

Abstract

Products derived from Noni fruit (*Morinda citrifolia*) have been commercialised in the USA since the 1990s and are increasingly distributed all over the world. A large number of beneficial effects have been claimed for Noni. Fruit juice of Noni has been approved as a Novel Food by the European Commission in 2003. This article reviews current knowledge on the phytochemistry, pharmacology, safety aspects of Noni fruit and Noni-derived products, and health-related claims and benefits. The knowledge on the chemical composition of Noni fruit has considerably increased over recent years. A number of *in vitro* and, to a certain extent, *in vivo* studies demonstrate a range of potentially benefi-

cial effects. However, clinical data are essentially lacking. To what extent the findings from experimental pharmacological studies are of potential clinical relevance is not clear at present. Based on a toxicological assessment, Noni juice was considered as safe. Due to recent reports of cases of hepatotoxicity, the safety issue has been re-examined in Europe. While the European Food Safety Authority sees no link between adverse effects on liver and consumption of Noni juice, a continuing monitoring of the situation is desirable and some vigilance advised.

Key words

Noni · *Morinda citrifolia* · Rubiaceae · novel food · phytochemistry · pharmacology · hepatotoxicity

Introduction

Products derived from the fruit of *Morinda citrifolia* (Noni) have gained considerable popularity and are sold worldwide as Food Supplements and Novel Food, mostly via the Internet. Current opinions regarding the value of Noni products differ considerably and range from very positive [1] to highly critical [2] or cautious [3]. The extraordinary transformation of Noni from a Polynesian ethnomedicine to a commercial food supplement with a wide spectrum of health-related claims was probably spurred by a publication in 1985 in the Pacific Tropical Garden Bulletin [4], in which the author claimed the presence of an active “alkaloid” named *xeronine*. This compound, for which no structure was given, was said to derive from a precursor, *proxeronine*. The author described a wide range of potential indications for Noni

juice including “high blood pressure, menstrual cramps, arthritis, gastric ulcers, sprains, injuries, mental depression, senility, poor digestion, atherosclerosis, blood vessel problems, drug addiction, relief of pain and many others.”

Noni products have been commercialised in the USA since the 1990s and are nowadays available in health food stores and on the Internet [5]. Products derived from leaves and fruits are being sold as capsules, teas, and as juice, the fruit juice being the predominant form. Juices may be pasteurised or obtained by a fermentation process; some of the Noni juices are flavoured by addition of other fruit juices to render the product more palatable. The popularity of Noni products in the USA has been attributed to claims of a “cure-all” for a variety of diseases [3]. Noni fruit juice is legally sold in the European Community since

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2003, and other products are readily available on the Internet. Reliable sale figures are not available, but it is claimed that the market has reached US\$ 1.3 billion in annual sales.

Morinda citrifolia L. belongs to the family Rubiaceae. The genus *Morinda* comprises some 80 species which all occur exclusively in tropical climate zones [6]. *M. citrifolia* is an evergreen tree or shrub 3 to 6 m high, with bright green ovate and deeply veined leaves which are 10 to 30 cm long. The tubular flowers are white. The unusual fruit has an ovoid shape covered by polygonal-shaped sections. It reaches a length of up to 12 cm and has the size of a potato. The immature fruit is hard and has a bright green colour. Upon ripening, the fruits become very soft and turn to a translucent yellowish or white. The ripe fruit has an unpleasant butyric and cheesy odour and soapy taste. The seeds are buoyant due to an air sac attached at one end and may germinate even after extended periods of drifting in the sea. This explains, in part, the wide distribution of the Noni tree in the Indo-Pacific Islands which was further favoured by the migration of seafaring Polynesians. *Morinda citrifolia* occurs from India through South-east Asia and Australia to Eastern Polynesia and Hawaii. More recently, the plant has been introduced to other regions with tropical climates. Commonly used vernacular names are "Indian Mulberry", "Noni" and "Nonu"; in Australia, the fruit is commonly known as "cheese fruit".

Morinda citrifolia has a long tradition as a medicinal plant in India and the Pacific Islands. All parts of the plants have been used including leaf, fruit, roots, bark, flower and seed. Typical uses have been reported as a treatment of boils and cures, abscesses, and inflammations of various origins, fungal infections, constipation as well as diarrhoea [3], [5]. Root and bark of the Noni tree have been used as natural yellow and red dyes, due to their content in anthraquinones. Ethnobotanical investigations on the dietary habits of aboriginal populations of Polynesia and Australia report on raw or cooked Noni fruit. However, its consumption was apparently limited to times of famine due to the unpleasant taste and flavour of the ripe fruits [3], [6].

To satisfy the increasing demand for Noni products, cultivation has been established in Polynesia and Hawaii. *M. citrifolia* is relatively easy to propagate, either from seeds or from cuttings. The tree grows at altitudes up to 400 m and is fairly undemanding once mature. Noni plants begin to bear fruits already one year after planting. Mature trees typically produce 120 – 250 kg of fruits per year. In Hawaii, average annual yields of 50 t per hectare are achieved [7]. Considering a 60% extraction rate, this would correspond to an annual production of 30 t of juice per hectare. Even though Noni farming seems profitable, it is no match to the staggering profits achieved at the wholesale and retail levels if one considers the current pricing of Noni products [8]. Noni juices are prepared by a variety of methods. Traditionally, mature Noni fruits are fermented in a collection vessel and the juice collected by drip-extraction. Non-fermented juices are obtained by squeezing or pressing mature fruits and preservation by pasteurization. Solid dosage forms such as capsules contain a powder obtained by evaporation of the juice and addition of non-hygroscopic excipients to avoid clumping of the highly hygroscopic dry extract [8].

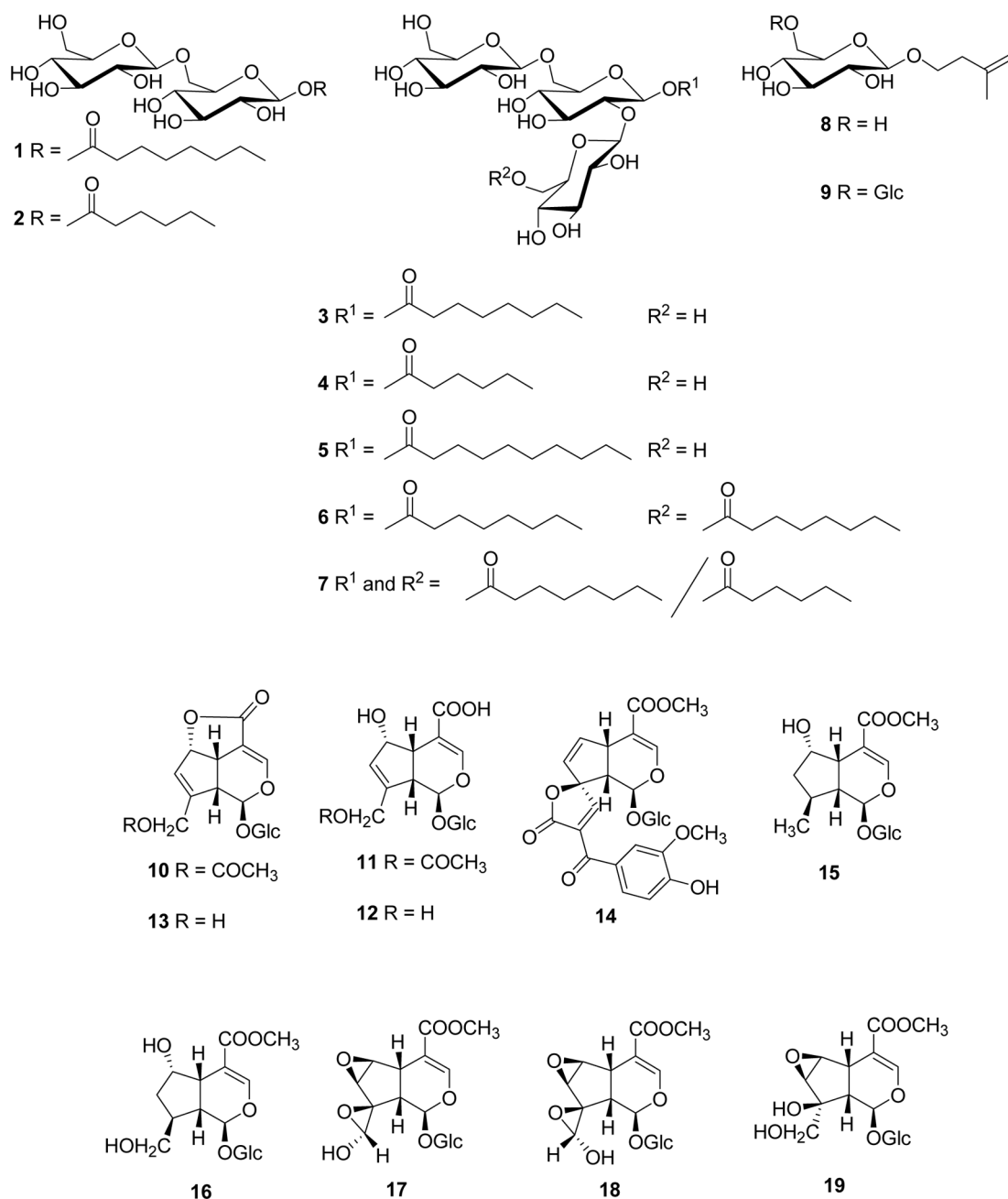
Phytochemistry of Noni Fruit

Early phytochemical investigations on *M. citrifolia* focussed on secondary metabolites in leaves, roots and bark. The roots contain a wide spectrum of anthraquinones such as rubiadin, damnacanthal and alizarin-1-methyl ether, naphthoquinone derivatives and sterols [9], whereas several iridoids, flavonol glycosides and triterpenes were reported from the leaves [10]. Plant cell cultures were analysed mainly for their capabilities for synthesis of anthraquinoid pigments. The interest in the constituents of the fruit was stimulated by the introduction of fruits juices as food supplement. Up to now, several classes of metabolites have been described, including polysaccharides, fatty acid glycosides, iridoids, anthraquinones, coumarins, flavonoids, lignans, phyto-sterols, carotenoids, and a range of volatile constituents including monoterpenes and short chain fatty acids and fatty acid esters.

Nutritional composition of unfermented Noni juice has been analysed. It contains approx. 10% of dry matter consisting mainly of glucose and fructose (3 – 4% each), protein (0.2 – 0.5%) and lipids (0.1 – 0.2%). The content in potassium is relatively high (30 – 150 ppm), followed by calcium, sodium and magnesium. Vitamin C contents reported varied from 30 – 155 mg/kg [11], [12]. The polysaccharide fraction consists primarily of the pectins homogalacturonan, rhamnogalacturonan I, arabinan, and type I and II arabinogalactans [13].

Among the phytochemicals reported so far in the fruits, the fatty acid glycosides (**1** – **7**) and alcohols (**8** and **9**) appear quite unique with respect to their structures and content in ripe fruits [14], [15], [16], [17] (Fig. 1). They consist of one, occasionally two short-chain fatty acids, or an alcohol attached to a sugar moiety consisting of one to three glucoses. Due to their structure, they possess more or less pronounced amphiphilic properties and may be, at least in part, responsible for the soapy taste of ripe fruits.

Noni fruit contains numerous iridoids. Main compounds are asperuloside (**10**) [18], asperulosidic acid (**11**) and deacetylasperulosidic acid (**12**) [19]. Minor iridoids include deacetylasperuloside (**13**), dehydromethoxygaertneroside (**14**), *epi*-dihydrocornin (**15**), 6 α -hydroxyadoxoside (**16**), citrifolinin B epimers a (**17**) and b (**18**), and 6 b ,7 β -epoxy-8-*epi*-splendoside (**19**) [10], [19], [20] (Fig. 1). A number of other compounds classes have been reported. Flavonol glycosides include rutin (**20**), narcissoside (**21**) and nicotifloroside (**22**) [10], [20]. Several known and new lignans such as 3,3'-bisdemethylpinoresinol (**23**), americanol A (**24**), americanin A (**25**), americanoic acid A (**26**), morindolin (**27**), isoprincepin (**28**) [21] and balanophonin (**29**) [22] have been isolated (Fig. 2). The coumarin scopoletin (**30**) has been identified [22]. Similar to other plant parts, the fruits also contain a wide spectrum of 1-hydroxyanthraquinones (**31** – **38**) [19], [22], albeit in much lower concentrations. These include new compounds such as 2-methoxy-1,3,6-trihydroxyanthraquinone (**31**), and 5,15-dimethylmorindol (**34**). Finally, miscellaneous compounds such as β -sitosterol (**39**) and its 3-*O*-glucoside (**40**) [20], [22], ursolic acid (**41**) and 19-hydroxyursolic acid (**42**) [10], cytidine (**43**) [10], [20], borreriagenin (**44**) [20] and epiborreriagenin (**45**) [16], iridoid derivative **46** [10], succinic acid diesters (**47** – **49**) [16], 4-hydroxy-3-methoxycinnamaldehyde (**50**) [22], β -hydroxypropiovanillone (**51**) [22] and vanillin (**52**) [22] have been isolated (Fig. 3). Morin-



dacin, previously reported as a new iridoid from Noni fruit [19] was recently shown to be identical with borreriagenin (**44**) [23].

The characteristic cheesy smell of mature Noni fruits instigated the study of the volatile components collected by solvent extraction, steam distillation or solid phase microextraction (SPME). Major volatile compounds were octanoic and hexanoic acids, and 3-methyl-3-buten-1-ol. Minor compounds include other free fatty acids, alcohols, aldehydes and ketones, esters, traces of monoterpenes, and a series of sulphur compounds [24], [25]. Unripe fruits contain mainly C₁₆ and C₁₈ fatty acids, whereas fatty acids of shorter chain length are dominant in ripe fruits and are mainly responsible for their unpleasant cheese-like flavour [10].

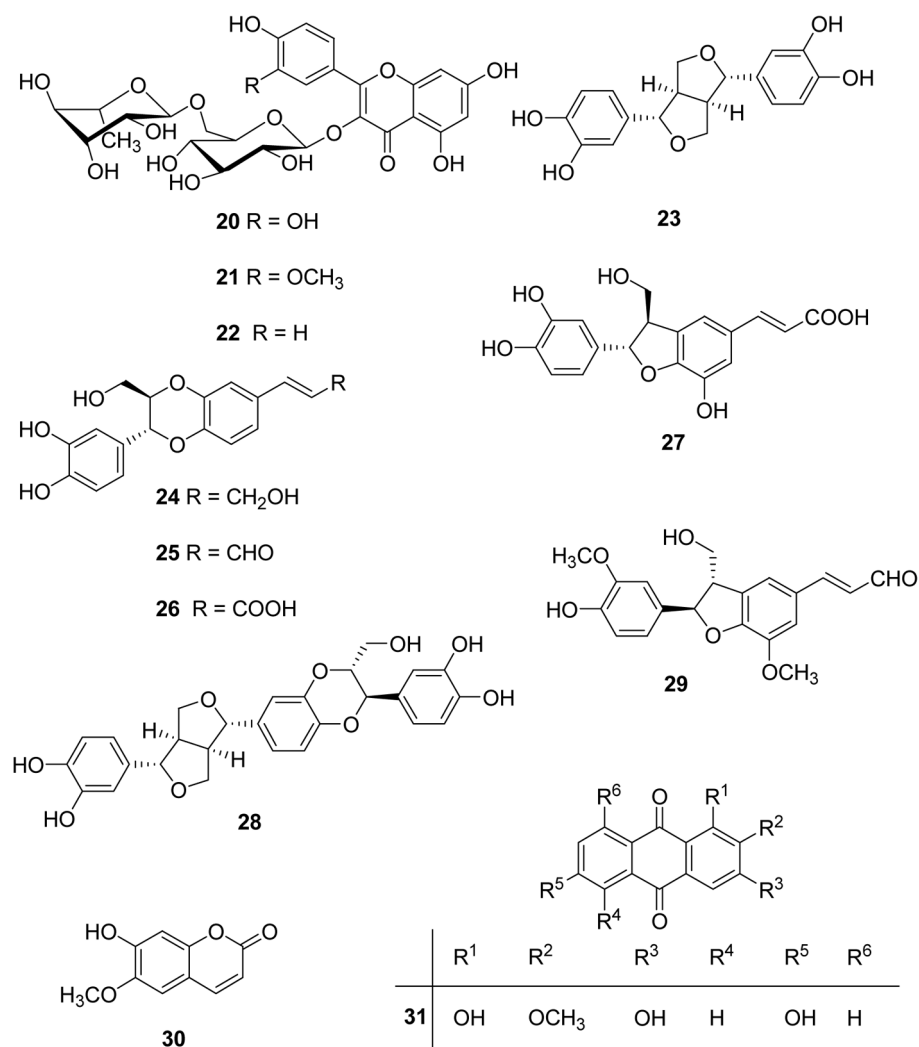
With the exception of a preliminary study [26], no methods for the control of authenticity and quality of Noni products have been published up to now. The authors used planar chromatog-

raphy for non-volatile compounds and headspace solid-phase microextraction (HS-SPME) GC-MS for analysis of volatile constituents. Chemometric data treatment revealed distinct differences in samples originating from Hawaii and Cook Islands, Tahiti, and of Noni juices mixed with other fruit juices.

Pharmacology

A growing number of pharmacological studies on Noni juice and isolated compounds from the fruit have been published in recent years. They are chiefly related to three areas: cancer, inflammation and metabolic diseases. Many of the reports are only available as congress abstracts and not (yet) as peer-reviewed research papers. Hence, the quality of the data and significance of findings cannot be fully assessed in these cases.

Fig. 2 Flavonoids, lignans, coumarins and anthraquinones in Noni fruit.

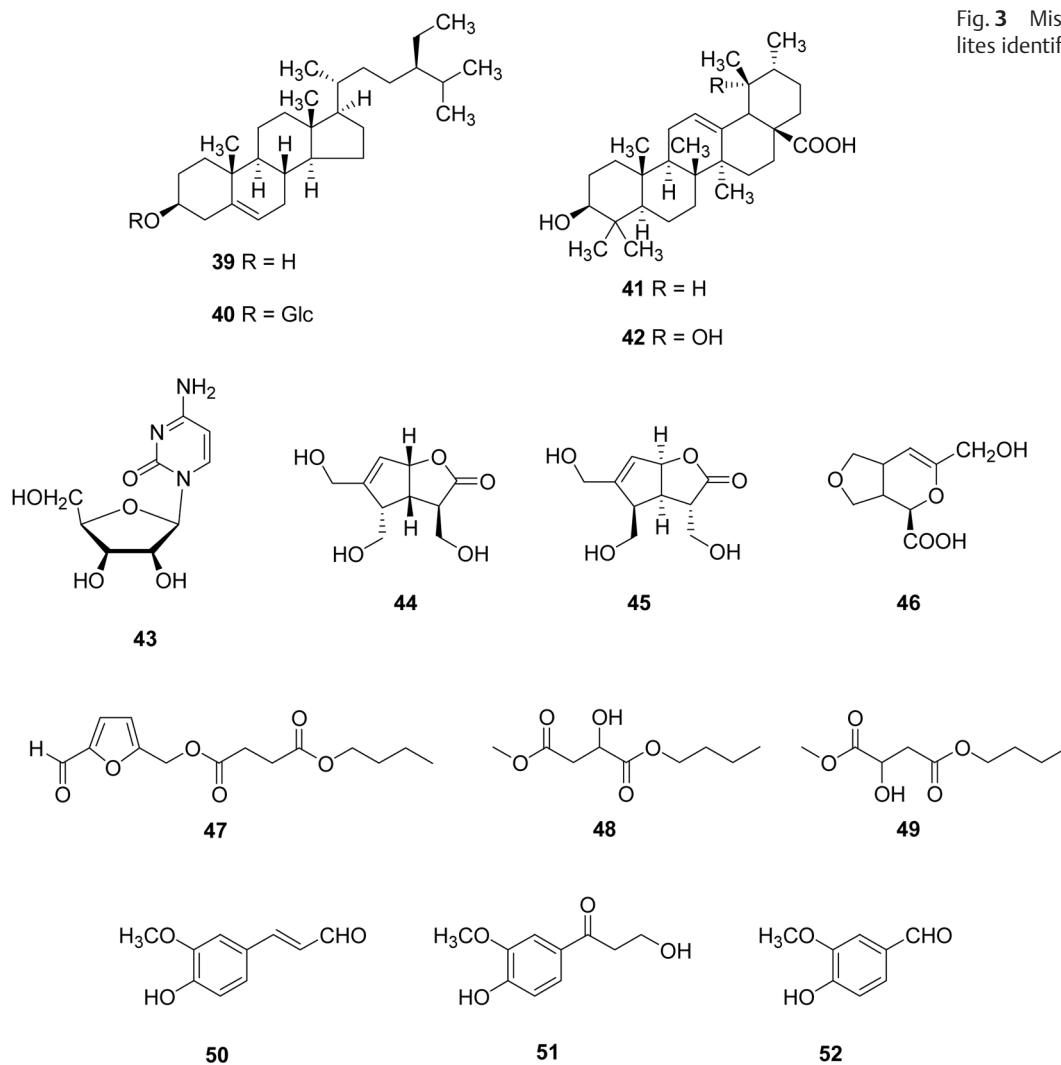


	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
31	OH	OCH ₃	OH	H	OH	H
32	OH	CH ₂ OH	H	OCH ₃	H	OH
33	OH	OCH ₃	OH	H	H	H
34	OH	CH ₃	H	OCH ₃	OH	H
35	OCH ₃	OH	H	H	H	H
36	OH	CH ₂ OCH ₃	H	OCH ₃	OH	H
37	OCH ₃	OH	OCH ₃	H	H	H
38	OCH ₃	OH	OCH ₃	H	OH	H

Fatty acid glycoside **1** and an iridoid, asperulosidic acid (**11**), were found to inhibit phorbol ester- and EGF-induced AP-1 (transcription activator protein-1) transactivation and cell transformation in mouse epidermal JB6 cells [27]. A polysaccharide-rich fraction, which was obtained from fruit juice by precipitation in ethanol, showed anti-tumour activity in the Lewis lung carcinoma model in mice. The precipitate also stimulated the release of certain cytokines such as TNF- α , IL-1 β , IL-10, and IF- γ , but not of IL-2 [28]. In a similar study, the precipitate showed anti-tumour activity against Sarcoma 180 ascites tumour in mice [29]. However, it should be mentioned that these two murine tumour models have been abandoned by the National Cancer Institute (NCI) many years ago in favour of human xenografts in nude mice.

Noni fruit reportedly had a preventive effect at the initiation stage of 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced mammary breast carcinogenesis in rats [30]. In a similar study using the same model, a synergistic effect of fruit juice and methylsulphonylmethane was observed [31], [32]. The juice also showed antimutagenic activity in ICR mice [33]. Anthraquinone **31** was identified as a potent inducer of quinone reductase activity, with a 40-fold higher potency than the well-known inducer sulforaphane. There was no discernible cytotoxicity at the highest dose tested [22]. Noni juice, at a concentration of 5%, strongly inhibited the initiation of new vessel sprouts from a model of placental vein explants. At a concentration of 10%, vessel degeneration and apoptosis in established capillary networks were ob-

Fig. 3 Miscellaneous secondary metabolites identified in Noni fruit.



served. This concentration was effective at inhibiting capillary initiation in explants from human mammary tumours, and led to degeneration of vessels in explants showing capillary sprouting [34]. Growth inhibition of breast cancer and neuroblastoma cell lines *in vitro* was reported for a methanolic extract from fruits at a concentration of 0.1 mg/mL, whereas non-cancerous cells were not inhibited at this concentration [35]. It should be noted, however, that the concentrations used in these experiments were high.

Noni fruit juice extract showed anti-inflammatory activity in the carrageenan-induced rat paw oedema when 10 or 200 mg were administered intraperitoneally. These doses were also effective in reducing the bradykinin-induced oedema in the rat paw [36]. Oral dosage of juice to neonatal equine foals (60 mL twice daily) was found to reduce the expression of COX-2 and several cytokines in LPS-stimulated monocytes in an *ex vivo* experiment. However, the number of animals was not sufficient for statistically significant findings [37]. An anthraquinone isolated from Noni fruit reportedly inhibited matrix metalloproteinase-I in primary cultures of human fibroblasts. In nude mouse skin, the compound increased the dermal type-I procollagen [38].

Noni juice reportedly lowered serum cholesterol and triglycerides in smokers [39]. In male adult Sprague-Dawley (SD) rats, an antithrombotic effect on jugular vein thrombosis induced by ferric

chloride was observed [40]. A fruit extract showed antioxidative activity in several *in vitro* test systems [41]. Lignans **23** – **28** isolated from the fruit inhibited Cu²⁺-induced oxidation of low-density lipoprotein particles *in vitro* [21]. Antioxidant activity of americanin (**25**) from a Noni fruit extract against 1,1-diphenyl-2-picrylhydrazyl (DPPH) and peroxy nitrite radicals was reported [20].

Potential antidiabetic and hepatoprotective properties have been investigated. Noni fruit extract reportedly inhibits phosphodiesterase 3 and shows agonistic activity at the P2Y receptor [42]. A protective effect against carbon tetrachloride-induced liver injury in female SD rats has been described [43].

Information on Clinical Studies

Testimonials on health beneficial properties of Noni abound on countless internet sites. Clinical data published in the scientific literature, however, are still scant. In two case reports a significantly prolonged survival of cancer patients taking Noni juice was claimed [44]. Of significantly higher interest is a Phase I clinical trial sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institute of Health (NIH). It was initiated in 2001 at the Cancer Research Center of Hawaii, Honolulu. Some information on the aims of the

study can be found at the website of the centre [45] and on the website of NIH sponsored clinical trials [46]. The hypothesis being tested is that Noni, at a specified dosing, provides cancer patients with a sufficient benefit to toxicity profile to be useful as a therapeutic. Principal aims at this point are to determine the maximum tolerated dose of a freeze-dried Noni fruit extract, to assess possible toxicities associated with the treatment, collect preliminary information on efficacy in tumour and symptom control, and identify of marker compounds for bioavailability and pharmacokinetics. Recently, preliminary data from the trial were reported. Toxicity and quality of life measures were assessed. A statistically significant decrease in pain interference with activities was observed, and a non-significant but consistent dose response effect for global health status. No tumour regression was noted [47]. According to the principal investigator, over 50 patients have entered the study at different dose levels which should be completed in 2007. The dose providing maximum quality of life should be identified in this Phase I trial, to be used subsequently in a Phase II efficacy study (B. Issell, personal communication).

Patenting Activities

A considerable number of patent applications have been filed in recent years, mainly by businesses commercialising Noni-based products. Chiefly, the claims extend to anticancer, anti-metastatic and cancer preventive properties, involving among others, aromatase inhibition and anti-angiogenetic effects [48], [49], [50], [51], [52], [53]. Use of Noni based products as antifungals, including treatment of candidiasis has been claimed [54], [55]. A third category of patents relates to rather general protective properties against cell damage [56].

Legal Status of Noni Products

Noni juice has been marketed in the USA since 1 July 1996 as a dietary supplement, as well as in Canada, Japan, Australia, Mexico, Norway and Hong Kong [3]. Noni-based products had no previous history of use in Europe. Therefore, distribution in countries of the EC required an approval either as drug or as food. The manufacturer of Tahitian Noni filed an application for approval as Novel Food which was granted by the European Commission in 2003 [57], on the basis of a report by the Scientific Committee on Food of 1 December 2002 [58]. The expert committee, however, noted that the recommended daily intake of 30 mL was rather uncommon for a fruit juice. The approval applies only to the juice of Noni fruit and not to other types of Noni products such as, for example, those based on dry extracts from fruits and leaves. Such preparations seem increasingly popular if one considers the range of products available in the USA. Some of these preparations are distributed in Europe via Internet sales. As per October 2005, the European Commission has received over 25 notifications for Noni juice as a novel food ingredient on the basis of a claimed equivalence.

Safety

A comprehensive review of safety aspects, including data from internal laboratory reports, has been recently published [59]. Neither in acute, subacute, nor subchronic testing in rats were signs of toxicity observed [60]. The LD₅₀ values of intraperitoneally injected aqueous and alcohol extracts were found to be 7500 mg/kg and 3500 mg/kg body weight, respectively, in mice [61]. This is in accord with previous reports of an LD₅₀ >1000 mg/kg in mice for an intraperitoneally injected methanolic extract of the fruit [62]. Oral toxicity tests with Tahitian Noni juice revealed no adverse effects at doses equivalent to 80 mL/kg body weight per day in rats [63], [64]. Assessment of genotoxicity in various *in vitro* and *in vivo* models did not reveal a genotoxic risk. No allergenic response was observed in guinea pigs when Noni juice was administered by gavage, intraperitoneal and intravenous application routes [59].

In 2005, two clinical case reports were published which associated consumption of Noni juice with three cases of acute hepatitis in Austria [65], [66]. While two patients recovered spontaneously after ceasing of intake, the third patient underwent liver transplantation. On 6 March 2006, the German Office for Risk Assessment (BfR) issued information on potential health risks related to consumption of Noni products. According to this document, a case of liver inflammation in relation to consumption of Noni juice has been reported in Germany [67]. Details on this case were published recently [68]: the patient who was treated with interferon-beta because of multiple sclerosis admitted to use Noni juice for "general immune system stimulation". She showed elevated transaminase and bilirubin levels which did not decrease after cessation of interferon-beta administration, but were normalised after stopping drinking Noni juice. However, the apparent causality of Noni juice has been recently contested by Tahitian Noni International, which concludes to a case of persisting interferon-beta hepatotoxicity [69]. A causal link of Noni intake and observed hepatotoxicity has also been questioned for the previously reported cases [64], [70]. In a recent publication, data from a single-centre, double-blind, placebo-controlled safety study with three dose levels of Noni juice were discussed [64]. According to this account, a daily dose of 750 mL for 28 days had no measurable effect on clinical parameters of liver function, on blood cell counts and serum chemistry. The authors also describe data from unpublished animal toxicity study in rats for determination of the "no observable adverse effect level" (NOAEL), which was determined to be > 80 mL/kg day. They argue that the ingested doses in the three cases of hepatotoxicity were 10 to 80 fold lower than the NOAEL and that the hepatotoxic reactions could, therefore, not be caused by Noni juice. At the same time, in a study reviewing the use of herbal products by patients with stage 5 chronic kidney disease, the authors cautioned that dialysis patients should avoid Noni juice because of its high potassium content [71].

The approval by the European Community of Noni juice as a Novel Food in 2003 was, among others, based on a review of the toxicological data available at that time [58]. In consideration of the reported cases of hepatotoxicity, the European Community requested the European Food Safety Authority (EFSA) to review the scientific elements and to consider whether the current sta-

tus would need to be amended [72]. The report adopted on 1 September 2006, concluded that there was no convincing evidence for a causal relationship between the hepatotoxicity described in the clinical case reports and the consumption of Noni juice [73]. A possible link between anthraquinones in Noni juice and hepatotoxic reactions, as suggested in the clinical case reports, was excluded in the EFSA report. While the anthraquinone content is relatively high in the roots (in earlier times, they were used for this reason as a natural red or yellow dye) their concentration in the fruits seems to be extremely low. No quantitative data have been published on the anthraquinone content in Noni juice, but in the analytical documentation submitted in the application for approval as Novel Food the genotoxic anthraquinones lucidin and rubiadin could not be detected (detection limit of the assay for rubiadin was 10 µg/kg) [58]. Chemical analyses performed recently by the Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH (AGES) confirmed the absence of detectable amounts of anthraquinones in different batches of Noni juice, including a sample involved in a case report [73]. The potential hepatotoxicity of other phytochemicals in Noni juice has not been considered so far.

Conclusions

The number of scientific publications on Noni fruit has been rapidly growing over the past few years, but the current state of knowledge is still far from satisfactory. First of all, a comprehensive phytochemical profiling is needed to provide sufficient qualitative data on the chemical composition. Secondly, tools for appropriate quality assessment of Noni products are lacking. Validated analytical methods are required for a comparative assessment of Noni products and for quantitative determination of important marker and/or putative bioactive compounds. Given that the Noni market is largely uncontrolled, a survey of the quality of available products is desirable from a perspective of consumer safety. Pharmacological studies of high quality are needed to shed light on putative modes of action. Past investigations on pharmacological properties of Noni juice and purified compounds have been mostly at the *in vitro* level and, quite often, with rather high concentrations. Some of the *in vivo* experiments have been using animal models which are no longer state-of-the-art. A large number of the pharmacological studies have been published only as congress abstracts and not yet as peer-reviewed research publications. Hence, the quality of these data cannot be adequately assessed. However, some interesting activities such as chemopreventive and anti-angiogenic properties warrant further investigation. To what extent the findings from the experimental pharmacological studies are of potential clinical relevance is not clear for the moment. There is a stark contrast between the sweeping claims on curative and disease preventive properties of Noni products and testimonials published on numerous websites, on one hand, and the almost complete lack of clinical data on the other. In that respect, the publication of a full account on the NIH-sponsored phase-I clinical study will be of major importance. The issue of potential hepatotoxicity needs to be followed up by further studies since Noni juice is sold in Europe as a food item. The adverse events seem rare and may be idiosyncratic in nature. While the causality of Noni consumption in the reported cases is doubtful, the current lack of

conclusive evidence of clinically relevant benefits has to be taken into account in the risk assessment.

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