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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.

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

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