

Review on the Bioactive Constituents, Health Benefits, and Safety Evaluation of Noni (*Morinda Citrifolia* L.): Implications for Development of New Health Products Derived from Noni

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Abstract Noni (*Morinda citrifolia* L.) holds a unique position in various regions such as foods, health products, and cosmetics as both a medicinal and edible plant. It is rich in various bioactive constituents, including anthraquinones, flavonoids, iridoid terpenoids, saccharides, and coumarins. These constituents along with crude noni extracts exhibit a variety of health benefits, such as anti-oxidant, anti-inflammatory, anti-hypertension, anti-diabetic and hepatoprotective effects, with great development potential in the fields of food and health products. Liver toxicity of noni juice has also been reported, and evaluation of safety and toxicity of noni become essential for future use. Nowadays, the innovation and application of noni products have expanded, particularly in the fields of skincare, health supplements, industrial applications, etc. This review provides an overview of recent advances in the bioactive constituents, health benefits, safety evaluation, and future applications and perspectives of noni, providing a scientific basis for the development of noni-based products.

Keywords: noni, bioactive constituents, health benefits, safety, application

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1. Introduction

Noni (*Morinda citrifolia* Linn.) is an evergreen tropical tree or shrub native to tropical regions. It is mainly distributed in the Southeast Asia and South Pacific Islands, including Hainan, Taiwan and Xisha Islands in China (Figure 1A). In these tropical regions, noni has been used as a traditional medicine for more than 2,000 years. In China, noni has been used and recorded in the Compendium of Materia Medica for a long history. It belongs to the genus *Morinda*, known for its ability to "dispel pathogens and strengthen vitality". Components of *Morinda officinalis* are found in several classical Chinese medicine prescriptions, including Baji Pill, Jingang Pill, and Zhenwu Decoction. In the latest Chinese Materia Medica Atlas, noni is described as having the medicinal properties of "tonifying kidney and liver, strengthening tendons and bones, and nourishing both qi and yin" [1].

Moreover, noni has particularly garnered significant attention in the domain of food and health care products. Noni fruits are often locally called as "magic fruit" and

"God's gift" due to their recognized health benefits. In the early 20th century, noni fruit juice was certified as a new food by the European Union, marking its entry into broader recognition, including in China. The China Ministry of Health classified "Noni pulp" as a "new resource food" in 2010 [2], which spurred significant research interest and attention from scholars. Noni fruit has gained international popularity, appreciated for its notable health benefits. Tahitian Noni Beverages Co., Ltd is among the first companies to commercialize noni juice, creating a product composed of 89% noni pulp and 11% blueberry and grape juice, marketed as a functional food and dietary supplement across many countries. Besides commercial juice, noni is also available in various forms such as tablets and capsules for health purposes. Noni fruit extracts or fermented fruit wines have been shown to promote lipid metabolism and help with weight loss by supporting the breakdown of adipose tissue [3].

Nowadays, as the cultivation of noni fruit trees has expanded, its potential value in various regions such as food, health products, and cosmetics has been continuously explored (Figure 1B). A series of derivative products, including noni juice, fruit powder, dried fruit,

and oil soap, has been developed, with innovations such as noni tea incorporating chinese tea-making technology, thereby filling the market gap for noni leaf-based products [4]. The fruits and leaves are edible, with the leaves also used for external applications, while the roots used as natural dyes. Given its excellent antioxidant and antibacterial properties, noni has also been incorporated into a growing range of skincare and oral hygiene products, such as natural mouthwashes and facial masks containing noni complex enzymes, which are gaining increasing popularity in the market [5,6]. In addition, noni extracts have many industrial applications. It has been discovered that noni leaf extracts can be incorporated into methylcellulose active films to enhance the freshness-preserving properties of food packaging materials [7].

Collectively, as both a health food and traditional medicinal plant, noni has been extensively used in various domains, particularly in food and health care domain, for a long period. The research and development of its extracts and bioactive constituents, hold significant implications for future expansion of noni's application. In this context, we have summarized the latest research on noni's extract constituents, health benefits, and safety, with the hope of contributing to its further development and application, particularly as food products.

2. Bioactive Constituents

To date, the bioactive constituents extracted from noni include anthraquinones, flavonoids, iridoids, saccharides, lignans, coumarins, terpenoids, and volatile compounds, among others. By 2025, over 300 compounds had been isolated and identified from various parts of the noni plant,

including its roots, stems, leaves, flowers, fruits, and bark (Figure 2). Below, we summarized some of the most recent research advancements regarding these bioactive components.

2.1. Anthraquinones

The quinones identified in noni primarily include anthraquinones and naphthohydroquinones, with anthraquinones being the most abundant, and the majority of the anthraquinones belong to the alizarin and emodin types. So far, more than 100 anthraquinones have been isolated and identified from Noni. The most of these compounds consist of a single anthraquinone parent structure, with substituents such as methyl-, ethyl-, hydroxyl-, methoxy-, and carboxyl-, etc. The novel anthraquinone compounds damnacanthal and nordamnacanthal were isolated from the noni root in the 20th century [8]. Recently, a novel anthraquinone compound, moricitrifone, along with seven known anthraquinone compounds, 1,3,5-trihydroxy-2-methoxy-6-(methoxymethyl)-9,10-anthracenedione, morindicinone, filamentos B, lasianthurin C, 3-hydroxy-1,2,4-trimethoxy-6-methylanthraquinone, plocamanone B and plocamanone C, were isolated from noni fruit [9]. Additionally, a new anthraquinone compound, 1,3-dihydroxy-2,5-dimethoxy-6-(methoxymethyl) anthracene-9,10-dione, was identified in noni seeds [10]. Anthraquinones are present in nearly all parts of noni, yet they are mainly concentrated in the roots. Importantly, the drying or freeze-drying fermented noni fruit and fruit juice does not affect the content of anthraquinones, facilitating the manufacture of noni fruit into diverse preparations that retain these bioactive ingredients.



Figure 1. (A) Map of the planting of Noni in the world; (B) the products of noni



Figure 2. Various parts of the noni plant which are rich in bioactive constituents

2.2. Flavonoid

To date, over 20 flavonoids and their glycosides have been isolated from the entire noni strain. The glycosides mainly consist of quercetin and kaempferol as aglycones, such as rutin, kaempferol-3-O- α -l-rhamnopyranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside, and quercetin-3-O- α -l-rhamnopyranosyl-(1 $\rightarrow$ 6)- β -D-glucopyranoside, etc. The total flavonoid content in noni fruit is extremely abundant, with the effect of combined extraction technique of enzymatic treatment and ultrasonication, yielding up to 47.19 ± 1.22 mg rutin/100 mL [11]. Flavonoids are prevalently present in noni and play a significant role in numerous diseases due to their potent antioxidant and free radical scavenging effects. Recently, it was discovered that the freeze-dried aqueous extract of noni exhibited excellent schistosomicidal activity, with rutin identified as the characteristic peak by HPLC chromatogram [12]. Additionally, epicatechin is another noteworthy flavonoid in noni. Researches have demonstrated that noni leaf extract is rich in epicatechin, catechin and scopoletin [13,14].

2.3. Iridoid Terpenoids

Noni contains a diverse range of iridoids, also referred to as iridosides, most of which exist in the form of glycosides. When iridoids were extract from noni using traditional solvents and deep eutectic solvents (DESS) respectively, the 70% ethanol extract of noni fruit had the highest total iridoid content (26.38 mg CE/g DW) [15]. Deacetylasperulosidic acid (DAA) and asperulosidic acid (AA) exist in the leaves, roots, seeds, and flowers of noni plants, which are regarded as the primary iridoid terpenoid constituents of noni fruit.

2.4. Saccharides

Recent research has identified at least 45 saccharides isolated from noni, and the most of them are isolated from the noni fruit. Notably, noni fruit is the main source of sugar, and the maturity of noni fruit has a considerable impact on the extraction yield, molecular weight, sugar acid content, sugar composition, monosaccharide profile, antioxidant capacity, and DNA protection of noni polysaccharides. The fully mature noni polysaccharides exhibited the highest extraction rate ($8.26 \pm 0.14\%$), the highest sugar content ($61.94 \pm 1.86\%$), and the strongest 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and 2,2-Azino-

bis(3-ethylbenzthiazoline-6-sulfonic acid (ABTS) radical scavenging effects, which might be attributed to its high content of fucose and rhamnose and a lower molecular weight [16]. Saccharides and polysaccharides are significant bioactive constituents in noni, which are demonstrating anti-inflammatory, immunomodulatory, anti-cancer, liver-protective, and hypoglycemic effects, benefiting human health.

2.5. Lignans

Lignans, a category of compounds formed from two phenylpropanoid molecules, are widely distributed in plants. It has been reported that 27 lignans were isolated from noni, primarily from fruits and leaves, and a smaller fraction in seeds [17]. Two lignans, (+)-3,4,3',4'-tetrahydroxy-9,7' α -epoxylignano-7 α ,9'-lactone and (+)-3,3'-bisdemethyltanegool were isolated from noni fruit [18]. Additionally, 50% ethanol extract of noni seeds (MCS-ext) exhibited a significant inhibitory effect on melanogenesis. Among which, 3,3'-bisdemethylpinoresinol and americanin A were identified as the active components of MCS-ext [19]. Recent studies have discovered two sesqueneolignans, namely (7S,8S,7'R,8'R)-isoamericanol B and americanol B, and two dineolignans, namely moricitrins A and moricitrins B, from the extract of noni fruit. Among them, americanol B, moricitrins A, and moricitrins B are novel compounds [20].

2.6. Coumarins and Other Bioactive Constituents

Coumarin, consist of a benzene and an α -pyranone ring, presents naturally in at least 150 different plant species. Coumarin is an important fragrance compound, and also exhibit great potential in fluorescence applications for many years [21]. Beside these constituents, noni extracts contain minor amounts of steroids, triterpenoids, aliphatic glycosides, organic acids, etc. The principal organic acids isolated from fresh noni fruit are malic acid (76.43 ± 2.72 mg/100 mL) and ascorbic acid (26.93 ± 1.17 mg/100 mL) [22]. Octanoic acid and caproic acid was the main organic acids contributing to the unfriendly odor of noni [23]. Recently, a new sterol compound 28-hydroxy-3 β -acetoxy-9-dehydrogramisterol and a new triterpene compound 3 β -acetoxy- taraxast-20(30)-ene-21-ol were identified from the ethanolic extract of noni fruit [24]. Additionally, four new alkaloids, nonialkaloids A-D, were isolated from noni juice, with nonialkaloids A and C exhibiting α -glucosidase

inhibition [25]. Five new compounds, cyanidin 3-(2 G-xylosylrutinoside), inulobiose, clausarinol, pectachol, and 4, 7-megastigmadien-9-ol, were discovered in the alcoholic extract of noni fruit [26]. Figure 3 illustrated the structures of these newly discovered compounds from noni over the past five years.

2.7. Nutrients

Noni is rich in abundant nutrients, containing 13

vitamins, 16 minerals, 8 trace elements, and over 20 amino acids, among which 9 amino acids are essential for human health. Among the 13 vitamins isolated from noni, the content of vitamin C was highest, with ripe noni fruits (76.24 ± 1.13 mg/100 g) containing more than unripe ones (53.19 ± 0.79 mg/100 g) [27]. These discoveries laid the foundation for screening natural noni extracts and nutrients for beneficial utilization as food and health sources.

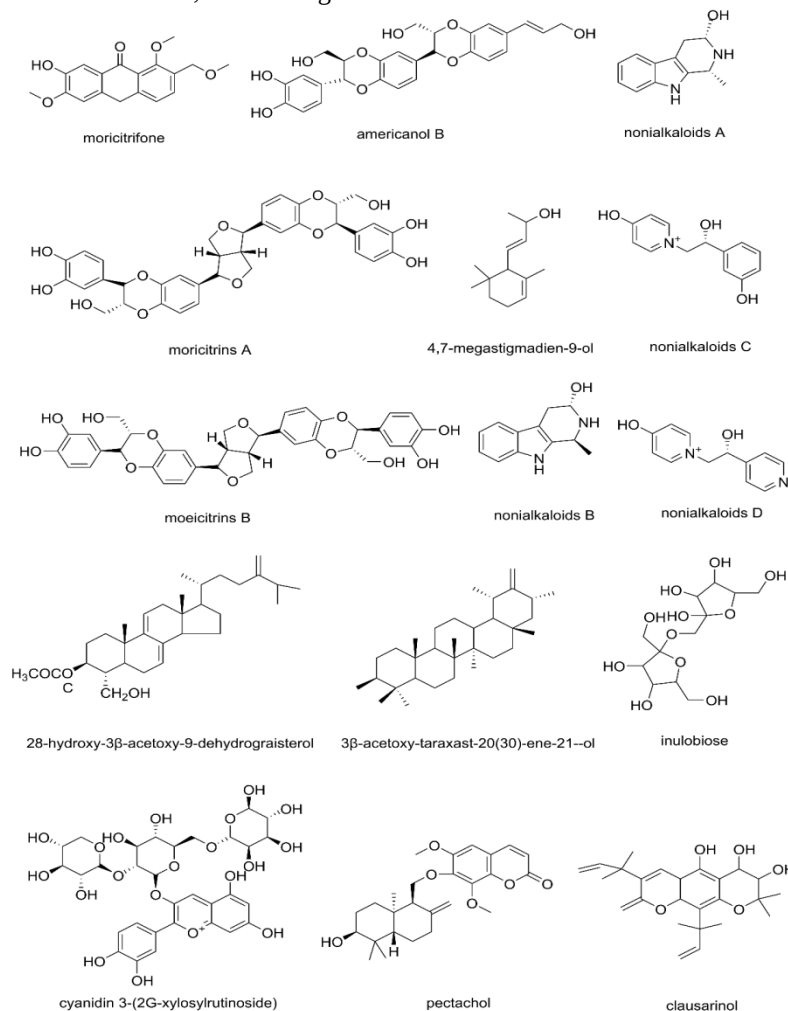


Figure 3. The structures of compounds newly discovered in noni over the past five years

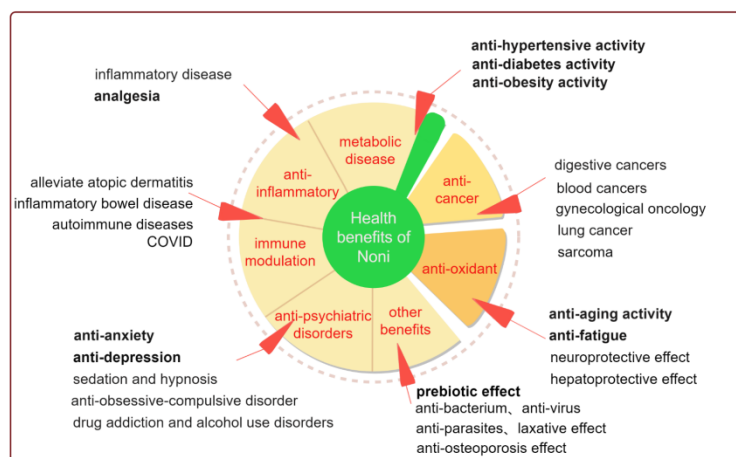


Figure 4. Illustration of the health benefits of Noni

3. Health Benefits

The health benefits of noni include anti-oxidative activity, anti-bacterial activity, anti-inflammatory activity, anti-hypertensive activity, anti-hyperglycemic activity, hepatoprotective activity, anti-parasites activity, anti-diabetes activity, immunomodulation, anti-psychiatric disorders, and neuroprotective activity, etc. Figure 4 illustrated the different beneficial effects of noni for human health.

3.1. Anti-oxidative Activity

Extensive literature has proved the excellent anti-oxidative properties of noni extracts in free radical scavenging and oxidative damage repair. A study revealed that noni juice alleviated oxidative DNA damage and aromatic DNA adducts in heavy smokers. Noni fruit at different ripeness stages exhibited different antioxidant capacities and protection against DNA damage. Noni polysaccharide that isolated from noni fruit at maturity stage 5 exhibited the highest DPPH and ABTS radical scavenging capabilities. Whereas, the polysaccharide that isolated from noni fruit at maturity stage 4 exhibited the greatest hydroxyl radical scavenging ability and DNA protection [16]. Fermentation studies further demonstrated enhanced antioxidant activity in fermented noni juice. After fermentation with lactic acid bacteria, the DPPH scavenging capability of noni juice increased significantly [28]. Moreover, the DPPH scavenging capability of the methanolic noni leaf extract increased, following inoculation and fermentation with *Lactobacillus plantarum* BP102 [29].

Noni extracts with the capability of scavenging free radicals contribute to oxidative stress mitigation, which is closely linked to the progression of diseases. Typically, as an antioxidant, noni can reduce the generation of free radicals in the inflammatory reactions, thereby alleviating inflammation. Oxidative stress and inflammation are also regarded as key elements in neurodegenerative disorders such as Parkinson's disease. Current studies have demonstrated that noni ethyl acetate extract exhibits antioxidant and anti-apoptotic effects on skeletal muscle cells in rotenone-induced Parkinson's rats [30]. Additionally, noni fruit extract demonstrated cardioprotective effects by reducing cardiomyocyte apoptosis and enhancing energy production in damaged cardiomyocytes, suggesting potential benefits in delaying heart failure progression [31]. Totally, further research on the antioxidant properties of noni fruit and the more potent noni root extracts is crucial for the development of novel drugs and nutraceuticals for disease prevention and treatment.

3.2. Anti-bacterial Activity

It has revealed that noni extracts effectively inhibit the growth of various bacteria, including common pathogens such as *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella* spp., and *Klebsiella*. The polarity and chemical characteristics of the solvents influenced the observed differences in the antibacterial efficacy. For instance, noni leaves extracted with different solvents

showed varying activity against *Bacillus subtilis*, *E. coli*, *Proteus vulgaris*, and *Staphylococcus aureus*, with the n-butyl alcohol extract displaying the strongest antibacterial activity [32]. Also, a lipid transfer protein isolated from noni seeds, *McLTP1*, exhibited significant antibacterial activity. In the cecal ligation puncture (CLP) mouse model of sepsis, *McLTP1* (8 mg/kg) treatment yielded 100% survival of the animals after 3 days and significantly alleviated sepsis-induced symptoms [33].

Ripe noni fruit resists decay and mold, gradually drying up without spoilage, thus it is called the "mummy" of fruits. This characteristic was attributed to antibacterial components and an essential oil containing octanoic acid (75.8%), caproic acid (12.8%), and isobutyl 4-pentenylcarbonate (3.1%). This essential oil at a concentration of 5 mg/mL could inhibit the growth of fungal mycelium through stable interactions with tyrosine-tRNA ligase in *S. cucurbitacearum* [34]. Noni extracts exhibited antibacterial activity against *Mycobacterium tuberculosis*. The 96% ethanol extract of noni fruit and its active components, including flavonoids, alkaloids, scopoletin, and anthraquinone, exhibited strong inhibitory effects on the *M. tuberculosis* strain H37RV [35]. However, some bacteria gradually acquired resistance to current antibiotics due to the extensive application of antibiotics in both the medical and agricultural domains. Recent research indicated that noni fruit extracts inhibited some drug-resistant bacterial strains. For instance, n-hexane, dichloromethane, and methanol extracts of noni seeds have shown antibacterial activity against methicillin-resistant *Staphylococcus* (MRS) strains and the *Staphylococcus aureus* ATCC 29213 strain [36]. 96% ethanol extract of noni fruit was also effective against multi-drug resistant tuberculosis strains (MDR-TB), inhibiting strains resistant to kanamycin, amikacin, and ofloxacin, suggesting a potential role in MDR-TB treatment [37]. These findings demonstrated the inhibitory activity of noni fruit extracts on drug-resistant bacteria and tuberculosis, which maybe potential source of novel antimicrobial drugs.

3.3. Anti-inflammatory Activity

Noni has been reported for the anti-inflammatory activity for a long history, with its fruits, leaves, and roots applied to a wide range of inflammatory diseases. Nowadays, the anti-inflammatory effects of noni have gradually gained recognition in modern medicine. Studies have demonstrated that some certain compounds contained in noni, such as asperulosidic acid, rutin, tricetin, anthraquinones, and naphthoates, possessed anti-inflammatory property [38]. Fermented noni fruit extract was shown to protect against colonic inflammatory diseases by improving colonic microbiota and exerting anti-inflammatory activities in Caco-2 cells, with the flavonoid compound quercetin identified as a mainly contributor. Noni leaf extract, abundant in scopoletin and epicatechin, has also been shown to inhibit the secretion of various inflammatory mediators [13].

Noni seed also exhibited anti-inflammatory activities. In LPS-stimulated RAW264 cells, noni seed extract, noni seed oil, noni leaf extract, and noni fruit extract decreased iNOS and tumor necrosis factor- α (TNF- α) [39]. It was

previously reported that *McLTP1* isolated from noni seed exhibited anti-inflammatory effect by regulating pro-inflammatory and anti-inflammatory cytokines. In carrageenan-induced foot edema mouse model, *McLTP1* (8 mg/kg) significantly modulated inflammatory cytokines in inflamed skin tissues. *McLTP1* also decreased the number and the migration of neutrophils in peritoneal cavity of the peritonitis model induced by dextran. In cerulein-induced acute pancreatitis, it mitigated pancreatic and related lung injury [40]. Also, *McLTP1* promoted wound healing in the mouse superficial burn model due to its favorable anti-inflammatory effects [41]. A recent study reported that moricitan A and 9'-ethyl americanol A isolated from noni seed exhibited significant inhibitory effect on LPS-induced NO production in RAW264.7 cells [10]. Nevertheless, as the seeds were eliminated and discarded during the production of noni juice, further exploration on noni seed extract and its active ingredients could provide valuable insights.

3.4. Anti-hypertensive Activity

In Indonesia, noni has been utilized as an herbal remedy to help control blood pressure for a long history. In China, *M. officinalis*, a related species, has long been included in traditional Chinese antihypertensive prescriptions, among which Erxian decoction and Jisheng Shenqi decoction exhibited high efficacy in the clinical treatment of hypertension. Key components of noni, including polyphenols, flavonoids, and iridoid terpenoids, were considered critical to its antihypertensive properties. Recent studies discovered that, deacetylaspatic acid isolated from noni juice extract (NJE), exhibited significant antihypertensive activity [42]. Flavonoids isolated from Noni also exhibited a significant role in cardiovascular diseases, which could modulate vasoactive factors related to blood pressure regulation and alleviate hypertension induced by inflammation [43]. Two flavonoids rutin and quercetin, identified in the extract of noni pulp, have been confirmed to inhibit ACE activity, and the combined effect of these two compound was more potent than either one alone [44]. Generally, the antihypertensive activity of mature noni juice was stronger than that of immature noni juice, as ripeness substantially impacted the bioactive components and functional efficacy of noni fruit [45].

Also, the antihypertensive effect of scopoletin (7-hydroxy-6-methoxy coumarin) isolated from noni fruit has been reported. It achieved the antihypertensive effect by dilating the narrowed blood vessels, and meanwhile exhibited no influence on the blood pressure of normal individuals. An *in vitro* investigation of rats with hypertension induced by L-nitroarginine methyl esterification (L-name) discovered that *Morinda Lucida* extract could normalize blood pressure [46]. Another *in vitro* study of dexamethasone-induced hypertensive rats revealed that ethanol extract of noni leaf (MCLEE), noni fruit (MCFEE), and their 1:1 combination (MCLFEE), could significantly decrease the blood pressure of hypertensive rats. The antihypertensive effect of MCLFEE was greater than either single extract, comparable to that of the positive control captopril. This enhancement was due to the synergistic effect of the unique metabolites in each extract, with rutin being the principal flavonoid in MCLEE and scopoletin being the

principal compound in MCFEE [47]. These founding offered unimaginable benefits for the treatment of hypertension by noni.

3.5. Anti-obesity Activity

It is well known that obesity is a risk factor for numerous chronic disorders, directly influencing the health and quality of life. Noni extracts exhibited potential anti-obesity effects, where some animal experiments indicated that noni extracts were beneficial in reducing body weight and fat accumulation. In high-fat diet induced Wistar rats, noni fruit extract (100 mg/kg and 200 mg/kg) notably increased level of low density lipoprotein (LDL), and meanwhile significantly reduced level of high density lipoprotein (HDL) compared to untreated rats [3]. Similarly, in another study of high-fat diet induced hyperlipidemia, 50 mg/kg and 100 mg/kg noni juice remarkably decreased levels of TC, TG, and the low-density lipoprotein-cholesterol (LDL-C) [48]. Additionally, noni wine could also prevent obesity induced by a high-fat diet in mice. 50 mg/kg noni wine per day significantly reduced body weight, body fat, and serum levels of TC, TG and LDL, and meanwhile increased energy consumption and physical activity in high-fat diet-fed mice.

The anti-obesity mechanism of noni extract might be multifactorial. Pancreatic lipase, a crucial lipolytic enzyme in lipid metabolism, is a target for obesity treatment, as its inhibition can inhibit fat absorption in patients with obesity, hypertriglyceridemia, or hypercholesterolemia [49]. Other study found that Bet-Gly (betaine: Glycerol extract, $IC_{50} = 14.47 \pm 0.61 \mu\text{g/mL}$) extract and 70% ethanol extract of noni fruit ($IC_{50} = 212.06 \pm 2.42 \mu\text{g/mL}$) exhibited higher inhibitory activity on pancreatic lipase than other solvents, though their activity was lower than that of orinoat ($IC_{50} = 5.91 \mu\text{g/mL}$), which might be attributed to their high phenols and iridoid terpenes content [15]. Totally, noni extract exhibited anti-obesity potential, which still need further study as functional food and medicinal agents.

3.6. Anti-cancer Activity

Increasing evidence indicated that noni extracts and their bioactive components possessed substantial antitumor activities *in vitro*. Noni fruit extract exhibited remarkably inhibitory effect on cholangiocarcinoma, bladder carcinoma, and hepatocellular carcinoma [26]. Moreover, noni shoot and leaf extract has demonstrated cytotoxic potential in colon, liver, lung, cervical, and breast cancer cells [50]. Accumulating evidence demonstrated that bioactive components extracted from noni, including epicatechin, rutin, 7-hydroxy-6-methoxycoumarin, rubiadin, chrysin, morindone, damnacanthal, exhibited antitumor activities. Chrysin, abundant in noni fruit water-EtOAc extracts, combined synergistically with apigenin could induce apoptosis and inhibit migration of human breast and liver cancer cells [51]. Morindone, an anthraquinone compound isolated from noni root, exhibited anticancer activity against HT29, LS174T, and HCT-116 cells [52]. Damnacanthal, another anthraquinone compound isolated from noni root, exhibited a wide range of inhibitory effect on various cancer cells [53]. The detailed anti-

cancer mechanisms of noni extracts were comprehensively depicted in Figure 5.

Noni extracts also exhibited anticancer potential in animal studies. In Ehrlich ascites carcinoma mice, silver nanoparticles (AgNPs) synthesized from noni fruit extract inhibited the infiltration of cancer cells into surrounding tissues [54]. In mice xenograft with human Jurkat leukemia cells, treatment with 100 or 200 mg/kg/day of noni leaf extract rich in epicatechin and scopoletin dose-dependently reduced the level of bone marrow myeloblasts without observe toxicity [55]. Compounds isolated from noni also exhibited anticancer effects. The anti-ovarian cancer effect of damnacanthal has been confirmed in an orthotopic SKVO3 ovarian cancer model

in nude mice [53]. It effectively inhibited the growth of colorectal tumor xenografts in nude mice, with tumor size and bioluminescence reductions approximately 3-to 5-fold higher than 5-FU [56]. Furthermore, noni extract acted synergistically with clinical drugs, potentially enhancing anticancer efficacy and reducing adverse reactions. When combined with 5-FU, two ethanol extracts of Noni juice (TNJ-Cr and TNJ-Bs) reduced the dose of 5-FU, while achieving greater tumor inhibition in CCA cell xenograft nude mice [57]. Similarly, noni juice in combination with cyclophosphamide (CYL) improved tumor suppression and mean survival time in breast cancer-bearing mice, mitigating CYL-induced bone marrow toxicity and liver toxicity [58].

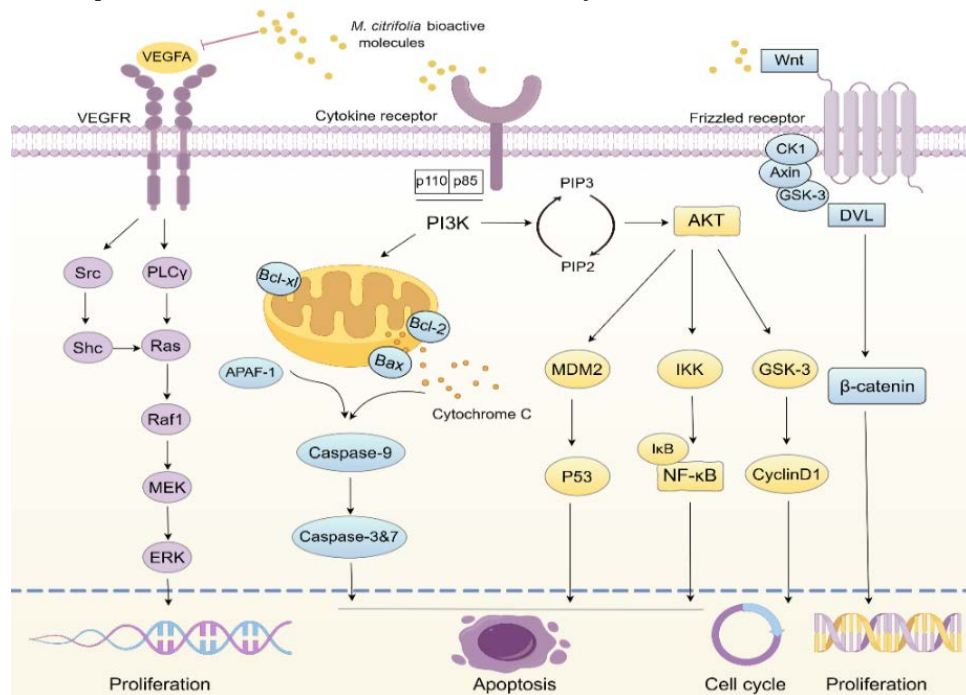


Figure 5. Anticancer mechanisms of noni extracts and their bioactive compounds

The anti-cancer property of noni extract has been widely studied in human clinical trials. A phase II clinical trial reported that 6.2 g/day of noni in capsule form for one year in men with very low or low-risk prostate cancer was feasible for long-term treatment. 50% of these participants had negative prostate biopsies after one year [59]. This study proved the potential of noni as a dietary intervention in human cancers, although this finding was based on case reports or single-arm pilot studies with limited sample sizes. Given the variability among individual patients, further larger-scale studies are needed to clarify therapeutic value of noni. These results revealed the potential therapeutic activities of noni extracts and active ingredients as promising candidates for anticancer drugs or dietary supplements.

3.7. Hepatoprotective Activity

Noni has proven to be a natural supplement for liver protection. Noni fruit juice was found to improve biochemical indicators including ALT and AST, and alkaline phosphatase (ALP), and mitigate the side effects of hepatotoxicity caused by cyclophosphamide in tumor-bearing mice [58]. In contrast to fresh juice, fermented

noni fruit juice also exhibited comprehensively preventive effect against alcohol-induced acute liver injury by alleviating hepatocyte oxidative stress [60]. Additionally, naturally fermented noni juice exhibited hepatoprotective effect on thioacetamide (TAA)-induced liver fibrosis in rats via reducing inflammation in the liver and enhancing hepatic antioxidant capacity [61]. Similarly, fermented noni juice has been found to reduce hepatocyte steatosis in streptozotocin (STZ)-induced diabetic rats.

Furthermore, other noni extracts also exhibited hepatoprotective effect. The iridoid glycosides in *M. officinalis* reversed disorders of lipid metabolism in collagen arthritis rats (CIA) treated with methotrexate (MTX), inhibited cell apoptosis, and reduced the levels of LDH, ALT, and AST, thus ameliorating MTX-induced liver injury in arthritis treatments [62]. In non-alcoholic fatty liver disease (NAFLD) induced by high-fat diet, it was discovered that the noni fruit polysaccharide may modulate the gut microflora and reduce the permeability of the colonic barrier and metabolic endotoxemia, thereby alleviating hepatic oxidative stress and inflammation in rats [63]. In a hepatic steatosis model of ovariectomized rats fed with thermoxidized palm oil (TPO) diet, noni ethanolic leaf extract exhibited hepatoprotective effect,

and confirmed by ultrastructural analysis for the first time [64]. Collectively, these findings suggested that noni extracts had significant hepatoprotective properties.

3.8. Anti-parasites Activity

In the latest revision of the List of Zoonotic diseases, leishmaniasis represents a significant public health problem. Accumulating evidence has revealed the anti-leishmanial activity of noni extracts and their bioactive constituents. In a double-blind randomized clinical trial, an ointment containing 1% methanol extract of noni leaf in petroleum jelly was administered to 40 patients with cutaneous leishmaniasis. 50% of the patients showed a favorable response and 30% showed considerable improvement. Lignin, a macromolecular, isolated from noni leaves exhibited anti-leishmanial activity ($IC_{50} = 29.56 \mu\text{g/mL}$) [65]. Additionally, noni juice also exhibited anti-leishmanial activity *in vitro*, acting directly on the parasite or by activating macrophages. *Leishmania* is an intracellular flagellate progressing through promastigote and the amastigote stages in the host. Noni juice was observed to promote the death of intracellular amastigotes by enhancing macrophage NO production. Further study demonstrated that noni juice exhibited stronger inhibitory effect on intracellular amastigotes ($IC_{50} = 201.3 \text{ g/mL}$) than promastigotes ($IC_{50} = 260.5 \text{ g/mL}$) [66]. In *Leishmania amazonensis*-infected C57BL/6 mice, noni juice extract at 500 mg/kg mitigated inflammatory infiltration in the foot pads [67].

Malaria is a parasitic disease caused by the plasmodium and has a profound impact on the low economic level countries. Recently, ethanol extract of noni leaves was also demonstrated to possess anti-malaria activity, however, there was no correlation between the dosage of this extract and the splenomegaly and hepatomegaly [68]. While these studies reveal the potential of noni extracts in the treatment of parasites, further exploration is necessary to elucidate the specific anti-parasitic compounds and to develop effective drugs.

3.9. Anti-diabetes Activity

Diabetes is a prevalent chronic metabolic disorder, particularly among the elderly [69]. Hyperlipidemia, a prevalent complication of diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), often accompanies aberrant lipid metabolism. Noni extract exhibited anti-diabetic effect via regulating metabolism of lipedema and glucose [70]. Both fermented noni fruit juice and noni leaf extract exhibited hypoglycemic and lipid-lowering activities in alloxan-induced diabetic mice and rats [71]. In mice with a high-fat/high-sugar (HFF) diet, high dose of noni fruit aqueous extract (AE) was found to improve glucose tolerance, exhibiting anti-diabetic effect [72]. In an 8-week human trial involving 20 patients with type 2 diabetes, twice-daily noni juice (2 mL/kg) administration significantly decreased fasting glucose levels and HbA_{1c}, enhanced insulin release, and importantly exhibited no influence on blood glucose in normal participants [73].

Additionally, noni extract exhibited anti-diabetic effect via regulating oxidative stress. Oxidative stress is closely linked to the occurrence of diabetes and its complications,

as it disrupts blood glucose homeostasis, promoting insulin resistance (IR) and hyperglycemia, eventually leading to T2DM. Noni extract, abundant in antioxidant components, could neutralize free radicals and mitigate oxidative stress, thereby protecting cells from oxidative damage. Fermented noni juice (FNJ) could promote glucose uptake and consumption, and improved intracellular and extracellular glucose imbalance and insulin resistance in IR-HepG2 cells by regulating the antioxidant defense system. In db/db mice, FNJ also exhibited hypoglycemic effect via interactions between Nrf2/ARE pathway and gut microbiota [74].

3.10. Immunomodulation

Recently, a considerable amount of research has revealed the immunomodulatory activity of noni extracts. Immunomodulation plays a key role in human health. It includes not only immune cell regulation, but also cytokine regulation, which is closely related to anti-inflammation. It has been reported that fermented noni can alleviate atopic dermatitis (AD) by restoring Th1/Th2 immune balance and enhancing skin barrier function [75]. Subsequent research further has found that the elevated levels of DAA in fermented noni not only inhibit the gene expression but also reduce the secretion of inflammatory cytokines and chemokines associated with AD [76]. The polysaccharide components in noni juice exhibited immunomodulatory properties via modulating inflammatory cytokines. Noni polysaccharides rich in galacturonic acid and rhamnose-galacturonic domain I (NFP) exhibited protective effect in a DSS-induced inflammatory bowel disease (IBD) mouse model, via decreasing serum levels of LPS, TNF- α , and IL-17 [77]. Further, it was verified that NFP also relieved colonic tissue damage in IBD mice, potentially linked to increase expression of galectin-3 (Gal-3) [78].

Noni extracts were also demonstrated to exhibit specific and non-specific immunomodulatory function in macrophages, lymphocytes and natural killer (NK) cells [79]. Specifically, the ethanol extract of noni fruit elevated levels of the interleukin family, IFN- γ and TNF- α , and enhanced NK cell-mediated cytotoxicity against YAC-1 cells (a T-cell lymphoma cell) in C30BL/57 mice [80]. *in vitro* studies also demonstrated that noni extract could enhance cellular and humoral immune responses in mice. Noni juice significantly reversed age-related declines of lymphocyte proliferation, and delayed decay of lymphocytes in aged F344 rats [81]. The immunomodulatory activity of fermented noni juice has also been verified in clinical trials. In a 28-day randomized clinical trial involving 188 patients with moderate to severe post-COVID syndrome, fermented noni fruit supplements significantly improved clinical symptoms and metabolism of the patients compared with the placebo. This treatment significantly enhanced neutrophils phagocytic activity, with pronounced effects in severe COVID patients [82]. These findings indicated that noni extract was capable of up-regulating beneficial cell-mediated immune responses and reducing detrimental pro-inflammatory responses, which were crucial for immune surveillance and diseases prevention.

3.11. Anti-psychiatric Disorders

Over the past few decades, noni extracts have shown potential in the treatment of depressive and anxiety disorders. The antidepressant effect of noni extract was linked to the serotonergic and noradrenergic systems. The methanol extract of noni fruit significantly reduced immobility duration in the tail suspension test (TST) in mice, which could be reversed by 5-HT receptor antagonists and norepinephrine synthesis inhibitors [83]. A latest study revealed that noni juice also had significant anti-depressive activity, alleviating depression- and anxiety-like behaviors in chronic unpredictable mild stress (CUMS)-induced mice [84]. Furthermore, it was revealed that noni fruit extract significantly reduced anxiety-related behavior in mice. For instance, methanol extract of noni significantly increased the time spent in open arms and entries in an elevated plus maze test, and meanwhile improved their behavior in a light box [83].

Sleep disorders, particularly insomnia, can exacerbate mental illnesses and elevate the risk of Parkinson's disease, cardiovascular disease, and other health conditions [85]. Sedative-hypnotic drugs play crucial roles in improving sleep quality, though accompanied by specific side effects, including tolerance, withdrawal reactions, and drug dependence for long term use. To minimize reliance and side effects of these drugs, traditional herbs and natural ingredients maybe alternative therapeutic approaches, where noni is an ideal candidate. In an experiment, the sedative activity was evaluated, where 500 mg/kg aqueous extract of noni fruit reduced spontaneous motor activity in mice, and prolonged ketamine-induced sleep time in a manner comparable to diazepam (1 mg/kg) [86], suggesting that the extract of noni fruit possessed sedative and hypnotic effects. Drug addiction and alcohol use disorders also present health challenges due to their impact on the central nervous system and associated mental disorders. Fortunately, noni fruit extract showed promise in reducing addiction-related behaviors. Recent research has found that methanol extract of noni fruit attenuated the rewarding effects of heroin and methamphetamine [87,88]. Bioactive compounds such as scopolamine and rutin in noni fruit or fruit juice were suspected to be responsible for this anti-addictive effect [89].

Recently, it has been shown that noni extract is potential to be a candidate drug for the treatment of obsessive-compulsive disorder (OCD), another chronic and complex mental disorder. It was found that administration of 100 and 200 mg/kg noni fruit extract improved behaviors in the marble-burying and nest-building tests in mice. Notably, there was a significant improvement in biogenic amine and serotonin levels in mice treated with noni fruit extract, and histopathology of brain, liver, and kidney tissues also showed normal morphological structures indicating no signs of toxicity or abnormalities [90]. These studies indicated that noni might be potential for the treatment of psychiatric disorders. However, systematic studies on noni as an anti-psychiatric drug are still at preliminary stage and the specific active ingredients and its long-term effects on humans need to be further explored.

3.12. Neuroprotective Activity

In a bioactivity assessment of five selected botanical dietary supplements consumed in the United States, noni, demonstrated neuroprotective effects in animals [91]. Noni exhibited neuroprotective effects via its antioxidant and anti-apoptotic activity. Noni juice, at concentrations of 1%-5% (v/v), could protect PC12 cells from hydrogen peroxide-induced oxidative damage [92]. Further analysis identified that both chloroform fractions (CF) and aqueous fractions (AF) of noni juice protected SH-SY5Y cells from t-Butyl hydroperoxide-induced oxidative damage [93]. The ethyl acetate extract of noni fruit (MCE) also exhibited neuroprotective effects against rotenone-induced apoptosis in striatal neurons of PD rats and increased the number of tyrosine hydroxylase (TH) positive neurons and alleviating rotenone-induced apoptosis [94]. A recent study discovered that the methanol extract of noni fruit exhibited neuroprotective effects on pentylenetetrazol (PTZ)-induced seizures in Kindled mice. It significantly reduced the seizure score and also restored their motor and cognitive dysfunctions [95].

3.13. Other Effects

3.13.1. Anti-fatigue Activity

Noni is valued for its anti-fatigue effects, potentially beneficial as a dietary supplement or healthcare product. In a weight-loaded swimming test conducted on mice, the water extract of noni leaf significantly extended exercise duration [96]. A clinical study on middle-aged male athletes revealed that noni juice supplementation post-exercise increased superoxide dismutase (SOD) activity and improved quality of life scores related to physical function and energy [97]. Moreover, noni juice enhanced fatigue time and workload in diabetic rats in the incremental workload running test. This might be associated with the enhanced energy efficiency promoted by chronic noni ingestion [98]. Recent studies revealed that flavonoids extracted from noni pomace by ultrasonic-assisted deep eutectic solvents also exhibited anti-fatigue activity [99].

3.13.2. Anti-aging Activity

Noni is abundant in antioxidants, vitamins, and minerals, supporting cellular protection against free radicals and potentially delaying the aging process. Noni leaf extract was found to delay aging process via modulating the levels of MDA, GSH, and SOD. Additionally, the accumulation of advanced glycation end products (AGEs) could accelerate aging and contribute to various chronic degenerative diseases, the n-butanol extracts of noni fruit appeared to suppress AGE-induced inflammatory reactions in endothelial cells [100]. Another significant factor influencing aging is the decline of growth hormone (GH) [101]. It was discovered that noni juice and dietary supplements containing noni extract boosted GH production [102]. Furthermore, in old F344 rats model, noni fruit juice exhibited anti-aging effect reversing the age-related decline of neuroimmune decline in the spleen [81].

3.13.3. Anti-virus Activity

Studies have revealed that noni exhibited antiviral activity. Noni fruit extract was reported to inhibit HIV-1 integrase activity and disrupt HIV-1 viral replication by inhibiting both "3 processing" (3P) and "chain transfer" (ST) processes. Moreover, noni leaf extract demonstrated antiviral activity against HIV-1 (IIIB) and HIV-2(ROD) in MT-4 cells, and exhibited anti-HCV activity attributed to the presence of chlorophyll a catabolites pheophorbide a and pyropheophorbide a in noni leaf [103]. In recent years, the novel coronavirus (COVID-19) caused by the SARS-CoV-2 virus presented huge challenges for public health worldwide, and octanoic acid extracted from noni exhibited binding affinity to SARS-CoV-2 protein in preliminary computer simulation analysis [104]. These findings lay the foundation for further *in vitro* and *in vitro* studies, while also provided new phytochemical components for the treatment of Covid-19.

3.13.4. Anti-osteoporosis Activity

Noni shows therapeutic potential in osteoporosis treatment. Scopoletin extracted from noni exhibited potential as a treatment for diabetes-related bone diseases, where it elevated plasma levels of osteoprotegerin, RANKL, and osteocalcin, as well as trabecular bone formation and epiphyseal disc thickness in diabetic mice [105]. Additionally, noni leaf extract was found to promote bone regeneration, and served as an effective bone-regeneration material in treating the periodontal intraosseous bone defects [106]. Besides the above effects, noni also exhibited other bioactive effects such as anti-allergic, prevention of postoperative nausea and vomiting, improvement of overactive bladder symptoms, and laxative effect. The anti-allergic effects of noni have been documented, with studies showing that its inhibition of mast cell degranulation and histamine release ameliorated symptoms in allergic conditions [107]. A recent study found that the methanol extract of noni fruit significantly shortened the time of the first defecation, increased the total number and weight of stools, and had good laxative activity in constipated mice [108].

4. Safety of Noni

Evaluation of the safety and toxicity of noni is essential to ensure its safe application in food and pharmaceuticals. Currently, there is no standardized dosage for the safe use of noni extract. In one study, 2 mL/kg of fermented noni juice administration over 20 days decreased blood glucose in STZ-induced type 1 diabetic rats without toxic impact on the liver [109]. However, a 60-day study in STZ-induced type 1 diabetic rats treated with the same dose of noni juice (2 mL/kg) noted reduced blood glucose, but the observed renal toxicity, raising concerns for clinical safety. Considering its need for prolonged administration for diabetic patients, larger clinical studies were required to determine the efficacy and safety of noni products [98]. Furthermore, genotoxicity assessments of noni fruits and seeds revealed no genotoxic effects in the Ames test (up to

5000 µg/plate) or the micronucleus assay (up to 2000 µg/plate), indicating a favorable safety profile under these experimental conditions. Chromosomal aberration assays with the fruit puree and the aqueous extract also showed no structural or numerical abnormalities at concentrations of 5000 and 4650 µg/mL, respectively [110]. These findings suggested a low risk of noni fruits and seeds for genetic damage or carcinogenicity.

While numerous studies revealed the hepatoprotective property of noni extract and its efficacy in mitigating liver injury induced by certain pharmaceuticals, such as cyclophosphamide and methotrexate, in the treatment of related diseases [58,62], a few investigations reported cases of acute hepatotoxicity associated with noni. Since 2005, 10 cases of noni induced liver injury have been reported globally, including one severe hepatotoxicity incident in a 14-year-old boy. Among these reported cases, one patient with noni caused hepatotoxicity required a liver transplantation, while most patients recovered spontaneously with supportive care [111]. In a chronic toxicity test, high dose of noni fruit extracts (2 mg/mL) over 6 months intake produced chronic toxic effects, as evidenced by liver histological damage and increased AST level, whereas noni leaf extracts showed no observable toxicity [112].

Accumulating evidence has indicated that a small amount of anthraquinones in noni fruit may contribute to hepatotoxicity, however, the specific compounds and metabolic pathways involved have not been thoroughly studied. Previous studies found no detectable levels of anthraquinone in noni fruit puree, from which seeds and skin fragments, the parts richest in anthraquinones, were removed [113]. Although a potential relationship between liver dysfunction and anthraquinones consumption exists, the commercial production of noni juice typically excludes seeds and peels, thereby minimizing the associated risk. Given the increasing consumption of noni fruit, further investigation into the metabolic pathways of anthraquinones is required to elucidate causality and assess safety implications. Meanwhile, processing methods such as fermentation might reduce the risk of hepatotoxicity. Fermentation could alter the composition and biological activity of active compounds, such as flavones and polyphenols, in noni juice, thereby producing different metabolite profiles with potentially different biological effects [114].

In addition, noni has been identified as a potential inhibitor of CYP3A4 and CYP1A2 enzyme. Cytochrome (CYP) P450 enzymes is an important metabolic enzyme in the human body, as they are responsible for metabolizing approximately 60% of commonly used clinical drugs. Consequently, noni can affect the metabolic processes of drugs or foods metabolized by these enzymes, and its use should be avoided in combination with such substances. Overall, current findings indicate that noni may be generally safe when consumed in moderation and even offer some protective effects. However, toxicological evaluation is a complex process involving multiple tests and long-term monitoring, especially for high-dose or prolonged usage, to ensure a thorough understanding of any potential health risks of noni and related products.

5. Future Applications and Perspectives of Noni

With the growing consumer preference for natural, healthy and environmentally friendly products, the innovation and application of noni products have expanded, particularly in the fields of skincare, health supplements, and industrial applications. In recent decades, functional foods have attracted accumulating attention due to their bioactive potential and relatively low adverse effects. Given the health benefits of noni, including antioxidant, antidiabetic, anti-inflammatory, anti-cancer, antibacterial, anti-obesity, hepatoprotective, and antiparasitic properties, noni supplement in diets will provide a series of health benefits, like anti-aging, diabetes and obesity prevention, and liver protection, emphasizing the implication of noni as functional food.

Besides, noni supplements can be used as prebiotics. Recent research has focused on the prebiotic effects of noni extract and its role in regulating gut microbiota. Polysaccharides, polyphenols and dietary fiber in noni are the main prebiotic components. These components are not directly digestible by the human body but interact with the gut microbiota to produce short chain fatty acids (SCFAs), such as acetic acid, propionic acid, and butyric acid, thereby regulating the composition and function of the gut microbiota [115,116]. Studies have found that noni fruit consumption affects the gut microbiota by decreasing the *Firmicutes/Bacteroidetes* ratio and increasing bacteria with prebiotic properties, such as *Prevotella* and *Ruminococcus* [115]. Additionally, fermented noni juice was found to alleviate the adverse effects of a high-fat diet on gut microbiota composition in juvenile yellow catfish, which was reflected in a reduction of *Proteobacteria* and *Bacteroides*, and an increase of *Firmicutes* [117]. These evidences highlighted the potential of noni fruit as a natural source of prebiotics, capable of modulating gut microbiota and improving host health.

As prebiotics, noni extract has demonstrated potential in the prevention and treatment of various metabolic diseases and inflammation by regulating intestinal microbiota. In HFD-induced obese mice, supplementation with noni fruit phenolic extract (NFE) improved the intestinal microbiota balance by increasing SCFA-producing bacteria and reducing LPS-producing bacteria, thus playing an important role in inhibiting obesity [116]. Besides, noni fruit polysaccharide (NFP) could regulate gut microbiota, increasing the relative abundance of *Lactobacillus* in HFD mice, improving bile acid metabolism, and reducing fat accumulation and dyslipidemia [118]. In HFD-induced NAFLD, NFE restored the composition of gut microbiota by increasing the relative abundance of *Parabacteroides*, *Lactobacillus*, *Roseburia*, and *Akkermansia*, and also improving liver inflammation and metabolic comorbidities [63]. Moreover, fermented noni juice and noni fruit phenolic extract have been shown to improve insulin resistance in T2D mice, with these effects attributed to the regulation of gut microbiota composition and their anti-diabetic effects [70,74]. Collectively, these investigations indicated the potential of noni products as prebiotics in the prevention of obesity, dyslipidemia, diabetes, and metabolism

disorders, emphasizing the application prospects of Noni as functional foods.

Furthermore, the antibacterial properties of noni are being explored for applications in the development of novel antibacterial products, such as oral care products wound dressings, and antimicrobial agents for agricultural products [5,119,120]. For example, a natural mouthwash product containing fermented noni plant juice, inhibited the pathogens in the oral cavity such as *E. coli*, *S. aureus* and *P. aeruginosa*, demonstrating potential benefits in reducing gum inflammation. Moreover, the combination of noni fruit extract and pandan leaf extract (1:1 v/v) inhibited 92.9% of bacteria isolated from dandruff [5], suggesting the potential for its application as a dandruff shampoo. Also, noni fruit extract could be employed as a natural fungicide for fresh agricultural products to enhance the microbial safety of fresh-cut agricultural products, which effectively inhibited the growth of foodborne *Listeria monocytogenes* and induced cell death by disrupting their cell membranes. When romaine lettuce, spinach and cabbage were washed with 0.5% noni fruit extract (NFE), the *L. monocytogenes* (ATCC, 19111 and 191115) were decreased by 1.47, 2.28 and 3.38 log CFU/g, respectively, surpassing sodium hypochlorite (100 ppm) and suggesting the role of noni as a natural fungicide for fresh produce [119].

The bioactive constituents of noni are diverse and their mechanisms of action are complex and multifactorial, often involving the collaborative action of multiple bioactive activities. It remains imperative to further investigate the active constituents and underlying mechanisms of noni, thus expanding the use of noni in functional food and therapeutic application in diseases. The application of advanced technologies, such as nanotechnology and proteomics, offers novel perspectives and methodologies for investigating noni. By integrating these methodologies, the development of new functional food and pharmaceuticals based on the new bioactive compounds and their new mechanisms of noni, represents a promising research direction for future. Despite some existing toxicological studies, the interaction of noni extract with other drugs or foods, along with its overall safety profile, requires further evaluation to support its broader and safer application in the future.

6. Conclusions

In summary, noni is a potential plant constituent pool with a large of diverse bioactive constituents, including anthraquinones, flavonoids, saccharides, iridoids, and coumarins. Moreover, noni has demonstrated a broad range of bioactive effects, including antioxidant, antidiabetic, anti-inflammatory, anti-cancer, antibacterial, anti-obesity, hepatoprotective, and antiparasitic properties. These bioactive constituents of noni and their bioactive effects emphasize the application prospects of Noni as functional foods and health products.

Data Availability

Data will be made available on request.

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