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Usage, biological activity, and safety of selected botanical dietary supplements consumed in the United States

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ABSTRACT

In view of the continuous growth of the botanical dietary supplement industry and the increased popularity of lesser known or exotic botanicals, recent findings are described on the phytochemical composition and biological activities of five selected fruits consumed in the United States, namely, açaí, noni, mangosteen, black chokeberry, and maqui berry. A review of the ethnomedicinal uses of these plants has revealed some similarities ranging from wound-healing to the treatment of fever and infectious diseases. Laboratory studies on açaí have shown both its antioxidant and anti-inflammatory activities *in vitro*, and more importantly, its neuroprotective properties in animals. Anthraquinones and iridoid glucosides isolated from noni fruit induce the phase II enzyme quinone reductase (QR), and noni fruit juice exhibited antitumor and antidiabetic activities in certain animal models. Antitumorigenic effects of mangosteen in animal xenograft models of human cancers have been attributed to its xanthone content, and pure α-mangostin was shown to display antineoplastic activity in mice despite a reported low oral bioavailability. Work on the less extensively investigated black chokeberry and maqui berry has focused on recent isolation studies and has resulted in the identification of bioactive secondary metabolites with QR-inducing and hydroxyl-radical scavenging properties. On the basis of the safety studies and toxicity case reports described herein, these fruits may be generally considered as safe. However, cases of adulteration found in a commercialized açaí product and some conflicting results from mangosteen safety studies warrant further investigation on the safety of these marketed botanical dietary supplements.

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1. Introduction

The popularity of botanical dietary supplements and their consumption continue unabated in the United States, as indicated by various demographic surveys and related expenditure reports.[1–3] According to the U.S. National Health Statistics Reports, non-mineral and non-vitamin dietary supplements, including botanical supplements, have consistently held the first place among the most popular complementary health approaches used between the years 2002-2012.[1] Moreover, sales of herbal dietary supplements represented 18% of the U.S. supplement industry sales in 2015 and continued to expand for the thirteenth consecutive year in 2016 reaching nearly $7.5 billion USD.[4,5]

The popularity of these products has been associated with their perceived health-promoting properties based on ethnobotanical uses, scientific reports, and even speculative marketing claims in the media. Consumers turn to botanical dietary supplements for reasons including promotion and maintenance of general well-being, weight loss, disease prevention, as an immune system boost, or as perceptually “safer” natural alternatives to conventional drugs.[6,7]

While some botanicals may indeed fulfill some of these expectations, caution should be taken before assuming that they are all safe to use. Considering that several of the approved conventional drugs associated with dose-limiting toxicities are derived from natural sources including plants, botanical dietary supplements and/or the secondary metabolites therefrom could induce some adverse effects or drug interactions. In fact, the steady rise in the

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consumption of these products has been associated with an increase in the incidence of related cases of hepatotoxicity,[8,9] and some botanicals have been linked to this problem.[10,11] Case reports on liver, kidney, and heart toxicities related to dietary supplements have been documented in a recent series of reviews.[12–14] Therefore, investigating the chemical components, and evaluating the biological activities and potential toxicity of these products constitute essential steps in order to confirm or determine their health benefits and to ensure the safety of consumers. Several such studies have been undertaken, and they include research on food products, such as fruits and vegetables.

A considerable body of evidence has been gathered regarding the positive impact of the consumption of berry fruits on human health, resulting in a growing interest in this area of research, notably on their effects on diabetes, cardiovascular diseases, and cancer.[15,16] These fruits include the commonly consumed berries in North America, such as blueberry, cranberry and strawberry, as well as the "exotic" fruits and berries that have more recently gained in popularity in the U.S., including mangosteen, açaí and maqui berry.[15] Investigation of the potential chemopreventive phytochemicals from various botanicals, including açaí, noni, mangosteen, black chokeberry, and maqui berry has been carried out, and results from the study of the first three of these fruits have been discussed in a previous review.[17] Thus, in the present contribution, additional reports on the phytochemistry of and recent biological findings on these fruits are discussed. Research performed on black chokeberry and maqui berry is also summarized. In addition, the discussion of all five fruits will include their ethnomedicinal properties, commercial uses as botanical dietary supplements, and their potential toxicity, if any.

2. Açaí

2.1. Traditional and dietary supplement uses

Açaí [*Euterpe oleracea* Mart. (Arecaceae)] is a palm tree growing in the Amazon basin, of which the berries are prepared into beverages or consumed as a staple food by the local populations.[18] In addition, the core of the trunk, known as the palm heart, is sliced and canned for consumption as a popular vegetable.[18] Ranking among the top thirty best-selling dietary supplements in 2015 in the United States,[19] açaí holds a high economic value both in its native South American regions and in several countries worldwide, notably the U.S.[20] Various parts of this plant have been used in local folk medicine for the treatment of a variety of ailments, including fever, gastrointestinal and skin conditions, pain, and infectious diseases (Table 1).[21–23] For example, the fruits are applied topically to treat skin ulcers, while the fruit juice is used against influenza, and the fruit oil is utilized as an antidiarrheal agent.[21,22] On the other hand, an infusion from the seeds serves as a febrifuge (medicine to treat fever) and preparations from the roots are used to treat jaundice, malaria, and kidney disorders.[21]

In the U.S., açaí has received major attention as a "superfood", following reports of its remarkable antioxidant potential, and thus, it has been used as a dietary supplement in the form of tablets or powders, and as an ingredient for energy drinks and cosmetic products.[18,20,22] For instance, açaí fruit pulp exhibited a total antioxidant capacity (TAC) of 1027 μmol Trolox equivalents (TE)/g (dry weight),[24] largely surpassing the corresponding antioxidant capacities of several known antioxidant-rich fruits, such as cranberry (by 11-fold) and blackberries (by 17-fold).[25]

2.2. Phytochemistry and biological studies

The antioxidant properties of açaí, mainly attributed to its phenolic content, in particular the anthocyanins and flavonoids, have been studied over the years quite intensively. Also investigated have been several related *in vitro* (Table 2) and *in vivo* (Table 3) bioactivities germane to cancer chemoprevention, as well as potential anti-inflammatory and cardioprotective effects.[22,25]

The antioxidant as well as the cytoprotective activities of several neolignans from *E. oleracea* have been previously reported.[17,26] More recently, two new neolignan glucoside enantiomers (**1**, **2**) and a new phenolic glucoside (**3**) (Fig. 1) were isolated from the freeze-dried powder of this fruit.[27] While these compounds showed potent antioxidant activity by inhibiting reactive oxygen species (ROS) formation in HL-60 leukemia cells, in term of a potential protective effect against cancer cell lines growing *in vitro*, they had modest to no cytotoxic activity for the same cell line.[27] Moreover, four flavonoids were reported from *E. oleracea* for the first time, including velutin (**4**), which showed potent anti-inflammatory capacity by blocking the production of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) through inhibition of the nuclear factor-κB (NF-κB) activation and the phosphorylation of p38 mitogen-activated protein kinase (MAPK) and *c*-Jun *N*-terminal kinase (JNK) in murine macrophages.[28,29]

In view of its antioxidant and anti-inflammatory capacity and a

Table 1
Ethnomedicinal uses of açaí, noni, mangosteen, black chokeberry, and maqui berry.

Botanical	Part used	Uses	Reference
Açaí (*Euterpe oleracea*)	fruits	skin ulcers, influenza (juice), antidiarrheal (oil)	21,22
	seeds	febrifuge (infusion)	21
	roots	jaundice, antimalarial, treatment of kidney diseases	21
Noni (*Morinda citrifolia*)	fruits	mouth sores, toothaches, treatment of fever, diabetes, intestinal worms, fungal infections, tuberculosis	38,39
	leaves	cough, topical burns, rheumatic joints, ulcers	38
	bark	urinary disorders, antihelmintic, stomachaches, antibacterial	38
	roots	cancerous swellings, sore throat, febrifuge	38
Mangosteen (*Garcinia mangostana*)	fruit pericarp	wound-healing, skin infections, diarrhea	55,56
	leaves and bark	eczema, psoriasis	56
Black chokeberry (*Aronia melanocarpa*)	fruits	common cold	77
	bark	astringent	77
	not specified	antihypertensive, atherosclerosis, hemorrhoids	78
Maqui berry (*Aristotelia chilensis*)	fruits	dysentery, diarrhea, wound-healing	77
	leaves	sore throat, antitumor, fever	77
	unspecified	stomach ulcer, kidney pain, antitumor, scars, hemorrhoids, diarrhea, migraines	23,92

Table 2
Highlights of *in vitro* bioactivity of açaí, noni, mangosteen, black chokeberry, and maqui berry.

Botanical	Test sample	Cell line/bioassay	Results	Reference
Açaí	new neolignan glucosides (**1**,**2**), phenolic glucoside (**3**) from freeze-dried fruit powder	PMA-stimulated HL-60 human leukemia cells	antioxidant activity by blocking ROS production	27
	velutin (**4**)	LPS-treated RAW-blue and RAW-264.7 murine macrophages, or C57BL/6 mouse peritoneal macrophages	anti-inflammatory activity: inhibition of SEAP secretion NF-κB activation, and p38-MAPK and JNK phosphorylation resulting in inhibition of pro-inflammatory cytokines (TNF-α and IL-6) expression	28,29
	fruit pulp extract and fractions	LPS-activated murine BV-2 microglial cells murine E18 embryonic and HT22 hippocampal neurons	anti-inflammatory by inhibition of iNOS, p38-MAPK, TNF-α, NF-κB, and COX-2 production restoration of autophagy and calcium homeostasis	30,31
Noni	pure Costa Rican noni juice	LPS-activated J774 macrophages, ovine COX-1 and -2	moderate reduction of NO and PGE_2 production, and inhibition of COX-1 and -2	46
	americanin A (**11**)	MRC-5 normal human lung epithelial cells HCT116 human colon cancer cells	no toxicity in normal cells ($IC_{50} > 100$ μM) inhibition of HCT116 proliferation	49
Mangosteen	α-mangostin	DMBA-induced preneoplastic mouse mammary glands	inhibition of preneoplastic lesions ($IC_{50} = 2.4$ μM)	43
Black chokeberry	hyperin (**20**), melanodiol (**21**) and melanodiol-4″-*O*-protocatechuate (**22**)	hydroxyl-radical scavenging assay	antioxidant activity ($ED_{50} = 0.17–0.75$ μM)	86,87
	protecatechuic acid (**16**) melanodiol (**21**) and melanodiol-4″-*O*-protocatechuate (**22**)	murine hepa1c1c7	induction of quinone reductase phase II enzyme (CD = 3.1–8.8 μM)	86,87
Maqui berry	fruit methanol extract	DPPH and ABTS radical scavenging assay, FRAP and FIC activity assays	antioxidant activity 28, 19, 25 g TE/kg (for DPPH, ABTS, and FRAP) and 0.12 g EDTAE/kg (FIC)	98

PMA: phorbol 12-myristate-13-acetate. ROS: reactive oxygen species. LPS: lipopolysaccharides. SEAP: secreted embryonic alkaline phosphatase; DMBA: 7,12-dimethylbenz[α] anthracene; DPPH: (2,2-diphenyl-1-picrylhydrazyl); ABTS: 2,2- azino-bis(3-ethylbenzothyazolin-6-sulfonic ammonium)-salt; FRAP: ferric reducing antioxidant power; FIC: ferrous ion chelating.

claimed "anti-ageing" benefit, *E. oleracea* has been further investigated for its potential protective role in age-related neurodegenerative diseases, as many of these are associated with oxidative stress and inflammation. Accordingly, açaí pulp extract prevented the inflammatory stress caused by the lipopolysaccharide (LPS)-induced activation of mouse brain microglial cells through inhibition of the pro-inflammatory p38MAPK signaling cascade involved in the production of the inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2).[30] These results positively correlated with the activity of the açaí component velutin (**4**) described above. Moreover, açaí may help attenuate the neurotoxic accumulation of calcium ions and dysregulation of autophagy in brain cells, which contribute to neuronal cell death and the loss of cognition during aging.[31] These *in vitro* protective results were confirmed in animal models, in which aged rats fed with açaí displayed an increase in the production of antioxidant markers such as the transcription factor Nrf2 in the hippocampus and frontal cortex.[32] In addition, these animals displayed improved working memory and behavioral performance.[33]

2.3. Safety

Although *E. oleracea* is not on the U.S. FDA generally regarded as safe (GRAS) list, it is considered safe and has been only regarded as possibly unsafe if used in patients with autoimmune disorders, as açaí may counteract the effects of immunosuppressant agents.[21] In addition, neither the açaí pulp and fruit oil nor the açaí-enriched beverage MonaVie Active® displayed acute or subchronic genotoxicity in mice.[34–36] Interestingly, the former even protected murine cells against doxorubicin-induced genotoxicity.[34] However, concerns over the safety of certain açaí-containing products adulterated with prescription drugs have led the FDA to issue warning letters to manufacturing companies.[22] For instance, the weight loss product "Dream Body Advanced + Acai Weight Loss & Cleanse" was shown to be adulterated with the appetite-suppressing drug sibutramine and the antidepressant fluorexetine.[37]

While progress has been made in determining the pharmacological properties of *E. oleracea*, more advanced studies in animals and subsequently in the clinic are imperative to further confirm these preliminary data.

3. Noni

3.1. Traditional and dietary supplement uses

Morinda citrifolia (Rubiaceae) is a tropical tree believed to have originated from South Asia, and is now found in Africa, the Caribbean, and several countries in the Pacific region, including Hawaii and Tahiti, where it is cultivated for commercial production.[38] Certain parts of the plant have been used traditionally in several countries for medicinal purposes, and these have been presented in detail in previous reviews.[38,39] Examples of these ethnobotanical uses include the treatment of mouth sores, cancer, urinary and gastrointestinal tract disorders, such as stomach ulcers and diarrhea, tuberculosis, and bacterial and fungal infections (Table 1).

In the last few decades, *M. citrifolia* has gained in popularity as a dietary supplement, owing to its claimed beneficial health effects as a tonic, anticancer, and anti-inflammatory product.[17] Noni dietary supplements have been sold in the form of pills, tablets, powders, purees, and most commonly as juice blends of varying noni concentrations.[38–40]

Table 3
Examples of *in vivo* bioactivity studies of açaí, noni, mangosteen, black chokeberry, and maqui berry.

Botanical	Test sample/compound	Animal model	Delivery route/dose/duration	Outcome	Reference
Açaí	freeze-dried açaí powder	19-month old Fischer rats (n = 15–20/group)	oral, ad libitum (2% of diet for 6–7 weeks)	increased production of antioxidant marker Nrf2 in hippocampus and frontal cortex improved working memory and behavior	32,33
Noni	fermented fruit exudates and fractions	S180 sarcoma tumor-challenged C57BL/6J mice (n = 4–8/group)	oral, ad libitum (0.2 mL i.p. or 5% of drinking water 3d-4 weeks)	inhibition of tumor development and suppression of existing tumor cells	44
	Tahitian Noni® juice	MMTV-neu transgenic mice (n = 30–45/group)	oral, ad libitum (10% v/v drinking water, maximum 14 months)	reduction of mammary tumor growth but not incidence	45
	pure Costa Rican noni juice	carrageenan-induced acute paw edema rat model (n = 8/group)	by gavage (14.8 and 37 mg/kg, one time) or i.p. (7.4 and 37 mg/kg, one time)	reduction of acute and chronic inflammation	46
		asthmatic rat model (ovalbumin-induced, n = 8/group)	oral (4.6 mL/kg) and i.p. (2.3 mL/kg) (7 days)	reduced number of inflammatory cells in bronchoalveolar lavage	47
	americanin A (11)	HCT116 tumor xenograft mice (n = 6/group)	i.p. (5 or 10 mg/kg, 3 times/week for 41 days)	tumor volume reduction by 45%–56%	49
Mangosteen	α-mangostin	HT-29 human colon xenograft mice (n = 18/group)	oral, ad libitum (900 mg/kg added to diet, 3 weeks)	attenuation of tumor growth, and reduction of apoptotic proteins (BcL-2 and β-catenin) concentrations in tumor mass	67
Black chokeberry	CellBerry® (spray-dried fruit extract)	Rats fed fructose-rich diet (n = 6/group)	oral, ad libitum (100 or 200 mg/kg BW/d added to drinking water, 6 weeks)	reduced cholesterol, blood glucose modulation of adipogenesis and insulin signaling pathways	84
	Commercial spray-dried fruit ethanol extract	apolipoprotein E knockout mice fed high-fructose diet (n = 10/group)	oral, ad libitum (0.005 or 0.05% diet, 4 weeks)	reduction of plasma cholesterol improved hepatic and plasma antioxidant function	83
Maqui berry	fruit methanol extract anthocyanin-rich fraction of methanol fruit extract	ischemia/reperfusion rat model obese hyperglycemic mice (n = 4–10/group)	i.p. (10 mg/kg, single dose) by gavage (50–500 mg/kg single doses)	cardioprotective effect reduction of blood glucose levels and improved glucose tolerance	97 100

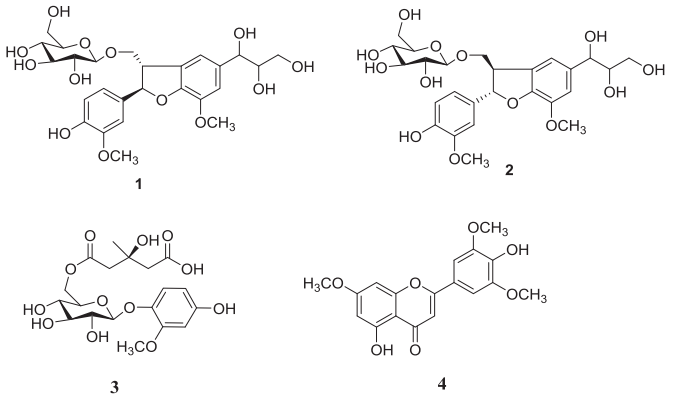

Fig. 1. Structures of representative compounds isolated from *Euterpe oleracea*.

3.2. Phytochemical and biological studies

The phytochemical composition of noni has been extensively studied, with approximately 200 compounds previously reported.[38] Moreover, noni extract and its constituents have been evaluated in various biological tests related to potential antioxidant, anti-inflammatory, cardiovascular, analgesic, antimicrobial, anticancer, and neuroprotective effects, among others (Table 2 and 3).[39–41]

A previous review highlighted the cancer chemopreventive potential of *M. citrifolia*, reporting several isolated compounds and their respective quinone reductase (QR)-inducing activities reflecting possible cancer protective properties *in vitro*.[17] Of particular significance was the isolation of the minor fruit constituent, 2-methoxy-1,3,6-trihydroxyanthraquinone (**5**) (Fig. 2), which proved to be nearly 40 times more potent than the positive control, L-sulforaphane, in the QR induction assay, and was not toxic to the host cells.[42] More recently, three new compounds, namely, 2-*O*-(β-D-glucopyranosyl)-1-*O*-(2*E*,4*Z*,7*Z*)-deca-2,4,7-trienoyl-β-D-glucopyranoside (**6**), 10-dimethoxyfermiloside (**7**), and 2-caffeoyl-3-ketohexulofuranosonic acid γ-lactone (**8**), along with a few known substances, were isolated from a fermented fruit exudate (juice secreted by the fruits through fermentation) of this plant.[43] Although these isolates only displayed moderate inhibitory activity against the inflammatory transcription factor NF-κB, the known iridoid glucosides, scandoside methyl ester (**9**) and rhodolatouside A (**10**), showed good potency in inducing the QR enzyme in Hepa1c1c7 murine hepatoma cells.[43] Mice administered with a similar preparation of noni fruits and its obtained butanol-soluble fraction both intraperitoneally and orally were protected against S180 sarcoma tumor challenge in preventive and therapeutic. The fermented noni fruit exudates and its fraction prevented tumor development, and eradicated up to 75% of existing tumor cells, leading to tumor-free animals for the rest of their lifespan.[44] Another animal study evaluated the effect of a commercial Tahitian Noni® juice product (percentage content of noni not specified) on tumor development and metastasis in a breast cancer model. This noni juice product was composed of the fruit puree, devoid of the skin and seeds, and standardized in terms of its iridoid content and complemented with grape and blueberry juices.[45] This preparation, when given orally, inhibited tumor growth but not tumorigenesis and showed no toxicity to the liver and kidney in a MMTV-neu transgenic mouse model, a close equivalent of the human HER2$^+$ breast cancer, and a very aggressive form of this disease.[36] While the investigators speculated on the potential of this commercial noni-based beverage as a complementary therapy to enhance survival in women with HER2$^+$ breast cancer, further study is warranted to validate this proposal. A pure Costa Rican noni juice sample obtained from the fruit puree inhibited COX-1 and COX-2 in LPS-activated murine macrophages *in vitro*,[46] and

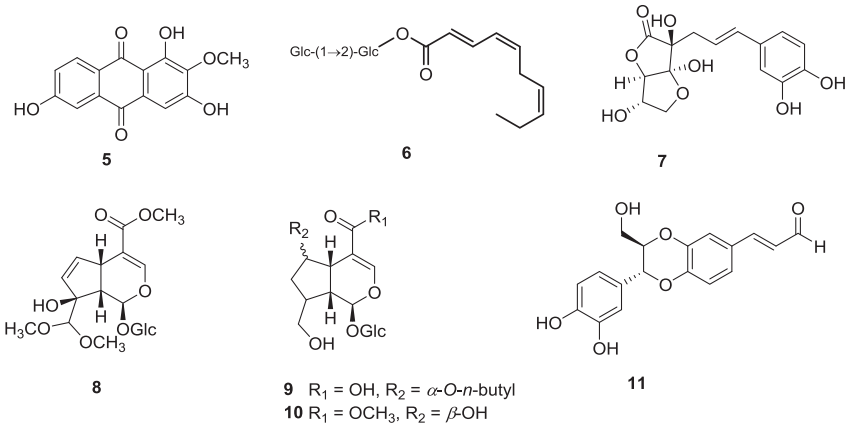

Fig. 2. Structures of representative compounds isolated from *Morinda citrifolia*.

when administered orally and intraperitoneally, it reduced acute and chronic inflammation in rat models of carrageenan-induced paw edema and ovalbumin-triggered asthma, respectively.[46,47] Since COX-2 plays a key role in neu-induced carcinogenesis, it was proposed that the anti-inflammatory property of noni could be a possible antitumor mechanism.[45] In an independent study, americanin A (**11**) (Fig. 2), a previously reported component of noni fruits,[48] inhibited tumor growth in a xenograft human colon cancer HCT116 mouse model with no apparent toxicity observed in the mice or in normal MRC-5 human lung epithelial cells *in vitro*.[49] Its mechanism of action involved modulation of several markers in the signaling pathways leading to G2/M cell cycle arrest and apoptosis.

The previously mentioned fermented noni juice preparation also showed potential antidiabetic properties in animal studies, as it reduced body weight and blood glucose and insulin levels in high-fat-diet-fed mice, and it beneficially modulated the expression of genes involved in gluconeogenesis and glycolysis, such as the phosphoenolpyruvate C kinase (PEPCK) and the forkhead box-O1 (FoxO1), respectively, in diabetic rats.[50] Phytochemical work on a commercially available dried noni powder geared toward the isolation of insulin-mimetic compounds led to discovery of additional new lignans and neolignans.[51] Some of these isolated compounds inhibited the protein tyrosine phosphatase 1B (PTP1B), and represented new lead compounds using this drug target for the treatment of type 2 diabetes and obesity, and stimulated glucose uptake in adipocyte cells.[42] However, these results have yet to be confirmed by *in vivo* evaluation. Interestingly, noni fruit juice has shown higher potencies in antidiabetic models compared to other plant parts, yet only the potential antidiabetic compounds from the roots, mostly anthraquinones, have been reported.[52]

3.3. Safety

Cases of toxicity associated with noni have been reported, and more recently, the consumption of noni juice was attributed as the cause of acute hepatotoxicity in two individuals. In one case, liver injury was suspected to have resulted from a noni-phenobarbital drug interaction,[53] while in the second case, the individual, a 14-year old male, was healthy with no family history of liver disease.[54] A review by Brown presenting a perspective on the safety of noni juice (Tahitian noni® juice), refuted the direct association of this noni juice to the toxicity case studies on the basis of the reported pre-existing medical conditions of the patients affected and the lack of adverse events in published animal and human safety studies.[39] Nevertheless, as a result of these observations, it has been recommended that patients with pre-existing cardiac, renal, or liver problems should avoid the consumption of noni juice.[39]

4. Mangosteen

4.1. Traditional and dietary supplement uses

Mangosteen [*Garcinia mangostana* L., (Clusiaceae)], also known as the “queen of fruits”, is a tropical tree indigenous to South and Southeast Asian countries, including India, Malaysia and Thailand.[55] The fruits and other parts of this plant have been used traditionally in these countries to treat various medical conditions including fever, parasitic diseases, skin disorders, diarrhea, chronic ulcers, and for wound-healing (Table 1).[55,56] Similar to the fruits mentioned earlier, mangosteen has been heavily marketed as a “superfruit”, following claims of its health-promoting properties,[57] and commercial products containing mangosteen fruits are readily available for sale online, in the United States, in the form of extract powders or capsules, and juices.

4.2. Phytochemical and biological studies

Mangosteen has also drawn much interest from the scientific community in the last few years as indicated by the large number of reports on its phytochemistry and biological activities *in vitro* (Table 2), *in vivo* (Table 3), and in humans. Mangosteen is mostly known for its content in xanthones, which have been extensively characterized, with over 60 of these compounds isolated previously.[17] In an initial study, two new xanthones, mangostingone and 8-hydroxycudraxanthone G, were isolated from *G. mangostana* fruit pericarp, and α-mangostin (**12**) (Fig. 3) was found to inhibit 7,12-dimethylbenz[α]anthracene (DMBA)-induced preneoplastic lesions in a murine mammary organ culture assay ($IC_{50} = 2.4\ \mu M$).[58] In recent years, additional derivatives, including mangostanaxanthones I and II (**13, 14**) were isolated (Fig. 3).[59,60] Mangosteen fruit extracts as well as some purified xanthones, notably the most abundant representative, α-mangostin (**12**), have been reported to exhibit a wide range of biological activities, inclusive of antioxidant, anti-inflammatory, antibacterial, and antiproliferative effects at the cellular level and in animal models, and potential mechanistic pathways responsible for these effects have been described.[55,56,61–63] Several antitumorigenic activities of xanthones from *G. mangostana* have been reported in various xenograft models of human cancers, including glioblastoma, prostate, and colorectal subtypes.[57] In addition, compound **12** showed potential in modulating metabolic diseases, as it induced body weight loss

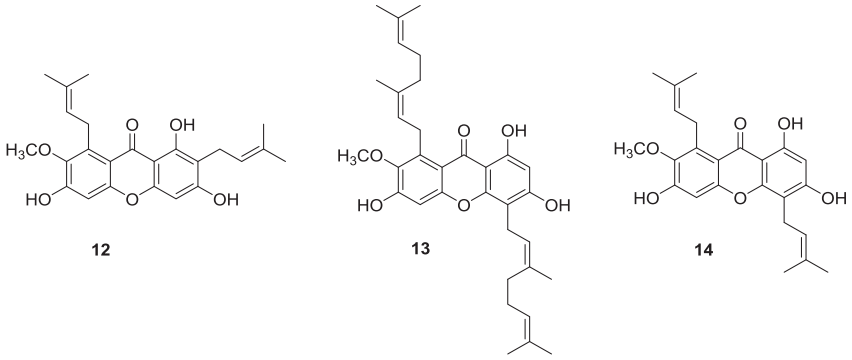

Fig. 3. Structures of representative compounds isolated from *Garicinia mangostana.*

without affecting food intake in obese mice, positively regulated their lipid metabolism, and also reduced hepatic steatosis.[64]

Following the investigation of the potential chemopreventive activity of xanthones from the freeze-dried pericarp of *G. mangostana* fruits through their hydroxyl radical-scavenging, quinone reductase-inducing, and aromatase-inhibiting effects,[17] bioavailability studies of *G. mangostana* extract and α-mangostin in animal models and in human subjects have been conducted. A first *in vivo* pharmacokinetic study showed that while the intravenous administration of α-mangostin (2 mg/kg) in rats led to a rapid distribution followed by a slow elimination, the oral administration (20 mg/kg) caused an intensive first pass metabolism, resulting in an overall very low bioavailabilty.[65] In a similar study comparing the pharmacokinetic properties of pure α- and γ-mangostin to that of the *G. mangostana* fruit extract, the pure xanthones had a comparable distribution. However, γ-mangostin was eliminated faster when given intravenously, though it had a slower conjugation and elimination rate when orally administered. On the other hand, elevated amounts of the unconjugated xanthones were present in the serum when a mangosteen fruit extract was given, suggesting that higher concentrations of the active "free" compounds would reach the target tissues.[66] Another report showed that α-mangostin was bioavailable in both healthy and tumor-bearing athymic mice as both the free and conjugated forms of α-mangostin and its biotransformed derivatives were detected in the serum, tumors and liver of the mice.[67] In the same study, α-mangostin caused a reduced tumor mass in the treated mice, showing antineoplastic activity despite the previously reported low oral bioavailability.

A clinical study further confirmed the bioavailability of xanthones from mangosteen in humans when the fruit juice was consumed with a high-fat meal.[68] In addition, consumption of a commercial mangosteen-containing beverages showed bioavailability of α-mangostin, as well as an increased antioxidant capacity and beneficial modulation of anti-inflammatory markers in humans in two different studies.[69,70] A third randomized controlled clinical study, conducted with 59 subjects suggested beneficial effects of the intake of Mangosteen Plus™ with Essential Minerals® on the immune system.[71] However, the mangosteen-based drink used in the above three studies contained green tea, *Aloe vera*, and some multivitamins, which synergistically could be partly responsible for the observed biological effects, and therefore question the extent of the effect of mangosteen. Similarly, a gel formulation containing a crude extract of mangosteen pericarp applied topically resulted in reduction of periodontal inflammation in human subjects, but the gel composition and mangosteen percent concentration used were not specified.[72]

4.3. Safety

Animal toxicity studies on mangosteen and its xanthones have been conducted, and these have resulted in conflicting reports. For instance, α-mangostin at a single dose of 1 g/kg body weight (BW) given by oral gavage showed no adverse effect in mice, and the long-term oral administration of ethanol or hydroethanolic extracts of mangosteen for a daily dose of up to 1 and 1.2 g/kg BW, respectively, showed no toxicity.[63] However, α-mangostin induced the production of pro-inflammatory TNF-α in normal and activated monocyte-derived human macrophages *in vitro*.[73] Moreover, α-mangostin aggravated induced colitis in mice, caused a shift in the gut microbiota favoring the abundance of pathogenic bacteria in healthy animals, a profile found in ulcerative colitis, and increased their colonic inflammation.[74] Interestingly, no liver toxicity was observed in the animals in this study, and the dose of α-mangostin used was deemed safe and effective in a previous antitumor study by the same group.[67] Similar dysbiosis and adverse colonic effects were observed in other strains of mice having different microbiomes, showing that the adverse effect of α-mangostin was strain independent.[75] In light of these diverging findings, it is clear that further toxicological studies are warranted, especially those relating to mangosteen juice consumption in humans. Nevertheless, it seems that caution should be taken when consuming xanthone-rich mangosteen supplements regularly, notably in patients with inflammatory bowel conditions.[74]

5. Black chokeberry

5.1. Traditional and dietary supplement uses

Aronia melanocarpa (Michx.) Elliott (Rosaceae), or black chokeberry tree, is a shrub native to northeast regions of the United States including the Appalachians and New England.[76] The berries were consumed as food by Native Americans, while infusions prepared from the fruits were used to treat colds, and the bark as an astringent.[77] Black chokeberry was introduced to Russia and Eastern European countries in the 20th century, where it became a popular food ingredient for the industrial production of jams, juices, liquor and wines, as well as food colorant. This plant was also grown as an ornamental shrub and used in Eastern Europe as an herbal medicine for the treatment of hypertension, atherosclerosis, and hemorrhoids, among other conditions.[78] Additionally, the fruits of *A. melanocarpa* were prepared as health-promoting beverages and dietary supplements, notably with their increased popularity related to their antioxidant property.[78]

5.2. Phytochemical and biological studies

Several studies have been reported on the beneficial biological effects associated with the high phenolic composition of *A. melanocarpa*, and the findings have been extensively reviewed.[78–82] These reports highlighted studies covering various disease conditions *in vitro*, and in animal and human studies, and the resulting potential protective effects of black chokeberry exemplified by its antiproliferative (against a variety of cancer cells), antimutagenic, hepatoprotective (against chemically induced liver damage), anticoagulant, cholesterol-lowering activities, and insulin modulation to name a few (Tables 2 and 3).[78–84] Phytochemical profiling of *A. melanocarpa* revealed that polymers of 10 or more (epi)catechin subunits, and cyanidin derivatives with galactose, glucose, arabinose, and xylose as the sugar units, constituted the major proanthocyanidins and anthocyanins, respectively, and the two most abundant phenolic compound classes in black chokeberries. In addition, hydroxycinnamic acids, and flavonols, such as quercetin and its derivatives have been identified from these fruits.[85]

In a search for potential cancer chemopreventive agents, a bioactivity-guided fractionation of a fruit sample of *A. melanocarpa* showed potent hydroxyl-radical scavenging and QR-inducing activity of the ethyl acetate-soluble extract. Further purification of this extract led to the isolation of a new depside (**15**) (Fig. 4), a class of compound rarely found in higher plants, but quite common in lichens, along with two of its analogs, and 24 known isolates. Among these secondary metabolites, 19 were reported in black chokeberry for the first time, with compounds **15**–**20** (Fig. 4) occurring at the highest abundance.[86] The hydroxyl-radical scavenging potencies were significant for 17 of the isolated compounds, with ED_{50} values ranging from 0.17 to 6.4 μM, and hyperin (**20**) being the most potent substance. On the other hand, protecatechuic acid (**16**), neochlorogenic acid methyl ester, and quercetin were found to be potent in inducing QR *in vitro*, with CD (the concentration required to double the QR activity) values of 3.1–6.7 μM.[86] Two additional new flavonoid derivatives with a novel fused pentacyclic core skeleton were further identified, namely, melanodiol (**21**) and its 4′-*O*-protocatechuate derivative (**22**) (Fig. 4).[87] It is worth mentioning that the structural determination of these compounds was facilitated by the computer-assisted structure elucidation (CASE) software to assist conventional spectroscopic data interpretation. Both **21** and **22** displayed potency as hydroxyl-radical scavengers, with ED_{50} values of 0.75 and 0.71 μM, and as QR inducers *in vitro* with CD values of 8.8 and 7.4 μM, respectively.[87] Considering the reported low bioavailability and extensive metabolism of *A. melanocarpa* anthocyanins, it is possible that the observed activities *in vivo* are due to the metabolites and catabolites of these flavonoids as well as other constituents of this fruit.[80,88,89] Therefore, the newly identified and isolated bioactive components of black chokeberry could potentially contribute to its overall *in vivo* health benefit.

5.3. Safety

No toxicity associated with the consumption of black chokeberry products has been found in published reports.[78,81] However, rats (six animals per treatment group) co-administered with 8 mL/kg BW of a 100% *A. melanocarpa* fruit juice over a period of 28 days and a single dose of the carcinogen *N*-nitrosodiethylamine (150 mg/kg BW delivered intraperitoneally on day 27) exhibited more DNA damage than those treated with the carcinogen alone.[90]

6. Maqui berry

6.1. Traditional and dietary supplement uses

Aristotelia chilensis (Molina) Stuntz (Elaeocarpaceae) or maqui, is a shrub indigenous to Chile and distributed in other South American regions, the Pacific area, and Asia.[91] The fruits of this plant, constituting berries of a dark purple color, have been added to the family of the so-called “superfruits” based on their high antioxidant capacity and perceived health benefits resulting therefrom.

Both the leaves and the berries of maqui have been used in folk medicine for the treatment of various conditions (Table 1). For instance, preparations made from the leaves were used to relieve sore throats, or applied topically to treat tumors, while the fruits were used to alleviate diarrhea and dysentery.[77] Other medicinal uses include the management of migraine headaches, fever, kidney pain and ulcers.[23,92] In addition to their medicinal properties, the

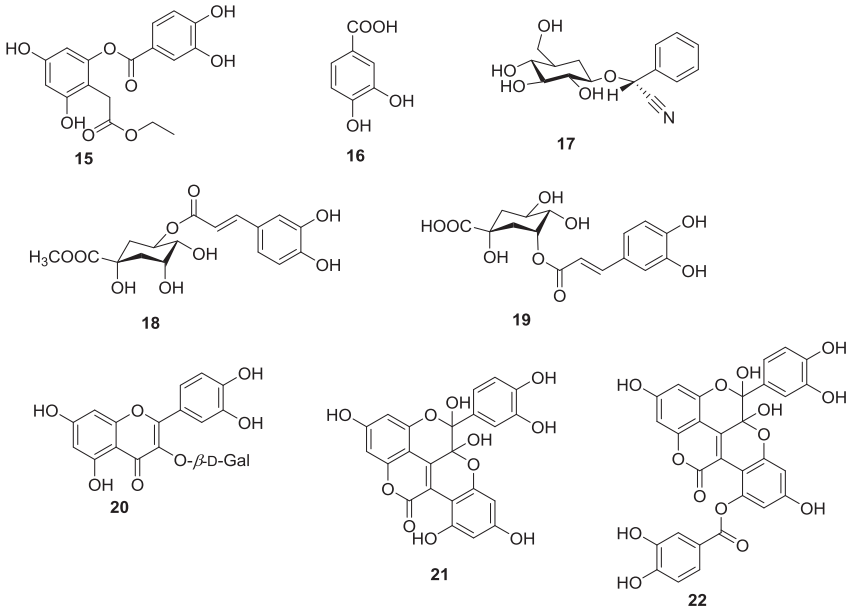

Fig. 4. Structures of representative compounds isolated from *Aronia melanocarpa*.

fruits of *A. chilensis* are consumed as fresh fruits or in the form of jams, wine, tea, and juice. Moreover, these berries represent a source of natural dye used in food coloring.[23,93,94]

Similar to other "superfruits", *A. chilensis* has been used as an ingredient of dietary supplements marketed in Western countries, including the United States. These products are sold in various forms including functional beverages such as Maqui Superberry™, topical formulations (composition not specified),[23] capsules of the fruit extracts, such as Delphinol® (a maqui berry extract standardized to 35% total anthocyanins, 28% delphinidins, and containing maltodextrin and dietary minerals in trace amounts).[95,96] Claims of antioxidant, anti-inflammatory, weight loss-promoting and skin protecting benefits have been ascribed to maqui-berry-based supplements, in their promotion to consumers.[91]

6.2. Phytochemical and biological studies

Investigation of the health benefits of maqui berry extracts have been conducted *in vitro* (Table 2) and *in vivo* (Table 3), and they have shown the potential of this fruit as an antioxidant,[97,98] cardioprotective,[97] anti-inflammatory,[99] antidiabetic,[100] and antibacterial.[98] For example, one study reported that *A. chilensis* fruit extracts and fractions showed hydroxyl radical-scavenging, antioxidant and anti-inflammatory activity in murine macrophage cells, by reducing lipid peroxidation and down-regulating the expression of both iNOS and COX-2.[92] Moreover, a methanol extract of maqui berries exhibited a cardioprotective effect in an ischemic/reperfusion model in rats, and this effect was associated with the observed antioxidant properties.[97] In another study, the anthocyanin-rich extract of the fruits of *A. chilensis* reduced the blood glucose levels in insulin-resistant obese hyperglycemic mice, and increased glucose uptake in muscle cells.[100] The antidiabetic potential of this fruit extract was correlated to that of delphinidin-3-*O*-sambuboside-5-*O*-glucopyranoside isolated in the same study. Clinical studies on a delphinidin-enriched maqui berry supplement Delphinol® have speculated on the beneficial effects of this commercialized extract as an antioxidant, and as a modulator of glycemia in prediabetic individuals.[95,101]

Alkaloids have been reported mainly from the leaves of *A. chilensis*, while more recent studies on the berries have revealed the presence of phenolic compounds, including proanthocyanins, anthocyanins, and flavonols, with delphinidin derivatives being the major anthocyanins that occur.[23,91,98] While most analytical reports have concentrated on the chemical profiling of maqui berry phenolic compounds, mainly anthocyanins, using various analytical techniques coupled in some cases with some biological testing, reports on the isolation of secondary metabolites from the fruits are still scarce.[93,94,98,102,103] Among the few such studies is the isolation of 3-hydroxyindole, which was found to possess antioxidant capacity,[104] and the aforementioned bioactive delphinidin-3-*O*-sambuboside-5-*O*-glucopyranoside isolated from an anthocyanin-rich extract of maqui berry.[100]

In an effort to investigate the potential cancer chemopreventive activity of maqui berry and the corresponding secondary metabolites responsible thereof, the first bioactivity-guided isolation of a commercially available *A. chilensis* fruit sample, using hydroxyl-radical scavenging and QR induction bioassays has been recently conducted. Sixteen small molecules, comprising one new natural product (**23**) (Fig. 5) and 15 known compounds, were isolated, structurally characterized, and evaluated in the above two bioassays.[105] These isolates included 13 phenolic compounds, two furan derivatives and one organic acid. Interestingly, the new compound, 2-*O*-*β*-D-glucopyranosyl-4,6-dihydroxybenzaldehyde (**23**), although it had not been previously reported as a natural product, has been generated as a synthetic intermediate for the preparation of anthocyanin, at a time when no spectroscopic data were available.[106] Fourteen of the isolated compounds exhibited hydroxyl-radical scavenging activity with ED_{50} values ranging from 0.13 to 1.9 μM, with cyanidin-3-*O*-*β*-D-glucopyranoside (**24**) displaying the greatest potency, while in the QR induction assay, four compounds were active with CD values that ranged from 4.1 to 19.2 μM. In addition, using the most abundant bioactive isolates [**16** (Fig. 4), and **25**–**27** (Fig. 5)] as chemical markers, a LC-DAD-MS-based chemical profiling procedure for the utilized maqui berry sample was developed and validated, providing a suitable method for quality control of this dietary supplement ingredient.[105]

6.3. Safety

No study investigating the toxicity associated with the consumption of maqui berry has been reported, to the best of the knowledge of the present authors, and despite the various biological evaluations on *A. chilensis* described above, these are still considered preliminary investigations. Thus, further rigorous preclinical and clinical studies assessing the health-promoting effects and possible toxicity are required on *A. chilensis*.

7. Conclusion

The consumption of botanical dietary supplements in the United States continues to increase, as reflected by the continuous growth in the annual sales of these products over the years, and, more recently, "exotic" fruits have been incorporated in this trend. This developing interest has been closely associated with the perceived need of consumers for the betterment of health, and claims for the health-promoting effects of these botanicals are usually linked to their historical uses in traditional medicine and some preliminary scientific findings. In this review, five less common or exotic fruits or fruit berries, namely, açaí, noni, mangosteen, black chokeberry, and maqui berry, have been described based on their traditional and local uses (Table 1), as well as their roles as dietary supplements, their presently known phytochemical components, the biological significance resulting from recent scientific investigations (Tables 2 and 3), and any existing reports on their potential toxic effects.

According to the data gathered, in addition to their "exotic" feature, these five botanicals share many similarities including their uses as foods, their ethnobotanical applications, and possibly related biological effects, notably their antioxidant potential, despite some differences in their phytochemical profiles. Notwithstanding the numerous compounds previously isolated from açaí, noni and mangosteen, a continued interest in these botanicals has led to the discovery of additional new secondary metabolite constituents. Recent work focusing on bioactive compounds from black chokeberry and maqui berry, for which previous chemical isolation reports were limited, has resulted in the identification and isolation of several new and known small-molecule constituents in each case.

Concerning the biological studies conducted on these botanical products, due to the large number of reports and their diverse nature, the majority of the available information has been summarized briefly for each plant in this review, while some findings are discussed in more detail. In particular, açaí was found to exhibit neuroprotective properties with *in vitro* studies being confirmed *in vivo*, and more evidence was found in the potential antitumor activity of noni based on animal and mechanistic studies. Moreover, pharmacokinetic studies have confirmed the bioavailability of mangosteen and its xanthones in animals and humans. Since the oral bioavailability of the major xanthone, α-mangostin, was low in a rat model when in the pure form, consideration of its observed

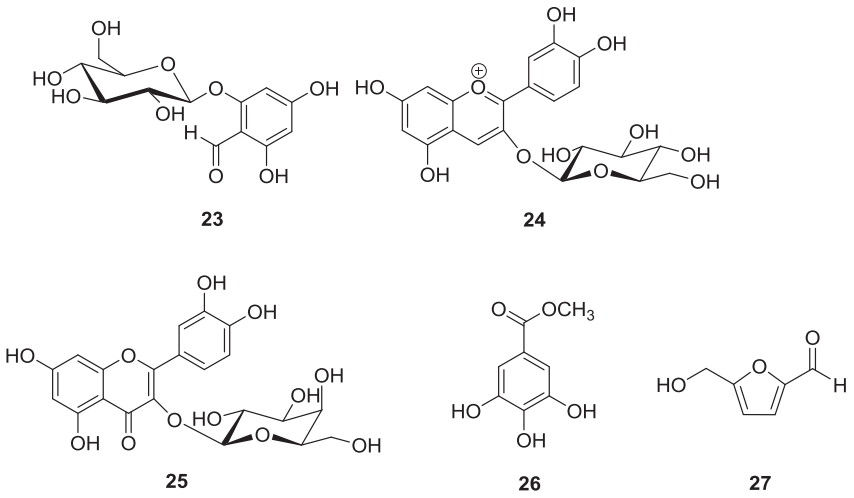

Fig. 5. Structures of representative compounds isolated from *Aristotelia chilensis*.

biological activity *in vivo* will require, in the future, the investigation of the activities of its conjugated and biotransformed xanthone derivatives.

While all the botanicals mentioned above are consumed as foods, they have also been used for medicinal purposes, and based on their observed pharmacological effects, it is crucial to have their potential adverse effects evaluated. Açaí was qualified as being generally safe, but a case of adulteration has been reported. Toxicity studies on noni juice suggest its safety in healthy individuals, while consumption is discouraged in patients with a medical history of liver, kidney, or cardiac conditions. Moreover, pure α-mangostin was shown to induce some toxicity in mice, while a mangosteen extract was regarded as non-toxic. Although the lack of consistency in the toxic effect of α-mangostin used at the same dose in mice in a further study is intriguing, the difference found for the extract versus the pure compound is perhaps not surprising. However, since α-mangostin is the major xanthone constituent of mangosteen, it is possible that higher doses of this supplement could cause some toxic effects. Finally, toxicity studies on maqui berry, if existing, are limited, and this is possibly due to the lack of comprehensive investigations conducted thus far.

In light of the results presented above, it is evident that more extensive research should be developed to confirm the efficacy and evaluate the safety of dietary supplements including the few selected herein. It is hoped that this compilation of findings will stimulate additional research in these directions.

Conflicts of interest

The authors declare no conflicts of interest.

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