Keywords: Aristotelia chilensis; Nutraceuticals; Antioxidants; Anti-diarrheal; Anthocyanins

Introduction

A nutraceutical is a product made from a food, which besides having a nutritional role by providing nutrients and energy, is capable of delivering the body other active ingredients beneficial to health, differing from a functional food in the form of presentation and administration [1].

In recent years, both in the market of American nutraceuticals as in Chile, there have been a number of products whose formulation containing Aristotelia chilensis. This fruit and leaves have shown an important range of biological actions, including antioxidants, anti-inflammatory and analgesic effects. These effects have led to use these products as complementary therapeutic agents in the treatment of various chronic and degenerative disorders. The fruits of Aristotelia chilensis have a high content of anthocyanins, of indole alkaloids and flavonoids, which makes them an attractive resource to produce antioxidant extracts for use in functional foods or nutraceuticals [1,2].

The Aristotelia chilensis (Mol.) Stuntz, belongs to the family of Elaeocarpaceae, a Chilean native species, popularly known as Maqui. It is a small tree that does not grow beyond 4-5 meters high, evergreen, with reddish stems, thin, flexible branches. Its bark is smooth and soft. Its leaves are stalked, lanceolate, with serrated edges, measuring 4-9 cm. It has small, whitish flowers arranged in axillary inflorescences. Its fruits are small berries of about 5 mm, bright blue or black color. The Maqui grows wild and is distributed from Limari in Region IV to Region XI Aysén in Chile. It thrives in moist soil, invading ravines, slopes of hills and forest edges [1-4].

In Chile, this species is known for the use given to the fruit in the diet. However, little has been used for medicinal purposes [5]. Only native peoples (mainly Mapuches) have used its leaves as a tea for therapeutic purposes in the treatment of diarrhea, acute tonsillitis, throat and mouth ulcers [6].

In recent years there has been an active interest in the berries, which are a group of fruits red, violet or purple, with a high content of polyphenols. Among the highlights are cranberries, myrtle, raspberries, grapes, caulk and also maqui or blackberry [7].

Traditional Medical Purposes

Among the traditional medicinal uses, fruits and juices, as well as Maqui leaves have been used [1,6,8]. Internally, the fruits have been used as a tonic that has anti-diarrheal, anti-inflammatory, healing, digestive, diaphoretic, expectorant, laxative and diuretic properties. Infusions of the leaves can be administered as gargling in inflammation of the oropharyngeal mucosa [8]. The Mapuches used the fruits of maqui externally to treat infected wounds and burn dry leaves as healing [1,6,8].

Nutritional Composition

In 1990 Schmidt-Hebbel et al. published tables of chemical composition of Chilean foods where maqui is included as a native fruit [9]:

Schmidt-Hebbel et al. Composición Química de Alimentos Chilenos, 8ªEdición. Universidad de Chile. According to Damascos et al. the maqui contains a significant amount of ascorbic acid. Native shrub fruits had higher content of Br, Zn, Co, Cr, Fe, Mo, and Na than those of the exotic naturalized species. The fruit nutrient content found in the studied species was similar or higher than other values reported for fruits of temperate and tropical species in the world [10].

Maqui mature leaves contain a lower amount of potassium than the young leaves and increased sodium content. The content of magnesium, chlorine, calcium, titanium and vanadium does not vary between leaves of different sites with different annual rainfall [1].

Chemical Composition

The Maqui has mainly anthocyanins, indole alkaloids, flavonoids, coumarins [11] caffeic and ferulic acid [12]. However, it has released the presence of gallic acid, gentisic, sinapic, hydroxybenzoic, vanillic, makanine, 8-oxo-9 dehydrohobartine and 8-oxo-9 dehydromakomakine [11,13].

Anthocyanins, flavonoids and phenolic acids are compounds which occur very often in many plant families. Their different biological activities, including antioxidant, antimicrobial, carcinogenic, cytotoxic, anti-inflammatory, analgesic, and antithrombotic properties, have been extensively reported. These biological activities are attributed to their chemical composition, rich in polyphenols, which are a group of secondary plant compounds with antioxidant properties [14].

References

1. Schmidt-Hebbel, et al. Composición Química de Alimentos Chilenos, 8ªEdición. Universidad de Chile. 1990.
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anti-inflammatory and mutagenic properties, make them interesting objects of research [2].

The most revealing anthocyanidins are 3-glycosides, 3,5-diglycoside, 3-sambubioside 5- and 3-glycosides sambubioside of cyanidin and delphinidin. The anthocyanidin at higher rates proved to be the delphinidin 3-glucoside sambubioside-5 (34% of total) [14,15].

The most important flavonoids are quercetin 5,3'-dimethyl ether, malvidin, petunidin, friedelin and ursolic acid. It has also been obtained in the methanol extract; quercetin 3-O-B-D-glucoside and kaempferol [1,12,15].

Among the indole alkaloids identified include the following: aristone, aristoteline, aristotelene, aristoteline, aristoteline, protopine, serratoline, hobartinol, 8-oxo-9-dehydro-hobartine, makonine, 8-oxo-9-dehydromakonine, 9-dehydro-8-oxo-makomakine [16-18].

**Pharmacological Activities**

**Antioxidant activity**

Polyphenolic compounds maqui fruit have shown to possess potent antioxidant effects in *vitro* [19,20]. Maqui juices showed prevent lipid peroxidation induced by copper on human endothelial cells. The mechanism is explained by the effect of polyphenols maqui juice and by their antioxidant effect against oxidative stress [21].

Similarly, combining maqui juice with lemon juice important antioxidant effect against DPPH radicals, superoxide anion and hydroxyl were evidenced. The results suggested that lemon juice enriched with berries could be of potential interest in the design of new drinks with a nutritive related function on health for chronic diseases [22].

The new isotic blends with lemon and anthocyanins-rich berries showed an attractive colour, especially in maqui samples, which is essential for consumer acceptance. Significantly higher antioxidant and biological effects were determined in the new blends, in comparison with the commercial isotic beverages [23].

In general, aqueous and methanolic extracts of the fruit of the *A. chilensis* have shown antioxidant effects on *in vitro* models and xanthine oxidase inhibiting DPPH, fluctuating in the range of 52.9 and 62.7% respectively [12].

Crude extracts of leaves and fruits also showed antioxidant activity. Their polyphenols inhibit alpha-glucosidase enzyme. This enzyme is essential for the metabolism of carbohydrates and using these crude extracts, can be a useful mechanism in the management of diabetic patients. However, is necessary to make more research for warrants a potential dietary use of this berry in therapies to treat diabetes symptoms [24,25].

The Anthocyanins from *A. chilensis* improve fasting blood glucose levels and glucose tolerance in obese diabetic mice. Decreased glucose production and enhanced insulin-induced gene expression of glucose-6-phosphatase was observed in liver cells. For other hand, the Delphinidin 3-sambubioside-5-glucoside (D3SSG) was identified as principal anthocyanin of Maqui berry and responsible for these effects on glucose utilization [25,26].

The Aristotelene, aristone, serratoline and hobartinol were isolated from mixture of alkaloids (ALK-MIX). Ursolic acid, friedelin and quercetin 5,3'-dimethyl ether were present in the dichloromethane extract while quercetin 3-O-B-D-glucoside and kaempferol were present in the methanol extract. From aqueous extract (INFU) were isolated protopine, aristoteline and caffeic and ferulic acids. The effects of *A. chilensis* are here in demonstrated, validating its use in traditional medicine. Protopine was reported for the first time in Elaeocarpaceae for Muñoz in 2011[12].

Phenolics compounds are well-known antioxidants and their regular ingestion contributes to improve antioxidant status of plasma. Phytochemical findings describe phenolics compounds of leaves in *Aristotelia chilensis* (Molina) Stuntz, show that their administration in herbal teas may support the prevention of diseases whose etiology lies in the oxidative stress. The extracts obtained with polar solvents showed the stabilizing capacity of free radicals and the antioxidant capacity of plasma which, after taking *A. chilensis* tea, increased to 30.27% as an average. Herbal tea and extracts from *A. chilensis* exhibited antioxidant capacity under the described conditions [5]. The methanol extract (MeOH) from mature fruits of *Aristotelia chilensis* (Mol) Stuntz, showed antioxidant activities and cardioprotective effects on acute ischemia/reperfusion in rat heart in *vivo*. On the other hand, the methanolic extract of the fruits was able to prevent these harmful events in the animal’s heart by diminishing lipid oxidation. Antioxidant activities of MeOH were strongly correlated with total polyphenol content. Consistent with this finding, MeOH had the greatest ORAC and FRAP values as percentage of activity. These results show that these fruits could be useful as antioxidant, cardioprotective and nutraceuticals sources (Table 1) [27]. The presence of the compound indole-3-OH showed significant antioxidant effects and may explain the chemopreventive, anti-inflammatory and cardiopreventive activities this fruit [2].

**Anti-inflammatory and analgesic activities**

Folk medicine attributes to the leaves of this species, analgesic and anti-inflammatory properties to be backed by scientific studies and has also determined that the leaves have antimicrobial and antioxidant activities [3,12,28]. The lack of effective and safe long-term therapies to treat the inflammatory process is an important problem in animal health. Thereby, the discovery of new anti-inflammatory alternatives is imperative. We have determined the anti-inflammatory effects of *Aristotelia chilensis* fruit concentrate in rats subjected to subplantar acute inflammation induced by carrageenan [29].

A bioguided study was carried out on serial extracts (hexane, dichloromethane, methanol, INFU and crude ALK-MIX). All extracts were evaluated for: a) topical administration against both arachidonic acid and 12-deoxyphorbol-13-decanoate (TPA)-induced inflammation in mice b) per-os administration against inflammation by delta-carrageenan- induced paw oedema in guinea-pigs and c) topical analgesia in tail flick and formalin model and per-os writhing test in mice. Greater anti-inflammatory effects were obtained against TPA with dichloromethane extract and methanol extract (63.9% and 66% respectively). INFU showed the most potent effect (56.2%) against arachidonic acid. Greater effects were obtained in the writhing test hexane and dichloromethane extracts (89.2%) [12].

In the topical analgesia models, all the extracts and ALK-MIX and the methanol extract were the most active (58.2 and 55.2%, respectively). In relation to the tail formalin assay, the methanol extract (74.1%) was the most active [12].

| Calories | Protein | CHO | Fibre | Ash | Calcium | Phosphorus | Iron | Potassium |
|---------|--------|-----|-------|-----|---------|------------|------|-----------|
| 150     | 0.8 g  | 40.8 g | 0.8 g | 1.2 g | 87 mg   | 44 mg      | 30.5 mg | 296 mg    |

**Table 1**: Nutritional composition of *Aristotelia chilensis* in 100 g of edible part.
The proposed mechanism of action for analgesic activity of the hexane extracts, is considered which would be modulated by L-arginine serotoninergic receptors (5-HT3), adrenergic (a-1), cholinergic-muscarinic (ACh-M) and via/NO (nitric oxide). Instead antinociceptive activity of dichloromethane extract would be modulated by the opioid, serotoninergic, adrenergic and nitridergic pathways. In the analgesic effect of methanol extract were involved the opioid systems, adrenergic, muscarinic cholinergic and L-arginine/NO. Alkaloids (Aristone, aristotelone, aristoteline and aristotelinine) demonstrated relax intestinal smooth muscle, explaining its anti-inflammatory and antispasmodic actions [3,28].

In general these compounds that occur in these Aristotelia species have been considered as the active principles of many anti-inflammatory plants. Thus, many phenolic acids, anthocyanins and flavonoids type have shown inhibitory activities on nitric oxide implicated in physiological and pathological process as chronic inflammation. These finding shows that the anthocyanins, flavonoids and phenolic acids may be responsible of the anti-inflammatory activity of this fruit. Actually, researchers are working in the kinetic of inhibition of these plant extracts and compounds as anti-inflammatory and they are dissecting the sites and mechanism of action as iNOS, Cyclooxygenase (COX), and TNF, among others [14].

Likewise, these extracts were able to reduce the production of nitric oxide (3.7-25.5%) and prostaglandin E2 (9.1-89.1%) and the expression of inducible oxide nitric synthase (9.8-61.8%) and cyclooxygenase-2 (16.6-62.0%) in RAW 264.7 macrophages stimulated by lipopolysaccharide [30].

Anthocyanins have effect during the inflammatory process, since they act by inhibiting the COX. Besides its antioxidant purpose and it inhibits adhesion of leukocytes to endothelial reaction to suppress the expression of molecules VCAM cells. They also inhibit mast cell degranulation and decreased levels of IL-2, IFN-y, and TNF-α [31]. It has been shown that anthocyanins inhibit the secretion of inflammatory cytokines such as IL-8, MCP-1, IL-1B-1 in neutrophil chemotactic cytokine-induced and IL-6 in cell and animal model after an inflammatory stimulus [32,33]. This suggests that it is feasible to use a formulation of dermatological use with A. chilensis to treat inflammatory skin diseases such as rosacea, sunburn and more circumscribed inflammatory lesions [34]. Other studies have suggested that supplementation with anthocyanins in vivo inhibits activation of NF-κB regulates many pro-inflammatory chemokines, cytokines and inflammatory mediators [35].

Anthocyanins exhibit a wide range of antioxidant protection and beneficial therapeutic effects including genomic DNA integrity, cardiovascular protection, neurological protection, anti-inflammatory and anti-cancer and can significantly reduce the production of NO, reducing oxidative stress in the anti-inflammatory process [29].

On the other hand, the tannins of the maqui have astringent properties and anti-diarrheal and the polyphenols of the leaves showed effects anti-hemolytic in vitro [24].

An experimental study evaluated the neuroprotective potential of an extract made from maqui polyphenols in Alzheimer’s disease model induced by soluble oligomers B-amyloid.

Neurons cultures of rat hippocampus were used and neuroprotection was observed when neurons were incubated with amyloid B (0.5 uM) more maqui extract for 24 hrs. In the mechanism of action was observed a recovery in the frequency transients calcium channel, compared with the control group receiving only B-amyloid (Only B-amiloid=72 ± 3% and B-amiloid+Maqui= 86 ± 2%; n=5). This was positively correlated with observed in spontaneous synaptic activity and the preservation of dendritic branches changes. The antioxidant activity of maqui is primarily responsible for these changes [37]. Alzheimer’s disease is characterized by the presence of different types of extracellular and neurotoxic aggregates of B-amyloid. Recently, bioactive compounds extracted from natural sources showing neuroprotective properties have become of interest in brain neuroregeneration. The results suggest that the maqui induces changes in the aggregation kinetics of Aβ producing variations in the nucleation phase. In conclusion, the maqui induces a potent neuroprotection by direct interaction with the B-amyloid aggregates, generating far less toxic species and in this way protecting the neuronal network [37].

The use of methanol extract of the ripe fruit provides cardioprotective activity in models of acute ischemia reperfusion in an in vivo study in rats [27]. Metabolically, has been evaluated in vitro the ability the some extracts of maqui, in reducing adipogenesis and lipid accumulation in adipocytes. In this regard, the phenolic extracts showed inhibit lipid accumulation between 4 to 10.8% in mature adipocytes and between 5.9 and 37.9% in those in differentiation state [1,38]. Concentrated juice of Aristotelia chilensis has a high content of phenolic compounds with antioxidant capacity, which protect both LDL from oxidation and endothelial cells from intracellular oxidative stress, suggesting that Aristotelia chilensis could have anti atherogenic properties [36].

Obesity is characterized by an increase in the infiltration of monocytes into the adipose tissue, causing an inflammatory condition associate with, for example, the development of insulin resistance. Thus, anti-inflammatory based treatments could emerge as a novel and interesting approach. It has been reported that Chilean native fruits maqui (Aristotela chilensis) and calafate (Berberis microphylla) present high contents of polyphenols, which are known for their antioxidant and anti-inflammatory properties. The extracts of these fruits present important inhibitory-like features over the inflammatory response of the interaction between adipocytes and macrophages, comprising a potential therapeutic tool against comorbidities associated with obesity development [39].

One study showed the protective effect of topical formulations containing quercetin on damage caused by oxidative stress induced by ultraviolet radiation. Two different formulations were used; a non-ionic emulsion with high lipid content and other anionic emulsion with low concentration of lipids. The results showed that the inflammatory damage induced by ultraviolet radiation decreased with both formulations, with better results when using non-ionic formulation rich in lipids [34].

In search of a nutraceutical formulations or a functional food based on A. chilensis

Infusions of its leaves have long been used in the traditional native...
The maqui is characterized as an important source of phenolics compounds [24] and a product with a high content of polyphenols of natural origin, is a healthy product and considered functional [44].

The fruit of the maqui is considered the healthiest berry exotic, because of its particularly high concentration of bioactive polyphenols [27,38] and the use of this fruit rich in polyphenols in preparing of other foods, showed a reduction in the use of artificial additives antioxidants obtaining thus healthier foods [44,45].

The polyphenols, can prevent heart disease, by possessing vasodilatory effects, antibiotics, anti-inflammatory, anti-apoptotic, anti-atherogenic. Also could be prevent colon cancer [36,46], and providing a possible protective effect in preventing diseases of the retina [47]. Regardless of the course to follow; develop functional foods or nutraceuticals, the Maqui is a super food capable of providing innovative alternatives in food and natural product for health.

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