Plant Foods for Human Nutrition
https://doi.org/10.1007/s11130-019-00746-6

REVIEW ARTICLE

A Review of the Potential of Chilean Native Berries in the Treatment of Obesity and its Related Features

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Abstract
Obesity is a major worldwide health threat. It is characterized by an abnormal adipose tissue overgrowth together with increased monocytes infiltration, causing inflammation and oxidative stress, events associated with several illnesses. Investigations have focused on the benefits of native fruit consumption, claiming these to be natural sources of bioactive compounds with antioxidant and anti-inflammatory characteristics. It has been widely stated that berries are a source of the most antioxidant compounds, and, thus, seem highly promising to endure research efforts on these vegetal matrices. The present article describes botanical, chemical and biomedical features of the Chilean native berries, *Aristotelia chilensis*, *Ugni molinae*, and *Berberis microphylla*. This work aims to potentiate incoming research focused on the search for novel treatments for first-order diseases with these particular plant sources.

Keywords Antioxidants · Bioactive compounds · Chilean native berries · Polyphenols · Obesity

Introduction

South America presents a rich biodiversity of fruits, some of them with an important economic role in the countries where they are found. However, the culture of native fruits in this area has been less developed and their properties less studied. In this regard, several features have been reported in the literature due its secondary metabolites and their potential effects on human health.

Numerous epidemiological studies [1–3] indicate that a diet rich in fruits and vegetables has been associated with a lower risk of several chronic conditions, including obesity, cancer, cardiovascular diseases, among others. Fruits, widely contain micro and macronutrients such as vitamins, minerals, and fiber; however, their beneficial biological properties have been attributed mainly to the presence of bioactive compounds, as well as to the synergies among them [4]. Data suggests that the consumption of these fruits has been associated with a lower incidence of chronic diseases due to the chemopreventive and antioxidant properties of bioactive compounds, such as vitamin C, polyphenols, minerals, *etc*. [5–7]. These constituents are profoundly valuable due to their antioxidant and anti-inflammatory features. The antioxidant activity of these compounds is manifested by their scavenging ability against reactive oxygen species (ROS), such as hydrogen peroxide, hydroxyl, peroxide radicals and singlet oxygen [8, 9]. On the other hand, they can also act on enzyme function, receptor activities, and gene expression, among others [10].

A major issue that affects the daily lives of individuals the most is body weight increment. Even though human beings require the presence of adipose tissues in the organism, there are several harmful consequences when this tissue develops excessively [11]. Obesity has claimed the spotlight worldwide, emerging as one of the major global health threats that affects our society nowadays [12, 13]. Indeed, it is well known that an excessive body fat accumulation, which defines this disease, is a source of several associated clinical manifestations such as type 2 diabetes (T2D), metabolic syndrome

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Published online: 05 July 2019

features, cardiovascular events, arthritis, *etc*. [14, 15]; and, regrettably, its worldwide prevalence (from 40 years ago) is only increasing [16]. In 2016, according to the World Health Organization (WHO), 39% of the world's adults aged >18 years were overweight and 13% obese, being this number tripled from 1975 [17]. Despite the essential and well-established tools that we have to fight, namely caloric restriction and exercise promotion, psychological approaches, and even pharmacological and surgical methods, the positive obesity trend has been maintained year after year. Thus, novel complementary strategies that come from nature are welcome to be tried out.

One of the main physiological characteristics of the adipose tissue in obesity is the presence of a chronic inflammatory state [18]. When adipose tissue hypertrophy occurs, adipocytes secrete inflammatory signals, such as monocyte chemoattractant protein-1 (MCP-1), which are responsible for monocyte infiltration and M1 polarization of macrophages [19]. The increase of resident macrophages in the adipose tissue yields major circulating levels of tumor necrosis factor-α (TNF-α), which by stimulation of the nuclear factor-kappa B (NF-κB) in adipocytes, establishes a self-perpetuating cycle of increased inflammatory cytokine release. Moreover, increased levels of TNF-α reduce adiponectin expression and secretion [20] and activate inducible nitric oxide synthase (iNOS), resulting in increased levels of nitric oxide (NO) [21] and affect insulin sensitivity because of a disruption of the insulin receptor signaling [22]. Hence, the search for compounds, which could ameliorate the pathogenesis of chronic inflammatory state in obesity, preventing the onset of related-diseases, associated with adipose tissue mass augmentation, is of great importance.

In Chile, several fruits from native plants have been considered, from ancient times, to have a wide range of health benefits. Among them, Maqui (*Aristotelia chilensis*), Murtilla (*Ugni molinae*), and Calafate (*Berberis microphylla*) are some of the most recognized. The use of native South American fruits has been claimed internationally [23] since the presence has been shown of elevated levels of antioxidant compounds and, consequently, highly beneficial effects on human health [24]. The healthy properties of these fruits may rely on their polyphenolic compositions since these compounds are found in significant proportions in such fruits. Among these, anthocyanins are known to be the most common type, and have been reported to possess antioxidant and anti-inflammatory properties, and happens to have the highest concentration among berries [25, 26]. Thus, regarding the above, and according to evidence reported in the literature, the present review summarizes the contents of major bioactive compounds and the health-promoting effects of the consumption of and treatment with native berries of Chile, such as *Aristotelia chilensis*, *Ugni molinae*, and *Berberis microphylla* (Table 1).

Aristotelia chilensis (Mol.) Stuntz (Maqui)

Overall Characteristics

Aristotelia chilensis is a fruit-bearing shrub that thrives in the temperate forests stretching from central to southern Chile and western Argentina. It belongs to the Elaeocarpaceae family and is commonly known as "Maqui." It is an evergreen shrub, reaching 3–5 m in height. *A. chilensis* yields a small edible purple/black berry averaging 5 mm in diameter and typically having three to four seeds [44].

Bioactive Compound Content

Its leaves and fruits have been usually used for the treatment of a wide range of illnesses [45]. Its several healthy effects have been attributed mainly to the high content of polyphenols in its fruits [46, 47]. Among these, the Maqui berry is reported to have a relatively high anthocyanin content (137.6 mg/100 g fresh weight (FW)), found mainly in the glycosylated forms of delphinidin and cyanidin. Furthermore, analyses of anthocyanidin constituents identified the presence of delphinidin-3-sambubioside-5-glucoside [26, 31, 33, 46, 47]. This compound was the most abundant, covering 34% of the total anthocyanins [46]. Other anthocyanins reported were delphinidin, delphinidin gallate [47], delphinidin-3-sambubioside, delphinidin-3-glucoside, delphinidin 3,5-diglucoside, cyanidin 3-sambubioside, cyanidin 3-glucoside, cyanidin 3-sambubioside-5-glucoside [26, 31, 33, 46] and cyanidin 3,5-diglucoside [26, 33, 46]. These compounds were also identified by Cespedes et al. [30, 47] in extracts, fractions, and subfractions of fruit pulps. Thus, the most abundant anthocyanins from this species have been previously quantified (in mg equivalents of delphinidin-3-glucoside / 100 g DW): from 46.4 ± 0.1 to 101.05 of delphinidin-3-sambubioside-5-glucoside, 23.7 ± 0.2 to 49.8 of delphinidin-3,5-diglucoside, 18.7 ± 0.2 to 20.73 of cyanidin-3,5-diglucoside/cyanidin-3-sambubioside-5-glucoside, and 17.1 ± 0.2 to 32.53 of delphinidin-3-glucoside [46, 47].

The phenolic compound content of Maqui extracts has a significant positively correlation with the total antioxidant capacity of the extracts [28, 30]. Moreover, it was observed that the beneficial effects of Maqui extract could probably also be attributed to an elevated content and variety of phenolic acids, such as gentisic, ferulic, gallic, *p*-coumaric, sinapic, *p*-

Table 1 Common name, origin, main bioactive compounds and reported biomedical features of the species revised

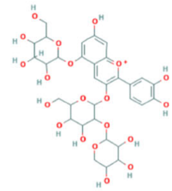
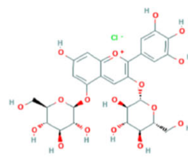
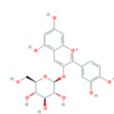
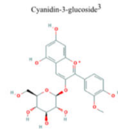
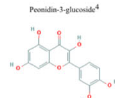
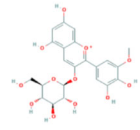
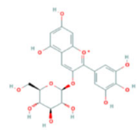
Specie	Common name	Picture	Family	Origin	Main polyphenolic groups	Chemical structure of most abundant compounds	Reported biomedical features	References
Aristotelia chilensis	Maqui		Elaeocarpaceae	Argentina	Anthocyanins		Oxidative stress protection of human endothelial cells	[27]
				Chile	Phenolic acids			
					Flavonoids		Antioxidant, anti-inflammatory and cardioprotective effects in rat heart	[28]
						Delphinidin-3-sambubioside-5-glucoside[1]	Antioxidant features on plasma oxidative stress markers after a meal intake (beverage and burger) prepared with a concentrate berries mix (containing Maqui)	[29]
							Anti-inflammatory effects in TPA-induced formation of ear rat enema	[30]
						Delphinidin-3,5-diglucoside[2]	Anti-lipogenic effect in 3T3-L1 adipocytes and anti-inflammatory features in RAW264.7 macrophages	[31]
							Antioxidant properties	[32]
							Ameliorating effects on T2D development in both animal (C57BL/6J mice) and cellular (H4IIE and L6 cell) models	[33]
							Inhibiting effects on α-glucosidase and α-amylase activity in diabetic patients	[34]
							Prevention of RAW264.7 macrophage activation and improving effects on 3T3-L1 adipocytes apoptosis	[35]
							Increased GSH levels and GSH/GSSG ratio, prevented caspase-3 induction, decreased MCP-1 gene expression, and improved IRS-1 phosphorylation on differentiated 3T3-L1 treated with conditioned media from activated macrophages	[36]
							Different mixtures, fractions, and subfractions of methanolic extracts presented inhibitory effects on inflammatory mediators in murine macrophages	[37]
							An isolated tetracyclic indole alkaloid induces vasodilation in rats aorta through modulation of calcium transport	[38]
Ugni molinae T.	Murta		Myrtaceae	Chile	Anthocyanins		Anti-inflammatory effects in TPA- and AA-induced formation of mouse ear enema	[39]
	Murtilla			Argentina	Phenolics acids			
	Chilean guava			Bolivia		Cyanidin-3-glucoside[3]	Increment of plasmatic antioxidant capacity in healthy subjects	[40]
					Flavonoids			
	Chilean cranberry				Ellagitannins		Protection against oxidative damage induced *in vitro* in human erythrocytes	[41]
	Uñi					Peonidin-3-glucoside[4]	Regulation of oxidative stress and carbohydrate metabolism in human red blood cells	[34]
	Mortillo							
						Quercetin[5]	Reduced ROS, lipid peroxidation and anion superoxide production in human endothelial cells	[42]

Table 1 (continued)

Berberis microphylla	Calafate		Berberidaceae	Argentina	Anthocyanins	 Petunidin-3-glucoside[6]	Inhibition of chloramphenicol-induced ROS production in human blood cells	[43]
	Barberry			Chile	Flavonols		High antioxidant capacity	[26]
	Mulun					 Delphinidin-3-glucoside[7]	Prevention of RAW264.7 macrophage activation	[35]
							Improving effects on 3T3-L1 adipocytes apoptosis and insulin-sensitivity induced by conditioned media from activated macrophages	[36]

TPA, tetradecanoylphorbol acetate; T2D, type 2 diabetes; GSH, reduced glutathione; GSSG, oxidized glutathione; MCP-1; monocyte chemoattractant protein-1; IRS-1, insulin receptor substrate; AA, arachidonic acid; ROS, reactive oxygen species. Chemical structures: [1]Shinbo, Y., et al. KNApSAcK: a comprehensive species-metabolite relationship database. Plant Metabolomics. 2006. 165–181; [2]NCBI, PubChem Database, CID = 10,100,905, https://pubchem.ncbi.nlm.nih.gov/compound/10100905 (accessed on Apr. 27, 2019); [3]NCBI, PubChem Database, CID = 441,667, https://pubchem.ncbi.nlm.nih.gov/compound/441667 (accessed on Apr. 27, 2019); [4]NCBI, PubChem Database, CID = 443,654, https://pubchem.ncbi.nlm.nih.gov/compound/443654 (accessed on Apr. 27, 2019); [5]NCBI, PubChem Database, CID = 5,280,343, https://pubchem.ncbi.nlm.nih.gov/compound/5280343 (accessed on Apr. 27, 2019); [6]NCBI, PubChem Database, CID = 443,651, https://pubchem.ncbi.nlm.nih.gov/compound/443651 (accessed on Apr. 27, 2019); [7]NCBI, PubChem Database, CID = 443,650, https://pubchem.ncbi.nlm.nih.gov/compound/443650 (accessed on Apr. 27, 2019)

hydroxybenzoic [47] and vanillic acid [30], flavonoids (quercetin, myricetin, rutin, (+)-catechin and (+)-epicatechin and gallocatechin gallate) and proanthocyanidins [30, 47]. Moreover, the presence of flavan-3-ol polymers and flavonols, such as glycosylated quercetin and kaempferol [34], was detected in crude extracts of Maqui leaves. The oxygen radical absorbance capacity (ORAC) value of Maqui has been determined to be 37,174 μmol Trolox equivalent (TE)/100 g DW [48]. Recently, a bioassay-guided isolation of antioxidant constituents from this fruit confirmed the presence of cyanidin 3-O-β-D-glucopyranoside, delphinidin 3-O-β-D-glucopyranoside, cyanidin 3-O-β-D-sambubioside, caryatin (3,5-di-O-methylquercetin), hyperoside (quercetin-3-O-galactoside), quercetin 3-O-α-L-arabinofuranoside, quercetin 3-O-β-D-xylopyranoside, gallic acid, gallic acid methyl ester, protocatechuic acid, protocatechuic acid methyl ester, hydroxymethylfurfural, acetyloxymethylfurfural, and 1,5-dimethyl citrate [49].

Finally, and as expected, the method that is applied to isolate and characterize these compounds has a significant impact on the constituents detected (and also on the antioxidant capacity) [50]. Moreover, it is important to mention that the presence of other food compounds could have an implication on the bioaccessibility of the main bioactive compounds (anthocyanins) occurring in Maqui (or other fruits), *e.g.*, previous results published related to different dietary fiber content [51].

Antioxidant and Anti-Inflammatory Features: Role in Obesity-Related Features

Regarding the antioxidant activities of fruits and/or leaves of this shrub, it was observed, for instance, that fruit extracts induced a reduction in lipid oxidation and thiobarbituric acid reactive substance (TBARS) concentration and presented significant antioxidant and cardioprotective effects on acute ischemia/reperfusion performed in vivo on rat hearts [28]. Moreover, it has been reported that Maqui leaf extracts present antioxidant features detected by 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) decoloration and xanthine oxidase activity inhibition [32]. Finally, it has been described that subfractions of Maqui induced inhibition of copper-induced oxidation of low-density lipoprotein (LDL) which protect against hydrogen peroxide-induced intracellular oxidative stress in human endothelial cells [27]. Furthermore, a standardized Maqui berry extract, Delphinol®, have an effect on oxidized low-density lipoprotein (ox-LDL) and 8-iso-prostaglandin F2α oxidative stress biomarkers. Results showed that Delphinol® supplementation improved oxidative stress not only in healthy subjects but in those overweight and smokers as well [52]. Besides, a berry concentrate mix (prepared from Maqui and several others berry samples) was administered to healthy male volunteers, as a beverage (6% of the mix), and also in combination with a ground turkey burger (prepared with 5% of the mix). Before meal intake, and at every hour for six hours after intake, a venous blood sample was collected in order to analyze markers of oxidative stress (MDA and DPPH). The authors observed a significant decrease in oxidative stress indicators for both types of meals, related to control one [29]. Moreover, in line with an improved oxidized environment related to decreasing cardiovascular malfunction (*e.g.*, low oxLDL), it has been reported recently that horbatine ((1R)-3-[(1S,5S)-(4,4,8-trimethylbicyclo[3.3.1]non-7-en-2-yl)methyl]-2,3-dihydro-1H-indole), a tetracyclic indole alkaloid extracted from Maqui leaves, induce vasodilation in rats aorta through modulation of calcium transport, indicating a possible protective role in this type of disturbances [38].

On the other hand, regarding glycemic control, Rojo et al. [33] described the ameliorative effects of an anthocyanin-enriched fraction of Maqui fruit on T2D features in both animal and cellular models. It was observed that this formulation improved fasting glucose and glucose intolerance in diet-induced hyperglycemic obese C57BL/6 J mice. These results were comparable with the effects of metformin. Regarding rat cellular models, it was observed that this anthocyanin formulation diminishes glucose production and improves insulin-stimulated glucose-6-phosphatase inhibition, suggesting effects on gluconeogenesis in H4IIE liver cells, and increases basal and insulin-stimulated glucose uptake in L6 myotubes. Similar results were observed with delphinidin 3-sambubioside-5-glucoside, a Maqui characteristic anthocyanin, which was explicitly isolated. Finally, it was observed that crude extracts of Maqui fruit presented inhibiting effects on α-glucosidase and α-amylase activity, suggesting a possible delaying effect in carbohydrate digestion, reducing the glucose absorption rate and, thus, improving post-prandial glucose tolerance in diabetic patients [34]. Complementing this, Hidalgo et al. [53] reported that Delphinol®, a standardized Maqui berry extract, reduced post-prandial blood glucose. This was seen in individuals with moderate glucose intolerance and streptozotocin-diabetic rats. In this double-blinded trial, subjects fasted for 12 h received a single 0.8 mg/mL dose of Delphinol® before the rice was given for consumption. A glucose tolerance test was performed immediately, and after seven days, when subjects received a placebo. The results showed that Delphinol® intake before rice consumption significantly lowered post-prandial blood glucose and insulin compared to placebo. The authors identified inhibition of the Na^+−dependent glucose transport by delphinidin, the principal anthocyanin of Delphinol® [53]. Both works showed that Maqui reduced blood glucose levels by either targeting enzymes involved in carbohydrate metabolism or by inhibiting the Na^+−dependent glucose transporter.

Regarding obesity features and the adjacent pro-inflammatory environment, it has been reported that a polyphenolic extract of Maqui inhibited lipid accumulation in differentiating 3T3-L1 cells, suggesting an anti-lipogenic effect, and that it also inhibited the production of NO, prostaglandin E2 (PGE2), and the expression of iNOS and cyclooxygenase-2 (COX-2) in RAW264.7 macrophages, suggesting anti-inflammatory properties [31]. Moreover, Ojeda et al. [54] reported that Maqui juice reduced COX-2 expression, as well as TNF-α-induced NF-κB activity in the Caco-2 cell line. It was also observed that cytoplasmic kappa light polypeptide gene enhancer in B cell NF-κB inhibitor alpha (IκBα) levels were reduced and extracellular signal-regulated kinase 1/2 (ERK1/2) and protein kinase B phosphorylation were increased, further supporting this anti-inflammatory effect.

Moreover, it was demonstrated that subfractions of Maqui showed inhibitory effects in tetradecanoylphorbol acetate (TPA)-induced formation of mouse ear edema [30] and that different mixtures, fractions, and subfractions of methanolic extracts of this fruit present major anti-inflammatory features over inflammatory mediators in murine macrophages [37]. Lastly, a crude extract of Maqui was shown to inhibit the inflammation explicitly linked to the pathogenic interaction between adipocytes and macrophages. The gene expression of iNOS and TNF-α was inhibited; meanwhile, interleukin-10 (IL-10) was induced by incubating an adipocyte/macrophage co-culture with the Maqui extract [35]. Moreover, in differentiated 3T3-L1 cells that were treated with conditioned media from activated macrophages, Maqui extracts increased reduced glutathione (GSH) levels and the GSH/oxidized glutathione (GSSG) ratio, prevented caspase-3 induction, decreased MCP-1 gene expressions, and improved a specific insulin receptor substrate-1 (IRS-1) phosphorylation [36].

Ugni molinae Turcz (Murtilla)

Overall Characteristics

Ugni molinae Turcz belongs to the Myrtaceae family. It is an evergreen shrub, and it is also known as Murtilla, Murta, Chilean cranberry or Chilean guava, and as Uñi in the Mapuche language of Southern-Chile inhabitants [55]. This fruit is native of Chile, western Argentina, and certain regions of Bolivia. Murtilla is a well-known regional plant that bears aromatic, red globular fruits. The berries typically possess a diameter of 0.7–1.3 cm and weight between 0.25 and 0.40 g [56].

Bioactive Compound Content

So far, it has been determined that *Ugni molinae* possesses a complex mixture of polyphenols ranging widely in molecular weights, such as phenolic acids, flavanols, flavonols and hydrolyzable tannins (ellagitannins) [55, 57, 58], which have been mainly studied in leaves [40]. In this context, Rubilar et al. [57] isolated from leaves alcoholic and aqueous extracts, myricetin, kaempferol glucoside, glycosylated forms of myricetin and quercetin (dirhamnoside, glucoside, rhamnoside, and xyloside), and epicatechin and gallic acid. Later, the same authors reported the presence of high-molecular-weight procyanidins and flavan-3-ol polymers in their monomeric forms (catechin or epicatechin). However, despite previous characterizations, Ruiz et al. [26] found anthocyanin in *Ugni molinae* fruits, such as cyanidin-3-

glucoside (2.4–4.5 mg/100 g FW) and peonidin-3-glucoside (6.0–7.0 mg/100 g FW), comprising an important source of these compounds [55]. Complementing this, Junqueira-Gonçalves et al. [59] determined the phenolic compounds of *Ugni molinae* fruit extracts by liquid chromatography mass spectrometry. The ethanolic extract showed the presence of three major compounds: caffeic acid 3-glucoside, quercetin-3-glucoside, and quercetin, while the methanol acid extract showed cyanidin-3-glucoside, pelargonidin-3-arabinose and delphinidin-3-glucoside [59]. The ORAC value of Murtilla was determined to be 43,574 TE/100 g DW [59]. Finally, it has been recently reported that the concentration of flavonoids in leaves was three times the content of the fruit (2.32 mg antioxidants/g fruit vs. 6.81 mg antioxidants/g leaves) [60].

It is worth mentioning that alongside abiotic conditions (soil, climate) and agronomic management, the genotype of cultivars is an issue that should be addressed and taken into account in order to standardize possible solutions coming from this type of vegetal material. A Chilean research group has studied for several years different genotypes of *Ugni molinae*, and they recently published that different genotypes were responsible for the differences between ellagitannins, gallic acid derivatives, and flavonol compositions on the leaves of this specie (keeping all other variables constants) [61].

Antioxidant Features: Possible Role in Obesity-Related Features

The antioxidant properties of *Ugni molinae* were studied back in 2004 using samples obtained from both, continental Chile and Juan Fernandez island. Healthy volunteers were given a 1% (*w*/*v*) infusion twice a day for three days. An increase in plasmatic antioxidant capacity was observed [40]. Moreover, Chilean guava leaf infusion treatment protected against oxidative damage induced *in vitro* by hypochlorous acid on human erythrocytes [41].

Moreover, extracts of Chilean guava fruits and leaves presented interesting counteracting activity to oxidative stress and carbohydrate metabolism regulation features by the inhibition of α-glucosidase and α-amylase activities [34]. Thus, this plant presents promising activities for blood glucose level control. It has also been described that extracts of Chilean guava leaves presented anti-inflammatory effects on TPA- and arachidonic acid (AA)-induced ear edema formation in mouse [39]. Recently, Jofre et al.[42] corroborated the anti-oxidative effect of *Ugni molinae Turcz* fruit by detecting diminished ROS, lipid peroxidation and anion superoxide production in human endothelial cells.

Berberis microphylla G. Forst. (Calafate)

Overall Characteristics

Berberis microphylla (*Berberis buxifolia*), also known as Calafate and Barberry, belongs to the Berberidaceae family and is native to the Patagonian area of Chile and Argentina [55]. Calafate is an evergreen or semi-evergreen shrub or small tree, which grows under a wide range of environmental conditions. Calafate fruits are dark purple, black or bluish berries [26].

Bioactive Compound Content

Literature data on edible *Berberis* species is scarce. According to Pomilo [62] and Ruiz et al. [26], phenolic compounds in Calafate fruit are mainly anthocyanins in their glycosylated forms (3-glucoside conjugates), such as petunidin-3-rutinoside-5-glucoside, petunidin-3-gentobioside, delphinidin-3-rutinoside, delphinidin-3-glucoside, petunidin-3-rutinoside, peonidin-3-glucoside, malvidin-3-glucoside and malvidin-3-rutinoside [62]. Later, Ruiz et al. [26] found anthocyanins that were different from the ones described above. These were: delphinidin-3,5-dihexoside, delphinidin-3-rutinoside-5-glucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside, cyanidin-3,5-dihexoside, petunidin-3-glucoside, petunidin-3,5-dihexoside, peonidin-3-rutinoside, peonidin-3,5-dihexoside, malvidin-3,5-dihexoside and malvidin-3-rutinoside-5-glucoside, and glycosylated flavonols such as myricetin-3-rutinoside-7-glucoside, myricetin-3-glucoside, myricetin-3-rutinoside, quercetin-3-rutinoside-7-glucoside, quercetin-3-galactoside, quercetin-3-rutinoside, quercetin-3-glucoside, quercetin-3-(6′-acetyl)-hexoside, quercetin-3-rhamnoside, isorhamnetin-3-rutinoside-7-glucoside, isorhamnetin-3-galactoside, isorhamnetin-3-rutinoside, isorhamnetin-3-glucoside, and isorhamnetin-3-(6′-acetyl)-hexoside. Nevertheless, the most abundant anthocyanins found in the Calafate fruit are petunidin-3-glucoside (21.6 ± 0.22 mg / 100 g DW) and delphinidin-3-glucoside (14.7 ± 0.55 mg / 100 g DW) [36]. The total content of anthocyanin and flavonol in Calafate berries have been estimated to be about 17.1 and 0.16 μmol g-1, respectively.

Ruiz et al.[63] evaluated the compositions of flavonols and alkaloids found in the pulp, skin, and seed of Calafate and other berries. Samples were collected from several locations in southern Chile. Flavonols were detected in all samples and quercetin-3-rutinoside was the most abundant. Calafate pulp and skin showed higher flavonol concentrations than seeds. Interestingly, the maturation process decreased the flavonol concentration [63].

Role in Obesity-Related Features

The high content of polyphenolic compounds in Calafate has been correlated with a high antioxidant capacity [26]. In fact, the ORAC value for this fruit was determined at 72,425 μmol TE/100 g DW, positioning it as the vegetable matrix with the highest antioxidant capacity consumed in South America [48]. In this regard, it has been observed that chloramphenicol-induced ROS production was inhibited by water *Berberis* extracts in human isolated blood cells [43].

On the other hand, and as observed for Maqui, Calafate inhibits inflammation linked to the pathogenic interaction between adipocytes and macrophages. Thus, a Calafate extract reduced the expression of iNOS and TNF-α, meanwhile, increased IL-10, when applied to an adipocyte/macrophage co-culture, suggesting a potential anti-inflammatory role [35]. Moreover, it was recently reported that a Calafate extract inhibits the inflammatory response and stimulates glucose uptake in 3T3-L1 cells treated with conditioned media from activated macrophages [36]. These results can be considered as a promising first approach over obesity-derived insulin resistance.

In our laboratory, it has been observed that a purified polyphenol-rich Calafate extract administered to mice fed a high fat diet prevents the development of obesity (Soto-Covasich et al.—unpublished data). Therefore, it is of great interest to evaluate a role for Calafate in the obesity-induced inflammatory state and to determine whether Calafate might prevent or overcome insulin resistance, and also its role in the development of obesity itself. Despite its antioxidant properties, the potential of Calafate remains poorly studied, and further work must be done to determine its real therapeutic potential.

Conclusions

The studies reviewed showed a rich and diversified composition of bioactive compounds in native fruits of Chile and their relationship with health-promoting properties vis-a-vis obesity-related illnesses, such as cardiovascular diseases, dyslipidemia, T2D, and on the etiopathogenesis within. Maqui, Murtilla, and Calafate plant species exhibited an important diversity of phytochemicals, mainly phenolic compounds. The main effects of these compounds are related to antioxidant and anti-inflammatory activities. Understanding the role of these bioactive compounds in the maintenance of health is nowadays a cutting-edge field of study.

It is worth mentioning that the effect of their intake might not be the result of a single bioactive compound but may arise from the synergy of compounds. Thus, it may be worthwhile to encourage an increased consumption of these berries and to include these fruits in food products in order to enhance the diet's bioactive compound content. Currently, some research groups are beginning to review the antioxidant capacity and health promoting features of some drinks enriched with this type of fruits [64]. On the other hand, they are trying to identify the sub-compounds that are present in the organisms (in tissues or plasma), after the intake of this matrices, as it was described recently for Calafate on gerbils [65]. The last approach intends to focus the research on a single or a specific combination of sub-compounds and, thus, to unveil which of the original polyphenols present in the vegetal matrix is the most potent in each investigative context. This knowledge could, then, significantly improve the practical solutions, which could in future be derived and administered to subjects as a validated complementary therapy.

Summing up, future research is still needed to understand the possible mechanisms of action of the bioactive compounds contained in this type of berries, and their potential use in the formulation of functional foods, supplements, and nutraceuticals for use on human health.

Acknowledgements This work was supported by the National Commission for Scientific and Technological Research (CONICYT, Chile; FONDECYT Grant 11110219).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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