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Chemical compounds, pharmacological activity and toxicity of *Morinda citrifolia:* A review

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Abstract

Morinda citrifolia L. (Rubiaceae), popularly known as noni, is widely used in Tahiti, Hawaii, Polynesia and different Asian countries to treat and prevent different pathophysiology such as high blood pressure, bacterial, fungal and viral infections, wounds, dyslipidemia and diabetes, cancer, among others. In some countries, including Brazil, the use of noni (all plant parts and/or noni herbal medicines) has been banned by the National Health Surveillance Agency. What makes noni a differentiated plant that requires special attention is its hepatotoxic potential. However, the indiscriminate use of noni by many Brazilians from the northeastern region of the country is currently increasing, as this plant species is easily cultivated in this region of Brazil due to its favorable climate for cultivation. Despite its easy cultivation, the use of noni based on empirical knowledge can determine therapeutic effects but can also be extremely hazardous to human health. This article is a review of the literature, which aims to present the latest findings on the therapeutic potential of this plant according to studies already developed mainly on its pharmacological activity and toxicity, aiming to contribute to the disclosure of the risk and benefit of empirical use of this plant and its derivatives and biological constituents.

Key words: *Morinda citrifolia*, Chemical compounds, Pharmacological potential, Toxicity, Experimental Models

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1. Introduction

The history of the use of medicinal plants since ancient times has shown that they are part of human evolution and were the first therapeutic resources used by people. It can be said that the habit of resorting to the healing virtues of certain vegetables is one of the first manifestations of man's age-old effort to understand and to use nature as a response to one of its earliest concerns, that caused by sickness and suffering. The use of *Morinda citrifolia* L. commonly known as Noni, Mulberry India, Iada, Ninth, Canary, Wood or Mengkudu has been growing rapidly in Brazil, although it is a native plant of Southeast Asia, Indonesia and Polynesia [1]. Endemic in tropical regions, *M. citrifolia* has long been used in Polynesian therapy for the treatment of various diseases such as diabetes, cancer, hypertension, menstrual disorders, arthritis, as well as antimicrobial, anti-inflammatory, antioxidant, among others [2-4]. The plant has adapted well to Brazil's edaphoclimatic characteristics and is appropriately applied to the problem of irrational plant use. Considering that there is still insufficient evidence to prove its effectiveness, much research on the therapeutic action of Noni is in although the results are quite controversial. Publications with the species, in most of them, deal with results obtained in vivo or in vitro models, which do not answer the question: under what conditions is the use of Noni safe for human consumption?

This article presents a review of the literature available in public scientific databases on the species *M. citrifolia*. The botanical, chemical, pharmacological and toxicological aspects stand out to present updated source of information to those interested in developing researches that help in the complex assessment of the risk/benefit ratio of the therapeutic use of Noni and, consequently, the promotion of the rational use of this plant in folk medicine. It is important to highlight that the result presented is by the conclusions of the authors of each article analyzed.

2. Methodology

This is a literature review, and the identification of articles of interest was performed using the US National Library of Medicine PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), from the predefined keyword *Morinda citrifolia*, Phytotherapy, Pharmacological potential, and Toxicity. The search

expression used was the Boolean operator "AND". Limiting the search to the title or abstract words in English and Portuguese, studies on humans and animals published in the last 10 years. To ensure the quality of articles, only indexed publications were included in this database. Articles that presented title and abstract according to the theme were included and those that did not fit were excluded.

3. Results

3.1. Botanical Aspects

The species *Morinda citrifolia* L. belongs to the Rubiaceae family; subfamily Rubioideae; to the genus *Morinda* and is of the species *M. citrifolia*. The tree can be 3 to 10 meters tall in its adult form. According to the literature, there are two recognized varieties of *M. citrifolia*, *M. citrifolia* var. citrifolia and *M. citrifolia* var. bracteata [5]. However, in most publications, this distinction is not made and the nomenclature observed is only *M. citrifolia*. Botanical characteristics differ slightly between species so that a lay observer does not distinguish them.

3.2. Chemical Aspects

The procedures for the preparation of the extracts from noni leaves and fruits are diverse, especially maceration and decoction, using alcoholic and aqueous solvents, respectively. Also, most sources surveyed report previous drying procedures such as lyophilization and spray drying to treat fruits, roots, and leaves before extraction. As noted (Table 1), the main classes of *M. citrifolia* isolated compounds belong to flavonoids [6], lignans, triterpenoids [7], iridoids [8] and anthraquinones, as well as benzophenone-derived compounds, called moritrinfolins A (1) and B (2) [9]. The compounds americanin D, loganic acid, 4-ethyl-2-hydroxy succinate rhodolatoside were first identified [10]. Natural products with important biological activities in different systems were also isolated from noni. Among them, a chlorophyll metabolite called pheoforbide is of potential interest as a photosensor in photodynamic therapy for cancer treatment [11]. Many studies on this topic are being published, which reflects the relevance of this molecule as a therapeutic alternative, developed with the help of nanotechnology [12]. Pheoforbide acts in a selective cytostatic manner compared to normal cells in glioblastoma cells with IC50 in the order of micrograms/mL [13]. Moreover, antiproliferative activity has been observed in other cell lines, such as breast cancer, melanoma, bowel cancer [14] and more recently in mouth tumors [15-16].

Also noteworthy is the occurrence of 6-methoxy-7-hydroxycoumarin, also called scopoletin, a metabolite that occurs in several plant families. This coumarin is relevant because promising biological activities have been reported, such as: antiangiogenic [17], hepatoprotective [18], antioxidant [19], spasmolytic [20], and antiproliferative in human prostate cancer [21]. In a recent study, the antineovascularization potential in the colorectal tumor was reported, demonstrating in vivo antitumor activity with 0.06 μM IC50 [22]. Additionally, anthraquinone damnacanthal, which occurs in noni and other species of the Rubiaceae family, can be highlighted. Interest in this metabolite is due to its antitumor potential, as it has an important inhibitory activity of different tyrosine kinases at nanomolar concentrations [23-25]. Different mechanisms of action in vitro and in vivo have been proposed, including cell cycle inhibition and apoptosis induction in oral and breast cancer cells [26-27] and, also, inhibition of D1 cyclin expression [28]. Some damnacanthal inhibited tyrosine kinases are related to angiogenesis. Thus, a recent study demonstrated in vitro, in vivo and ex vivo antiangiogenic activity [25].

Therefore, it is observed that relevant and currently investigated bioactive molecules occur in Noni, allowing us to hypothesize that the consumption of this plant can have positive and negative impacts on the user's health according to the form of consumption. In this way, we reiterate the need for scientific studies that can contribute to clarifying under which conditions the consumption of noni is effectively safe.

3.3. *M. citrifolia*: ethnopharmacology

The species *M. citrifolia* has been widely used by the Polynesian population for over 2000 years in the use of noni fruit juice for various purposes, such as antibacterial, antiviral, antifungal, antitumor, antihelmintic, analgesic, hypotensive and anti-inflammatory. According to population reports and available literature, the most widely used parts of Noni in traditional medicine are fruits, followed by roots and leaves. According to the literature, the leaves and fruit are marketed as tablets and teas; however, most of the consumption is in the form of fruit juice [29]. In Hawaii, this is the second most-consumed species by the population. Outside Brazil noni is seen as food, recognizing that it has some pharmacological activities when compared to other juices, according to the Scientific Committee on Food. Noni juice® and Tahitian Noni® are trade names of the manufactured product, which are composed of noni fruit juice (89%) and grape (11%), published by the European Commission (2002). Scopoletin and (2E, 4Z, 7Z)-decatrienoic acid (DTA) are used to verify the authenticity of industrialized juices sold and the minimum required content is not indicated [30].

There are no reports of when noni was introduced in Brazil, however, this species has adapted very well to our climate and is currently grown in home orchards especially in the Northeast. Given the widespread reports of the benefits of noni among the population, it has been widely consumed in the state of Rio Grande do Norte. Users defend some properties, such as antihyperlipidemic, hypotensive, anti-inflammatory, healing, anti-allergic, pro rejuvenation, and sexual stimulant, among others. According to the

literature, each part of the plant is assigned a different medicinal property [31]. It is mostly consumed along with grape juice to mask the noni flavor and unpleasant smell. Still, some popular mix of fruit with alcohol to get better results. There are reports of the use of flour, produced from the leaves as a multi-blend, with slimming properties. This situation becomes relevant and problematic, since the popular use of noni is not described in safe sources and, since it is an exotic plant has no traditional use reported by Brazilian communities. On the other hand, there is a lot of information and printed materials being broadcast in open markets to highlight the healing properties of the homemade juice of the fruit of the plant, propagate only benefits, many of them without scientific proof.

To date, there are no scientifically accurate bibliographic references to confirm the properties attributed to any preparation made from noni. Some positive, though not clinical, the evidence is found for the commercial Noni Juice® or Tahitian noni® product which is a functional food and not a therapeutic alternative. The official pronouncement of the Sanitary Surveillance Agency regarding noni shows that, due to the lack of consumption history in Brazil, the commercialization of any food containing this ingredient will only be allowed after proof of its safe use and registration.

3.4. Biological effects: pharmacological and toxicological activity

Due to the widespread ethnopharmacological use of noni, especially in some countries and also as Noni Juice®, the search for scientific evidence of plant properties through in vitro and in vivo testing is growing. Some pharmacological testing methodologies demonstrate the potential for noni, although the lack of clinical studies persists. As summarized (Table 2), the main activities verified are: antioxidant, dyslipidemic, hypotensive, healing, antimicrobial, analgesic, dopaminergic and improvement in sexual performance [4], [30], [32-37]. Also, the Noni Clinical Research Journal, in its first edition, reports that noni has immunosuppressive activity when used by patients immunocompromised by the AIDS virus. On the other hand, it increased the immune response when tested in rats, with a greater number of macrophages and lymphocytes [38]. What makes noni a differentiated plant that requires special attention is its hepatotoxic potential, according to studies listed in table 3. The sanitary surveillance agency of Brazil substantiates its recommendation not to use noni also based on reports of human toxicity.

At the beginning of 2005, two cases were reported in which they presented hepatotoxicity related to noni juice consumption. A 29-year-old man with a history of drug hepatitis presented acute liver failure. The patient had a massive attack after consuming 1.5 liters of Tahitian Noni® juice in the previous three weeks and ingested daily a nine-day blend of Chinese herbs containing: Bupleuri, Pinellia, Scutellaria, Codonopsis, Glycyrrhiza, Schizonepeta and Paeonia. The cause of this liver disease could be related to the consumption of noni juice. However, the components of the herbal blend should also be evaluated for toxicity.

Another case reported was from a 62-year-old female patient with acute hepatitis. In an earlier period, the patient was diagnosed with leukemia and treated until remission. During this time, liver function was normalized. However, two months before being hospitalized, the patient reported having ingested 2 liters of Tahitian Noni® juice. After ingestion of the juice, the patient had an increase in transaminases and clinical suspicion led to a diagnosis of viral hepatitis. However, tests ruled out this diagnosis. The discontinuation of the use of juice made the transaminases return to normal, showing again a relationship between noni consumption and liver disease [41].

In 2006 a case has reported a case where the patient had an intoxication after ingestion of the juice, also pointed out that this patient was in an endemic region of hepatitis E, where the symptoms are confused with those of the disease. As no hepatitis tests were performed, it cannot be said that hepatotoxicity was caused by noni juice [42]. The following year it was reported that a patient arrived at the hospital with abdominal pain, mild jaundice, nausea, and vomiting. Anamnesis of the patient was performed and the symptoms indicated an alleged diagnosis of hepatitis since the patient had elevated total bilirubin (BT) and direct bilirubin (BD), as well as the other ALT, AST, GGT and prothrombin transaminases. After the examinations, doctors continued to investigate, when the patient reported that two weeks before her internment she had ingested an herbal preparation named NONI in Ecuador. After a few weeks of treatment, the clinical picture returned to normal [43]. The toxicity tests described in the literature are quite controversial, which indicates the need for a further and better-standardized investigation to generate reliable results. It is noteworthy that there are few studies on toxicity or biological activity that use the fruit in the form of juice to reproduce the main form of popular consumption. This fact becomes relevant because the substances vary qualitatively and quantitatively according to the extraction procedure employed and the part of the vegetable used. This study highlights the need for studies on juice consumption over long periods, and discussions on the impacts of acute and chronic toxicity, in addition to the great need for clinical studies.

Table 1. Chemical compounds already reported *M. citrifolia*

Plant part	Extract Type	Purification	Classified metabolites	Isolated compounds	References
Leaves	Not described	Not described	Iridoid Glycosylated flavonoid Triterpene	Not described	[4]
Leaves	Ethanol extract	Not described	Phenolic Compounds	5,15-dimethylmorindole, ferulic acid, *p*-hydroxycinnamic acid, methyl 4-hydroxybenzoate, methyl ferulate, and methyl 4-hydroxycinnamate	[44]
Leaves	Methanolic	Not described	Not described	Pheoforbide	[45]
Fruits	Aqueous, ethanol, methanol/acetone	Not described	Flavonoids, anthocyanins, carotenoids, vitamin C	Not described	[46]
Fruits	Methanol, Dichloromethane	Liquid-liquid partition, *N*-butanol	Glycosylated Flavonoids, Anthraquinones, Lignanas	O-(β-d-glucopyranosyl)-1-O-octanoyl-β-D-glucopyranose, 2-O-(β-O-glucopyranosyl)-1-octanoyl β-D-glucopyranose, 2,6-di-O-β-D-glucopyranosyl-1-O-hexanoyl-β-D-glucopyranose, 2,6-di-O-(β-D-glucopyranosyl) -1-O-hexanoyl-β-D-glucopyranose	[47]
Fruits	Methanolic	Liquid-liquid partition Ethyl acetate	Anthraquinones Coumarins	Morinaphthalenone, Scopoletin 1,3-dimethoxy anthraquinone 1,2-dihydroxy anthraquinone	[48]

Table 1. Chemical compounds already reported *M. citrifolia* (continued)

Plant part	Extract Type	Purification	Classified metabolites	Isolated compounds	References
Fruits	Watery and hydroalcoholic	Soxhlet Ethanol Chloroform	Polysaccharide Anthraquinone Alkaloid	Not described	[49]
Noni juice	Not described	Liquid-liquid partition Hexane Ethyl acetate *N*-butanol	Polysaccharides Iridoid	1-O-(3'-methylbut-3'-enyl)-α-D-glycopyranose 1-*N*-Butyl-4- (5'-formyl-2'-furanyl) methyl succinate 4-epi-borreriagenin Asperulosidic Acid Acetylsperulosidic Acid 1-*N*-Butyl-4-methyl-2-hydroxysuccinate 1-*N*-Butyl-4-methyl-3-hydroxysuccinate	[50]
Fruit Pulp (Powder)	Methanolic	Liquid-liquid partition Ethyl acetate *N*-butanol	Iridoid Polysaccharides Terpenoids	Scopoletin Quercetin Rutin	[51]
Root	Aqueous extract	Not described	Not described	Bajijiasu	[52]

Table 1. Chemical compounds already reported *M. citrifolia* (continued)

Plant Part	Extract Type	Purification	Classified metabolites	Isolated compounds	References
Root	Methanolic	Liquid-liquid partition Chloroform Ethyl acetate *N*-butanol	Iridoids Anthraquinones	Diacetylperulosidic Acid Asperulosidic Acid Damnacantal-3-O-β-D-primeveroside Lucidine 3-O-β-D-primeveroside Morindone 6-O-β-D-primeveroside	[8]
Root	Ethanolic	Not described	Polyphenols Glycosides Lignana Coumarin	Scopoletin 7-hydroxycoumarin 4-hydroxycoumarin	[53]
Seed	95% Ethanolic	Liquid-liquid partition Petroleum ether Ethyl acetate *N*-butanol	Flavonoids Triterpenes Lignins Iridoids Anthraquinones	Americanine D Americanine Loganic Acid Rhodolatoside 4-ethyl-2-hydroxysuccinate	[6]
Juice	Ethanolic	Not described	Polysaccharides	Not described	[54]

Table 2. Pharmacological activity of *Morinda citrifolia*

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Morinda citrifolia and placebo capsules	Not described	Not described	400 mg	Randomized double blind study. 100 women from 18 years old during 3 menstrual cycles	There was an improvement in signs and symptoms in both groups, but when compared to the test group with the control group there was no significant improvement	[40]
Fresh leaves	Aqueous extract	Not described	10 µl in each ear	Induced ear edema in male albino rats	Experimental results allow for possible preclinical validation of anti-inflammatory activity	[55]
Leaves	Aqueous extract	After the juice of the leaf was distilled water, it was filtered and lyophilized and the extract was dissolved in 0.1% (v/v) DMSO in PBS	750 µg/mL	Raw 264.7 macrophage cells	This study demonstrates and suggests *M. citrifolia* as a possible therapeutic agent against inflammatory diseases.	[56]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Leaves	Not described	Not described	150 mg/kg or 300 mg/kg	Rats	The extract significantly increased lymphocyte count in the blood and reduced epidermal growth factor receptor (EGFR) gene expression, which is a biomarker of lung adenocarcinoma.	[57]
Leaves	Methanol and Ethanol extract	Extraction performed with methanol at 50 ° C for 6h	20.6 mg/mL	Huh 7.5 cells and pFL-J6/JFH-1 plasmid	The extracts were effective against hepatitis C virus replication.	[58]
Leaves	Not described	Not described	70 mL	Patients 29 to 47 years old infected with *Plasmodium* sp	Significant differences were observed in patients who were treated with the extract compared to their control group (patients who were not treated with the extract)	[59]
Leaves	Aqueous extract	Not described	0,025% and 5%	Third or premolar tooth cells. Patients aged 17 to 25 years	Therapeutic potential related to periodontal bone and tissue regeneration was observed	[60]
Leaves	Ethanol extract	Not described	500 mg/L	*Metarhizium anisopliae* fungi Against malaria vector, *Anopheles stephensi*	The extract is a promising larvicidal and pupicidal agent against the malaria vector	[61]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Leaves	Hydroethanolic extract	Not described	10 mL/ kg/ 4h/ 14 days	Acute toxicity/mice	The study showed no weight loss or acute toxicity	[3]
Leaves	Ethanolic extract	Qualitative- saponins, tannins, triterpenes, alkaloids and flavonoids	150 mg/kg/day	Rats	*M. citrifolia* showed healing activity, where 70% of the injured animals treated with the extract had a fast healing, as well as a shorter time for tissue epithelialization	[30]
Leaves	Aqueous extract	Not described	5 mg plant/95 mL AgNO3 at different temperatures for 10 days	*Escherichia coli, Pseudomonas aeroginosa, Klebsiella pneumoniae, Enterobacter aerogenes*	The extract has high activity against pathogenic bacteria	[62]
Leaves and seeds	Alcoholic extracts, Hexanes, Chloroform and ethyl acetate.	Not described	100 mg	Strains of *Escherichia coli* and *Staphylococcus aureus coli*, and *Candida* sp	All tested extracts of *M. citrifolia* leaves and seeds had antimicrobial activity against the studied strains	[34]
Fruits	Aqueous extract	Not described	1000 µg, 500 µg, 250 µg, and 100 µg	*Candida albicans*	The extract has a dose dependent fungicidal effect	[63]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Fruits	Chopped fresh fruits	Not described	100 g/calf /day	Calf	Reduction in total cholesterol, triglycerides, glucose, serum creatinine and urea levels was observed	[64]
Fruits	Not described	Not described	Doses were administered according to groups 9 mL (15 g) every 8 hours for 2 days for the first group and for the second dose 18 mL (30 g) every 8 hours for 2 days	Randomized parallel clinical trial with patients 18 to 50 years old.	The maximum analgesic activity of the extract is dose dependent	[35]
Fruits	Industrialized fruit juice	Not described	5 mL/24 h	*Enterococcus faecalis*	The disinfectant capacity of the extract is satisfactory and less traumatic for the patient when compared to NaOCl suggesting its use in orthodontic procedures	[65]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Fruits	Fermented aqueous extract	Not described	Dosage not described, treatment for 20 days	Rats	The extract has hypoglycemic and hepatoprotective activity	[66]
Fruits	Ethanolic extract	Not described	10 mL/kg/1h before the experiment	Oxidative stress in the scopolamine-induced amnesia model in rats	The mechanism of action of *M. citrifolia* against memory loss is still unclear but may be due to its central cholinergic action by AChE inhibition	[67]
Fruits	Ethyl acetate extract	Not described	200 and 400 mg/ kg	Mice	Extract determines significant increase in short-term and long-term memory that may be associated with positive modulation of serotonin and dopamine levels	[68]
Ripe fruits	Aqueous extract	Not described	1000 µg/mL	*Streptococcus mutans* Strains MTCC 497, *Streptococcus mitis* MTCC 2696	The results obtained show that *M. citrifolia* has an inhibitory effect against oral mucosa streptococci.	[69]
Ripe fruits	Methanol extract	Maceration occurred for 4 h and was concentrated and vacuum at 37° C	200 mL	Adipocyte Cells SW872 (ATCC HTB-92)	Cell studies have shown that *M. citrifolia* was able to counteract oxygen accumulation	[70]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Ripe Fermented Fruits	Ethanolic extract	Fermented extract under anaerobic conditions for 48 h at 37° C	25, 50, 100, 200 mg/mL	CACO-2 human colon epithelial cell line (ATCC; HTB-37)	The extract promotes the growth of endogenous probiotics that increase immunity	[71]
Fruits	Methanolic extract	Not described	10 and 200 mg	Rat (paw edema)	The extract stimulates ap-1 (activated protein transcription), which induces cell transformation in the rat epidermis with an anti-tumor, anti-inflammatory and antioxidant effect. In addition the extract showed antidiabetic and hepatoprotective effect	[4]
Fruits	Aqueous extract	Aqueous extract 1 kg/ 4 L ethanolic extract 4 L (95%)/7 days	200 mL (human) and 0.5 g/kg (rats)	Nonrandomized Experimental Trial - men, and women 18 to 45 years old; *Wistar* rats	The aqueous extract showed activity against stomach acidity in human and rats	[72]
Fruits	Methanolic extract	Oven dried at 60° C for 2 days and reduced to dust	Not described	Permeation membrane	The extract showed free radical scavenging activity	[32]
Fruits	Not described	Not described	50 and 100 mg/kg/day	*Wistar* rats weighing 150 g-200 g	Decrease in total cholesterol, triglycerides and VLDL-c at both doses	[73]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Fruits	Ethanol extract	Not described	For antitumor activity doses of 10 mg / mL, and for antimicrobial activity doses of 1 mg/mL *Staphylococcus aureus*, and 10 mg/mL for *Escherichia coli*	Melanoma B16-F10 cells and strains of *Staphylococcus aureus* and *Escherichia coli*	The extract decreased cellular activity and inhibited 45% of the B16-F10 melanoma cell proliferation rate treated during the study period.	[74]
Fruits	Fermented aqueous extract	3.000 g pasteurized at 80° C / 15 min stored at -20° C	Distilled water and aqueous extract 3, 6 and 9 mL / 6 weeks	Hamsters	The extract has antioxidant activity and determines increased body weight	[75]
Fruits and Leaves	Ethanolic extract	Not described	Not described	Not described	Fruit and leaf extract increases tyrosinase and elastase activity. Thus, the plant can be a potential product for cosmetic development	[76]
Fruits and Leaves	Ethanolic extract	Not described	2 µM during 24-72 h	B16 Melanoma Cells	Inhibition of the tyrosine kinase enzyme was observed in B16 melanoma cells with the use of *M. citrifolia*	[77]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Fresh fruits	Ethanolic extract	Not described	100, 200, 250 and 1000 mg/kg	Rat/streptozotocin-induced diabetes	Elevated glucose, glycosylated hemoglobin, urea and serum creatinine levels in diabetic rats were reverted to near normal values after treatment. The dose with the best effect was 300 mg/kg for 30 days	[2]
Ripe fruits	Fruit juice	Not described	1.5 mL/4 kg during 7 days	Mice	Extract facilitates insulin release after ischemic stress	[78]
Ripe fruits	Not described	Not described	5.0 mg/kg and 10.0 mg/kg/24 h	Rats	The rats treated with *M. citrifolia* presented higher liquid excretion when compared to the control group, but this excretion was not higher when compared to the group that used furosemide	[79]
Ripe fruits	Methanolic Extract	Ethyl acetate, *N*-butanol	0.096, 0.19, 0.45, 0.82 and 1.41 mg/mL	*Candida albicans*, *Escherichia coli* and *Staphylococcus aureus* culture	The strains tested were sensitive to the iridoid derivatives: deacetyl perulosidic acid and asperulosidic acid. This suggests a potential antimicrobial effect of these compounds	[80]
Ripe fruits	Aqueous extract in KH_2PO_4	Not described	1 mL/ 200 g/kg	Rats	*M. citrifolia* extract and scopoletin have anti-ulcer action perhaps by inhibiting acetylcholine-mediated acid secretion	[81]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Dry fruits	Hexane and ethyl acetate	Not described	Not described	Rat (paw edema)	Inhibition of cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) is more effective with juice than with indomethacin. Juice-induced inhibition: COX-1 and COX-2 32.7 ± 9.3% and 23.1 ± 4.0%, respectively. Indomethacin-induced inhibition: COX-1 and COX-2 26.8 ± 6.7% and 89.6 ± 0.5%, respectively	[83]
Fresh green fruits	Methanol extract	Not described	< 40 mg / mL and < 50mg / mL	Rats	Dopaminergic agonist and antagonist effects, in a dose-dependent manner	[36]
Green fruits	Ethanolic extract	Not described	0.5 mL/30 min	Lipoprotein LPL from beef milk	The extract showed LPL inhibitory activity after 30 min	[84]
Fruits, leaves and roots	Alcoholic extract	Not described	1000 mg/kg	Rats	The extract showed antidislipidemic and hypotensive activity	[33]
Tahitian Noni® puree	Ethyl acetate extract	Not described	1 mL /4 h	Rat macrophages and liver carcinoma cells	The extract with scopoletin and rutin demonstrated anti-inflammatory and anticancer activity	[85]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Roots	Aqueous extract	Not described	40 g/kg	Rats	The extract improves sexual performance, increased testosterone and decreased LH and GnRH levels	[37]
Root	Not described	Not described	Not described	Colon cells	The 10 types of anthraquinones isolated from this extract showed antitumor activity	[86]
Root	Methanolic/ Butanolic extract	Not described	MeOH, BuOH (3 g/kg), Damnacantal (10-100 mg/kg)	Rat (paw edema)	The extract has antinociceptive and anti-inflammatory action, where these effects can be attributed to damnacanthal	[87]
Root	Methanolic Extract	Not described	3 g/kg/5 h	Rat/streptozotocin-induced diabetes	After 5 hours of treatment with the extract, glycemic levels reached normal values	[8]
Root	Aqueous extract	Not described	20 µg per rat	Rats	Increased testosterone levels	[52]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Root	Hydroethanolic extract	Not described	0.3 mg/mL and 0.06 mg/mL of the extract	Rabbit, Rat, Guinea pig, and Mice. Jejunum aorta, and atrium	In the rabbit jejunum there was a spontaneous inhibition causing relaxation, dependent on the extract concentration. In rabbit aorta, the extract determined dose-dependent vasodilation. In guinea-pig atria inotropism was dose-dependent suppressed. In mice, the extract did not cause any mortality or behavioral changes at a dose of up to 10 g/kg	[88]
Roots, fruits, and leaves	Ethanolic extract	Not described	Not described	Antioxidant potential Ferric thiocyanate and thiobarbituric acid test	The extract showed antioxidant activity, however, this activity is significantly lower than the antioxidant activity determined by BHT and α-tocopherol	[89]
Noni juice	Not described	Not described	10%	SiHa (HPV16 +) Cervical Cancer Cell Line	*M. citrifolia* increased expression of DNA repair genes alone and in combination with cisplatin	[90]

Table 2. Pharmacological activity of *Morinda citrifolia* (continued)

Plant part	Extract Type	Standardization of the extract	Dose / treatment time	Experimental Model	Results	References
Noni juice Tahitian Noni®	Aqueous extract	10 mL/kg/ day	0.4, 2.0 and 20 mg/kg	Rats	The juice impaired the ossification process of bone tissue	[91]
Fruit juice	Not described	Not described	0.9% *M. citrifolia* in NaCl and 3 mg/kg doxurrubicin/14 days	Ehrlich ascites tumor in BALB/c rats	Fruit juice determined antitumor activity by modulating the caspase-3 pathway similarly to doxurrubicin	[92]
Tahitian Noni® juice (TNJ)	Concentrated juice	Not described	1.5 mg/mL for 16 days	Rats	TNJ modulates the immune system by activating CB2 receptors and IL-4 suppressing factors but increased IFN production stimulates cytokine gene expression	[93]

Table 3. *Morinda citrifolia* toxicity reports

Extract Type	Standardization of the extract	Dose/treatment time	Experimental Model	Results	References
Mashed Fruit	Not described	1500 µg/mL/24 h (human) 10 mL/kg/24 h (rats)	Human liver cell strain and rats	*M. citrifolia* showed no toxic activity for HEP G2 strain nor induced hepatotoxicity in rats	[94]
Mashed Fruit	Not described	150 µg/mL oral dose 1.72, 3.43, 6.86 kg/mL	HEPG2 cell strain (rats)	*M. citrifolia* exhibited no toxicity to HEPG2 cells	[95]
Pasteurised ground fruit	Not described	900 mL/kg	Rats	The tests did not determine morphological alterations in the rats organs	[94]
Syrup (concentrate)	Not described	0.1 to 10%	*Wistar* rat hepatocyte tissue and mutagenicity test with *Salmonella* sp	Toxic effects were observed only at the highest concentration tested, i.e. 0.5%. When added grape juice that is rich in quercetin (a bacterial mutagen) the mutagenic incidence was higher than when the extract was tested alone	[96]

Table 3. *Morinda citrifolia* toxicity reports (continued)

Extract Type	Standardization of the extract	Dose/treatment time	Experimental Model	Results	References
Fruit Infusion	Not described	1 g/250 mL deionized water for 10 min	*E. coli* DNA and female/male rat	The use of leaf infusion does not suggest a potential risk	[97]
Methanolic Fruit Extract	Room temperature/7 days	Not described	Hepa lclc7 (Hepa-1) murine hepatoma cells	Hydroxyanthraquinone is mutagenic to adenomas and adenocarcinomas of the colon and determines liver neoplasms in rats fed a 1% hydroxyanthraquinone diet. However, the approximate percentage of hydroxy anthraquinone in this fruit is 0.0002% w/w	[9]

4.

Final considerations

The information available in the literature so far is insufficient to guarantee that the use of *M. citrifolia* does not determine toxic effects in humans when used as herbal medicines and/or as folk remedies. Although many studies show the main chemical constituents extracted from different parts of the plant and their pharmacological effects in different in vivo and in vitro experimental models, further clinical studies are needed to prove their therapeutic effect and the safety of their use in humans. The Brazilian population should be aware that the National Health Surveillance Agency advises against the use of *M. citrifolia* and that the already reported toxic effects should be propagated as a warning to prevent the occurrence of toxic effects due to the indiscriminate use of this plant as natural medicine.

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