role of carcinogens (Physical, chemical and infections) to trigger the transformation of a normal cell into an immortal cell where the growth is uncontrolled.⁸⁰ This is followed by unregulated growth and multiplication of the cancer cells: process of angiogenesis where they attract blood vessels for nutrition, and finally its ability to invade nearby tissues and metastasis. During the last decade, novel synthetic chemotherapeutic agents clinically have not shown therapeutic efficacy despite the considerable cost of their development. Therefore, there is an utmost need to develop novel, effective, and affordable anticancer drugs.^{81,82} Plant products have increasingly become popular over the past 30 years for their potential as novel cancer preventive and therapeutic agents.^{83,84,85} Prevention of the initiation of carcinogenesis, antimutagenic activity, inhibition of angiogenesis with capillary vessel degeneration and

apoptosis has also been reported by Noni.⁴² Two constituents of Noni, a fatty acid glycoside and an iridoid have been reported to inhibit neoplastic cell transformation.⁴² Damnacanthal, a phytochemical anthroquinone constituent of Noni, acts as a tyrosine kinase inhibitor, interferes with the growth of *ras* gene activation and prevents tumorigenesis.⁸⁶ Noni also promotes apoptosis in human colorectal cancer cell lines.⁸⁷ Limonene (aromatic terpene) prevents mammary, liver, and lung cancers by stimulating thymus gland to secrete T cells which destroy the carcinoma cells²¹ and Ursolic acid inhibits the growth of cancerous cells by inducing apoptosis.⁸⁸ Sulphated polysaccharides in Noni destabilize the interaction between glycosaminoglycan and other proteins, therefore preventing metastasis.⁸⁹ Alizarin (dihydroxy anthraquinone) has an antiangiogenic effect, which is beneficial in treatment of highly vascularized cancers.⁹⁰

Based on the clinical studies, significant amount of cancer related mortality could be prevented by avoiding tobacco products, decreasing alcohol consumption, maintaining a normal body and mass index by adopting a healthy life style.^{91,92} Interestingly, several constituents of Noni have been effective against various types of tumor and cancer.^{93–98} Thus, systematic clinical studies with Noni derived substances can significantly strengthen cancer therapy around the world.

4.2. Inflammatory disorders (arthritis)

While the exact cause of arthritis is unknown, researchers believe a combination of genetic, environmental, and hormonal factors play an essential role in the pathophysiology of the disease.⁹⁹ The current therapy focusses more on pain management and reduction of inflammation, consequently the outlook for those diagnosed with inflammatory arthritis is significantly better than it was 20–30 years ago.¹⁰⁰ However still there are poor prognosis and higher drug-induced adverse effects associated with arthritis therapy.¹⁰¹ The tissue damage is triggered by the formation of tissue degrading metalloproteinases (MMP), which are secreted by immune-functional cells during the inflammation process.¹⁰² Osteoarthritis is mostly treated with non-steroidal anti-inflammatory drugs (NSAID).¹⁰³ Although quite effective, these drugs often have severe side effects on the stomach, liver, kidneys and other organs.^{104,105} The destruction caused by the MMPs is not reversed by the drugs used for the treatment of arthritis and responsible for the progression of the disease, characterized by a permanent loss of the functionality of the joints. Possible alternatives to NSAIDs may come from plant derived medicines.

Several medicinal plants like devils' claw (*Harpagophytum procumbens*), cat's claw (*Uncaria tomentosa*) and ginger (*Zingiber officinale*) have demonstrated their effectiveness in reducing symptoms of arthritis 100. Noni extracts due to the presence of scopoletin, 13 quercetin, and ursolic acid (major anti-inflammatory constituents) inhibited COX/ lipoxygenases (LOX-5) and therefore have been effective for the treatment of inflammatory diseases such as arthritis. Noni inhibits the metalloproteinases and thus inhibits the cartilage destruction during arthritis.^{106,107} The lack of typical side effects of NSAIDs after use of noni juice may be due to the less pronounced inhibition of functional prostaglandins by this combinatory effect.

The various comorbid conditions coexisting with arthritis are heart disease, diabetes mellitus, hypertension, obesity, anxiety and depression.^{108,109} Henceforth, a botanical such as Noni with multipotent therapeutic value with minimal contraindications and hypersensitivity reactions will be a more suitable approach to treat arthritis.

4.3. Menstrual disorders

Dysmenorrhea, or painful menstruation, is a common gynecological problem that affects women of reproductive age and can cause severe disability.¹¹⁰ Risk factors for dysmenorrhea include nulliparity, heavy menstrual flow, smoking and depression.^{111,112} The pain of dysmenorrhea is believed to be mediated by the release of prostaglandin F2

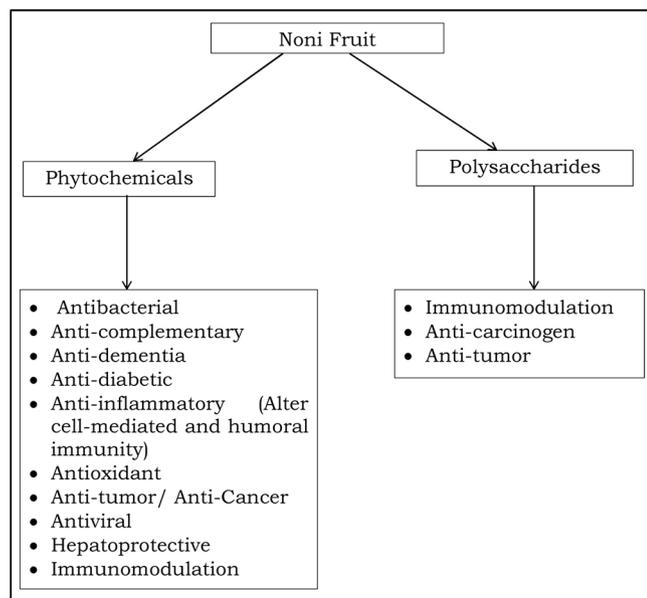


Fig. 2. Biological activities of Noni fruit polysaccharides and phytochemicals.

Table 2
Active ingredients and Molecular Mechanisms of Noni to alleviate various diseases.

Disease	Important Feature	Actions of Noni
Cancer	<ul style="list-style-type: none"> ● Important Features: ● Leading cause of death and morbidity of in adults ● Increased risk: ● Familial and genetic factors ● Geographical & cultural factors ● Environmental factors (tobacco use, alcohol abuse, certain viral infections, chemicals and toxins) ● Current Focus: ● Early diagnosis ● Suitable treatment: Radiation, Chemotherapy, Surgery ● Palliative care ● (iv) Identify new and novel synthetic and botanicals to reduce cancer 	<ul style="list-style-type: none"> ● Anti-cancer bioactive compounds in Noni: ● Fatty acid glycoside ● Iridoid ● Anthroquinone ● Polysaccharides ● Molecular Mechanisms of action: ● Prevention of the initiation of carcinogenesis ● Anti-mutagenic activity ● Inhibition of angiogenesis with capillary vessel degeneration and apoptosis
Inflammatory disorders (Arthritis)	<ul style="list-style-type: none"> ● Important Features: ● Commonly misunderstood due to the inability to differentiate between inflammatory and non-inflammatory arthritis ● Onset is gradual, but symptoms progress rapidly ● Tissue degrading metalloproteinases (MMP) ● Increased Risk: ● Combination of genetic, environmental, and hormonal factors ● Current Focus: ● Early diagnosis ● Treatment is crucial to limiting the scope of potential joint damage ● NSAID 	<ul style="list-style-type: none"> ● Anti-inflammatory bioactive compounds in Noni: ● Scopoletin ● Quercetin ● Ursolic acid ● Molecular Mechanism of Action: ● COX and LOX inhibition ● Inhibits the metalloproteinases ● Lack of typical side effects of NSAIDs due to the less pronounced inhibition of functional prostaglandins by this combinatory effect
Menstrual disorders- Dysmenorrhea (painful menstruation)	<ul style="list-style-type: none"> ● Important Features: ● Common gynecological problem affecting women of reproductive age ● Leading cause of recurrent school absence in adolescent girls ● Primary dysmenorrhea occurs in the absence of identifiable pelvic pathology ● Secondary dysmenorrhea occurs in the presence of a pelvic pathology, such as endometriosis, adenomyosis, uterine leiomyomata, or chronic pelvic inflammatory disease ● Increased Risk: ● Nulliparity ● Heavy menstrual flow ● Smoking ● Depression ● Major Mediator: PGF2α, leukotrienes, Hormones ● Current Focus: ● Therapy: NSAIDs, combination of oral contraceptives and depot medroxyprogesterone acetate, topical heat, vitamin E, fish oil supplements, acupuncture, low-fat vegetarian diet, and Japanese toki-shakuyaku-san 	<ul style="list-style-type: none"> ● Anti-inflammatory bioactive compounds in Noni: ● Scopoletin ● Quercetin ● Ursolic acid ● Molecular Mechanism of Action: ● COX and LOX inhibition ● Inhibit the formation of pro-inflammatory cytokines ● Possesses tranquilizing properties
Gastro-intestinal diseases	<ul style="list-style-type: none"> ● Important Features: ● Common chronic upper gastrointestinal diseases ● Retrograde flux of gastric contents into the esophagus for prolonged periods of time ● With increasing severity, it may be associated with erosions, ulceration and formation of strictures ● Increased Risk: ● Smoking ● Diet ● Helicobacter pylori ● Mediators: Reactive oxygen species; TNF-α, IL-1β, IL-6, PGE2 ● Current Focus: ● Acid-suppressive therapy ● Major Problem with the acid-suppressive therapy: impotence, gynaecomastia, hypergastrinemia and haemopoietic changes 	<ul style="list-style-type: none"> ● Anti-inflammatory bioactive compounds in Noni: ● Scopoletin ● Quercetin ● Ursolic acid ● Molecular Mechanism of Action: ● COX and LOX inhibition ● Inhibit the formation of pro-inflammatory cytokines ● Decreases Serotonin ● Anti-inflammatory activities ● Antioxidant activities ● Anti-secretory agent ● Prokinetic agent ● Antiemetic activity

(continued on next page)

Table 2 (continued)

Disease	Important Feature	Actions of Noni
Metabolic disorders: Dyslipidemia Diabetes Mellitus	<ul style="list-style-type: none"> ● Important Features: ● Growing health ● Constitutes one of the major risk factors for the development of cardiovascular diseases ● Leads to atherosclerosis and myocardial infarction ● Elevation of total cholesterol, LDL, triglyceride, HDL ● Problems of Anti-diabetic mellitus therapy: Hypoglycemia, weight gain and secondary failure ● Increased Risk: ● Smoking ● Alcohol ● Diet ● Unhealthy Life-style 	<ul style="list-style-type: none"> ● Anti-dyslipidemic and anti-diabetic mellitus bioactive compounds in Noni: ● Deacetylasperulosidic acid ● Oleuropein ● Saponins ● Rutin
CNS disorders	<ul style="list-style-type: none"> ● Current Focus: ● Life-Style ● Pharmacological approaches ● Important Features: ● Memory enhancing activity ● Major CNS disorders: brain tumors, epilepsy, Parkinson's disease, dementia, anxiety depression and psychosis ● Increased Risk: ● Inflammation ● Oxidative stress ● Mitochondrial dysfunction ● Alteration of hormones &/or neurotransmitters 	<ul style="list-style-type: none"> ● Molecular Mechanism of Action: ● Inhibits HMG-CoA Reductase and acyl Coenzyme A acetyltransferase ● Lowered LDL, hs-CRP, and homocysteine ● Secretagogues by enhancing insulin secretion ● Increases glucose uptake ● Increase the expression of AMP-activated protein kinase ● Inhibition of intestinal α-glucosidase and α-amylase ● Regulates Akt/phosphatidylinositol-3-kinase (PI3K) pathway and subsequent inhibition of forkhead boxO transcription factor 1 (FoxO1) ● Regulate hepatic gluconeogenesis
	<ul style="list-style-type: none"> ● Current Focus: ● Reduce oxidative stress, Inflammation and improve mitochondrial function 	<ul style="list-style-type: none"> ● Neuroprotective bioactive compounds in Noni: ● Rutin ● Scopoletin
		<ul style="list-style-type: none"> ● Molecular Mechanism of Action: ● Anti-inflammatory effect ● Antioxidant action ● Inhibits acetylcholinesterase activity ● Acts on GABA-A receptor ● Anxiolytic action ● Sedative effects ● Dopamine antagonist

alpha (PGF2 α)¹¹³ and leukotrienes.¹¹⁴ The treatment of choice for initial management is NSAIDs in patients suspected to have primary dysmenorrhea. Other treatment options include the combination of oral contraceptives and depot medroxyprogesterone acetate. Some patients do not desire hormonal contraception hence alternative remedies such as topical heat, vitamin E, fish oil, acupuncture, low-fat vegetarian diet, and Japanese toki-shakuyaku-san have been tried. In another etiology, menstrual disorders occur due to complex interactions among hormones and neurotransmitters.¹¹⁵ Noni has been used extensively in folk medicine by Polynesians for centuries and has been reported to have a wide range of therapeutic benefits in dysmenorrhea.^{13,25,64,116,117} Noni has the ability to inhibit the formation of pro-inflammatory cytokines and also possesses tranquilizing properties similar to narcotic agents which contributes to the analgesic effect in dysmenorrhea.^{13,118}

4.4. Gastrointestinal diseases

Gastroesophageal reflux disease and peptic ulcers are common chronic upper gastrointestinal diseases. The current therapy focusses on acid-suppressive therapy (with or without prokinetic agents).¹¹⁹ Nevertheless, a considerable number of patients do not achieve complete mucosal healing or suffer from either sustained symptoms or complications. But most of these drugs exhibit serious adverse effects such as impotence, gynaecomastia, hypergastrinemia and haemopoietic changes.¹²⁰ Furthermore, ulcer relapse after long-term treatment has also been reported. Reactive oxygen species; pro-inflammatory cytokines [TNF- α , IL-1 β and IL-6]; pro-inflammatory mediators PGE2 and nitric oxide generated from the induction of inducible nitric oxide

synthase (iNOS)], have been proposed to play a part in the pathophysiology.^{119,121} In addition; abnormal gastric motility, associated with rapid or delayed gastric emptying also contributes to gastric ulcer development. Noni has shown to exhibit anti-secretory and prokinetic agent. These properties may be beneficial as a potential preventive and therapeutic agent for gastroesophageal inflammation. In addition, Noni enhances the mucosal defensive mechanisms through suppression of serotonin, free radicals and cytokine-mediated inflammation. Moreover, Noni possess antiemetic activity and have been shown to reduce incidence of postoperative nausea and vomiting.¹²² Scopoletin, a coumarin derivative, is one of the main compounds in Noni has pharmacological activity in controlling the serotonin level in the body,¹²³ along with anti-inflammatory^{40,124,125} and antioxidant activities.¹²⁶ The antiemetic activity may be due to its effect on serotonin. Noni can also be used as a carminative, appetite stimulant, reliever of gum diseases and heartburn reducer.¹²⁷ Therefore, Noni can considerably possess protective effects against gastrointestinal disorders.

4.5. Metabolic disorders

4.5.1. Metabolic disorders-dyslipidemia

Dyslipidemia, individually as a disease, has emerged as a growing health concern as it constitutes one of the major risk factors for the development of cardiovascular diseases, such as atherosclerosis and its complications like myocardial infarction.²¹ It is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency and manifested by elevation of the total cholesterol, low-density lipoprotein (LDL), triglyceride and a decrease in the high-density

Table 3
Various parts of Noni and their Health Benefits.

Various Parts of Noni	Uses
Bark	<ul style="list-style-type: none"> • Asthma • Cancer • Diabetes Mellitus • Fabric dyes • Nausea • Pain • Preparation to aid childbirth • Tuberculosis
Root	<ul style="list-style-type: none"> • Cancer • Dyslipidemia • Fabric dyes • Hypertension • Neurological diseases • Pain (Headache, Migraine, Body) • Spasm • Topical ailments
Leaves	<ul style="list-style-type: none"> • Arthritis • Bone and joint problems • Cancer • Dyslipidemia • Dysmenorrhea • Headache • Hypertension • Improves wound healing • Liver disease • Neurological diseases • Pain (Headache, Migraine, Body) • Reduces burns, sores • Spasm • Topical ailments
Fruit	<ul style="list-style-type: none"> • Arthritis • Cancers • Cardiovascular disease: atherosclerosis, cardiac problems • Cataract • Cough • CNS disease: depression, senility, addiction, Convulsion • Diabetes-Mellitus • Gastrointestinal disorders: colic, ulcers and poor digestion, • Hypertension • Infection: AIDS, Cold, Small pox • Liver disease • Menstrual Problem, • Neurological diseases • Pain (Muscle, Headaches)
Stems	<ul style="list-style-type: none"> • Bone disease • Cardiovascular disease • Diabetes Mellitus • Leishmanial
Flowers	<ul style="list-style-type: none"> • Fabric dye • Neurological diseases

lipoprotein (HDL). Despite various treatment modalities available, these medications are limited by dose dependent side effects of which hepatotoxicity and myopathy are a concern.¹²⁸ Noni has antioxidant, vasodilatory and angiotensin converting enzyme inhibitor activities which suggest its beneficial effect towards the cardiovascular system.¹²⁹ Noni has been shown to have inhibitory effects on HMG-CoA Reductase and acyl Coenzyme A acetyltransferase enzymes.¹³⁰ Noni lowered LDL, hs-CRP, and homocysteine. Deacetylasperulosidic acid, asperulosidic acid, Oleuropein, the active ingredients in Noni may contribute to the dyslipidemic effects.^{97,131,132,133} Noni treatment reduced total cholesterol, triglycerides and LDL in a high fat diet induced dyslipidemic murine model.^{63,134} Based upon the above studies, Noni can prevent major cardiovascular diseases.

4.5.2. Metabolic disorders- anti-diabetic mellitus agent

Type 2 diabetes mellitus consists of an array of dysfunctions

characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion.²³ In spite of various treatment options available, lack of adequate glucose control and the associated side effects like hypoglycemia, weight gain and secondary failure has prompted researchers to investigate the role of complementary and alternative medicine. Once such natural product is Noni, which has been suggested to exhibit anti-diabetic mellitus effect due to the stimulatory effect on the remnant β -cells of Langerhans to secrete more insulin.¹³⁵ Saponins as well as flavonoids (rutin) in Noni acts as secretagogues by enhancing insulin secretion.¹³⁶ Noni increases glucose uptake by increasing the expression of AMP-activated protein kinase, a known sensor of cellular energy and contributes to improved peripheral insulin resistance. Improvement of postprandial glucose can be done by delaying carbohydrate absorption from the intestine, which may help to regulate insulin release. This can be achieved through the inhibition of intestinal α -glucosidase and α -amylase.¹³⁷ Noni has the ability to modulate the transcription factors (FoxO1) and regulate the gluconeogenesis process. Gluconeogenic genes which are regulated by insulin, including phosphoenolpyruvate C kinase and glucose-6-phosphatase, were also inhibited by Noni.¹³⁸ Inhibition of hepatocyte fatty degeneration was also speculated as one of the mechanisms to lower plasma glucose among streptozotocin-induced diabetic rats.¹³⁶ Chronic inflammation is considered a critical etiological factor in Type-2 diabetes mellitus. Due to its anti-inflammatory properties, Noni has direct correlation between anti-inflammatory effects and amelioration of diabetes mellitus. Patients with type 2 diabetes mellitus supplemented with Noni juice resulted in significant reduced mean blood glucose levels.¹³⁹ The suggested anti-diabetic mellitus mechanisms involve modulation of genes involved in gluconeogenesis and glycolysis, such as the phosphoenolpyruvate C kinase (PEPCK) and the forkhead box-O1 (FoxO1).^{138,140,141}

4.6. CNS disorders

The most common neurological disorders are brain tumors, epilepsy, Parkinson's disease, dementia, anxiety depression and psychosis. Neurological diseases significantly affect the neurons, nerves and/ or glial cells in the central nervous system and peripheral nervous system. Inflammation, oxidative stress, mitochondrial dysfunction and alteration of hormones &/or neurotransmitters are the main cause for various neurological disorders. Noni has exhibited antioxidant and anti-inflammatory effect. Interestingly, memory enhancing activity of Noni is due to the presence of rutin, scopoletin which inhibits the acetylcholinesterase activity²⁸ and also due to antioxidant activities.^{142,143} Components of Noni can bind to the GABA-A receptor and exhibit anxiolytic and sedative effects.^{40,144,145} It also exhibits dopamine antagonist effect and hence used as antipsychotic.^{146,147}

4.7. Other pharmacological effects (eye, mouth, fatigue, liver)

Free radicals have shown to increase the risk of cataract and other ophthalmic pathologies. Noni by exhibiting antioxidant effect has shown to protect the human cataractous lens epithelial cells.¹⁴⁷ Noni has exhibited significant ergogenic (anti-fatigue) effect by enhancing strength, stamina and physical performance.^{147,148} The anti-fatigue effect can be attributed to the cardioprotective and stimulatory effects of Noni.^{147,149,150} In rodents, Noni has exhibited hepatoprotective effects chemically-induced (CCl4) hepatotoxicity.^{147,151} Furthermore, Noni reduces smoking-induced adverse effects and reduce gum diseases.¹⁴⁷

5. Toxicological effects

Noni has shown to increase the risk for hyperkalemia due to the high content of potassium¹⁴⁷ and therefore it should be avoided in patients with chronic kidney disease.¹⁴⁷ There are several cases of

hepatotoxicity due to Noni juice consumption.^{147,152–156} Hence, U.S. Food and Drug Administration has issued warnings to noni manufacturers regarding unsupported health claims.

6. Discussion and conclusion

Noni exhibits a rich traditional value and is a nutraceutical that has been accepted globally. Essentially each part of the Noni has prophylactic and therapeutic values. The current article emphasizes the novel beneficial health effects and the immunomodulatory activities of Noni associated with its bioactive substances, the phytochemicals and polysaccharides (Tables 2 and 3). However, one of the key limitations of this study is the lack of large data from human clinical trials utilizing Noni in various diseases. More investigations are required to extensively study the active components of Noni in wide range of concentrations and their specific pharmacological mechanism of action. As a long-established and validated botanical remedy, Noni is a plant with multiple benefits ranging from traditional usage of its wood for making tools to its juice being used as a first aid or for treating critical illnesses. Due of its therapeutic benefits this Polynesian botanical has become a quite popular recently.

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