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Antibacterial Activity of *Morinda citrifolia* (Noni) Fruits against Selective bacterial Pathogens

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ABSTRACT

Noni (*Morinda citrifolia* L.) is an edible and medicinal fruit distributed in Tirunelveli, India. The antibacterial activities of the extracts of water, petroleum ether, ethyl acetate, chloroform, and n-butanol were assayed by the disk diffusion method. The results showed that the extracts from Noni fruit possessed antibacterial effects against *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, and *Staphylococcus aureus*. Among 5 different extracts, the Butanol extract produced the best antibacterial activity. The samples were first extracted by ethanol, and the primary compounds in the fraction of ethanol extract Butanol extract was further isolated and identified. Six phenolic compounds, including 5, 15-dimethylmorindol, ferulic acid, p-hydroxycinamic acid, methyl 4-hydroxybenzoate, methyl ferulate, and methyl 4-hydroxycinnamate, were identified by NMR. The results indicated that the phenolic compounds might significantly contribute to antibacterial activities of Noni fruit.

Keywords: antibacterial activity, isolation and identification, *Morinda citrifolia* (Noni) fruit

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INTRODUCTION

Noni (*Morinda citrifolia L.*), belonging to the family Rubiaceae, is an ageless shrub distributed across the Pacific islands, Australia, Hawaii, Southeast Asia, and the islands of French Polynesia, as well as several other tropical and subtropical regions (Deng, and others 2007)[1]. It has large, dark, glossy, prominently veined, elliptical to oblong fruit (Motshakeri, and others 2015)[2]. Noni fruit have been spent as a vegetable by multiple cultural groups. The safe use of Noni fruit as a food was corroborated in 2007(West and others 2007)[3]. In 2008, the Panel on Dietetic Products, Nutrition, and Allergies of the European Food Safety Authority (EFSA) decided that the use of dried and roasted noni fruit for the preparation of infusions at the anticipated levels of consumption is also safe (Bresson, and others 2008)[4]

In Samoa, Noni fruit was common fruit, and in Burma, the fruit was cooked in seasonings or eaten raw with salt. In 1943, Merrill[32] described *Morinda citrifolia* L as an edible fruit in a technical manual of edible and poisonous plants of the Pacific Islands, and fruits could be used as emergency food. Abbott[31] also stated that Noni had been used as a food, drink, medicine, and colorful dye. The medicinal history and accrued scientific studies, to date, have revealed and confirmed the Polynesian's claim of the health benefits of Noni. The medical knowledge and pharmacopoeia of the Polynesians is now believed to have been fairly complex and modern scientific and medical communities are beginning to study the fruits compiled from this knowledge base. The Noni fruit is a small evergreen tree found growing in open coastal regions at sea level and in forest areas up to about 1300 feet above sea level. The fruit is often found growing along lava flows. It is identifiable by its straight trunk, large, bright green and elliptical fruit, white tubular flowers, and its distinctive, ovoid, "grenade-like" yellow fruit. The fruit can grow in size up to 12 cm or more and has a lumpy surface covered by polygonal-shaped sections. The seeds, which are triangular shaped and reddish brown, have an air sac attached at one end, which makes the seeds buoyant. This could explain, in part, the wide distribution of the fruit throughout the Polynesian islands.

The synthetic preservatives are harmful to humans to differing degrees, such as cause poisoning, allergic reactions, teratogenicity, and even cancer (Lowery, and others 2009)[5]. So, consumers have become concerned about the safety of synthetic preservatives used in food. As a result, there is an urgent need for the development of new preservatives and preservative systems with fewer side-effects to human health. Some herbs with antimicrobial natural products have the advantages of safety and nutrition, which can serve as alternative food preservatives to inhibit bacterial and fungal growth in order to improve food quality and prolong shelf-life. Lou and others, 2010[29]; (Tajkarimi and others 2010)[6]. Therefore, there is considerable potential for the utilization of natural antimicrobials from fruits in foods (Xiong and others 2013)[7].

Noni fruit are well-known for their strong antioxidant activity (Chan-Blanco and others 2006)[8], however the additional studies reveal that extracts of Noni fruit can antagonize pathogenic fungi and bacteria. For instance, the Australian Noni leaf possessed the antimicrobial activities against *Salmonella sp*., *Enterica serovartyphi* (S76), *Staphylococcus aureus* (B313), and *Myco.phlei* CSL, which was attributed to the presence of phenolic compounds, such as acubin, l-asperuloside, alizarin, and scopoletin(Assi and others 2015)[9]. Sunder and others (2011)[10] reported that the best antibacterial activity was found in extract from *M. citrifolia* seed followed by its leaf extract and fruit extract. Sharma and Sharma (2010)[11] found that ethyl acetate extract of Noni fruit showed pronounced antimicrobial activity and ethanol extract exhibited the weak activity, but petroleum ether extract failed to inhibit the test pathogens.

Noni is a small tree that grows at a normal height of around 10 feets. The fruit of this plant or thick Shiny dark green with 3 to 5 inches long over it and all is white become quick tender at maturity. This noni fruit have outstanding medicinal value and used as traditional medicine and play vital role in curing many diseases.

MATERIALS AND METHOD

Fruit material

Noni fruits were collected from Sadakathullah Appa college, Tirunelveli. The samples were dried in the shade 25 °C for 7 days and grinded into a powder. The powder was stored in a desiccator after passing through mesh sieve.

Test strains, chemicals and reagents

The Gram-positive bacteria *Staphylococcus* aureus, Bacillus subtilis, as well as the Gram-negative bacteria *Escherichia coli*, Proteus vulgaris were used as the test bacterial strains, which were obtained from the microbiology laboratory of Southwest University, China. High-Performance Liquid Chromatography (HPLC)-grade acetonitrile was purchased from HI media. Water for HPLC analysis was produced by a Double distilled Water Purification System. All the other chemicals and reagents were of analytical grade purchased from the Merk.

Preparation of Noni fruit extracts

The Noni fruit were extracted with 4 times the volume of 50% ethanol for 24 h at room temperature. The solution was centrifuged at 5000 rpm for 10 min. Then the residue was re-extracted twice using the same method. The combined supernatants were concentrated at 45°C in vacuum using a rotary evaporator and freeze-dried to afford the crude extract (CE). The CE was further fractionated through solvent partitioning extraction. Different fractions were got using 5 solvents with polarity from low to high, petroleum ether, chloroform, ethyl

acetate, n-butanol, and water. Their extracts were stored in dark bottles at 4 °C after evaporation and freeze-drying. considerable amount of petrochemical compounds extracted from the noni fruits , and the extraction ratio was expressed in percentage.

Assay of antibacterial activity

Sensitivity of different bacterial strains to the different concentration of the noni fruits extract was measured by to disk agar diffusion assay to get inhibition zones (Obad and others 2015)[12]. Briefly, the bacterial strains were incubated at 37 ± 1°C overnight. The bacterial suspensions were diluted to 1X 106 CFU/ml. Three millilitres of sterile liquid agar medium (0.2% agar) were added to petri dishes containing 15 ml of Mueller-Hinton agar medium 200 µl volume of the standard inoculum of the test bacterial strain (Patel and others 2009)[13]. The extract samples were dissolved in the same extract solvents and diluted to 2.0 and 0.5 mg/ml, respectively. Sterilized Whatman No.1 filter paper discs (6 mm diameter; Whatman Plc, Kent, UK) with 20 µl of each sample were placed on the surface of the agar and incubated at 37 ± 1 °C for 24 h. After incubation, the inhibition zones around the disks (diameters in mm) were measured. Inhibition zone above 6 mm were considered to be Sensitive. The same solvents without extraction were used as negative control and sterile 50% ethanol was used as blank control. Each test was conducted in triplicate.

Preliminary analysis of antibacterial compounds by LC/TOF-MS Major types of antibacterial compounds in the analyzed with LC/TOF-MS. The ethanol extract of Noni fruit was dissolved in methanol and diluted to 100 mg/mL. Mobile phase A was a mixture of 0.8% acetonitrile and 0.005% formic acid in ultrapure water, whereas mobile phase B was acetonitrile. A gradient elution used was 0 to 5 min, 5% B; 5 to 20 min, 35% B; 20 to 25min, 35 to 90% B. The running temperature was 30 °C and the injection volume was 10 µL. The detection was monitored with UV-Vis (200 to 600 nm) at a flow rate of 0.7 mL/min. MS analysis was carried out using a mass spectrometer fitted with an electrospray interface. A drying gas of 800 L/h was applied for ionization using nitrogen from generator. The scan range of ESI-MS was m/z 200 to 2000. Ion source temperature was 120 °C. The ESI voltage was 3.0 kV in negative ion mode, and the normalized collision energy was 35 to 40Ev. Isolation and identification of antibacterial compounds the method of extraction was similar to above mentioned. The Noni fruit (10 kg) were extracted with the same volume of ethanol three times. The extract was further extracted with petroleum ether, ethyl acetate, and n-butanol, respectively, and incubated at room temperature for 48 h. The solvent was removed under reduced pressure to yield petroleum ether extract (9.2 g), ethyl acetate extract (37.7 g), and n-butanol extract (39.6 g), respectively. The antibacterial fractions (n-butanol extract) were further purified on D101 microporous resin column using 20% methanol and 70% Methanol, respectively. The 20% methanol soluble phase was chromatographed on SiO_2

column chromatography (CC) using CHC_{l3}/ methanol gradient (100:0 to 0:100) to give 7 fractions (fraction A to G). The C fraction was subjected repeatedly to CC using a hexane/EtOAc gradient to yield compound 1 (20.0 mg). The E fraction yielded compound 2 (9.0 mg) and 3 (8.0 mg). Whereas the 70% methanol soluble phase was subjected to CC chromatographed to give 6 fractions (fraction H–M). The J fraction yielded compound 4 (14.0 mg), and the M fraction yielded compound 5 (11.0 mg) and 6 (6.0 mg).

RESULTS AND DISCUSSION

Extraction yield and antibacterial activity of different extracts

The extraction yield of the antibacterial compounds (amount of total extractable compounds) depends on the polarity of the compounds. The extraction yield of WE, BE, EAE, CE, and PEE was 0.54, 0.64, 0.60, 3.42, and 0.15 g, respectively. Their extraction ratios were 0.36%, 0.43%, 0.40%, 2.28%, and 0.10%, respectively.

Table 1 : Antibacterial activity of different extract from Noni Fruits.

Extract	Concentration (mg/ml)		Microorganisms			
			Bacillus subtilis	***Staphylococcus aureus***	***Escherichia coli***	***Proteus vulgaris***
Inhibition zone (mm)	PEE	0.5	-	-	-	-
		2.0				
	CE	0.5	-	-	-	-
		2.0				
	EAE	0.5	-			
		2.0	7.0± 0.1	7.5± 0.7	6.8±0.4	7.9±0.6
	BE	0.5	7.4±0.0	7.2±0.5	7.6±0.4	6.8±0.2
		2.0	14.5±2.4	12.5±2.2	15.4±2.1	12.0±1.2
	WE	0.5	7.6±0.5	7.7±0.5	8.5±0.5	8.0±0.5
		2.0				

PEE- Petroleum Ether Extract; CE, Chloroform Extract; EAE, Ethyl Acetate Extract; BE, n-butanol extract; WE, Water Extract.

Table 2: LC-MS data and maximum absorption wavelength of each peak in extract from Noni Fruits.

Peak	RT (min)	Wavelength(nm)	(M-H)- m/z	MS/MS (m/z)	Compound
1	2134	235	389	227209	Deacetylasperulosidic acid
2	3933	233	431	269251	Asperulosidic acid
3	6927	255352	741	609301	Quercetin derivative
4	7753	254352	609	301	Rutin
5	10850	265345	593	285	Kaempferol-3-O-rutinoside

The antibacterial activity of the various extracts diverse with the solvents used. The antibacterial activity of 5 different extracts was shown in Table 1. Three extracts displayed considerable antibacterial activity against the tested bacteria. Different extracts contained different constituents because of the solvent polarity, therefore their antibacterial activity

varied. The strongest inhibition was found in BE, followed by EAE and WE. However, PEE and CE had no antibacterial properties. The antibacterial activity of BE to 4 microorganisms was E. coli > B. subtili s> S. aureus > P. vulgaris. Inhibition zone was P. vulgaris > S. aureus > B. subtilis > E. coli for EAE, while E. coli > P. vulgaris > S. aureus > B. subtilis for BE. Reports presented that the antimicrobial activity of Tahitian M. citrifolia fruit in a methanol divided with n-butanol extract was assessed in an in vitro assay on E. coli, Candida albicans and S. aureus. Candida albican was the most sensitive to M. citrifolia antimicrobial activity, while S. aureus sensitivity was the lowest (West and others 2012)[14].

The present study, the best result was obtained with BE, followed by EAE and WE. The variation in the antibacterial activity of the various solvents is due to the nature of the polarity of the solvents (Sunder and others 2011)[10]. It showed that BE and EAE produced the best antibacterial activity. Since, n-butanol has high polarity it could dissolve both polar and nonpolar compounds and produced best activity. It could be speculated that the BE fraction exhibited the strongest antimicrobial activity, and the antibacterial substances of Noni fruit mainly existed in BE, EAE, and WE. Therefore, the BE fraction was further isolated and identified using HPLC and NMR spectroscopy.

Preliminary analysis of compounds of ethanol extract from Noni fruit

Ethanol is having higher polarity and thus they have a tendency to dissolve different compounds from the plant materials dipped in them. Reports revealed that ethanol and methanol are commonly used for extraction of antibacterial compounds (Karaman and others 2003; Wei and others 2008)[15,16]. The primary phenolic compounds were identified using HPLC-MS by comparison with phenolic standards and related literature data. LC-MS data showed that phenolic compounds in ethanol extract from Noni fruit were mainly phenolic acids and flavonoid glycosides with high polarity. Table 2 listed identified compounds, including deacetylasperulosidic acid, asperulosidic acid, quercetin derivative, rutin, and kaempferol-3- O-rutinoside. Previous studies have shown that the *Morinda citrifolia* plant has beneficial antimicrobial effects which are attributed to its phenolic compounds, including acubin, L-asperuloside, alizarin, scopoletin, and other anthraquinones (Chan-Blanco and others 2006)[8], however, these compounds were not detected in our LCMS data.

Isolation and identification of antibacterial compounds

Six pure compounds were isolated and identified from the ethanol extract, that is 5, 15-dimethylmorindol (1), ferulic acid (2), p-hydroxycinamic acid (3), methyl 4-hydroxybenzoate (4),methyl ferulate (5), and methyl 4-hydroxycinnamate (6) 5,15-Dimethylmorindol (1): Yellow amorphous powder (20 mg); ESI-MS: m/z[M]+ 314.08 (Calcd for C17H14O6: 314.0790). 1H-NMR (DMSO-d6, 400 MHz): δ7.79 (1H, d, J = 8.5Hz, H-3), 7.79 (1H, d, J = 8.5Hz, H4), 7.35 (1H, d, J = 8.5Hz, H-7), 7.35 (1H, d, J = 8.5Hz, H-8), 4.64 (2H, s,

CH2OCH3), 4.03 (3H, s, OCH3), 3.51 (3H, s, OCH3); 13C-NMR (DMSO-d6, 100 MHz): δ187.8(C-9), 181.9(C-10), 159.5(C-1), 156.1 (C-6), 146.9(C-5), 134.5(C-3), 134.0(C-2), 133.3(C-13), 127.0(C-12), 125.8(C-11), 125.6(C-8), 120.1(C-7), 119.0(C-4), 114.9(C-14), 68.6(C-15), 62.4(C-17), 58.9(C-16). The structure of compound 1 was established as 5, 15-Dimethylmorindol according to the literature (Kamiya and others 2005)[17]. Ferulic acid (2): White crystal (9 mg); ESI-MS: m/z [M] + 154.06 (Calcd for C10H10O4: 154.0597). 1H-NMR (DMSO-d6,400 MHz): 7.17 (1H, d, J = 8.5Hz, H-3), δ7.06 (1H, d, J = 8.5Hz, H-5), δ6.81 (1H, d, J = 8.4Hz, H-6), 6.31 (1H, d, J = 8.4Hz, H-8), 3.89 (3H, s, OCH3); 13C-NMR (DMSOd6, 100 MHz): δ171.3(C-9), 150.5(C-1), 149.5(C-2), 146.7(C7), 128.0(C-4), 124.0(C-5), 116.9(C-6), 116.6(C-8), 111.9(C-3), 56.6(C-10). The structure of compound 2 was established as ferulic acid according to the literature (Li and others 2008)[18]. P-hydroxycinamic acid (3): White crystal (8 mg); ESI-MS: m/z[M]+ 164.05 (Calcd for C9H8O3: 164.0473). 1H-NMR (DMSO-d6, 400 MHz): δ6.79(1H, d, J = 8.5Hz, H-2), δ7.44 (1H, d, J = 8.5Hz, H-3), δ7.44 (1H, d, J = 8.4Hz, H-5), 6.79 (1H, d, J = 8.4Hz, H-6), 7.58 (1H, d, J = 3.2Hz, H-7), 6.27 (1H, d, J = 3.2Hz, H-8); 13C-NMR (DMSO-d6, 100 MHz): 150.5(C1), 116.9(C-2), 131.1(C-3), 127.4(C-4), 131.7(C-5), 116.9(C-6), 146.6(C-7), 116.6(C-8), 171.3(C-9). The structure of compound 3 was established as p-Hydroxy-cinnamic acid according to the literature (Zhang and others 2006)[28]. Methyl 4-hydroxybenzoate (4): White dendritic crystal (14 mg); ESI-MS: m/z[M]+ 152.05 (Calcd for C8H8O3: 152.0473). 1HNMR (DMSO-d6, 400 MHz): δ7.86 (1H, d, J = 8.5Hz, H5), δ7.86 (1H, d, J = 8.5Hz, H-3), 6.81 (1H, d, J = 8.4Hz, H-6), 6.81 (1H, d, J = 8.4Hz, H-2), 3.76 (3H, s, OCH3); 13C-NMR (DMSO-d6, 100 MHz): δ168.8(C-7), 163.6(C-4), 132.8(C-2), 132.8(C-5), 122.3(C-1), 116.2(C-3), 116.2(C-6), 52.3(C-8). The structure of compound 4 was established as methyl 4-hydroxybenzoate according to the literature (Ren and Yang 2001)[19]. Methyl ferulate (5): Colourless oil (11 mg); ESI-MS: m/z[M]+ 208.07 (Calcd for C11H12O4: 208.0736). 1H-NMR (DMSO-d6, 400 MHz): 7.61 (1H, d, J = 8.5Hz, H-7), 7.18 (1H, d, J = 8.5Hz, H-3), δ7.06 (1H, d, J = 8.5Hz, H-5), δ6.81 (1H, d, J = 8.4Hz, H6), δ6.37 (1H, d, J = 8.4Hz, H-8), 3.89 (3H, s, COOCH3), 3.76 (3H, s, OCH3); 13C-NMR (DMSO-d6, 100 MHz): δ169.8(C9), 150.8(C-1), 149.3(C-2), 146.8(C-7), 127.8(C-4), 124.1(C5), 116.6(C-6), 115.3(C-8), 111.9(C-3), 56.6(C-11), 52.0(C-10). The structure of compound 5 was established as methyl ferulate according to the literature (Liu and Wang 2011)[30]. Methyl 4-hydroxycinnamate (6): Colourless oil (6 mg); ESI-MS: m/z[M]+ 178.06 (Calcd for C10H10O3: 178.0630).1HNMR (DMSO-d6,400 MHz): δ6.79 (1H, d, J = 8.5Hz, H-2), δ7.45 (1H, d, J = 8.5Hz, H-3), δ7.45 (1H, d, J = 8.5Hz, H-5), δ6.79 (1H, d, J = 8.4Hz, H-6), δ7.61 (1H, d, J = 3.2Hz, H-7), 6.32 (1H, d, J = 3.2Hz, H-8), 3.75 (3H, s, CH3); 13C-NMR (DMSO-d6, 100 MHz): δ169.8(C-9), 150.8(C-1), 116.9(C-2), 146.6(C-7), 127.2(C-4), 131.7(C-5),

116.9(C-6), 115.0(C-8), 131.7(C-3), 52(C-10). The structure of compound 6 was established as methyl 4-hydroxycinnamate according to the literature (Chang and Gong 2005)[20].

Noni fruit have been utilized in a variety of commercial products for their health benefits. It was previously reported that there are many useful phytochemicals associate with biological activities of Noni fruit. For example, flavonoids have potential to be used as a favorable antimicrobial (Chan-Blanco and others 2006)[8]. Lignan is larvicidal and antioxidant, while triterpenoids are anticancer (Kovendan and others 2012, 2014)[21,22]. Sterols can lower blood cholesterol and stimulate immune system, while chlorophyll derivatives can lower blood glucose levels (Shovic and Whistler 2001; Wang and others 2002)[23,24]. Iridois can suppress UVB-induced activator protein-1 (AP-1) activity, and scopoletin has anti-proliferative effects on cancer (Assi and others 2015)[9].

Noni fruit contain a large number of phenolic components, in particular coumarins and flavonoids (Mohd and others 2007)[25]. These phenolic compounds also attributed to the antimicrobial activities of the Noni fruit (Assi and others 2015)[9]. Phenolic compounds were antimicrobial because they possessed antioxidant effects, possibly involving proton exchange processes in the antimicrobial activity (Elo and others 2015)[26]. Previous studies reported flavonoids in Noni fruit, particularly quercetin and its derivatives had antimicrobial properties in vitro and in vivo, which maybe play an important role in its bacterial defense system (Chan-Blanco and others 2006)[8]. In the present study, 3 kinds of extracts from Noni fruit exhibited antibacterial activities against *B.subtilis, E.coli, S.aureus, and P.vulgaris*. In addition, 6 phenolic compounds were isolated from the extract, which might be the major antimicrobial component. Anthraquinones and saponins present in plant (for example, gherkin) are used for antibacterial and antifungal activities against clinical pathogens (Kumar and Kamaraj 2010)[27]. One anthraquinone, 5,15-Dimethylmorindol, was obtained from Noni fruit in this study, which was also isolated in previous study (West and others 2007)[14]. They found that the contents of 5,15- dimethylmorindol ranged from 11.3 to 42.6 mg/kg in dried and roasted Noni fruit, while 5.8 to 20.9 μg/L in infusions from dried and roasted Noni fruits. In addition, anthraquinones also possess antiviral, antioxidant and anticancer properties. Another group of polyphenols, phenolic acids have also been realized for their free radicals-scavenging activities and antibacterial against pathogens (Lin and others 2008)[18].

CONCLUSION

The extracts from Noni fruit possessed antibacterial effects against B. *subtilis, E. coli, S. aureus, and P. vulgaris*. In addition, 6 phenolic compounds, including 5, 15-dimethylmorindol, ferulic acid, p-hydroxycinamic acid, methyl 4-hydroxybenzoate, methyl ferulate, and methyl 4-hydroxycinnamate, were isolated from bioactive ethanol extract, which

might be the major antimicrobial compounds in Noni fruit. Further studies invivo and clinical research are needed to explore the antibacterial and antifungal mechanism in the future.

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