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Review Article

Review of the ethnobotany, chemistry, biological activity and safety of the botanical dietary supplement *Morinda citrifolia* (noni)*

Alison D. Pawlus and A. Douglas Kinghorn

Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612, USA

Alison D. Pawlus†

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210, USA

Alison D. Pawlus,
A. Douglas Kinghorn

Correspondence: A. D. Kinghorn, Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210, USA. E-mail: kinghorn.4@osu.edu

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†**Present address:** Department of Experimental Therapeutics, University of Texas, M.D. Anderson Cancer Center, Houston, Texas 77030, USA.

Abstract

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. A relatively large number of scientific publications on noni have been published in recent years, including a number of review articles. The goals of this review are to provide an updated categorization of the phytochemical constituents found in noni and to provide perspective for its extensive utilization as a major botanical dietary supplement. Included herein are a comprehensive list of known ethnobotanical uses and common names of *M. citrifolia*, a brief summary of relevant biological studies and a discussion of the safety of noni as a supplement.

Introduction

Morinda citrifolia L. (Rubiaceae), known popularly as noni, is a small evergreen tree or shrub, native to South Asia, that currently grows throughout the tropics (Abbott & Shimazu 1985). The fruits of *M. citrifolia* are very distinct and easy to recognize (Figure 1). The white tubular flowers form in clusters on the young fruit. The syncarpous fruit grow to be about 5–10 cm long and turn from a greenish to a translucent yellowish-white colour when fully ripe (Nelson 2003). The surface of the fruit is covered with polygonal segments that surround postfloral nectarines, which continue to function during the development of the fruit (Keller 1985).

Noni has a long history of use as a medicinal plant in Polynesia, South and Southeast Asia, Northeastern Australia and the Caribbean, and has been used to treat a wide variety of ailments. While applications have been reported for all parts of the plant, the leaves have the most prevalent traditional use and the plant is usually used topically. This contrasts with the current popular use where the fruit juice, and less commonly the leaves and roots, are primarily consumed orally. Responding to noni's ethnobotanical and popular use, a substantial number of biological and chemical studies have been performed on this species dating back more than 100 years. Many secondary metabolites of noni have been established. These include iridoid glycosides and triterpenoids, such as ursolic acid, which are the major constituents of the fruit, and a number of anthraquinones, which primarily accumulate in the roots, but have also been found in trace quantities in the fruit.

There are currently two recognized varieties of *M. citrifolia* (*M. citrifolia* var. *citrifolia* and *M. citrifolia* var. *bracteata*) and one cultivar (*M. citrifolia* cultivar Potteri). The most commonly found variety, *M. citrifolia* var. *citrifolia*, has the greatest economic importance. It is morphologically diverse with both large and small fruits and its leaves exhibit a wide range in size and shape, being variously described as elliptical, long and strap-like, and ovate or rounded. *M. citrifolia* var. *bracteata* has smaller fruits subtended by bracts and is found in countries between the Indian and Pacific Oceans. *M. citrifolia* cultivar Potteri is an ornamental plant distributed throughout the Pacific, with green and white leaves (McClatchey 2002b; Nelson 2003). Variations among *M. citrifolia* trees are known by traditional healers, who use leaf size and shape in addition to fruit odour to differentiate among individual trees. In at least some situations, local healers preferentially select specific trees,

Figure 1 Photographs of *M. citrifolia* fruits.

based on their morphology or odour, for a particular purpose (McClatchey 2002a, b). However, most research has not distinguished between the different noni varieties and this review paper will not attempt to make such distinctions. The first section will review the documented ethnobotanical uses and common names of *M. citrifolia*. The second section will describe its current usage as a dietary supplement. The third section presents a compilation of the chemical constituents. In the fourth section, published data on the biological activity of noni extracts or pure compounds will be presented and in the fifth section, the safety and toxicity of noni will be discussed. Various aspects of the uses, phytochemical profiles and biological activity of *M. citrifolia* have been reviewed previously (Wang et al 2002; Pawlus et al 2005b; Chan-Blanco et al 2006; Potterat & Hamburger 2007). This review covers literature published on noni through March 2007.

Ethnobotanical uses of noni

Originating in South Asia, noni has spread across the tropical world and is known to local populations throughout this area for its medicinal properties. Table 1 presents a long, but necessarily partial, list of its traditional uses. The majority of the entries in the table are local to South and Southeast Asia and the South Pacific, reflecting noni's geographic origin, but there are also traditional uses in east Africa, the Hawaiian Islands and the Caribbean. Noni's medical applications are as diverse as its geography. Its root, stem, bark, leaves and fruit can be used externally as a poultice, internally as an infusion or applied directly to the body. It is also prepared, in some cases through fermentation, and administered orally. Its external indications primarily consist of sores, cuts and inflammation, but also include stings from poisonous fish and even headaches. The internal uses are even more diverse, ranging from regulation of menstruation to the treatment of cancer. Paralleling this wide range of traditional uses, Western consumers have also been turning to noni for the treatment or prevention of a wide variety of ailments. This will be discussed in the next section.

Noni as a botanical dietary supplement

The use of noni has recently grown tremendously in North America, Western Europe and elsewhere and it is now widely available in health food stores, pharmacies, grocery stores and through the Internet. According to the Nutrition Business Journal (www.nutritionbusiness.com), noni juice was number one in 2005, for sales of single herbs in the USA, with sales estimated at $250 million, up from $33 million in 1999. It is cultivated for commercial use in the Pacific islands, particularly in Tahiti and Hawaii, as well as Australia, and, more recently, Florida. A description of the growing, harvesting and processing of noni can be found in the recently published book by S. C. Nelson and C. R. Elevitch (Nelson & Elevitch 2006).

Noni's rise in popularity as a dietary supplement is most likely due to the increase in its publicity and marketing as a general cure-all or panacea for a number of chronic conditions (Solomon 1998; Elkins 2002; Fairchild 2004), as well as to the growing number of scientific studies reporting data, however preliminary, on its potential benefits (see Table 3). The popular publicity, in the form of books, marketing pamphlets and Internet sites, promotes a wide number of indications for noni, such as cancer, depression, diabetes, drug addiction, heart disease and obesity, and presents anecdotal evidence claiming somewhat miraculous cures obtained through its use. A significant portion of these advertisements and informational publications attribute these wide-ranging benefits to an alkaloid called xeronine, which is reported to exist in noni as its precursor, proxeronine (Heinicke 1985). A number of books and web-sites make scientifically astounding claims about the benefits of xeronine, complete with cartoons and schematics showing xeronine converting sickly cells into healthy, robust-looking cells (e.g. Solomon 1998). This xeronine theory began with a 1985 publication in a botanical journal by Dr Heinicke. Unfortunately, this publication lacks supporting data and, to date, the presence of xeronine and proxeronine has not been confirmed in any peer-reviewed scientific publication. Furthermore, the structures of xeronine and proxeronine have never been provided.

Table 1 Common names and ethnobotanical uses of *Morinda citrifolia*

Location	Common Name[a]	Part used	Use	Reference
Africa	Bungbo, Bumbo	Leaves	As a purge.	von reis Altschul (1973); Lassak & McCarthy (1990); Morton (1992)
Australia	Awl Tree, Canary Wood, Cheesefruit, Great Morinda, Leichhardt's Tree	Rootbark	As an antiseptic.	
Brunei	Mengkudu	Fruits	Used against tooth decay.	Haji Mohiddin et al (1992)
		Root	Decoction is taken orally to regulate menstruation.	
		Leaves	Heated and used for cough and enlarged spleen.	
China	Je Shu, Hai-ba-ji	Whole plant	Extract or tincture is taken to relieve aching bones.	Perry (1980); Li (2002); Hu (2005)
		Root	Treatment of beri-beri, cancer, lumbago, cholecystitis, and to increase leucocyte count, and stimulate the endocrine system.	
Cook Islands	Nono	Fruits	Included in infusion for treating urinary tract ailments and associated pains and used with other medicinal plants in treating diaphragmatic hernia and other abdominal swellings and gonorrhea.	Whistler (1985); Holdsworth (1991); Ross (2001)
		Root	Solution of grated root is applied to the top of the head in treating stings from the stonefish. Used externally for cancerous swellings and to localize infections.	
		Bark	Orally with *Calophyllum inophyllum* and water from green coconut for diabetes.	
		Leaves	Orally with other plants to treat gonorrhea.	
Dominica	Pain-Killer, Feuille Froide	Leaves	Used as a poultice and to wrap around rheumatic joints.	von reis Altschul (1973)
Fiji	Kura, Achi	Fruit	Liquid from young fruit is instilled into each nostril for bad breath and a raspy voice. Placed directly to mouth ulcers and haemorrhoids. Treat ringworm. Orally for depression, fever, seizures, tuberculosis, viral infection, and as a tonic.	Weiner (1976); Sing (1986); Aalbersberg et al (1993); Cambie & Ash (1994); Ross (2001)
		Stem	Pressed fluid is used to treat swollen testicles or hernia.	
		Leaves	Steam of boiling leaves is used to relieve pain from barbs of poisonous fish. Chewed and applied as a poultice for inflammation, rheumatism, and a steam bath made from the leaves is used to relieve stiffness. Warm leaves used for broken bones and sprains. Treat boils, gastric ulcers and remove pus from ear infections. Fresh leaf is used topically for burns. Used with *Psychotria* sp. to treat haemorrhoids and leaves of *Epipremnum pinnatum* to relieve pregnancy pains.	
		Leaves and flowers	Hot juice is squeezed into ulcers and leaves used as bandage.	
		Shoots	In coconut oil for treatment of ringworm, scabies, itching, and acute rheumatic pains.	
		Roots	Used with *Euodia hortensis* and *Geniostoma vitiense* to treat malnutrition.	
			Grated root mixed with coconut and wood ash is used to treat yaws. Infusion used for insect sting and inflammation.	
		Root and fruit	Grated and chewed morning and evening to treat sore throat.	
		Bark	Internally for urinary disorders.	
		Flower	For eye inflammation.	

(Continued)

Table 1 (*Continued*)

Location	Common Name[a]	Part used	Use	Reference
Futuna	Nonu	Bark	Orally as an abortifacient and for stomach pains in women.	Parsons (1985); Cambie & Brewis (1997)
		Fruit	Chewed and placed onto the lips of children with mouth ulcerations.	
Guyana	Pain Killer, Yaw-weed	Leaves	Macerated alone or mixed with *Pothomorphe peltata*, in coconut oil for an external rub to relieve arthritic and rheumatic pains.	DeFilipps et al (2004)
		Fruit	Mixed with vinegar to smooth a swollen spleen.	
Hawaii	Noni, Indian Mulberry, Large-leaved Morinda	Leaves and bark	Pounded, cooked, and strained and used as a tonic. Orally as abortifacient.	Tabrah & Eveleth et al (1966); Degener (1973); Wagner et al (1990); Locher et al (1995); Horowitz (2001); Ross (2001)
		Fruit	Used against tuberculosis with native blackstemmed sugar cane and root of *Piper methysticum*. As a poultice. Healing broken bones and deep cuts and bruises. Insecticide for hair. Orally for asthma. Rotten-ripe used for hypertension and lassitude of old age. Immature fruit juice internally for diabetes, hypertension, digestive disorders, menstrual cramps, and a general tonic. The mashed green fruit is used for skin conditions.	
India	Al, Ach, Achi, Achu, Achuka, Ainshi, Awl Tree, Bartundi, Bo-Aal, Dilo-K, Indian Mulberry, Kattapitelavam, Kattatogaru, Maddi, Mannanatii, Mara, Minamaram, Núna, Pindra, Surangi, Tagaru, Tagase, Tagate, Togari Wood, Togaru	Root	Cathartic, febrifuge.	Moorthy & Reddy (970); Kamboj (1988); Jain & DeFilipps (1991); Morton (1992); Ross (2001)
		Leaves	Juice applied externally for gout.	
			Internally as a tonic and fever.	
			Applied to wounds and ulcers.	
		Fruit	Throat and gum complaints, dysentery, leucorrhoea. Applied to spongy gums.	
		Fruit and leaves	Emmenagogue.	
Indonesia	Bengkudo	Bark	Antihelmintic.	Perry (1980); Ross (2001)
		Fruit	Intestinal worms in children. Emmenagogue.	
		Not stated[b]	Antirheumatic.	Perry (1980)
Indo-China Malaysia	Mengkudu, Nona	Fruit and leaves	Orally as abortifacient.	Morton (1992); Ross (2001)
Micronesia		Fruit	Included in a remedy to treat ulcerated feet.	Weiner (1976)
			Employed in treatment of diabetes.	
			Used when unripe in a drink for tuberculosis.	
		Root	Liquid is applied to boils.	
			Employed in a preparation on stonefish and sting-ray wounds. Salve for small-pox.	
		Leaves	Liquid is used as a rinse for injured eyes.	
		Shoots	Crushed and squeezed into baby coconuts in preparation of a liquid to treat eye infections.	
New Guinea	Noku, Mwagum Wagugn, Oko, Pemi, Te Non, Riro, Noko, Gomor, Val, Kotambul, Urarian, Pemii	Root	Juice is taken internally for fevers, including those caused by malaria. Root bark is used internally for skin disorders.	Weiner (1976); Cambie & Brewis (1997); Ross (2001)
		Leaves	Heated and applied to relieve headaches.	
			Young leaves are heated and applied to sores.	
			Old leaves are heated and used on sores of leprosy. Taken internally for stomach ache and dysentery.	

		Bark	Employed in a treatment to aid/induce labour during childbirth.	
		Unspecified[b]	Treatment of sores on the feet.	
Philippines	Apatol, Apalot, Bangkoro, Baĝuro, Bankoro, Bankundo, Bankgkudo, Pankundo, Nino, Kulit, Tumboĝaso, Lino, Mambog, Rukurok, Taing-Aso, Takpus, Taliantar, Tumbong-Aso	Root	Diarrhoea and dysentery.	Pardo de Tavera (1901); Perry (1980); Food and Agriculture Organization of the United Nations. Forest Resources Development Branch (1983); Morton (1992)
		Fruit	Emmenagogue and perhaps aperient.	
		Leaves	Mashed and applied to wounds and ulcers to hasten cicatrization. As a poultice to the enlarged abdomen of children.	
Rotuma	Ura	Fruits	Bacterial infections, fungal infections, viral infection preventative, fevers, oral sores, seizures, and tuberculosis.	McClatchey (1996)
		Leaves	Bacterial infections, fever, inflammation, and topical burns, and haemorrhage.	
		Bark	Bacterial infections.	
		Roots	Postparturition health, ictheotoxin/sting, inflammation, and pain.	
		Flowers	Inflammation of eyes.	
Samoa	Nonu	Leaves	Rheumatic aches, swelling of joints, boils, inflammation of breast. Swelling caused by the parasitic disease, filariasis. Externally for chest cold in infants. Orally for fevers including those caused by malaria.	Weiner (1976); Dittmar (1993); Cambie & Brewis (1997); Ross (2001); Whistler (2004)
			Chewed for inflamed, swollen and painful deep red gums; sore throat and pharyngitis.	
			Topically for centipede bite, elephantiasis, with *Artocarpus* spp. for septicaemia.	
			Used as dressing for wounds.	
		Flower	Juice is used in the eye for irritated, red, or sore eyes, conjunctivitis, sties. Coughs.	
		Bark	Orally for infant diarrhea, stomach complaints, cough, worms and woman's complaint.	
		Fruit	Orally for fever, tuberculosis, fever with vomiting. Topically for eye complaints.	
			Orally with the roots and leaves of *Boerhavia diffusa* for diarrhoea.	
			Orally with the root of *Polypodium powellii* for intestinal worms. As a mouthwash for inflamed, sore gums.	
		Roots	Toothache and jaundice.	
		Mixed[b]	Sore throat with cough, thrush, abscesses.	
			Topically or orally for spreading dark spots on the skin.	
Tahiti	Mona, Monii, Nono	Fruit	Used directly on stings from stonefish.	Parsons (1985); Whistler (1985); Morton (1992)
			Topically for swellings of limbs, neck, ears, and the lower bowel. Orally for swellings of the lower jaw, throat, and below the ears.	

(Continued)

Table 1 (*Continued*)

Location	Common Name[a]	Part used	Use	Reference
Thailand	Awl Tree, Indian Mulberry, Kura, Mataasuea, Nhau, Yae-Yai, Yo, Yor Ban	Root	Treatment of diseases causing cachexia. As a laxative.	Farnsworth & Bunyapraphatsara (1992); Morton (1992); Ross (2001); Chearskul et al (2004)
		Leaves	Treatment of diseases causing cachexia, gout, and as a pediculicide.	
		Fruits	For use after giving birth, as a cardiotonic, fainting, treatment of hiccough, hoarseness, gingivitis, diseases causing cachexia, heartburn, as a carminative, as a central nervous system stimulant, element tonic, appetite stimulant, blood purifier, and antiemetic.	
Tonga	Nonu	Not stated[b]	Treat diarrhoea in infants.	von reis Altschul (1973); Singh et al (1984); Cambie & Ash (1994)
		Leaves	Crushed and moistened with water, leaves are applied to aching joints or massaged into aching muscles. Leaves used in conjunction with other plants as a poultice to be applied to carcinomas, induration, and pain of the breast. Used in infusions for postpartum discharge, secondary amenorrhoea, and severe bleeding in early pregnancy. Used as a general tonic and boils.	
		Bark	Used for afterbirth, infertility, menorrhagia, postpartum haemorrhage and vaginal bleeding.	
Virgin Islands	Pain-Killer, Headache Tree	Not stated[b]	Heart trouble.	Oakes & Morris (1958)
Vietnam	Cây, Grand Morinda, Ngao, Nhàu, Nhau Lon, Nhau Nui, Nhàu Rùng	Root-bark	Internally for hypertension, osteodynia, and lumbago. Orally for fever, dysentery and diarrhoea.	Nguyen (1990); Morton (1992)
		Leaves	Poultice of pounded fresh leaves for furunculosis.	
		Fruit	Stomachic, aperient, active on dysentery, uterine haemorrhage, metrorrhoea, cough, coryza, oedema, and neuralgia.	
West Indies	Feuille Froide, Pain Killer, Rubarbe Caraibe, Bilimbi, Pomme Macaque	Leaves	Wrapped around rheumatic joints, as a poultice, and for headaches. Brewed and used externally for pain.	Ayensu (1981)
		Fruit	Heated and put on sores or inflammation.	

[a]Additional common names given to *M. citrifolia* where no reported medicinal uses have been found and, therefore, not listed in this table include: Barbados: forbidden fruit, wild pine, Cambodia: nhor prey, nhor thom, Cayman Islands: hog apple, mulberry, Cuba: mora de la India, Dominica: feuille froide, pain killer, Dominican Republic: baga, buñuela, coca, huevo de reuma, nigua, piña de Puerco, piñuela, El Salvador: ruibarbo caribe, Florida: limburger tree, French West Indies: bilimbi, Guadeloupe: rubarbe caraibe, ruibarbo caribe, Guam, Lada, Ladda (Safford 1905), Haiti: boi doleur, doleur, feuille douleur, fromagier, Jamaica: hog apple, Japan: Yaeyama-aoki, Laos: nho, Malaysia: awl tree, great morinda, mengkudu, menkudi besar, menkudu besar, Seychelles: mirier de Java, (Morton 1992; Takashima et al 2007).
[b]More specific information on plant part used was not provided in original publication.

While the fruits and leaves are sold as tablets and as herbal teas, noni is most commonly sold as a juice derived from the fruit. Such fruit juices are frequently prepared by diluting the dried powdered fruit with other juices, such as grape juice, to increase palatability. While it is not known which compounds may be most beneficial, some products report that they are standardized to a given percentage of polysaccharides. This presumably stems from studies demonstrating the potential anti-cancer activity of the polysaccharide-rich partition of the fruits in mice (Hirazumi et al 1994; Furusawa et al 2003). These investigations were performed by injecting a polysaccharide-rich fraction into the peritoneal cavity of mice with pre-injected cancer cells. While the results seem promising and warrant further investigation, it is still unknown whether beneficial anti-cancer activity would occur with oral administration in man.

Phytochemical constituents of *Morinda citrifolia*

Phytochemical investigations of *M. citrifolia* have resulted in the isolation of approximately 200 compounds, as summarized in Table 2. These primarily consist of a number of anthraquinones and anthraquinone glycosides, fatty acids and their derivatives, iridoids and iridoid glycosides, lignans, neolignans, flavonol glycosides, phenylpropanoids, saccharides, triterpenoids and fatty acids. The majority of these compounds have been isolated and identified through NMR spectroscopy and mass spectrometry while gas chromatography-mass spectrometry was used primarily in the identification of the fatty acids. The names of the compounds found are listed in Table 2 and the chemical structures of the majority of these isolates are shown in Figure 2. Additionally, the chemical structures of several iridoids have recently been revised by Schripsema et al (2006) as indicated by their previous names in parenthesis in Table 2.

M. citrifolia has also been evaluated for its nutritional content for potential use in geographical regions where specific nutritional deficiencies are prevalent. One 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). In another study, fruits from Australia were found to contain 158 mg of vitamin C and 2012 mg of potassium per 100 g of dry weight. These levels approximate the recommended daily allowance of these nutrients (Peerzada et al 1990). Recently, the polysaccharide content of noni fruits (noni-ppt) collected in Vietnam has been investigated using monosaccharide analysis and glycosyl linkage analysis. The most abundant monosaccharides found were arabinose (Ara*f*), galactose (Gal*p*), galacturonic acid (GalA*p*) and rhamnose (Rha*p*). The polysaccharide composition, deduced by the monosaccharide linkage data, was found to be mostly pectic polysaccharides, of which homogalacturonan (49.5%), type I arabinogalactan (12.3%) and rhamnogalacturonan I (10.8%) predominated (Bui et al 2006).

Biological activity of *Morinda citrifolia* extracts and pure constituents

A number of in-vitro and, to a lesser extent, in-vivo biological studies have been performed on both the crude extracts and several pure constituents of noni. These pertain to analgesic, antibacterial, anti-cancer, anti-inflammatory, antioxidant, anti-tubercular, cancer-chemopreventive and cardiovascular actions, as summarized in Table 3. The in-vivo results include the increase of lifespan of mice implanted with cancerous cells injected intraperitoneally with the EtOH-ppt, as mentioned above. In this study, the EtOH-ppt activity was shown to be blocked by immunosuppressants, such as ciclosporin, and increased survival by concurrent administration with chemotherapeutic agents, vincristine, 5-fluorouracil, cisplatin and adriamycin. This activity was demonstrated in several models, including mice injected with Lewis lung carcinoma cells and sarcoma 180 tumour cells (Hirazumi et al 1994; Furusawa et al 2003). Other in-vivo studies include the reduction of blood glucose levels in mice with streptozotocin-induced diabetes, hypotensive effects in dogs by the intravenous injection of the water-soluble extract from the roots and an analgesic effect of the aqueous extract injected intraperitoneally in mice (Youngken et al 1960; Younos et al 1990; Yamaguchi et al 2002; Nayak et al 2007). On the other hand, the subcutaneous injection of an aqueous extract of noni was found to be ineffective in the prevention of pregnancy in animal studies (Matsui et al 1967). The in-vitro studies demonstrated antioxidant and antibacterial effects of both noni extracts, but no antiviral activity has been demonstrated (Wang & Su 2001; Su et al 2005). In-vitro studies have also suggested noni may have anti-angiogenic activity, which could be important in preventing the spread of cancer (Hornick et al 2003). In addition, a methanol leaf extract upregulated low-density lipoprotein (LDL) receptors in HepG2 liver cells, a mechanism for reducing LDL blood levels, a risk factor for atherosclerosis (Salleh et al 2002).

Additionally, some promising biological activity was found with pure compounds, particularly anthraquinones and lignans. For example, in-vitro tests using a quinone reductase bioassay with hepa1c1c7 cells on the anthraquinone, 2-methoxy-1,3,6-trihydroxyanthraquinone (**27**), found it to be a highly potent phase II enzyme inducer and showed no toxicity to these cells (Pawlus et al 2005a). Damnacanthal (**11**) is another anthraquinone with potent biological activity in-vitro; it is a potent tyrosine kinase inhibitor and, similarly to morindone (**33**), exhibits topoisomerase II inhibition (Faltynek et al 1995; Tosa et al 1998). Several lignans from noni have demonstrated activity in antioxidant-related bioassays. For example, americanol A (**90**), 3,3′-bisdemethylpinoresinol (**92**), isoprincepin (**94**) and morindolin (**95**) all inhibited copper-induced LDL oxidation (Kamiya et al 2004). Additionally, americanin A (**88**) demonstrated DPPH free-radical scavenging activity and narcissoside (**64**) demonstrated antioxidant activity against the free-radical $ONOO^-$ (peroxynitrite) (Su et al 2005).

Safety, toxicity and adverse effects of *Morinda citrifolia*

There are several studies involving the administration of noni to laboratory animals with no perceived toxicity (West et al 2006; Westendorf et al 2007). There are however, several published case reports of possible toxicity in man. In one of these clinical reports, there was a suspected adverse event

Table 2 Compounds isolated from *Morinda citrifolia*

Compound structural class/name/code	Part	Reference(s)
Acids		
Acetic acid	Fruits	Farine et al (1996)
Ascorbic acid	Fruits	Peerzada et al (1990)
Benzoic acid	Fruits	Farine et al (1996)
Butanoic acid	Fruits	Farine et al (1996)
Decanoic acid	Fruits	Farine et al (1996)
(*Z,Z,Z*)-8,11,14-Eicosatrienoic acid	Fruits	Farine et al (1996)
Elaidic acid	Fruits	Farine et al (1996)
Heptanoic acid	Fruits	Farine et al (1996)
Hexanedioic acid	Fruits	Farine et al (1996)
Hexanoic acid	Fruits	Legal et al (1999)
13-Hydroxy-9,11,15-octadecatrienoic acid (**1**)	Leaves	Takashima et al (2007)
Lauric acid	Fruits	Farine et al (1996)
Linoleic acid	Fruits	Farine et al (1996)
2-Methylbutanoic acid	Fruits	Farine et al (1996)
2-Methylpropanoic acid	Fruits	Farine et al (1996)
3-Methylthiopropanoic acid	Fruits	Farine et al (1996)
Myristic acid	Fruits	Farine et al (1996)
Nonanoic acid	Fruits	Farine et al (1996)
Oleic acid	Fruits	Farine et al (1996)
Octanoic acid (**2**)	Fruits	Legal et al (1999)
Palmitic acid	Fruits	Farine et al (1996)
Ricinoleic acid (**3**)	Seeds	Daulatabad et al (1989)
Undecanoic acid	Fruits	Farine et al (1996)
Alcohols and phenols		
Benzyl alcohol	Fruits	Farine et al (1996)
1-Butanol	Fruits	Farine et al (1996)
Eugenol	Fruits	Farine et al (1996)
1-Hexanol	Fruits	Farine et al (1996)
3-Methyl-2-buten-1-ol	Fruits	Farine et al (1996)
3-Methyl-3-buten-1-ol	Fruits	Farine et al (1996)
(*Z,Z*)-2,5-Undecadien-1-ol	Fruits	Farine et al (1996)
Anthraquinones		
Alizarin (**4**)	Cell culture, heartwood	Thomson (1971); Leistner (1975)
Alizarin 1-*O*-methyl ether (**5**)	Roots	Simonsen (1920); Pawlus et al (2005a)
Anthragallol 1,2-di-*O*-methyl ether (**6**)	Roots	Thomson (1971)
Anthragallol 1,3-di-*O*-methyl ether (**7**)	Fruits	Kamiya et al (2005)
Anthragallol 2,3-di-*O*-methyl ether (**8**)	Heartwood	Thomson (1971)
Anthragallol 2-*O*-methyl ether (**9**)	Fruits	Kamiya et al (2005); Pawlus et al (2005a)
Austrocortinin (**10**)	Fruits	Kim et al (2005)
Damnacanthal (**11**)	Heartwood, roots	Thomson (1971); Hiramatsu et al (1993)
Damnacanthol (**12**)	Roots	Thomson (1971); Sang & Ho (2006)
5,6-Dihydroxylucidin (**13**)	Cell culture	Inoue et al (1981)
5,15-Dimethylmorindol (**14**)	Fruits, leaves	Kamiya et al (2005); Takashima et al (2007)
2-Ethoxymethyl-3-methoxy-1,5,6-trihydroxyanthraquinone (**15**)[a]	Cell culture	Leistner (1975)
2-Formylanthraquinone (**16**)	Roots	Sang & Ho (2006)
6-Hydroxyanthragallol-1,3-di-*O*-methyl ether (**17**)	Fruits	Kamiya et al (2005)
2-Hydroxyanthraquinone (**18**)	Stems	Siddiqui et al (2006)
1-Hydroxy-2-methylanthraquinone (**19**)	Roots	Sang & Ho (2006)
2-Hydroxy-1-methoxy-7-methylanthraquinone (**20**)	Roots	Rusia & Srivastava (1989)
3-Hydroxymorindone (**21**)	Cell culture	Inoue et al (1981)
Ibericin (**22**)	Cell culture, roots	Sang & Ho (2006)
Lucidin (**23**)	Cell culture	Leistner (1975);
Lucidin ω-methyl ether (**24**)	Cell culture	Inoue et al (1981)
2-Methoxyanthraquinone (**25**)	Stems	Siddiqui et al (2006)
1-Methoxy-3-hydroxyanthraquinone (**26**)	Roots	Sang & Ho (2006)

(Continued)

Table 2 *(Continued)*

Compound structural class/name/code	Part	Reference(s)
2-Methoxy-1,3,6-trihydroxyanthraquinone (**27**)	Fruits	Pawlus et al (2005a)
6-Methyl-anthrapurpurin (**28**)	Cell culture	Inoue et al (1981)
Morenone-1 (**29**)	Roots	Jain & Srivastava (1992)
Morenone-2 (**30**)	Roots	Jain & Srivastava (1992)
Morindicininone (**31**)	Stems	Siddiqui et al (2006)
Morindicinone (**32**)	Stems	Siddiqui et al (2006)
Morindone (**33**)	Heartwood, root, cell culture	Simonsen (1918); Thomson (1971); Leistner (1975); Inoue et al (1981); Srivastava & Singh (1993)
Morindone-5-*O*-methyl ether (**34**)	Fruits	Kamiya et al (2005); Pawlus et al (2005a)
Nordamnacanthal (**35**)	Cell culture and roots	Thomson (1971); Leistner (1975); Sang & Ho (2006)
Physcion (**36**)	Heartwood	Srivastava & Singh (1993)
Rubiadin (**37**)	Cell culture and roots	Thomson (1971); Leistner (1975); Inoue et al (1981); Sang & Ho (2006)
Rubiadin-1-*O*-methyl ether (**38**)	Roots and heartwood	Simonsen (1920); Thomson (1971)
Soranjidiol (**39**)	Roots	Thomson (1971)
Tectoquinone (**40**)	Roots	Sang & Ho (2006)
1,5,15-Trimethylmorindol (**41**)	Leaves	Takashima et al (2007)
Anthraquinone glycosides		
5,6-Dihydroxylucidin-3-β-primeveroside (**42**)	Cell culture	Inoue et al (1981)
6,8-Dimethoxy-3-methylanthraquinone-α-L-*O*-β-rhamnosyl glucopyranoside (**43**)	Flowers	Tiwari & Singh (1977)
3-Hydroxymorindone-6-β-primeveroside (**44**)	Cell culture	Inoue et al (1981)
Lucidin-3-β-primeveroside (**45**)	Cell culture	Inoue et al (1981)
2-Methyl-3,5,6-trihydroxyanthraquinone-6-β-primeveroside (**46**)	Cell culture	Inoue et al (1981)
Morindin (**47**)	Cell culture	Simonsen (1918); Inoue et al (1981)
Physcion-8-*O*-[{α-L-arabinopyranosyl (1→3)}-β-D-galactopyranoside] (**48**)	Heartwood	Srivastava & Singh (1993)
Carotenoids		
β-Carotene	Leaves	Aalbersberg et al (1993)
Chlorophyll derivatives		
13^2(*R*)-Hydroxypheophorbide a methyl ester (**49**)	Leaves	Takashima et al (2007)
13^2(*S*)-Hydroxypheophorbide a methyl ester (**50**)	Leaves	Takashima et al (2007)
15^1(*R*)-Hydropurpurin-7 lactone dimethyl ester (**51**)	Leaves	Takashima et al (2007)
15^1(*S*)-Hydropurpurin-7 lactone dimethyl ester (**52**)	Leaves	Takashima et al (2007)
Methyl pheophorbide a (**53**)	Leaves	Takashima et al (2007)
Methyl pheophorbide b (**54**)	Leaves	Takashima et al (2007)
Pheophorbide a (**55**)	Leaves	Takashima et al (2007)
13-*epi*-Phaeophorbide a methyl ester (**56**)	Leaves	Takashima et al (2007)
Esters		
1-*n*-Butyl-4-(5′-formyl-2′-furanyl)methyl succinate (**57**)	Fruits	Samoylenko et al (2006)
1-*n*-Butyl-4-methyl-2-hydroxysuccinate (**58**)	Fruits	Samoylenko et al (2006)
1-*n*-Butyl-4-methyl-3-hydroxysuccinate (**59**)	Fruits	Samoylenko et al (2006)
Ethyl decanoate	Fruits	Farine et al (1996)
Ethyl hexanoate	Fruits	Farine et al (1996)
Ethyl octanoate	Fruits	Farine et al (1996)
Ethyl palmitate	Fruits	Farine et al (1996)
Methyl decanoate	Fruits	Farine et al (1996)
Methyl elaidate	Fruits	Farine et al (1996)
Methyl hexanoate	Fruits	Farine et al (1996)
Methyl 3-methylthio-propanoate	Fruits	Farine et al (1996)
Methyl octanoate	Fruits	Farine et al (1996)

(Continued)

Table 2 *(Continued)*

Compound structural class/name/code	Part	Reference(s)
Methyl oleate	Fruits	Farine et al (1996)
Methyl palmitate	Fruits	Farine et al (1996)
Flavonoids		
Acacetin 7-*O*-β-D-glucopyranoside (**60**)	Flowers	Singh & Tiwari (1976)
5,7-Dimethyl apigenin 4′-*O*-β-D-galactopyranoside (**61**)	Flowers	Singh & Tiwari (1976)
Kaempferol (**62**)	Fruits	Deng et al (2007)
Kaempferol 3-*O*-β-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-β-D-galactopyranoside (**63**)	Leaves	Sang et al (2001a)
Narcissoside (**64**)	Fruits	Su et al (2005)
Nicotifloroside (**65**)	Fruits, leaves	Sang et al (2001a); Su et al (2005)
Quercetin (**66**)	Frutis	Deng et al (2007)
Quercetin 3-*O*-β-D-glucopyranoside (**67**)	Leaves	Sang et al (2001a)
Quercetin 3-*O*-β-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-β-D-galactopyranoside (**68**)	Leaves	Sang et al (2001a)
Rutin (**69**)	Fruits, leaves	Wang et al (1999); Sang et al (2001a)
Iridoids		
Asperuloside (**70**)	Fruits, leaves	Sang et al (2001b); Su et al (2005)
Asperulosidic acid (**71**)	Fruits, leaves	Wang et al (1999); Sang et al (2001b); Kamiya et al (2005); Su et al (2005); Samoylenko et al (2006)
Asperulosidic acid methyl ester (**72**)	Fruits	Sang et al (2002)
Borreriagenin (previously morindacin) (**73**)	Fruits	Kamiya et al (2005); Su et al (2005); Schripsema et al (2006)
4-*epi*-Borreriagenin (**74**)	Fruits	Samoylenko et al (2006)
Citrifolinin A-1 (**75**)	Leaves	Sang et al (2003)
Citrifolinin Ba (**76**)	Leaves	Sang et al (2001a)
Citrifolinin Bb (**77**)	Leaves	Sang et al (2001a)
Citrifolinoside A (**78**)	Leaves	Sang et al (2001b)
Citrifoside (**79**)	Leaves	Takashima et al (2007)
Deacetylasperuloside (**80**)	Fruits, leaves	Su et al (2005); Takashima et al (2007)
Deacetylasperulosidic acid (**81**)	Fruits	Kamiya et al (2005); Samoylenko et al (2006)
Deacetylasperulosidic acid methyl ester (**82**)	Fruits	Sang et al (2002)
Dehydroepoxymethoxygaertneroside (previously yopaaoside A, citrifolinin A and citrifolinoside) (**83**)	Leaves	Sang et al (2001c); Schripsema et al (2006)
Dehydromethoxygaertneroside (**84**)	Fruits	Su et al (2005)
6β,7β-Epoxy-8-*epi*-splendoside (**85**)	Fruits	Su et al (2005)
6α-Hydroxyadoxoside (**86**)	Fruits	Su et al (2005)
1,3a,4,7a-Tetrahydro-6-(hydroxymethyl)-3*H*-furo[3,4-*c*]pyran-4-carboxylic acid (**87**)	Fruits	Sang et al (2002)
Ketones		
2-Heptanone	Fruits	Farine et al (1996)
3-Hydroxy-2-butanone	Fruits	Farine et al (1996)
Lactones		
(*E*)-6-Dodeceno-γ-lactone	Fruits	Farine et al (1996)
(*Z*)-6-Dodeceno-γ-lactone	Fruits	Farine et al (1996)
Lignans		
Americanin A (**88**)	Fruits	Kamiya et al (2004); Su et al (2005)
Americanoic acid (**89**)	Fruits	Kamiya et al (2004)
Americanol A (**90**)	Fruits	Kamiya et al (2004)
Balanophonin (**91**)	Fruits	Pawlus et al (2005a)

(Continued)

Table 2 *(Continued)*

Compound structural class/name/code	Part	Reference(s)
3,3′-Bisdemethylpinoresinol (**92**)	Fruits	Kamiya et al (2004); Deng et al (2007)
3,3′-Bisdemethyltanegool (**93**)	Fruits	Deng et al (2007)
Isoprincepin (94)	Fruits	Kamiya et al (2004)
Morindolin (95)	Fruits	Kamiya et al (2004)
(−)-Pinoresinol (**96**)	Fruits	Deng et al (2007)
(+)-3,4,3′,4′-Tetrahydroxy-9,7′α-epoxylignano-7 α,9′-lactone (**97**)	Fruits	Deng et al (2007)
Nucleosides		
Cytidine (**98**)	Fruits	Sang et al (2002); Su et al (2005)
Saccharides		
Nonioside A (**99**)	Fruits	Wang et al (2000); Dalsgaard et al (2006)
Nonioside B (**100**)	Fruits	Wang et al (1999); Dalsgaard et al (2006)
Nonioside C (**101**)	Fruits	Wang et al (2000); Dalsgaard et al (2006)
Nonioside D (**102**)	Fruits	Wang et al (2000)
Nonioside E (**103**)	Fruits	Dalsgaard et al (2006)
Nonioside F (**104**)	Fruits	Dalsgaard et al (2006)
Nonioside G (**105**)	Fruits	Dalsgaard et al (2006)
Nonioside H (**106**)	Fruits	Dalsgaard et al (2006)
α- and β-Glucose	Fruits	Levand & Larson (1979); Samoylenko et al (2006)
Methyl α-D-fructofuranoside (**107**)	Fruits	Su et al (2005)
Methyl β-D-fructofuranoside (**108**)	Fruits	Su et al (2005)
1-*O*-(3′-Methylbut-3′-enyl)-β-D-glucopyranose (**109**)	Fruits	Samoylenko et al (2006)
Triterpenoids and sterols		
3-*O*-Acetylpomolic acid (**110**)	Leaves	Takashima et al (2007)
Barbinervic acid (**111**)	Leaves	Takashima et al (2007)
Campesta-5,7,22-trien-3β-ol	Leaves	Saludes et al (2002b)
Campesterol (**112**)	Cell culture	Dyas et al (1994)
Campesteryl linoleate	Cell culture	Dyas et al (1994)
Campesteryl palmitate	Cell culture	Dyas et al (1994)
Clethric acid (**113**)	Leaves	Takashima et al (2007)
Cycloartenol (**114**)	Cell culture, leaves	Dyas et al (1994); Saludes et al (2002b)
Cycloartenyl linoleate	Cell culture	Dyas et al (1994)
Cycloartenyl palmitate	Cell culture	Dyas et al (1994)
3,19-Dihydroxyursolic acid	Fruits	Sang et al (2002)
Hederagenin (**115**)	Leaves	Takashima et al (2007)
Isofucosterol (**116**)	Cell culture	Dyas et al (1994)
Isofucosteryl linoleate	Cell culture	Dyas et al (1994)
19α-Methylursolic acid (**117**)	Fruits	Sang et al (2002)
24-Methylenecholesterol	Cell culture	Dyas et al (1994)
24-Methylenecycloartanol	Cell culture	Dyas et al (1994)
24-Methylenecycloartanyl linoleate	Cell culture	Dyas et al (1994)
Oleanolic acid (**118**)	Leaves	Takashima et al (2007)
Rotungenic acid	Leaves	Takashima et al (2007)
β-Sitosterol	Leaves, cell culture	Ahmad & Bano (1980); Dyas et al (1994); Saludes et al (2002b); Pawlus et al (2005a)
Sitosteryl linoleate	Cell culture	Dyas et al (1994)
Sitosteryl palmitate	Cell culture	Dyas et al (1994)
Stigmasta-4-en-3-one (**119**)	Leaves	Saludes et al (2002b)
Stigmasta-4-22-dien-3-one (**120**)	Leaves	Saludes et al (2002b)
Stigmasterol	Cell culture, leaves	Dyas et al (1994); Saludes et al (2002b)
Stigmasteryl linoleate	Cell culture	Dyas et al (1994)

(Continued)

Table 2 *(Continued)*

Compound structural class/name/code	Part	Reference(s)
Ursolic acid (**121**)	Leaves	Ahmad & Bano (1980); Takashima et al (2007)
Miscellaneous compounds		
(Ethylthiomethyl) benzene	Fruits	Farine et al (1996)
Hexanamide (**122**)	Fruits	Farine et al (1996)
β-Hydroxypropiovanillone (**123**)	Fruits	Pawlus et al (2005a)
4-Hydroxy-3-methoxycinnamaldehyde (**124**)	Fruits	Pawlus et al (2005a)
Isoscopoletin (**125**)	Fruits	Deng et al (2007)
Limonene (**126**)	Fruits	Farine et al (1996)
1-Palmitin (**127**)	Fruits	Pawlus et al (2005a)
Peucedanocoumarin III (**128**)	Leaves	Takashima et al (2007)
Phytol (**129**)	Leaves	Takashima et al (2007)
Potassium	Fruits	Peerzada et al (1990)
Pteryxin (**130**)	Leaves	Takashima et al (2007)
Roseoside II (**131**)	Leaves	Takashima et al (2007)
Scopoletin (**132**)	Fruits	Saludes et al (2002a); Pawlus et al (2005a); Samoylenko et al (2006); Deng et al (2007)
Vanillin (**133**)	Fruits	Pawlus et al (2005a); Deng et al (2007)
Vomifoliol (**134**)	Fruits	Farine et al (1996)

[a]Suggested by the author to be an extraction artifact (Leistner 1975).

related to noni juice consumption from a patient with chronic renal insufficiency (Mueller et al 2000). This patient demonstrated elevated potassium levels despite claims of compliance with a low-potassium diet, but was reported to be taking a shot glass of noni juice before each meal. The authors found the potassium level of a specific noni juice product to be 56.3 $mEqL^{-1}$, which is similar to levels found in orange and tomato juices. The authors concluded that because the recommended dose is 1–3 oz of juice per day, noni juice does not pose a great threat of hyperkalaemia to those on a potassium-restricted diet unless they exceed the recommended dose. Unfortunately, they were unable to confirm which product the patient used or whether he was compliant with the manufacturer's recommended dosage. In a second report, a 41-year-old female developed coumadin resistance after beginning the daily consumption of noni juice product (Noni Juice 4 Everything) (Carr et al 2004). In a related report, noni juice has been found to inhibit angiotensin-I-converting enzyme (ACE) (Yamaguchi et al 2002). Since ACE inhibitors cause a decrease in potassium secretion, this activity, in addition to its potassium content, may contribute to hyperkalaemia in patients on potassium-restricted diets.

In addition to these reports of hyperkalaemia, there are several reports linking noni fruit juice consumption to hepatotoxicity. In one case at the Medical University of Innsbruck in Austria, a 45-year-old male patient presented with complaints of malaise and non-specific thoracic discomfort. Routine blood work showed a clinically significant elevation in liver enzymes, including transaminases and lactate dehydrogenase, suggesting some form of hepatic injury. This patient was not on any chronic medications but had begun taking a glass of noni juice every day for the previous few weeks. After excluding other potential causes of these elevated liver enzymes, the authors concluded that the toxic symptoms were most likely caused by noni juice. After discontinuing for one month, the patient's liver enzymes returned to normal (Millonig et al 2005). In 2005, Stadlbauer and co-workers at the Medical University of Graz in Austria reported on two patients suffering from hepatotoxicity while consuming noni juice (Stadlbauer et al 2005). In one case, a 29-year-old male patient presented with acute hepatitis. The patient was taking noni (1.5 L of the fruit juice), along with a mixture of herbal drugs from Chinese traditional medicine listed in the case report as bupleuri, condonopsis, glycyrrhizae, paeonia, pinellia, schizonepeta and scutellaria. This patient subsequently underwent a liver transplant. In the second case, a 62-year-old female presented with nausea and vomiting. Routine blood work showed an increase in liver enzymes, indicative of acute hepatitis, and a liver biopsy was consistent with the type of hepatitis found in idiosyncratic drug reactions. The patient reported taking 2 L of noni juice between April and July of that year. Nine months after discontinuing noni juice, the patient's liver enzymes returned to normal (Stadlbauer et al 2005). Another case involved a young female patient in Germany with multiple sclerosis who was being treated with interferon beta-1a. This patient presented with jaundice and high transaminase and bilirubin levels. Fine-needle aspirations were performed and autoimmune hepatitis was ruled out, but signs of drug-induced toxicity were found. The patient stated she had been consuming noni juice over the past four weeks and her liver enzyme levels returned to normal levels one month after discontinuing noni (Yüce et al 2006). Since the majority of these patients were also taking other medicines or herbs, any direct correlation with noni ingestion has been

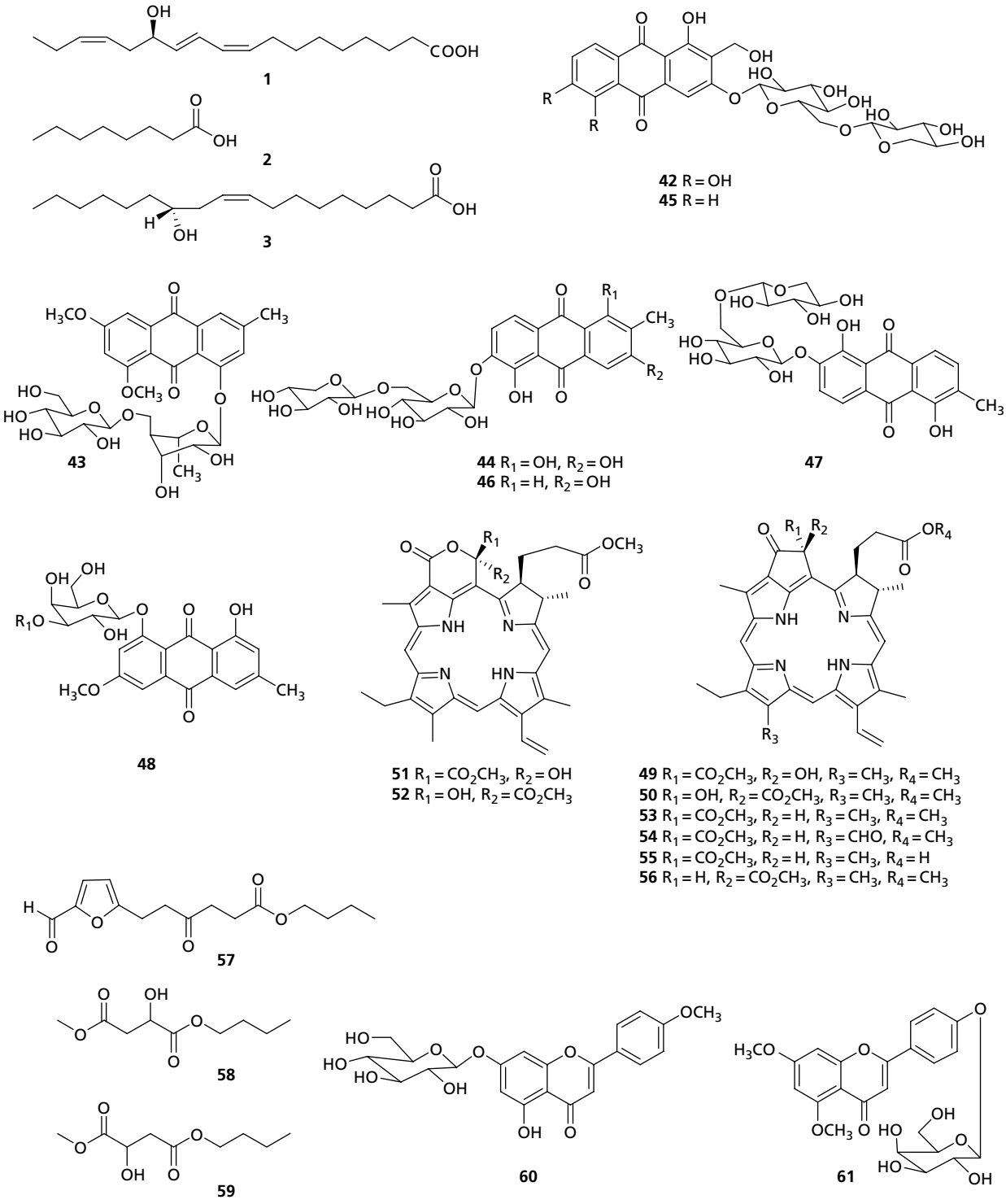
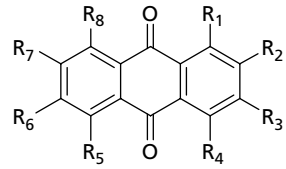


Figure 2 Chemical structures of compounds isolated from *Morinda citrifolia.*



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
4	OH	OH	H	H	H	H	H	H
5	OH	OCH_3	H	H	H	H	H	H
6	OCH_3	OCH_3	OH	H	H	H	H	H
7	OCH_3	OH	OCH_3	H	H	H	H	H
8	OH	OCH_3	OCH_3	H	H	H	H	H
9	OH	OCH_3	OH	H	H	H	H	H
10	OH	OCH_3	H	OH	H	H	CH_3	H
11	OCH_3	CHO	OH	H	H	H	H	H
12	OCH_3	CH_2OH	OH	H	H	H	H	H
13	OH	CH_2OH	OH	H	OH	OH	H	H
14	OH	CH_2OCH_3	H	H	OCH_3	OH	H	H
15	OH	$CH_2OCH_2CH_3$	OCH_3	H	OH	OH	H	H
16	H	CHO	H	H	H	H	H	H
17	OCH_3	OH	OCH_3	H	H	OH	H	H
18	H	OH	H	H	H	H	H	H
19	OH	CH_3	H	H	H	H	H	H
20	OCH_3	OH	H	H	H	H	CH_3	H
21	OH	CH_3	OH	H	OH	OH	H	H
22	OH	$CH_2OCH_2CH_3$	OH	H	H	H	H	H
23	OH	CH_2OH	OH	H	H	H	H	H
24	OH	CH_2OCH_3	OH	H	H	H	H	H
25	H	OCH_3	H	H	H	H	H	H
26	CH_3	H	OH	H	H	H	H	H
27	OH	OCH_3	OH	H	H	OH	H	H
28	OH	OH	H	H	H	CH_3	OH	H
29	OCH_3	H	OCH_3	H	H	OH	CH_3	H
30	OH	OCH_3	H	H	H	H	CH_3	OH
31	OCH_3	OH	H	H	H	H	CH_2OCH_3	OCH_3
32	OCH_3	H	OCH_3	CH_2OH	H	H	CH_2OCH_3	OCH_3
33	OH	OH	H	H	OH	CH_3	H	H
34	OH	CH_3	H	H	OCH_3	OH	H	H
35	OH	CHO	OH	H	H	H	H	H
36	OH	H	OCH_3	H	H	CH_3	H	OH
37	OH	CH_3	OH	H	H	H	H	H
38	OH	CH_3	H	H	H	OH	H	H
39	OCH_3	CH_3	OH	H	H	H	H	H
40	H	CH_3	H	H	H	H	H	H
41	OCH_3	CH_2OCH_3	H	H	OCH_3	OH	H	H

Figure 2 *(Continued).*

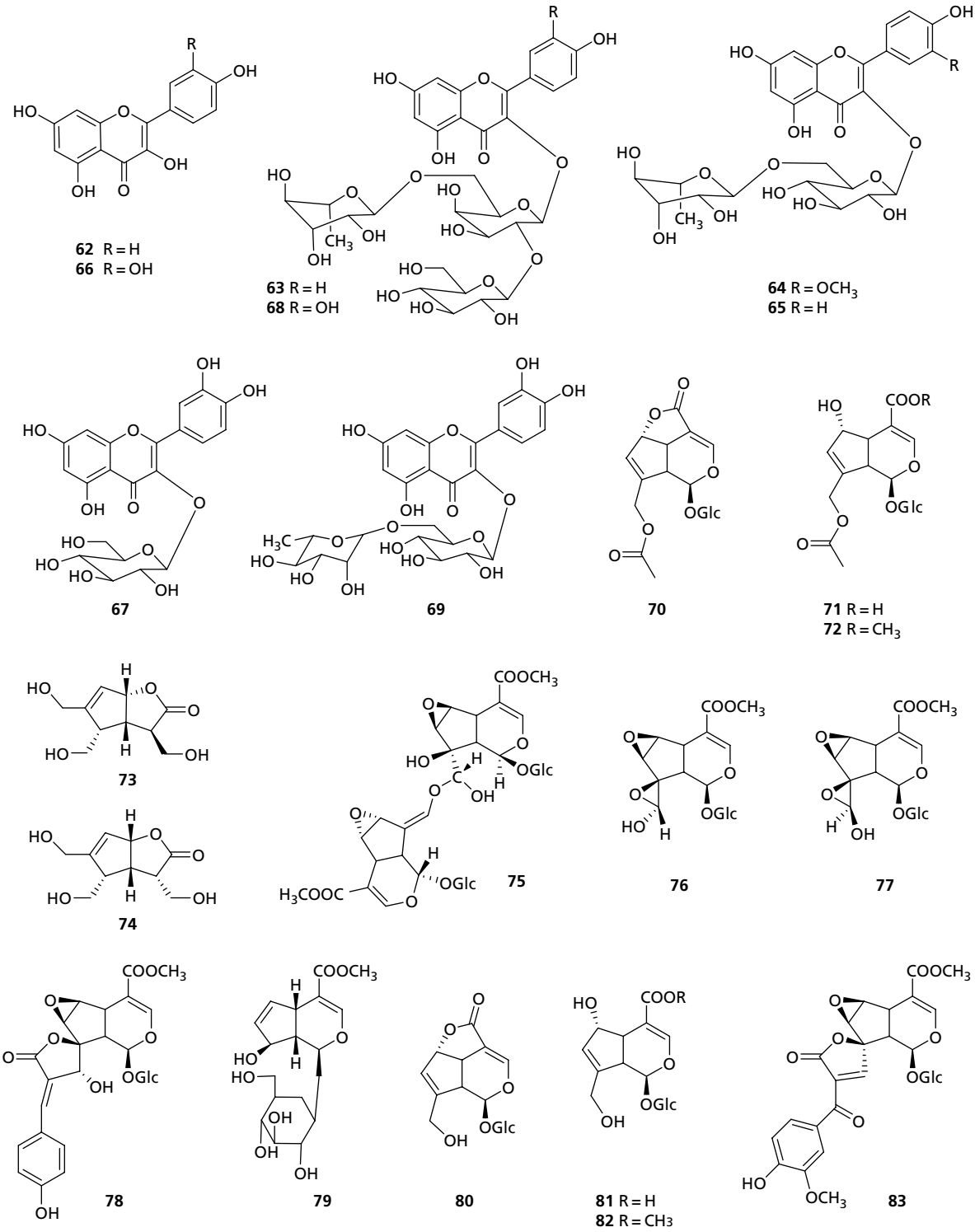


Figure 2 *(Continued).*

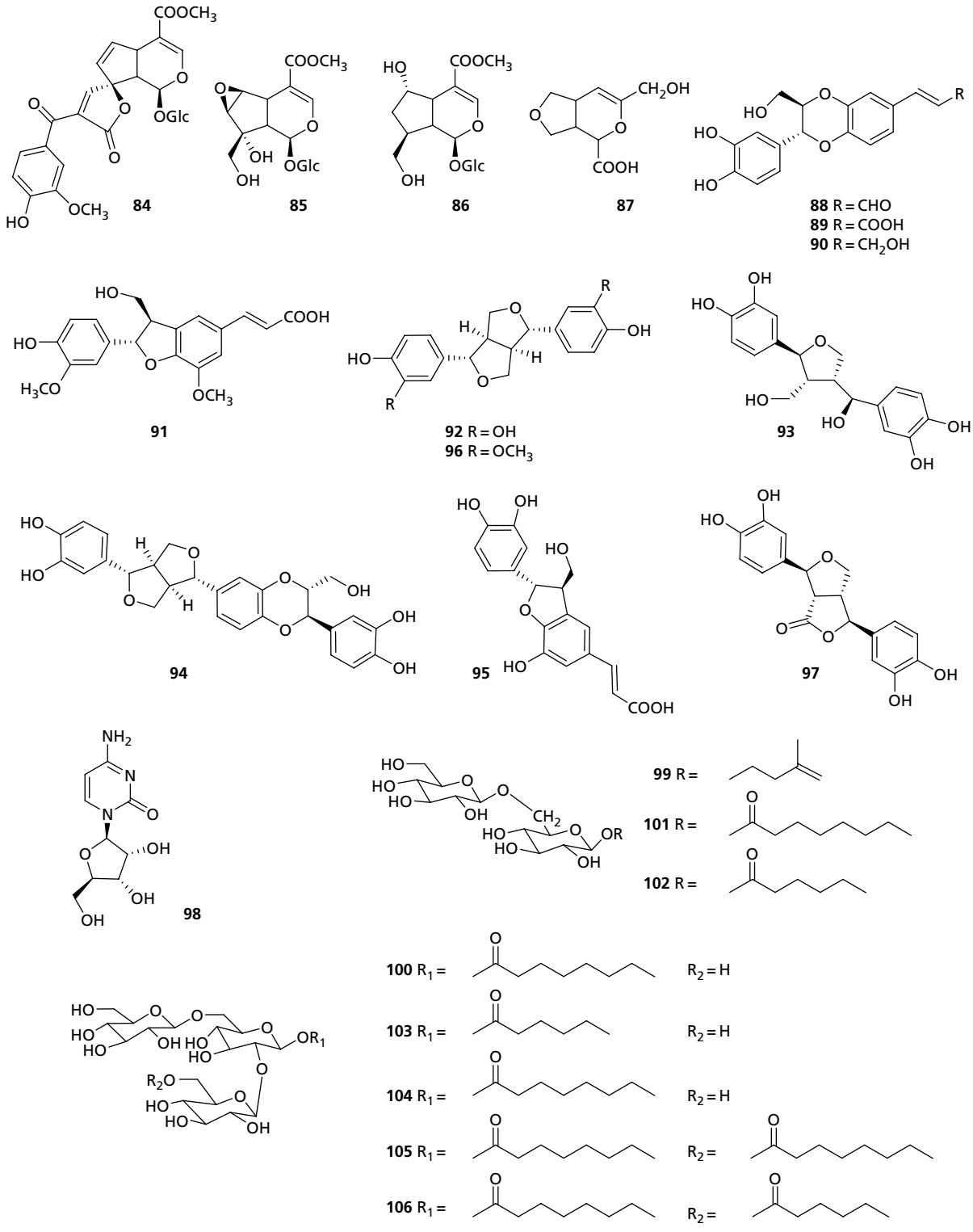


Figure 2 *(Continued).*

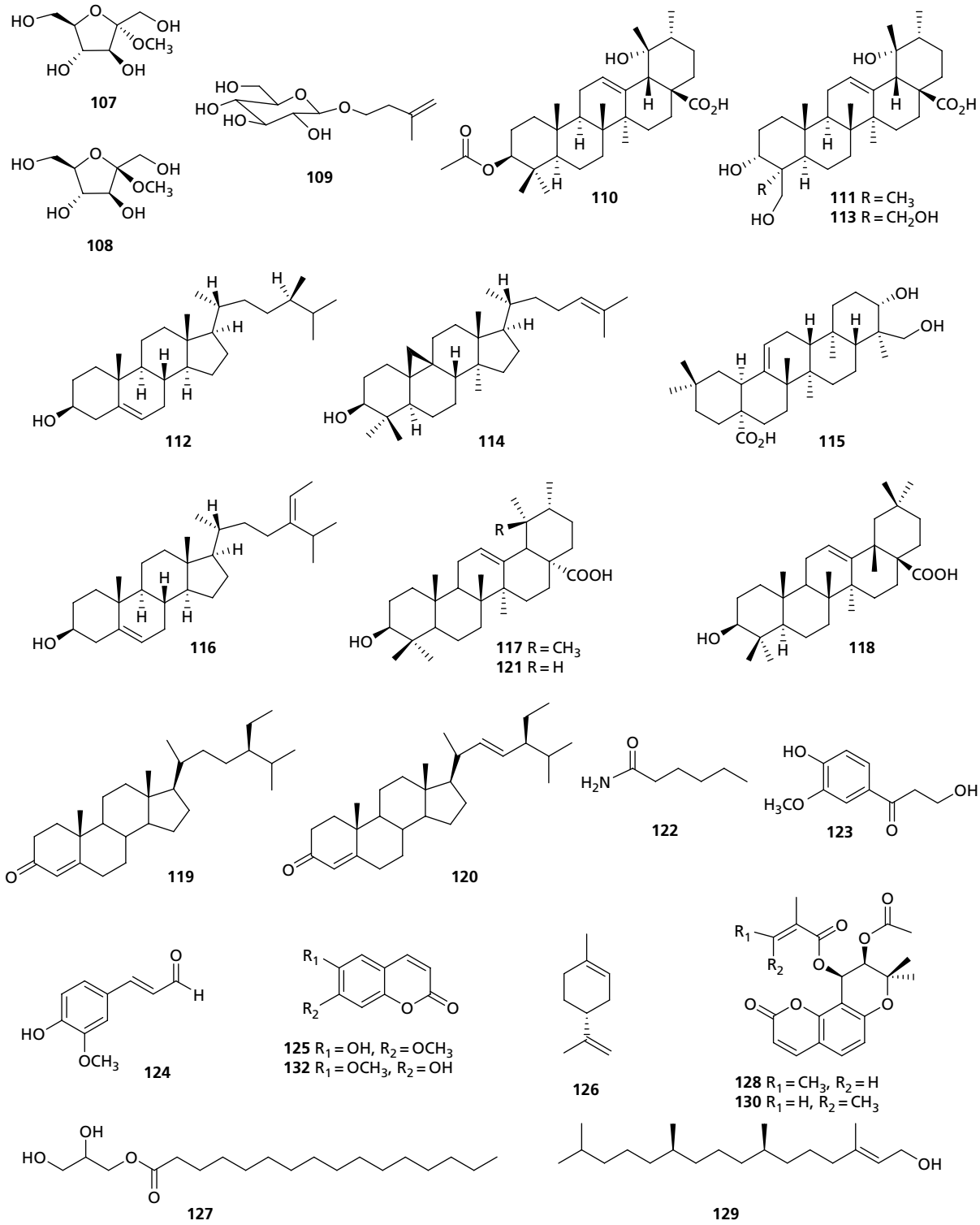
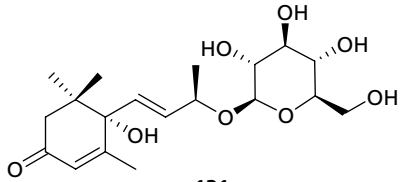


Figure 2 *(Continued).*



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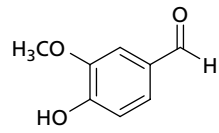

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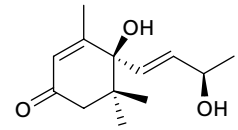

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Figure 2 *(Continued).*

challenged (Jensen et al 2006; West 2006; West et al 2006). In a safety review of noni by West et al (2006), the animal and human studies performed previously on noni were summarized, including those that examined the effect of noni on liver enzyme levels. Additionally, a list of reports in the literature of noni being used as a food was provided. The general conclusion was that the animal and human studies indicate that noni is safe for consumption (West et al 2006).

In a recently concluded phase I clinical trial, funded by the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health, Bethesda, MD, capsules containing freeze-dried noni fruit were administered to cancer patients at doses in the range 2–10 g. The purpose of this study was to determine possible benefits to these patients in addition to determining dosing, toxicity and biomarker compounds for bioavailability and pharmacokinetics studies. There was no observed toxicitiy or tumour response, but there was a significant alleviation in pain with activity, and an improvement, not considered statistically significant, in fatigue and physical functioning (Issell et al 2005). A full report on this clinical trial has yet to be published. With regard to its safety in pregnant and lactating women, noni has not been clinically evaluated. It has been reported that the ingestion of a large amount of the fruits can cause an abortion and the root bark has been used as an abortifacient in the Pacific island of Futuna. This activity has not been confirmed experimentally (Cambie & Brewis 1997).

Conclusions

Morinda citrifolia has been used as a medicinal plant for centuries and its use has continued to grow; it was disseminated throughout the tropics as a canoe crop, brought by early Polynesian settlers, and now has spread to the developed world as a popular dietary supplement. Noni's recent growth as a supplement is most likely due to marketing claims and is supported by at least some recent scientific studies suggesting broad potential health benefits from its use. Biological testing on crude extracts and pure compounds has been performed showing antioxidant, anti-inflammatory, antinociceptive, anti-cancer, anti-diabetic and antihypertensive activity. This activity was primarily found in preliminary in-vitro test systems and needs to be verified in more complex models. Additionally, the majority of the animal studies were undertaken by injecting the plant material into the test subject. Therefore, caution must be exercised before assuming that these results can be extrapolated to oral consumption in man.

Notwithstanding the need for caution, noni studies have provided several biological results that warrant further investigation. For example, the polysaccharide-rich precipitate should be further investigated. The relevant questions are whether the activity is specific to noni and whether it can be replicated orally. If not, further research would be necessary to afford a practical method of administration in man. However, these compounds are not the only ones in noni with promising biological activity. For example, according to in-vitro testing, the anthraquinone, 2-methoxy-1,3,6-trihydroxyanthraquinone (**27**), is one of the most potent quinone reductase enzyme inducers so far known and it did not demonstrate cell toxicity. This detoxifying enzyme (a phase II enzyme) is considered important in the prevention of the initiation phase of cancer. Although compound **27** is found at very low concentrations in the fruit, its biological properties make it such a promising candidate for further biological testing that chemical synthesis is warranted. Another promising area of further research is the use of noni for high blood pressure. Noni extracts demonstrated hypotensive activity when injected into animals and have been shown to have ACE-inhibitory activity. Since ACE inhibitors are commonly prescribed to treat high blood pressure, this activity points to a potential therapeutic use. However, it also points to the danger of drug and disease interactions, since ACE inhibitors cause potassium retention, which could explain the clinical report of coumadin resistance developing in a patient taking noni.

In addition to results from biological studies, ethnobotanical reports also provide promising leads for research. Some reported uses are common to a wide variety of cultures. This consistency makes it tempting to believe that noni will be useful for these ailments. In particular, its prevalent use for open sores and inflamed areas of the skin in multiple ethnic groups strongly suggest that it has efficacy for this purpose. This and other more exotic traditional uses of noni present promising areas for further research. Approximately 200 compounds have already been identified from noni, including anthraquinones, flavonoids, glycosides, iridoids, lignans and triterpenoids. While the structures of these compounds are known, their biological activity as pure entities and their significance when present as constituents of noni extracts are still just being elucidated. As the therapeutic and preventative effects of noni become better understood and as the active ingredients become more apparent, analytical methods for standardization of noni in terms of its active and major constituents can be developed. This would be an important step in the development of reproducible noni products for clinical testing, as well as the creation of monographs for chemical methods of quality control.

Table 3 Biological activity of *Morinda citrifolia* extracts and pure constituents

Anti-cancer and cancer chemopreventive activity		
Ethanol-insoluble precipitate of fruits	Increased lifespan of mice implanted with Lewis lung carcinoma cells that were injected intraperitoneally. This activity was blocked when given concurrently with the immunosuppressants 2-chloradenosine or ciclosporin. Also, there was an increased activity of chemotherapeutic agents, vincristine, 5-fluorouracil, cisplatin, and adriamycin compared with agent alone.	Hirazumi et al (1994)
Ethanol-insoluble precipitate of fruits, from Hawaii and Tahiti, injected intraperitoneally	Increased lifespan of mice implanted with sarcoma 180 cells. This activity was blocked when given concurrently with immunosuppressants, 2-chloroadenosine, anti-asialo GM1 antibody and ciclosporin.	Furusawa et al (2003)
Methanol extract from leaves	Inhibited Epstein-Barr virus activation induced by the tumor promoter, 12-*O*-hexadecanoylphorbol-13-acetate, on Raji human B-lymphoblastoid cells	Murakami et al (1995)
Fruit juice (Tahitian) supplied in drinking water (10%)	Decreased the amount of 7,12-dimethyl[*a*]benzanthracene-DNA adducts in the heart, lung, liver, and kidney, compared with negative controls, in female SD mice and male C57 Bl-6 mice when given for seven days prior to ingestion of carcinogen.	Wang & Su (2001)
Damnacanthal (**11**)	Potent inhibitor of specific tyrosine kinases, including $p56^{lck}$, in a cell-free system but not in a whole cell system. Induced normal morphology in cells expressing the *ras* oncogene, termed K-ras^{ts}-NRK cells, but not in cells expressing the *src* oncogene.	Hiramatsu et al (1993); Faltynek et al (1995); Hiwasa et al (1999)
Damnacanthal (**11**) and morindone (**33**)	Demonstrated strong topoisomerase II inhibition in a cell-free test system.	Tosa et al (1998)
Dichloromethane partition of the methanol extract of the fruits and 2-methoxy-1,3,6-trihydroxyanthraquinone (**27**)	The extract demonstrated significant phase II enzyme induction activity and the isolated compound, 2-methoxy-1,3,6-trihydroxyanthraquinone (**27**), was found to be a very potent phase II enzyme inducer in hepa1c1c7 murine hepatoma cells with no perceivable cytotoxicity.	Pawlus et al (2005a)
Dehydroepoxymethoxygaertneroside (**83**)	Prevented ultraviolet B-induced (UVB) activator protein-1 (AP-1) activity in cell culture.	Sang et al (2001c, d)
Asperulosidic acid (**71**) and nonioside C (**101**)	Suppressed 12-*O*-tetradecanoylphorbol 13-acetate and epidermal growth factor induced AP-1 transactivation in JB6 mouse epidermal cells.	Liu et al (2001)
Fruit juice at 5 and 10% in growth media	Noni juice was able to effectively suppress angiogenic initiation in an in-vitro angiogenesis model using placental vein explants and in human breast cancer explants.	Hornick et al (2003)
Anti-diabetic activity		
Fermented aqueous extract of fruits supplied in the drinking water	Decreased blood glucose levels in Sprague-Dawley rats with streptozotocin-induced diabetes compared with drinking water alone. There was also an increase in wound repair, of an inflicted excision wound, in these mice.	Nayak et al (2007)
Cardiovascular disease		
Methanol-soluble leaf extract	Did not demonstrate inhibition of LDL oxidation, but it caused an increase in LDL receptors in liver cells.	Salleh et al (2002)
Methanol extract and ethyl acetate partition of the fruits, 3,3′-bisdemethylpinoresinol (**92**), americanol A (**90**), morindolin (**95**) and isoprincepin (**94**)	Inhibited copper-induced LDL oxidation.	Kamiya et al (2004)
Water-soluble partition of roots	Demonstrated significant hypotensive activity when injected intravenously into a rabbit and dog. The alcohol-soluble partition was inactive.	Youngken et al (1960)
Juice of green and ripe fruit	Inhibited angiotensin I-converting enzyme (ACE) and oral administration reduced systolic lood pressure of male spontaneously hypertensive rats.	Yamaguchi et al (2002)
Antioxidant activity		
Fruit juice (Tahitian)	Demonstrated antioxidant activity in both lipid hydroperoxide and tetrazolium nitroblue assays.	Wang & Su (2001)
Leaf, root, and fruit methanol extracts and ethyl acetate partitions	The root methanol extract and the ethyl acetate partitions of all parts of the plant tested had antioxidant activity, similar to the positive controls, using the ferric thiocyanate method (FTC) and thiobarbituric acid test (TBA).	Zin et al (2002)
Fruit juice and polysaccharide-rich precipitate	No protection against superoxide-mediated tissue damage was afforded to rats given noni-precipitate or noni-juice.	Berg & Furusawa (2007)
Americanin A (**88**)	Demonstrated free-radical scavenging activity in a DPPH bioassay.	Su et al (2005)
Narcissoside (**64**)	Demonstrated free-radical scavenging in a $ONOO^-$ bioassay.	Su et al (2005)

(Continued)

Table 3 (*Continued*)

Anti-inflammatory and analgesic activity		
Ethanol extract of the bark, leaf, fresh fruit juice and fruit powder	The fruit powder had a "high" inhibition of cyclooxygenase-1 (COX-1) whereas the leaf extract had a "moderate" inhibition, as defined by the authors.	Li et al (2003)
Fruit juice (Tahitian)	Demonstrated higher selectivity to COX-2 than COX-1.	Wang et al (2002)
Aqueous extract of roots, injected intraperitoneally	Decreased the number of contortions in the writhing test, using acetic acid injection, and increased the reaction time in the hot-plate test in 9-week old male Swiss mice. The morphine antagonist, naloxone, reversed these effects. Also decreased locomotor activity in these mice.	Younos et al (1990)
Ethyl acetate partition of fruits, (+)-3,4,3′,4′-tetrahydroxy-9, 7′α-epoxylignano-7α,9′-lactone (**97**), (+)-3,3′-bisdemethyltanegool, quercetin (**62**) and kaempferol (**66**)	(+)-3,4,3′,4′-Tetrahydroxy-9,7′α-epoxylignano-7α,9′-lactone (**97**), (+)-3,3′-bisdemethyltanegool, quercetin (**62**) and kaempferol (**66**) strongly inhibited 15-lipooxygenase activity and quercetin also strongly inhibited 5-lipooxygenase activity.	Deng et al (2007)
Anti-infective activity		
Fruit juice, both ripe and unripe	The ripe fruits demonstrated zones of inhibition between 10 and 20 mm against *Salmonella typhosa, Salmonella montevideo, Salmonella schottmuelleri*, two *Shigella paradys* strains, *Micrococcus pyogenes, Escherichia coli* and *Pseudomonas aeruginosa*. The young fruits had similar zones of inhibition against *S. typhosa* and the two *S. paradys* strains.	Bushnell et al (1950)
The methanol partition of the ethanol extract of the root bark, stem bark and leaves	The root bark demonstrated a zone of inhibition of 7–15 mm against the Gram-positive bacteria, *Staphylococcus albus* and *Bacillus subtilis*, and the stem bark had a zone of inhibition of 7–15 mm against *S. albus* and zone of inhibition of 3–6 mm against *B. subtilis*. Both were inactive against the Gram-negative bacteria, *P. aeruginosa* and *Klebsiella pneumonia.*	Sundarrao et al (1993)
Hexane, methylene chloride, acetonitrile, methanol and water fruit extracts	Did not demonstrat in-vitro antiviral activity against Herpes Simplex-1; antibacterial activity against *Streptococcus pyogenes, Staphylococcus aureus, P. aeruginosa* and *E. coli*; and antifungal activity against *Microsporum canis, Epidermophyton floccosum* and *Trichophyton rubrum.*	Locher et al (1995)
Hexane partition of the ethanol extract of the fruits and leaves	Demonstrated in-vitro activity against *Mycobacterium tuberculosis.*	Saludes et al (2002a, b)
Ethanol extract, plant part not stated	Did not inhibit HIV-1 reverse transcriptase in-vitro.	Tan et al (1991)
Water and dichloromethane extract of fruits	Lacked antiviral activity against HIV-1 virus infected cells.	Locher et al (1996)
Effects on collagenase		
Fruit extract and austrocortinin (**10**)	Increased collagen synthesis in human dermal fibroblast cells via induction of type I procollagen and reduction of the collagenase, matrix metalloproteinase-1.	Kim et al (2005)
Fertility and oestrogenicity		
Aqueous extract injected subcutaneously, plant part not stated	No antifertility in female mice was found either pre- or post-mating.	Matsui et al (1967)
Aqueous and alcohol water extracts of unripe fruits injected intraperitoneally	Demonstrated very weak oestrogenic activity in immature female mice.	Chearskul et al (2004)
Genotoxicity		
Fruit alone or mixed with grape and blueberry juice, and the ethyl acetate partition	Demonstrated slightly mutagenic in Salmonella microsome assay in strain TA1537, reportedly due to the flavonoids, and was not mutagenic in V79 Chinese hamster fibroblasts. No DNA adducts or strand breaks were observed in rat studies.	Westendorf et al (2007)

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