Noni fruit (*Morinda citrifolia*) – Novel Food or Herbal Medicine? A Review on Safety, Pharmacology, Health-related Claims and Benefits

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Products derived from the fruit of *Morinda citrifolia* (Noni) (Fig. 1) are increasingly popular and sold worldwide as Food Supplements and Novel Food, mostly via the Internet (Fig. 2). Opinions on the value of Noni products differ considerably, ranging from very positive [1] to highly critical [2] or cautious [3]. The transition of Noni from a traditional Polynesian ethnobotanical to a commercial food supplement with a wide spectrum of health-related claims was probably spurred by a publication in the Pacific Tropical Garden Bulletin [4], in which the author claimed the presence of an active “alkaloid” named *xeronine*. This compound, which no structure was given for, was said to derive from a precursor, *proxeronine*. HEINICKE 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 commercialized in the USA in 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 tablets, teas, and as juice, the fruit juice being the predominant form. The popularity in the USA has been attributed to claims of a “cure-all” for a variety of diseases (Table 1). Noni fruit juice has been legally sold in the European Community since 2003, and other products are readily available on the Internet.

Background: Products derived from Noni fruit (*Morinda citrifolia*) were commercialized in the USA in the 1990s and are increasingly sold all over the world. A large number of beneficial effects have been claimed for Noni products. Fruit juice of Noni was approved as a Novel Food ingredient by the European Commission in 2003. **Objective:** To provide an overview on the current knowledge on chemical constituents, pharmacology and toxicology of Noni fruit and derived products. **Methods:** A systematic analysis of scientific and patent literature on Noni fruit. **Results:** Knowledge of 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 beneficial effects. However, clinical data are essentially lacking. Based on a toxicological assessment, Noni juice was considered as safe. Due to recent reported cases of hepatotoxicity, the safety issue is under investigation in Europe. **Conclusion:** Current knowledge on products derived from Noni fruit is incomplete. Comprehensive phytochemical profiles and a comparison of Noni products are needed. To what extent the findings from experimental pharmacological studies are of potential clinical relevance is not clear at present. Reported cases of hepatotoxicity need to be followed up by further studies.

Key words: Noni, *Morinda citrifolia*, Rubiaceae, novel food, health claims, constituents, anti-cancer, anti-inflammatory, angiogenesis, anti-diabetic, hepatotoxicity

Noni-Frucht (*Morinda citrifolia*) – Novel Food oder Phytopharmakon? Eine Übersicht zu Sicherheit, Pharmakologie, Wirkversprechen und Nutzen

Hintergrund: Produkte auf der Basis der Noni-Frucht (*Morinda citrifolia*) werden seit den 1990er Jahren zunächst in den USA und heute weltweit als Nahrungsergänzungsmittel propagiert und vertrieben. Eine Vielzahl von gesundheitsfördernden und protektiven Wirkungen wird angepriesen. Noni-Fruchtsaft ist seit 2003 im EU-Raum zugelassen unter der Novel-Food-Verordnung. **Zielsetzung:** Es soll eine Übersicht gegeben werden über den derzeitigen Kenntnisstand betreffend der Inhaltsstoffe, der pharmakologischen und toxikologischen Untersuchungen. **Methoden:** Systematische Auswertung der wissenschaftlichen Literatur und Patente zu Noni. **Ergebnisse:** Der Kenntnisstand zu den Inhaltsstoffen der Noni-Frucht hat sich in den letzten Jahren signifikant verbessert. Eine Vielzahl von *In-vitro*- und, seltener, *In-vivo*-Untersuchungen weisen auf potentielle Wirkung einzelner Inhaltsstoffe hin. Klinische Daten fehlen jedoch weitestgehend. Auf der Grundlage einer toxikologischen Prüfung wurde Noni-Saft im EU-Raum unter der Novel-Food-Verordnung zugelassen. Im letzten Jahr wurde jedoch über Fälle von Lebertoxizität berichtet, so dass die Sicherheitslage derzeit überprüft wird. **Schlussfolgerungen:** Der Kenntnisstand zu Noni-Frucht ist noch unvollständig. Eine umfassende phytochemische Analyse und ein Vergleich der verschiedenen Noni-Produkte fehlen. Eine mögliche klinische Relevanz der experimentell-pharmakologischen Befunde ist noch nicht klar. Die seltenen Fälle von beobachteter Lebertoxizität müssen genauer untersucht werden.

Schlüsselwörter: Noni, *Morinda citrifolia*, Rubiaceae, novel food, Inhaltsstoffe, Antitumor, Entzündungshemmung, Angiogenese, Diabetes, Hepatotoxizität

Fig. 1. *Morinda citrifolia* – unripe Noni fruit with flowers (photo: O. Potterat).

Fig. 2. A selection of Noni products sold via the Internet (photo: F. Dieterle).

Morinda citrifolia L. belongs to the family Rubiaceae. The genus *Morinda* includes some 80 species which all occur exclusively in tropical climate zones [6]. *M. citrifolia* is an evergreen tree or shrub 3 to 10 m high, with bright green elliptical leaves which are 10 to 30 cm long, and with white tubular flowers. The distinct 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 has bright green colour which turns to a translucent yellowish or white upon ripening. The ripe fruit has an unpleasant and cheesy odour. The seeds are buoyant due to an air sac attached at one end and germinate even after extended periods of drifting in the sea. This may explain, in part, the wide distribution of the Noni tree in the Indo-Pacific Islands. *Morinda citrifolia* occurs from India through Southeast 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. 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. 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 diets 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].

Constituents of Noni fruit

Early phytochemical investigations focussed on secondary metabolites in leaves, roots and bark. A wide spectrum of anthraquinones were reported, mostly from the root, together with iridoids, flavonoids, phytosterols and carotenoids [7, 8]. Plant cell cultures were analyzed mainly for their capabilities for synthesis of anthraquinoid pigments. The interest in the constituents of the fruit was stimulated by the introduction of fruit juices as food supplement. Up to now, several classes of metabolites have been described, including polysaccharides, fatty acid glycosides, iridoids, anthraquinones,

coumarins, flavonoids, lignans, phytosterols, carotinoids, and a range of volatile constituents including monoterpenes and short chain fatty acids and fatty acid esters.

Among these constituents, the fatty acid glycosides appear quite unique with respect to their structures and content in ripe fruits [9, 10]. The polysaccharide fraction consists primarily of the pectic homogalacturonan, rhamnogalacturonan I, arabinan, and type I and II arabinogalactans [11]. Iridoids such as asperulosidic acid, deacetylasperulosidic acid, morindacin, 6 α -hydroxyadoxoside, and a number of minor known compounds have been reported [7, 12, 13, 14]. Flavonol glycosides include rutin, narcissoside and nicotifloroside, and several known and new lignans such as americanin A, americanoic acid, morindolin and others were reported [14, 15]. The coumarin scopoletin has been identified [7]. A series of 1-hydroxyanthraquinones have been isolated from the fruits, including citrifolinin B, alizarin-1-methylether and related compounds [13, 14, 16]. In an extensive GC-MS analysis of the volatile components in ripe Noni fruit, a range of free fatty acids, methyl and ethyl esters of fatty acids, aliphatic and aromatic alcohols, ketones, lactones and traces of monoterpenes were identified [17, 18].

Table 1: Selected claims for modern Noni products (modified from [3])

Claims apparently based upon Polynesian traditional uses
<div>1. Inflammation (possibly extended to lupus)</div> <div>2. Headache</div> <div>3. Fever</div> <div>4. Arthritis</div> <div>5. Sore gums, gingivitis, toothache, abscess</div> <div>6. Respiratory disorders</div> <div>7. Sore throat with cough</div> <div>8. Infections (bacterial/fungal/viral/helminthic)</div> <div>9. Tuberculosis*</div> <div>10. Diarrhea</div> <div>11. Gastric ulcer</div> <div>12. Indigestion</div> <div>13. Diabetes*</div> <div>14. High blood pressure*</div> <div>15. Dermatological effects</div> <div>16. Childbirth</div> <div>17. Menstrual cramps</div>
Claims apparently based upon HEINICKE [4]
<div>1. Xeronine and proxeronine are active ingredients.</div> <div>2. Production of xeronine is promoted by noni juice.</div> <div>3. Xeronine can regenerate cells, causa cellular repair, (anti-aging).</div> <div>4. Mental depression</div> <div>5. Atherosclerosis, blood vessel problems</div> <div>6. Drug addiction</div> <div>7. Senility</div> <div>8. Analgesia</div>
Claims presumably of more recent origin
<div>1. Immune system stimulant</div> <div>2. Menstrual cycle regulation/pregnancy†</div> <div>3. AIDS</div> <div>4. Prevents activation of Epstein-Barr virus.</div> <div>5. Antitumor/anticancer activity, specifically, breast cancer</div> <div>6. Internal disorderst</div> <div>7. Kidney problemst</div> <div>8. Lupus</div> <div>9. Blood purifier/cleansert</div> <div>10. Weight lass</div> <div>11. Cleansingt</div> <div>12. Nervous system†</div>
<div>* Disease state that may not have been recognized in ancient Polynesia, but for which "traditional" remedies have recently been recorded.</div> <div>† Vague claim probably based upon one or more traditional uses.</div>

Predominant compounds were hexanoic and octanoic acids. Unripe fruits contain mainly C-16 and C-18 fatty acids, whereas fatty acids of shorter chain length are dominant in ripe fruits and are mainly responsible for their unpleasant cheese-like flavor [12].

Pharmacological studies

Pharmacological studies published so far were 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. A fatty acid glycoside and an iridoid, asperulosidic acid, from Noni fruit were found to inhibit phorbol ester- and EGF-induced AP-1 (transcription activator protein-1) transactivation and cell transformation in mouse epidermal JB6 cells [19]. A polysaccharide-rich fraction, which was obtained from fruit juice by precipitation in ethanol, showed antitumour activity in the Lewis lung carcinoma model in mice. The precipitate also stimulated the release of certain cytokines such as TNF- α , IL-1b, IL-10, and IF- γ , but not

of IL-2 [20]. In a similar study, the precipitate showed antitumor activity against Sarcoma 180 ascites tumor in mice [21]. However, it should be mentioned that these two 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 DMBA-induced mammary breast carcinogenesis in rats [22]. In a similar study using the same model, a synergistic effect of fruit juice and methylsulphonylmethane was observed [23, 24]. The juice also showed antimutagenic activity in ICR mice [25]. A new anthraquinone in Noni fruit 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 [16]. Noni juice, in 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 was observed. This concentration was effective at inhibiting capillary initiation in explants from human mammary tumors, and led to degeneration of vessels in explants showing capillary sprouting [26]. A tumour cell-line selective growth inhibition *in vitro* was reported for a methanolic extract from fruits, whereas non-cancerous cells were not inhibited [27]. However, the test concentrations were very high. Noni fruit juice extract showed anti-inflammatory activity in the carrageenan-induced rat paw edema when 10 or 200 mg were administered intraperitoneally. These doses were also effective in reducing the bradykinin-induced edema in the rat paw [28]. Oral dosage of juice to neonatal equine foals 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 statistically significant [29]. 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 [30].

Noni juice was found to lower serum cholesterol and triglycerides in smokers [31]. In male adult SD rats, an antithrombotic effect on jugular vein thrombosis induced by ferric chloride was observed [32]. Lignans isolated from the fruit inhibited Cu²⁺-induced oxidation of low-density lipoprotein particles *in vitro* [15]. Fruit extract showed antioxidative activity in several *in vitro* test systems [33]. Antioxidant activity of phenolic constituents from a Noni fruit extract against DPPH and peroxynitrite radicals was reported [14].

Potential antidiabetic and hepatoprotective properties have been investigated. Noni fruit extract reportedly inhibits phosphodiesterase 3 and shows agonistic activity at the P2Y receptor [34]. A protective effect against carbon tetrachloride-induced liver injury in female SD rats has been described [35].

Clinical studies

In two case reports a significantly prolonged survival of cancer patients taking Noni juice was claimed [36]. Recently, a phase I clinical trial with Noni juice was reported. It was a dose-finding study with a solid dosage from a capsule containing a dry extract of ripe Noni fruit. Toxicity and quality of life measures were assessed [37]. A statistically significant decrease in pain interference with activities was observed, and a non-significant but constituent dose response effect for global health status. No tumor regression was noted. Further information on an ongoing trial at the Cancer Research Center of Hawaii, Honolulu, can be found at the website of the Center [38]. The hypothesis to be tested is that Noni at a specified dosing provides cancer patients with a sufficient benefit to toxicity profile to be useful as a therapeutic.

Patent applications

Several patent applications have been filed in recent years mainly by busi-

nesses 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 [39, 40, 41, 42, 43, 44]. Use of Noni-based products as antifungals, including treatment of candidiasis has been claimed [45, 46]. A third category of patents relates to rather general protective properties against cell damage [47].

Legal status

Noni juice has been marketed in the USA since July 1, 1996, as a dietary supplement, as well as in Canada, Japan, Australia, Mexico, Norway and Hong Kong [3]. Since Noni-based products have no history of use in Europe, 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 [48], on the basis of a report by the Scientific Committee on Food of December 1, 2002 [49]. 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 Novel Food ingredient on the basis of a claimed equivalency.

Toxicological assessment and possible adverse effects

The approval of Noni juice as Novel Food was, among others, based on a review of toxicological data. Neither in acute, subacute and subchronic testing

in rats, signs of toxicity were observed. 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 was administered by gavage, intraperitoneal and intravenous application routes [49].

In 2005, two clinical case reports were published which associated consumption of Noni juice with three cases of acute hepatitis [50, 51]. While two patients recovered spontaneously after ceasing of the intake, the third patient underwent liver transplantation. On March 6, 2006, the German Office for Risk Assessment (BfR) issued an 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 [52]. The European Community requested the European Food Safety Authority (EFSA) to review the scientific elements and to consider whether the current status would need to be amended [53]. A report is expected later in 2006. In the clinical case reports the authors suggested anthraquinones in noni juice to be the likely hepatotoxic agent. While the anthraquinone content is relatively high in the roots (they were used for this reason in earlier times as a natural red or yellow dye) their concentration in the fruits seems low if one considers the isolation yields of new anthraquinones from Noni fruit as reported in recent publications [13, 16]. However, no quantitative data have been published on the anthraquinone content. In the analytical documentation submitted for the application for approval as Novel Food, it was claimed that the concentration of alizarin was below detection limit of [49]. The potential hepatotoxicity of other phytochemicals in Noni juice has not been considered so far. In a recent publication, the case reports above were questioned, and data from a single center, double-blind, placebo controlled safety study with three dose levels of Noni juice were discussed [54]. 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 an unpublished animal toxicity study in rats for determination of No Observable Adverse Effect Level (NOAEL), which was determined to be greater than 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.

First studies relating to toxicology were on the insecticidal properties of mature Noni fruit. The short chain fatty acids, in particular octanoic acid, showed significant insecticidal activity against *Drosophila* [17, 55]. 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 [56].

Conclusions

Despite a rapidly growing number of scientific publications on Noni fruit, the current state of knowledge is still far from being satisfactory. First of all, a comprehensive phytochemical profiling is needed to provide sufficient qualitative data on the chemical composition. Secondly, appropriate analytical tools are required for a comparative assessment of Noni products and for quantitative determination of important compounds. In a preliminary study, we found characteristic differences between the metabolite profiles of juices and dry extracts (unpublished). The investigations on pharmacological properties of Noni juice and purified compounds have been mostly at the *in vitro* level, and, to a lesser extent, with *in vivo* experiments. A large number of these 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 effects warrant further investigation. To what extent the findings from the experi-

mental pharmacological studies are of potential clinical relevance is not clear for the moment. Clinical publications are limited to case reports, and to a preliminary account on a NIH-sponsored Phase-I clinical study. 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 current lack of conclusive evidence of clinically relevant benefits has to be taken into account in the risk assessment.

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