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Review

Morinda citrifolia L. (Noni): A review of the scientific validation for its nutritional and therapeutic properties

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***Morinda citrifolia*, commonly called noni, has a long history as a medicinal plant and its use as a botanical dietary supplement has grown tremendously in recent years. This has prompted a concomitant increase in research on the phytochemical constituents and biological activity of noni. It has been reported for its antibacterial, antiviral, antifungal, antitumor, antihelminthic, analgesic, hypotensive, anti-inflammatory and immune enhancing effects. This plant has also been popular as a source of red, yellow and purple dyes. In order to encapsulate the medicinal value and therapeutic effects of the noni fruit and to summarize scientific evidence that supports the traditional claims, a literature review and recent advances in noni research has been detailed.**

Key words: *Morinda citrifolia.*

INTRODUCTION

During the last couple of decades the concepts of food in the developed world have been changing from past emphasis on survival, hunger satisfaction, and malnutrition to promising use of foods to promote better health and well-being to emasculate the risk of chronic illness and several kind of diseases such as cardiovascular diseases, certain types of cancers and obesity. An important part of this new “Healthy Eating Concept” is functional foods. Functional foods can be defined as a food which beneficially affects one or more target functions in the body, besides adequate nutritional effects, in a way that is relevant to either improved stage of health and well-being or reduction of diseases. The first wave of these "functional food" products, which involved noni juice had been commercialized in the USA in 1990s and are increasingly distributed all over the world (Dixon et al., 1999). The products derived from *Morinda citrifolia* fruits and leaves are being sold as capsules, teas, and juice, although the fruit juice being the predominant form. The various products, especially noni juice is being promoted for its nutraceutical and therapeutical properties, thereby emerging as major product of health and wellness industry. It has recently been the object of many claims concerning its therapeutical properties. One of the popular claims is by Heinicke (2005), who has claimed that noni fruit has the presence of an active “alkaloid” named xeronine, and is said to be derived from a precursor perxeronine for which no structure was given. The author described a wide range of potential indications for noni juice, including high blood pressure, menstrual cramps, hypertension, gastric ulcers, sprains, injuries, mental depression, atherosclerosis, blood vessel problems, drug addiction, relief of pain and many others. Various publications have shown that it can be used to relieve different diseases. The observed beneficial effects may result from certain compounds such as alkaloids, scopoletin, damnacanthal and lots of other reported molecules. As a result of this, the consumption of this fruit is currently high, not only in US but also in Japan, Europe and India. Although, reliable sales figures are not available, but it is claimed that the market has reached US $ 1.3 billion in annual sales (Potterat and Hamburger, 2007). Some companies producing flavored noni juices by addition of other fruit juices to render the product more embellish and yummy for making it more acceptable in market. Flavor compounds were also extracted from noni fruit juice (Wei et al., 2006).

In response to this demand, some countries including India have increased the commercial cultivation of noni. Recently, this plant has come up as a source of livelihood for farmers of Andaman and Nicobar Islands after Health

India Laboratories (HIL) entered into an agreement of contract farming with them (Singh et al., 2007). Noni juice has been recently accepted in European Union as a novel food (European Commission, Scientific Committee for Food, 2002). Despite the real market opportunities, there has been little scientific research to review the actual nutritional and functional properties of noni products. This has prompted a concomitant increase in research on the phytochemical constituents and biological activity. The goal of this review is to provide an updated categorization of the nutritional and phytochemical constituents and their biological activity for its extensive utilization in health and wellness industry.

NUTRITIONAL VALUE OF NONI

The complete physio-chemical composition of the fruit has not yet been reported and only partial information is available of noni juice (Table 1). The fruit contains 90% of water and the main components of the dry matter appear to be soluble solids, dietary fibres and proteins. The fruit protein content is surprisingly high, representing 11.3% of the juice dry matter, and the main amino acids are aspartic acid, glutamic acid and isoleucine (Chunhieng, 2003).

Minerals account for 8.4% of the dry matter, and are mainly potassium, sulfur, calcium, phosphorus and traces of selenium have been reported in the juice (Chunhieng, 2003). Recently, the polysaccharide content of the fruit has been investigated using monosaccharide and glycosyl linkage analysis. The most abundant monosaccharides found were arabinose (Ara*f*), galactose (Gal*p*), galacturonic acid (GalA*p*) and rhamnose (Rha*p*) (Bui et al., 2006). The vitamins reported in the fruit are mainly ascorbic acid (24 to 158 mg/100 g dry matter) (Morton, 1992; Shovic and Whistler, 2001) and provitamin A (Dixon et al., 1999).

CHEMICAL COMPOSITION OF NONI

Approximately 200 phytochemicals have been identified and isolated from different parts as summarized in Table 2. However, chemical composition differs largely according to the part of the plant. To date, several classes of metabolites have been described in different parts, including acids, alcohols and phenols, anthraquinone, anthraquinone glycosides, carotenoids, esters, flavonoids, iridoids, ketones, lactones, lignans, nucleosides, triterpenoids, sterols and several minor compounds. Anthraquinones are the major phenolic compounds that have been identified and isolated from different parts of *M. citrifolia* (Bowie and Cooke, 1962). Among the reported anthraquinones, damnacanthal appear quite unique with respect to their function for its anti-cancer and anti-HIV activity (Kamata et al., 2006; Hiramatsu et al., 1993), while similar anthraquinone damnacanthal is a potent tyrosine kinase and topoisomerase II inhibitor (Faltynek et al., 1995; Tosa et al., 1998).

Pawlus et al. (2005) identified and isolated an extremely potent quinone reductase inducer, 2-methoxy-1, 3, 6-trihydroxyanthraquinone, with a 40 fold higher potency than the well known inducer, sulforaphane. The reported molecule provides quinone reductase induction-mediated protective activity against chemical carcinogenesis. Although, the concentration is very low in the fruit, but its biological properties make it a promising biomolecule to prevent initiation phase of cancer (Pawlus et al., 2005). Sung-Woo et al. (2005) isolated an anthraquinone, 4-dihydroxy-2-methoxy-7-methylanthraquinone in fruits and established that this compound was a good candidate as an anti-wrinkle agent due to its strong induction of biosynthetic activity of extracellular matrix components.

Several studies have showed that cell culture are capable of accumulating substantial amounts of anthraquinones at a higher level than those in native plants through optimization of cultural conditions. This technique has immense potential for commercial exploitation of these valuable anthraquinones (Lucilla and Johannes, 1995; Marc et al.,, 2003; Lucilla et al., 1995).

Fatty acid glycosides and alcohols are one of the classes of phytochemicals that have been reported in the fruits (Wang et al., 1999, 2000; Samoylenko et al., 2006; Dalsgarrd et al., 2006). Due to their structure, they posses more or less pronounced amphiphilic properties and may be the region responsible for the soapy taste of ripe fruits.

Another study examined the carotenoid content in the leaves, bark and fruits and found that the leaves were a substantial source of carotenoids and had the potential to treat vitamin A deficiency (Aalbersberg et al., 1993). However, 51 volatile compounds have been identified in the ripe fruit by gas chromatography-mass spectrometry (GC-MS), which is very toxic to most *Drosophila* species (except *Drosophila sechellia*). The major compounds are carboxylic acids, especially octanoic and hexanoic acids, alcohols (3-methyl-3-buten-1-ol), esters (Methyl octanoate, methyl decanoate), ketones (2-heptanone), and lactones [(E)-6-dodeceno-glactone] (Farine et al., 1996; Sang et al., 2001). A new iridoid, named citrifolinin A-1 showing significant inhibition of activator protein-1 (AP-1) activity, has been isolated from the leaves (Guangming et al., 2001).

BIOLOGICAL ACTIVITY OF *M. CITRIFOLIA*

Widespread claims of the therapeutical effectiveness have have encouraged the researchers worldwide to further investigate some of these possibilities. By virtue of this, one can easily find out several research articles on the

Table 1. Physio-chemical composition of noni juice (Yanine et al., 2006).

Characteristic	Chunhieng (2003)[a]	Shovic and Whistler (2001)[a]	European Commission (2002)[b]	Indian Noni juice
pH-value	3.72	-	3.4-3.6	3.4-3.6
Dry matter	9.870.4%	-	10-11%	10-11%
Total soluble solids (Brix)	8	-	-	-
Protein content	2.5%	0.4 g/100 g	0.2-0.5%	0.2-0.5%
Lipid	0.15%	0.30 g/100 g	0.1-0.2%	0.1-0.2%
Glucose	11.970.2 g/L	-	3.0-4.0 g/100 g	3.0-4.0 g/100 g
Fructose	8.270.2 g/L	-	3.0-4.0 g/100 g	3.0-4.0 g/100 g
Potassium	3900 mg/100 g	188 mg/100 g	30-150 mg/100 g	30-150 mg/100 g
Sodium	214 mg/L	21 mg/100 g	15-40 mg/100 g	15-40 mg/100 g
Magnesium	14 mg/L	14.5 mg/100 g	3-12 mg/100 g	3-12 mg/100 g
Calcium	28 mg/L	41.7 mg/100 g	20-25 mg/100 g	20-25 mg/100 g
Vitamin C	-	155 mg/100 g	3-25 mg/100 g	3-25 mg/100 g

Chunhieng (2003)[a] Noni fruit; Shovic and Whistler (2001)[a] Noni fruit; Satapathy (2007) Indian Noni juice.

biological activities and pharmacological actions of *M. citrifolia* based on modern scientific investigation.

Antibacterial activity

Atkinson (1956) reported *M. citrifolia* antibacterial activity against certain infectious bacterial strains such as *Pseudomonas aeruginosa, Proteus morgaii, Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella* and *Shigella*. He accentuated that the anti-microbial effect observed may be due to the presence of phenolic compounds, such as acubin, *L*-asperuloside, and alizarin in the fruit, as well as some other anthraquinone compounds in roots. Bushnell et al. (1950) and Dittmar (1993) reported antimicrobial effect on different strains of *Salmonella, Shigella, and E. coli* which is in accordance with Atkinson (1956). Another study by Locher et al. (1995) showed that an acetonitrile extract of the dried fruit inhibited the growth of *P. aeruginosa, B. subtilis, E. coli*, and *Streptococcus pyrogene*. Furthermore, it also helps in stomach ulcer through inhibition of the bacteria, *H. pylori* (Duncan et al., 1998). Similar findings were also reported by Lee et al. (2008) in the methanol and aqueous crude extracts of the fruit against *E. coli*, *Streptococcus* species, *Vibrio alginolyticus,* and *Vibrio harveyi*. It has also been found that ethanol and hexane extract of this fruit provide protection against *Mycobacterium tuberculosis*. The major components identified in the hexane extract were E-phytol, cycloartenol and stigmasterol (Saludes et al., 2002).

Lee et al. (2008) showed that methanol extract of this fruit demonstrated zones of inhibition in a range of 7.7 to 26 mm against *Vibrio cholerae, Klebsiella, B. subtilis, Lactobacillus lactis, P. aeruginosa, Salmonella typhi, E. coli, S. aureus, Streptococcus thermophilus, Shigella flexneri, V. harveyi, Chromobacterium violaceum, Aeromonas hydrophila, Salmonella paratyphi A,* while ethyl acetate extract demonstrated zones of inhibition in range of 5.7 to 15.7 mm against *L. lactis, S. typhi, B. subtilis, E. coli, V. harveyi, S. aureus, S. flexneri, V. cholerae, A. hydrophila, C. violaceum, S. paratyphi A* (Jayaraman et al., 2008; Selvam et al., 2009; Natheer et al., 2012; Usha et al., 2010). In a related report, it has been found that methanol extract of fruit demonstrated zones of inhibition in the range of 7 to 15 mm against *E. coli*, *Streptococcus* spp., *V. alginolyticus* and *V. harveyi* (Lee et al., 2008).

In a study by Sundarrao et al. (1993), antimicrobial activity was tested against Gram positive (*Staphylococcus albus* and *B. subtilis*) and Gram negative (*P. aeruginosa* and *Klebsiella pneumonia*) bacteria using 37 crude drug samples from different parts of 24 plants. Most of them exhibited antibacterial activity only against Gram positive bacteria. Antitumor activities were screened in mice bearing sarcoma 180 cells. Five samples were found to mediate a significant increased in lifespan, indicating potential antitumor activity.

Other studies have reported a significant activity against *Salmonella typhosa, Salmonella montevideo, Salmonella Schottmuelleri* and *Shigella paradys* strains (Bushnell et al., 1950; Dittmar, 1993). Furthermore, they showed that the antibacterial effect is greater when the fruit is ripe. Lately, antibacterial activities of the fruit juice was compared with that of sodium hypochlorite (NaOCl) and chlorhexidine gluconate (CHX) to remove the smear layer of *Enterococcus faecalis* from the canal walls of endodontically instrumented teeth. The data from this experiment indicated that fruit juice and NaOCl treatment have similar effects (Murray et al., 2008). Similar findings were also reported by Bhardwaj et al. (2012) where they

Table 2. Compounds isolated from *M. citrifolia*.

Structural class	Name of the compound	Reference (s)
Acids	Acetic acid	Farine et al. (1996)
	Ascorbic acid	Peerzada et al. (1990)
	Benzoic acid	Farine et al. (1996)
	Butanoic acid	Farine et al. (1996)
	Decanoic acid	Farine et al. (1996)
	(*Z,Z,Z*)-8,11,14-Eicosatrienoic acid	Farine et al. (1996)
	Elaidic acid	Farine et al. (1996)
	Heptanoic acid	Farine et al. (1996)
	Hexanedioic acid	Farine et al. (1996)
	Hexanoic acid	Legal et al. (1999)
	Lauric acid	Farine et al. (1996)
	Linoleic acid	Farine et al. (1996)
	2-Methylbutanoic acid	Farine et al. (1996)
	2-Methylpropanoic acid	Farine et al. (1996)
	3-Methylthiopropanoic acid	Farine et al. (1996)
	Myristic acid	Farine et al. (1996)
	Nonanoic acid	Farine et al. (1996)
	Oleic acid	Farine et al. (1996)
	Octanoic acid	Legal et al. (1999)
	Palmitic acid	Farine et al. (1996)
	Undecanoic acid	Farine et al. (1996)
Alcohols and phenols	Benzyl alcohol	Farine et al. (1996)
	1-Butanol	Farine et al. (1996)
	Eugenol	Farine et al. (1996)
	1-Hexanol	Farine et al. (1996)
	3-Methyl-2-buten-1-ol	Farine et al. (1996)
	3-Methyl-3-buten-1-ol	Farine et al. (1996)
	(*Z,Z*)-2,5-Undecadien-1-ol	Farine et al. (1996)
Anthraquinones	Anthragallol 1,3-di-*O*-methyl ether	Kamiya et al. (2005)
	Anthragallol 2-*O*-methyl ether	Kamiya et al. (2005); Pawlus et al. (2005)
	Austrocortinin	Kim et al. (2005)
	5,15-Dimethylmorindol	Kamiya et al. (2005); Takashima et al. (2007)
	6-Hydroxyanthragallol-1,3-di-*O*-methyl ether	Kamiya et al. (2005)
	2-Methoxy-1,3,6-trihydroxyanthraquinone	Pawlus et al. (2005)
	Morindone-5-*O*-methyl ether	Kamiya et al. (2005);
Esters	1-*n*-Butyl-4-(5′-formyl-2′-furanyl) methyl succinate	Samoylenko et al. (2006)
	1-*n*-Butyl-4-methyl-2-hydroxysuccinate	Samoylenko et al. (2006)
	1-*n*-Butyl-4-methyl-3-hydroxysuccinate	Samoylenko et al. (2006)
	Ethyl decanoate	Farine et al. (1996)
	Ethyl hexanoate	Farine et al. (1996)
	Ethyl octanoate	Farine et al. (1996)
	Ethyl palmitate	Farine et al. (1996)
	Methyl decanoate	Farine et al. (1996)
	Methyl elaidate	Farine et al. (1996)
	Methyl hexanoate	Farine et al. (1996)
	Methyl 3-methylthio-propanoate	Farine et al. (1996)

Table 2. Contd.

	Methyl octanoate	Farine et al. (1996)
	Methyl oleate	Farine et al. (1996)
	Methyl palmitate	Farine et al. (1996)
Flavonoid	Kaempferol	Deng et al. (2007b)
	Narcissoside	Su et al. (2005)
	Nicotifloroside	Sang et al. (2001a); Su et al. (2005)
	Quercetin	Deng et al. (2007b)
	Rutin	Wang et al. (1999); Sang et al. (2001a)
Iridoids	Asperuloside	Sang et al. (2001b); Su et al. (2005)
	Asperulosidic acid	Wang et al. (1999); Sang et al. (2001b); Kamiya et al. (2005); Su et al. (2005); Samoylenko et al. (2006)
	Asperulosidic acid methyl ester	Sang et al. (2002)
	Borreriagenin (previously morindacin)	Kamiya et al. (2005); Su et al. (2005); Schripsema et al. (2006)
	4-*epi*-Borreriagenin	Samoylenko et al. (2006)
	Deacetylasperuloside	Su et al. (2005); Takashima et al. (2007)
	Deacetylasperulosidic acid	Kamiya et al. (2005); Samoylenko et al. (2006)
	Deacetylasperulosidic acid methyl ester	Sang et al. (2002)
	Dehydromethoxygaertneroside	Su et al. (2005)
	6β,7 β -Epoxy-8-*epi*-splendoside	Su et al. (2005)
	6α-Hydroxyadoxoside	Su et al. (2005)
	1,3a,4,7a-Tetrahydro-6-(hydroxymethyl)-3*H*-furo[3,4-clpyran-4-carboxylic acid	Sang et al. (2002)
Ketone	2-Heptanone	Farine et al. (1996)
	3-Hydroxy-2-butanone	Farine et al. (1996)
Lactone	(E)-6-Dodeceno—γ- lactone	Farine et al. (1996)
	(*Z*)-6-Dodeceno- γ -lactone	Farine et al. (1996)
Lignans	Americanin A	Kamiya et al. (2004)
	Americanoic acid	Kamiya et al. (2004)
	Americanol A	Kamiya et al. (2004)
	Balanophonin	Pawlus et al. (2005)
	3,3'-Bisdemethylpinoresinol	Kamiya et al. (2004); Deng et al. (2007b)
	3,3'-Bisdemethyltanegool	Deng et al. (2007b)
	Isoprincepin	Kamiya et al. (2004)
	Morindolin	Kamiya et al. (2004)
	(-)-Pinoresinol	Deng et al. (2007b)
	(+)-3,4,3′,4′-Tetrahydroxy-9,7′*a*-epoxylignano-7 *a*,9′-lactone	Deng et al. (2007b)
Nucleosides	Cytidine	Sang et al. (2002); Su et al. (2005)

Table 2. Contd.

Saccharides	Nonioside A	Wang et al. (2000); Dalsgaard et al. (2006)
	Nonioside B	Wang et al. (1999); Dalsgaard et al. (2006)
	Nonioside C	Wang et al. (2000); Dalsgaard et al. (2006)
	Nonioside D	Wang et al. (2000)
	Nonioside E	Dalsgaard et al. (2006)
	Nonioside F	Dalsgaard et al. (2006)
	Nonioside G	Dalsgaard et al. (2006)
	Nonioside H	Dalsgaard et al. (2006)
	α- and β-Glucose	Levand and Larson (1979); Samoylenko et al. (2006)
	Methyl α -D-fructofuranoside	Su et al. (2005)
	Methyl β-D-fructofuranoside	Su et al. (2005)
	1-*O*-(3′-Methylbut-3′-enyl)- β -D-glucopyranose	Samoylenko et al.
Triterpenoids and sterols	3,19-Dihydroxyursolic acid	Sang et al. (2002)
	19 α -Methylursolic acid	Sang et al. (2002)
Miscellaneous compounds	(Ethylthiomethyl) benzene	Farine et al. (1996)
	Hexanamide	Farine et al. (1996)
	β -Hydroxypropiovanillone	Pawlus et al. (2005)
	4-Hydroxy-3-methoxycinnamaldehyde	Pawlus et al. (2005)
	Isoscopoletin	Deng et al. (2007b)
	Limonene	Farine et al. (1996)
	1-Palmitin	Pawlus et al. (2005)
	Scopoletin	Sal.udes et al. (2002a); Pawlus et al. (2005); Samoylenko et al. (2006);
	Vanillin	Pawlus et al. (2005); Deng et al. (2007b)
	Vomifoliol	Farine et al. (1996)
Leaves		
Acids	13-Hydroxy-9,11,15-octadecatrienoic acid	Takashima et al. (2007)
Anthraquinones	5,15-Dimethylmorindol	Kamiya et al. (2005); Takashima et al. (2007)
	1,5,15-Trimethylmorindol	Takashima et al. (2007)
Carotenoids	β-Carotene	Aal.bersberg et al. 1993)
Chlorophyll derivatives	13^2(*R*)-Hydroxypheophorbide a methyl ester	Takashima et al. (2007)
	13^2(*S*)-Hydroxypheophorbide a methyl ester	Takashima et al. (2007)
	15^1(*R*)-Hydropurpurin-7 lactone dimethyl ester	Takashima et al. (2007)
	15^1(*S*)-Hydropurpurin-7 lactone dimethyl ester	Takashima et al. (2007)
	Methyl pheophorbide a	Takashima et al. (2007)
	Methyl pheophorbide b	Takashima et al. (2007)
	Pheophorbide a	Takashima et al. (2007)
	13-*epi*-Phaeophorbide a methyl ester	Takashima et al. (2007)
Flavonoids	Kaempferol 3-*O*—β- D-glucopyranosyl-(1→2)-[*a*-L-rhamnopyranosyl-(1→6)]-- β D- galactopyranoside	Sang et al. (2001a)
	Nicotifloroside	Sang et al. (2001a); Su et al. (2005)

Table 2. Contd.

	Quercetin 3-*O*- β -D-glucopyranoside	Sang et al. (2001a)
	Quercetin 3-*O*- β -D-glucopyranosyl-(1→2)-[*a*-Lrhamnopyranosyl-(1→6)]- β -D-galactopyranoside	Sang et al. (2001a)
	Rutin	Wang et al. (1999); Sang et al. (2001a)
Iridoids	Asperuloside	Sang et al. (2001b); Su et al. (2005)
	Asperulosidic acid	Wang et al. (1999); Sang et al. (2001b); Kamiya et al. (2005); Su et al. (2005); Samoylenko et al. (2006)
	Citrifolinin A-1	Sang et al. (2003)
	Citrifolinin Ba	Sang et al. (2003)
	Citrifolinin Bb	Sang et al. (2003)
	Citrifolinoside A	Sang et al. (2003)
	Citrifoside	Takashima et al. (2007)
	Deacetylasperuloside	Su et al. (2005); Takashima et al. (2007)
	Dehydroepoxymethoxygaertneroside	Sang et al. (2001c); Schripsema et al. (2006)
Triterpenoids and sterols	3-*O*-Acetylpomolic acid	Takashima et al. (2007)
	Barbinervic acid	Takashima et al. (2007)
	Campesta-5,7,22-trien-3 β -ol	Sal.udes et al. (2002b)
	Clethric acid	Takashima et al. (2007)
	Cycloartenol	Dyas et al. (1994);
	Hederagenin	Takashima et al. (2007)
	Oleanolic acid	Takashima et al. (2007)
	Rotungenic acid	Takashima et al. (2007)
	β-Sitosterol	Ahmad and Bano (1980); Dyas et al. (1994); Sal.udes et al. (2002b); Pawlus et al. (2005)
	Stigmasta-4-en-3-one	Sal.udes et al. (2002b)
	Stigmasta-4-22-dien-3-one	Sal.udes et al. (2002b)
	Stigmasterol	Dyas et al. (1994); Sal.udes et al. (2002b)
	Ursolic acid	Ahmad and Bano (1980); Takashima et al. (2007)
Miscellaneous compounds	Peucedanocoumarin III	Takashima et al. (2007)
	Phytol	Takashima et al. (2007)
	Pteryxin	Takashima et al. (2007)
	Roseoside II	Takashima et al. (2007)
Seed		
Acids	Ricinoleic acid	Daulatabad et al. (1989)
Roots		
Anthraquinones	Alizarin 1-*O*-methyl ether	Simonsen (1920); Pawlus et al. (2005)

Table 2. Contd.

	Anthragallol 1,2-di-*O*-methyl ether	Thomson (1971)
	Damnacanthal	Thomson (1971); Hiramatsu et al. (1993)
	Damnacanthol	Thomson (1971); Sang and Ho (2006)
	2-Formylanthraquinone	Sang and Ho (2006)
	1-Hydroxy-2-methylanthraquinone	Sang and Ho (2006)
	2-Hydroxy-1-methoxy-7-methylanthraquinone	Rusia and Srivastava (1989)
	Ibericin	Sang and Ho (2006)
	1-Methoxy-3-hydroxyanthraquinone	Sang and Ho (2006)
	Morenone-1	Jain and Srivastava (1992)
	Morenone-2	Jain and Srivastava (1992)
	Morindone	Simonsen (1920); Thomson (1971); Leistner (1975)
	Nordamnacanthal	Thomson (1971); Leistner (1975)
	Rubiadin	Thomson (1971); Leistner (1975); Inoue et al. (1981)
	Rubiadin-1-*O*-methyl ether	Simonsen (1920); Thomson (1971)
	Soranjidiol	Thomson (1971)
	Tectoquinone	Sang and Ho (2006)
Stems		
Anthraquinones	2-Hydroxyanthraquinone	Siddiqui et al. (2006)
	2-Methoxyanthraquinone	Siddiqui et al. (2006)
	Morindicininone	Siddiqui et al. (2006)
Flowers		
Anthraquinone glycosides	6,8-Dimethoxy-3-methylanthraquinone-*a*-L-*O*- β -rhamnosyl glucopyranoside	Tiwari and Singh (1977)
Flavonoids	Acacetin 7-*O*- β -D-glucopyranoside	Tiwari and Singh (1977)
	5,7-Dimethyl apigenin 4′-*O*- β -D-galactopyranoside	Tiwari and Singh (1977)
Heartwood		
Anthraquinone	Alizarin	Thomson (1971)
	Anthragallol 2,3-di-*O*-methyl ether	Thomson (1971)
	Damnacanthal	Thomson (1971)
	Morindone	Thomson (1971)
	Physcion	Srivastava and Singh (1993)
	Rubiadin-1-*O*-methyl ether	Thomson (1971)
Anthraquinone glycosides	Physcion-8-*O*-[{*a*-L-arabinopyranosyl (1→3)}- β -Dgalactopyranoside	Srivastava and Singh (1993)
Cell culture		
Anthraquinone	Alizarin	Leistner (1975)
	5,6-Dihydroxylucidin	Inoue et al. (1981)
	2-Ethoxymethyl-3-methoxy-1,5,6-trihydroxyanthraquinone	Leistner (1975)

Table 2. Contd.

	3-Hydroxymorindone	Inoue et al. (1981)
	Ibericin	Sang and Ho (2006)
	Lucidin	Leistner (1975)
	Lucidin ώ-methyl ether	Inoue et al. (1981)
	6-Methyl-anthrapurpurin	Inoue et al. (1981)
	Morindone	Inoue et al. (1981)
	Nordamnacanthal	Leistner (1975);
	Rubiadin	Leistner (1975);
Anthraquinone glycosides	5,6-Dihydroxylucidin-3-β-primeveroside	Inoue et al. (1981)
	3-Hydroxymorindone-6- β -primeveroside	Inoue et al. (1981)
	Lucidin-3- β- primeveroside	Inoue et al. (1981)
	2-Methyl-3,5,6-trihydroxyanthraquinone-6- β -primeveroside	Inoue et al. (1981)
	Morindin	Inoue et al. (1981)
Triterpenoids and sterols	Campesterol	Dyas et al. (1994)
	Campesteryl linoleate	Dyas et al. (1994)
	Campesteryl palmitate	Dyas et al. (1994)
	Cycloartenol	Dyas et al. (1994)
	Cycloartenyl linoleate	Dyas et al. (1994)
	Cycloartenyl palmitate	Dyas et al. (1994)
	Isofucosterol	Dyas et al. (1994)
	Isofucosteryl linoleate	Dyas et al. (1994)
	24-Methylenecholesterol	Dyas et al. (1994)
	24-Methylenecycloartanol	Dyas et al. (1994)
	24-Methylenecycloartanyl linoleate	Dyas et al. (1994)
	β -Sitosterol	Dyas et al. (1994)
	Sitosteryl linoleate	Dyas et al. (1994)
	Sitosteryl palmitate	Dyas et al. (1994)
	Stigmasterol	Dyas et al. (1994)
	Stigmasteryl linoleate	Dyas et al. (1994)

found that chlorhexidine gel showed the maximum antibacterial activity against *E. faecalis*, whereas calcium hydroxide showed the least. Among the natural intercanal medicaments, *M. citrifolia* gel consistently exhibited good inhibition followed by aloe vera gel and papain gel. Another study showed that iridoids from noni fruit appear to be active against yeasts, Gram negative, and Gram positive bacteria (Brett et al., 2012).

Antifungal activity

Candida albicans live in 80% of the human population with no harmful effects, although overgrowth from cellular yeast to a filamentous form results in candidiasis, which was often observed in immunocompromised individuals such as AIDS, cancer chemotherapy and organ or bone marrow transplantation.

Recent research has demonstrated that it contains a water-soluble component or components that interfere with the morphological conversion of C*andida* albicans and may have potential therapeutic value with regard to candidiasis (Banerjee et al., 2006; Usha et al., 2010). Other studies showed that methanol extract of the dried fruit exhibited maximum percentage of inhibition against *Trichophyton mentagrophytes* (79.3%), while approximately 50% activity was recorded against *Penicillium*, *Fusarium* and *Rhizopus* species (Jayaraman et al., 2008; Jainkittivong et al., 2009).

Antiviral activity

Viral protein R (Vpr) is one of the human immunodeficiency virus type 1 (HIV-1) accessory protein, that contributes to multiple cytopathic effects, G2 cell cycle arrest and apoptosis. The mechanisms of Vpr have been intensely studied because they trigger HIV-1 pathogenesis. A team from National Institute of Health (USA), identified damnacanthal a component of noni fruit,

as an inhibitor of Vpr induced cell death. The mechanism(s) of damnacanthal, which inhibits Vpr induced apoptosis is currently unknown and need to be elucidated (Kamata et al., 2006).

Antihelmintic activity

Alcoholic extracts of tender leaves showed good *in vitro* anthelmintic activity against human *Ascaris lumbricoides* (Raj, 1975). Similar findings were also reported by Khuntia et al. (2010) and they showed that the alcoholic extract produced more significant anthelmintic activity than petroleum ether extract and the activities are comparable with the reference drug piperazine citrate. Traditionally, it has been used in the Philippines and Hawaii as an effective insecticide (Morton, 1992).

Antioxidant activity

Many degenerative human diseases have been recognized as being a consequence of free radical damage. Studies have shown that high consumption of fruits and vegetables containing phenolic antioxidants, inhibit the oxidation of low density lipoprotein (LDL), thus slow the process of atherosclerosis and also reduce the risk of cancer and many other diseases. It is encouraging to see that all the chromatographic fractions obtained from the root, fruit and leaf demonstrated high antioxidative activity when compared with either butylated hydroxytoluene (BHT) or α-tocopherol (Mohd et al., 2006).

It has been reported that ethyl acetate extract of fruit exhibited higher antioxidative activity than mannitol or vitamin C, while the petroleum ether and n-butanol extracts showed lower activities as compared to mannitol. Three antioxidant phenolic compounds, isoscopoletin, aesculetin and 3, 3′, 4′, 5, 7-pentahydroxyflavone (quercetin) have been isolated from the ethyl acetate extract by several chromatography techniques for the first time (Chang-hong et al., 2007). Recently it has also been reported that *M. citrifolia* (noni) seed extract exhibit significant antioxidant activity in the Oxygen Radical Absorbance Capacity (ORAC) and Ferric Reducing Antioxidant Power (FRAP) tests (Brett et al., 2011).

Hepatoprotective activity

Fruit juice from Tahiti has been examined on carbon tetrachloride (CCl_4) induced liver injury in female Sprague-Dawley (SD) rats. This study evaluated that noni juice may be effective in protecting the liver against acute CCl_4 toxicity and it was also observed that necrosis of to normalize liver function after acute exposure to CCl_4 (Mian-Ying et al., 2008) or streptozotocin (Nayak et al., 2011).

A few reports have suggested the involvement of noni juice in the development of chemically induced hepatitis in a limited number of cases in Europe. Further, an official European investigation of these cases determined that no relationship between noni juice and hepatitis was evident; therefore, consumption of noni juice is unlikely to induce adverse human liver effects (EFSA European, 2006). It may thus be an efficacious natural hepato-protective nutritional supplement even at very high doses (West et al., 2006a, b).

Antiobesity and hypoglycemic effects

While most of the research focuses on cancer, inflammation and antimicrobial functions, there are some other aspects, of which one of them is the rate of gastric emptying in rats (Pu et al., 2004). In effect, noni juice reduced the rate at which food exited the stomach when taken as a juice for seven consecutive days. Although, the mechanism is not clear, it may mean that it acts like an appetite suppressant, useful for weight loss if future studies show a similar effect in humans. Another study (Adrienne and Pratibha, 2007) showed that noni juice reduced body weight by 40%, when a mice fed a control diet and whereas 25% in high-fat-diet (HFD). It also reduced adipose tissue weights, plasma triglyceride levels and improved glucose tolerance in these animals. A Japanese research team has also studied more specifically the hypoglycemic effects of the anthraquinone damnacanthol-3-O-beta-D-primeveroside and lucidin 3-O-beta-D-primeveroside by roots on streptozotocin (STZ)-induced diabetic mice and result showed that these molecules are responsible for the hypoglycemic effects. Further work is required to elucidate cellular and molecular mechanisms involved in anti-obesity and hypoglycemic effects (Kamiya et al., 2008).

Analgesic activity

The lyophilized aqueous extract of the roots was screened for analgesic activities in mice through writhing and hot plate tests. The data from this experiment showed that analgesic efficacy of the extract is 75% as strong as morphine, yet non addictive and also proved to be non-toxic (Chafique et al., 1990). Similar findings were also reported by Punjanon and Nandhasri (2005) in the alcoholic extract of fruits.

The analgesic activity of noni fruit puree on mice was investigated using the hot plate test. A 10% solution of freeze concentrated noni fruit puree in the drinking water of mice reduced the pain sensitivity comparably to the central analgesic drug tramadol. This effect was only partly reversed by the application of the morphine antagonist naloxone. An alcohol extract of noni fruit puree

also caused an inhibition of MMP-9 release from human monocytes after stimulation with lipopolysaccharide (LPS). This effect was comparable to hydrocortisone (10^{-5} M).

The findings of Basar et al. (2010) suggest that the preparations of noni fruits are effective in decreasing pain and joint destruction caused by arthritis. Further studies are necessary for the identification of the active compounds and mechanism of action.

Anxiolytic activity

Recent research has demonstrated the effects of fruit on preventing anxiety disorders, affecting an estimated 25% of the adult population at some point during their lifetime (Kjernised and Bleau, 2004). Methanol crude extract of fruit showed significant affinity to the gamma-amino butyric acid A (GABAa), the commonest inhibitory neurotransmitter in the central nervous system and displayed 75% binding inhibition as an agonist and thus induce its anxiolytic and sedative effects. Further work is required to identify compounds, which are responsible for the activities measured (Deng et al., 2007).

Anti-inflammatory activity

The aqueous extract of the fruit was investigated for anti-inflammatory activity against bradykinin and carrageenan induced oedema in the rat paw. The results showed that the bradykinin-induced inflammatory response was inhibited and subsided rapidly in rats that were pretreated either orally or intraperitoneally with fruit juice extract, whereas a higher dose of extract was required to completely inhibit the inflammatory response to carrageenan (Marsha-lyn et al., 2002).

Another study showed that ethanol extract of fruit powder has a selective inhibition effect on cyclooxygenase-1 (COX-1). Its IC_{50} value (163 µg/ml) was lower than those produced by aspirin (241 µg/ml), whereas much higher than indomethacin (1.2 µg/ml) used as the reference COX-1 inhibitors in this study. By contrast, It should be noted that it did not exhibit (*in vitro* and *in vivo*) nitric oxide (NO*) scavenging activity, a key mediator in the phenomenon of inflammation (Rachel et al., 2003).

Akihisa et al. (2007) reported that new saccharide fatty acid ester 2-O-(beta-D-glucopyranosyl)-1-O-octanoyl-beta-D-gluropyranose extracted from the fruits has got highly promising anti-inflammatory candidate.

Wound healing activity

The ethanol extract of the leaves (150 mg/kg/day) was used to evaluate the wound-healing activity in rats, using excision and dead space wound models. The result showed that the extract-treated animals exhibited 71% reduction in the wound area when compared with controls which exhibited 57%. The mass and hydroxyl-proline content in the dead space wounds of granulation tissue were also increased significantly in noni-treated animals when compared with controls (Shivananda et al., 2007). In a similar study, wound-healing activity of fruit juice was evaluated in streptozotocin-induced diabetic rats. The data from this experiment indicated that fruit juice significantly reduces blood sugar level and hasten wound healing activity (73%) in diabetic rats as compared to diabetic controls (63%) (Nayak et al., 2007).

An anthraquinone was isolated and identified as 1, 4-dihydroxy-2-methoxy-7-methylanthraquinone from fruit. It showed significantly increased elaboration of procollagen type I C-terminal peptide and glycosaminoglycans and reduced or inhibited expression of the collagenase matrix metalloproteinase-I in primary cultures of human fibroblasts. Furthermore, in a clinical trial this molecule was found to increase the dermal type I procollagen in nude mouse skin. These results suggest that identified anthraquinone is a good indispensable candidate for use as a new anti-wrinkle agent due to its strong induction of biosynthetic activity of extracellular matrix components (Kim et al., 2005).

Hypotensive activity

Youngken et al. (1960) found that the total extract of the roots has a hypotensive effect. Later on, Moorthy and Reddy (1970) found that the ethanol extract of the roots lowered the blood pressure in an anesthetized dog. Recently, it has been reported that noni juice contains angiotensin-I-converting enzyme (ACE) (Yamaguchi et al., 2002). Since ACE is commonly prescribed to treat high blood pressure, therefore this can be recognized as a therapeutical intervention for lowering blood pressure.

Cardiovascular activity

5-lipoxygenase and 15-lipooxygenase are responsible for production of leukotrienes that instigate asthmatic and allergic reactions and act to sustain inflammatory reactions. Recent research has showed the role of 5-lipoxygenase in cardiovascular and neuropsychiatric illnesses (Radmila and Hari, 2004).

Oxidation of LDL has been recognized as playing an important role in the initiation and progression of atherosclerosis. Methanol and ethyl extract of fruit showed 88 and 96% inhibition, respectively of copper-induced oxidation of low density lipoprotein particles *in vitro*. Six lignans were isolated from ethyl extract of the fruit and has been showed to have inhibiting effect of copper-induced LDL oxidation in a dose-dependent manner (Kamiya et al., 2004).

Deng et al. (2007b) isolated two new lignans, (+)-3,4,3',4'-tetrahydroxy-9,7'alpha-epoxylignano-7 alpha,9'-

lactone and (+)-3,3'-bisdemethyltanegool as well as seven known compounds from the fruits which are responsible for inhibition of 5- or 15-lipoxygenase (Deng et al., 2007a).

Two new anthraquinones, 1,6-dihydroxy-5-methoxy-2-methoxymethylanthraquinone (1) and 1,5,7-trihydroxy-6-methoxy-2-methoxymethylanthraquinone (2), and one new lignan isoamericanoic acid A (3) were isolated from the fruits of *M. citrifolia* along with 11 known compounds (Lin et al., 2007)

Recently, it has been reported that antispasmodic and vasodilatory activities of *M. citrifolia* root extract are mediated through blockade of voltage-dependent calcium channels and it showed antidyslipidemic effects and it can be used as a potential medicine for cardiovascular diseases. However, further studies are required to prove the safety and efficacy of *M. citrifolia* and its constituents in actual clinical settings (Saf-ur et al., 2010)

Estrogenic activity

M. citrifolia has been reported to have very weak estrogenic activity *in vivo*. According to Chearskul et al. (2004), the relative estrogenic potency of alcohol and water extracts of *M. citrifolia* was 1:1,000 and 1:10,000 respectively, indicating that the estrogenic activity is only seen at low doses, and even then it has very low potency in comparison to estradiol, suggesting that the beneficial effects of noni are not closely linked to estrogen mediated action.

A variety of phytoestrogens have been identified, which bind to the estrogen receptor and comprises protective effects on estrogen-related conditions, such as menopausal symptoms and estrogen-related diseases, namely prostate and breast cancers, osteoporosis and cardiovascular diseases (Cos, 2003).

A German research team has also studied the estrogenic properties of the fruit in two *in vitro* assays, the estrogen receptor binding assay with both estrogen receptors, ER-*α* and ER-*β*, and the estrogen-receptor dependent induction of alkaline phosphatase in Ishikawa cells. Hexane extracts prepared from the fruit exhibited high activity in both systems (Basar et al., 2006). Besides the aforementioned investigations, the chemical nature of phytoestrogen in noni is still mysterious and needs further investigations.

Immunological activity

Recent research examined the mechanisms involved in immunological properties of Tahitian Noni Juice (TNJ) and noni fruit juice concentrates (NFJC) in mice. The result showed that both modulate the immune system via the activation of the CB2 receptors and suppression of the IL-4, but increasing the production of IFN-gamma cytokines (Palu et al., 2008).

In a related report, it has been found that ethanol precipitation of the fruit contains a polysaccharide-rich fraction which showed antitumour activity in the Lewis lung carcinoma model in mice. It also stimulate the release of several potential mediators, including TNF-α, IL-1β, IL-10, IL-12 p70, IFN-γ and nitric oxide, but had no effect on IL-2 and suppressed IL-4 (Hirazumi and Furusawa, 1999).

Anti-cancer activity

It has been reported that methanol extract of the fruit at a concentration of 0.1 mg/ml exhibited cytotoxic activity against breast cancer (MCF7) and neuroblastoma (LAN5) cell lines at 29 and 36%, respectively in 3-(4,5-dimethythiazol-. 2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay (Arpornsuwan and Punjanon, 2006).

Another study showed that the ethanol precipitated polysaccharide-rich substance of noni juice possesses immunomodulatory and antitumour activity against Sarcoma 180 ascites tumour in mice (Furusawa et al., 2003). Wang et al. (2001) studied cancer preventive effect of TNJ in Sprague-Dawley (SD) rats. In this study, a chemical carcinogen 7, 12-dimethylbenz [a] anthracene (DMBA) was used to induce cancer in specific organs of rats. Results showed that 10% TNJ reduced DMBA-DNA adduct formation by 30% in the heart, 41% in the lung, 42% in the liver, and 80% in the kidney in one week.

One of the current strategies for the treatment of human cancer is to activate the cellular apoptotic death program. Along this line, Hornick et al. (2003) found that noni juice in concentrations of 5% or greater was highly effective for inhibiting the initiation of new vessel sprouts from model of placental vein explants. At higher concentration of 10%, it was able to induce vessel degeneration and apoptosis in established capillary networks within a few days of its application.

An anthraquinone damnacanthal isolated from the chloroform extract of the root was found as new inhibitor of *ras* function and thus suppressed *ras*-expressing tumors (Hiramatsu at al., 2003). It also showed potent inhibitory activity towards tyrosine kinases such as Lck, Src, Lyn and EGF receptor and might be related to the stimulatory effect on ultraviolet-induced apoptosis (Takaki et al., 1999).

Other studies have reported that the two novel glycosides, 6-*O*-(b-D-glucopyranosyl)-1-*O*-octanoyl-b-D-glucopyranose and asperulosidic acid, extracted from the juice of the fruits were effective in suppressing 12-*O*-tedtradecanoylphorbol-13-acetate (TPA) or epidermal growth factor (EGF), thereby inducing cell transformation and associated AP-1 activity (Guangming et al., 2001).

FUTURE STRATEGY

New compounds with high levels of pharmacological activity are urgently required for a wide range of human disorders

and diseases. A number of scientific publications showed that this plant contains several nutritional and functional compounds, but the current state of knowledge is still far from satisfactory. The most important compounds identified are damnacanthal and some other phenolic compounds. However, its activity as chemopreventive and anti-HIV needs further investigation. A drug development programme should be undertaken to develop modern drugs with the compounds isolated, but before that, a comprehensive phytochemical profiling, extensive investigation of its bioactivity, mechanism of action, pharmacotherapeutics, toxicity and clinical trials are needed to provide sufficient data. In addition, research should be initiated for identification of elite chemotypes, quality control of produces through marker development such as TLC, HPTLC, standardization of cell culture techniques for production of bioactive compounds and identification of pathway related to the production of potent bioactive compounds. In order to realize these goals a number of projects have been initiated by academic institutions and pharmaceutical companies.

In nut shell, we can say that the combination of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology are needed to exploit the vast diversity of chemical structures and their biological activities for the development of new pharmacological agents. Eventually my personal suggestion to those companies which are involved in production and merchandise of noni juice should provide relevant information regarding bioactive components present in juice. Which results, primarily, would motivate consumers to purchase noni juice that contains such substances, and secondary, it would inspire food processors to retain these bioactive compounds.

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