Maqui (*Aristotelia chilensis*) berry and its major polyphenol delphinidin: Relevance for skin photo-protection and anti-aging

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Healthy ageing involves the interaction between genes, the environment, and lifestyle factors, particularly diet. Diet-regulated genes play a crucial role in the onset and progression of several chronic disorders including skin diseases and dietary interventions can be used to mitigate these diseases but also to maintain health. The nutrient regulation of key genes involved in ageing may prevent oxidation and inflammation, reducing cellular damages to proteins, membranes, and mitochondria. In recent years there has been a growing interest, supported by a large number of experimental and epidemiological studies, about the beneficial effects of some commonly used food-derived products, including macro-and micronutrients and dietary phytochemicals. In particular, fruits, spices and herbs often contain active phenolic substances endowed with potent antioxidant and chemo-preventive properties. Among polyphenols, anthocyanins, a subfamily belonging to the flavonoid group, have shown to modulate a variety of biochemical/signalling pathways involved in promoting organism physiology and general health status, including vasculo-protective effects, cognitive process enhancement, anti-cancer activity and skin photo-protection. Among the anthocyanin species, delphinidin [2-(3,4,5-trihydroxyphenyl)chromenyl-3,5,7-triol] represents the most potent antioxidant. The richest known natural source of delphinidin is the maqui berry (*Aristotelia chilensis*), a super-fruit indigenous to Chile. We have recently performed a randomized double-blind nutritional trial, and demonstrated the in vivo ability of maqui polyphenols to protect lipids from oxidative damages. This and other studies have begun to provide a basis for considering the use of maqui and delphinidin in the development of novel nutritional interventional strategies for health management and against specific age-associated diseases. In this review we will provide an overview of the current literature emphasizing antioxidant and anti-inflammatory pathways modulated by maqui berry and its polyphenolic components, mostly delphinidin. Moreover, we will focus on experimental studies showing that delphinidin of maqui may have a positive impact on skin health.

KEYWORDS: Maqui; Aristotelia chilensis; Polyphenols; Delphinidin; antioxidants.


**ABSTRACT**

Healthy ageing involves the interaction between genes, the environment, and lifestyle factors, particularly diet. Diet-regulated genes play a crucial role in the onset and progression of several chronic disorders including skin diseases and dietary interventions can be used to mitigate these diseases but also to maintain health. The nutrient regulation of key genes involved in ageing may prevent oxidation and inflammation, reducing cellular damages to proteins, membranes, and mitochondria. In recent years there has been a growing interest, supported by a large number of experimental and epidemiological studies, about the beneficial effects of some commonly used food-derived products, including macro-and micronutrients and dietary phytochemicals. In particular, fruits, spices and herbs often contain active phenolic substances endowed with potent antioxidant and chemo-preventive properties. Among polyphenols, anthocyanins, a subfamily belonging to the flavonoid group, have shown to modulate a variety of biochemical/signalling pathways involved in promoting organism physiology and general health status, including vasculo-protective effects, cognitive process enhancement, anti-cancer activity and skin photo-protection. Among the anthocyanin species, delphinidin [2-(3,4,5-trihydroxyphenyl)chromenyl-3,5,7-triol] represents the most potent antioxidant. The richest known natural source of delphinidin is the maqui berry (*Aristotelia chilensis*), a super-fruit indigenous to Chile. We have recently performed a randomized double-blind nutritional trial, and demonstrated the in vivo ability of maqui polyphenols to protect lipids from oxidative damages. This and other studies have begun to provide a basis for considering the use of maqui and delphinidin in the development of novel nutritional interventional strategies for health management and against specific age-associated diseases. In this review we will provide an overview of the current literature emphasizing antioxidant and anti-inflammatory pathways modulated by maqui berry and its polyphenolic components, mostly delphinidin. Moreover, we will focus on experimental studies showing that delphinidin of maqui may have a positive impact on skin health.

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Proper nutrition is a direct factor affecting wellbeing, health and proper skin condition. Beyond the nutritional value, nutraceuticals and functional foods contain health-promoting components with specific beneficial effects on skin. The human skin is subject to constant change, which is why dietary supplements can complement the normal diet by providing properly balanced nutrients. A number of efficient micronutrients are capable of contributing to the prevention of UV damage in humans and a growing body of scientific evidence is becoming available to support that food derived compounds with antioxidants and anti-inflammatory activities contribute to endogenous photo protection and are crucial for the maintenance of skin health. Spices and herbs often contain active phenolic substances endowed with potent antioxidative and chemopreventive properties (1). All of these compounds appear to have a number of different molecular targets, impinging on several signalling pathways, and showing pleiotropic activity on cells and tissues. A possible general mechanism of polyphenols healing activity, relate to their ability to overexpress highly protective inducible genes, involved in the cellular stress response. Several data from our and other laboratories, have previously shown that different classes of polyphenols, such as an-
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tochyanins, epicatechins and curcuminoids, strongly induce heme-oxygenase-1 (HO-1) expression and activity in skin cells via the activation of heterodimers of nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant responsive element (ARE) pathway (2). Many studies clearly demonstrate that activation of Nrf2 target genes, and particularly HO-1, is strongly protective against inflammation, oxidative damage, and cell death, in skin and in several tissues (3). Furthermore, most of these compounds, have been shown to efficiently inhibit the activation of Nuclear Factor kB (NFkB), the master regulator of cellular pro-inflammatory events (4). This double pathways interference by polyphenols-Nrf2 activation/-NFkB inhibition, induce an over expression of endogenous antioxidants, and inhibit the production or expression of pro-inflammatory mediators including cytokines, chemokines and matrix metalloproteinases (Figure 1). These studies have begun to provide a basis for considering the use of such polyphenols in the development of novel nutritional interventional strategies for skin health management and against specific age-associated diseases, including photo carcinogenesis.

In this review we have examined the nutritional value of a super fruit, the berries of Aristotelia chilensis ([Molina], Stuntz), also known as maqui (Figure 2), and its promising effects against skin aging and skin inflammatory diseases, with a special focus on delphinidin[2-(3,4,5-trihydroxyphenyl)chromenylium-3,5,7-triol], a specific polyphenol highly contained in this fruit (Figure 3).

**MAQUI: FROM TRADITIONAL USE TO PHYTOCHEMICAL CHARACTERISTICS.**

Maqui belongs to the family of Elaeo-
carpaceae, with 10 genera and about 400 species, is a plant native to the Valdivian temperate rainforests of Chile. Maqui berries, very similar to blueberries, are rich in anthocyanins, in particular delphinidin, antioxidants responsible for their purple coloration and, in all likelihood, for many of the medicinal properties attributed to it. Maqui’s therapeutic qualities have been known for centuries to the Mapuche indigenous people who have traditionally lived in the southern part of Chile. According to the conquistadors the Mapuche warriors ate very little solid food and drank both a fresh and a fermented beverage called “chicha” made from maqui berry which might have contributed to the strength and stamina that the warriors exhibited. The Mapuche Indians have used maqui’s berry leaves, stems, fruits and wine medicinally for thousands of years. Traditionally, it is believed to heal wounds, relieve sore throats and as analgesic. Today, maqui berry is regarded as “super fruit” due to its superior antioxidant properties. Currently berries maqui are marketed in the form of juices and infusions, and supplements are also derived from the maqui.

Phytochemical screening of maqui extract (fruits or leaves) revealed the presence of anthocyanins and other flavonoids, alkaloids, cinnamic and benzoic acid derivatives, other bioactive molecules, and mineral elements. There are several reports concerning the anthocyanins chemical composition of A. chilensis indicating relatively high anthocyanin content (~135 mg for 100 g fresh weight). Anthocyanins are glycosides of anthocyanidins, and are widely distributed in colored fruits and berries. Anthocyanins are water soluble and non-toxic pigment, divided in five major groups: malvidin, delphinidin, petunidin, cyanidin, peonidin. Delphinidin, that contains 3 hydroxilations in the B ring, posses the highest antioxidant activity. The total anthocyanin content in the maqui berry extracts (MBE) was ~35%, of which the anthocyanin proposition is ~80% of delphinidin, and malvidin, petunidin, cyanidin, peonidin derivatives being the rest (5). Recently Delphinol® (trademark owned by MNL Chile) an high polyphenols standardized extract of maqui berries, bearing ≥ 25% delphinidin, has been introduced in the European and Japanese supplement market (5).

**MAQUI BIOLOGICAL ACTIVITIES.**

Regarding biological activity, maqui shows good responses in terms of antioxidant, anti-inflammatory anti-diabetic, anti-photo aging, etc. The broad range of activities of the fruits indicates that multiple mechanisms are responsible for its biological healing properties, linked to their characteristic phenolic content, and suggesting a very attractive potential for skin photo-aging and photo carcinogenesis.

**Antioxidant activity**

In vitro antioxidant potential of maqui berries have been widely explored. Maqui fruits represent a rich source of antioxidant compounds, considering that they show high activity with respect to the DPPH. decoloration assay. This is due to their high anthocyanins content as demonstrated by the positive and direct correlation between DPPH. and total anthocyanins content (TAC). Maqui fruits show higher oxygen radical absorbance capacity (ORAC) values than over 100 different kinds of foods, including fruits, vegetables, nuts, dried fruits, spices and cereals (20 times stronger.
than lemon, 3.5 times stronger than blackcurrant, and 2.9 times stronger than wild blueberry).

The effect of anthocyanins on lipid peroxidation was examined in vitro (using artificial membrane lipid bilayer model). Results showed that anthocyanins strongly inhibited lipid peroxidation by Fe2+ ion, particularly, delphinidin demonstrates powerful inhibitory effect.

Hydrogen peroxide is the simplest peroxide with powerful oxidizing capacity, hence a highly reactive oxygen species. The effect of anthocyanins on hydrogen peroxide was examined on membrane lipids (using rat brain homogenate). Delphinidin exhibits strongest inhibitory effect on hydrogen peroxidation of membrane lipids with lowest ID50.

The antioxidant effects of A. chilensis, with its exceptionally high content of phenolics, have been studied in different cellular models. Maqui extract has been shown to protect both LDL from oxidation and endothelial cells from intracellular oxidative stress (6), suggesting that it could have anti-atherogenic properties (7), being atherosclerosis a possible consequences of oxidative stress on LDL cholesterol in the vascular wall. Oxidized LDL support foam cells formation and represent a potent inducer of inflammatory molecules, which leads to apoptosis of vascular endothelial cells, thus to progression of atherosclerosis.

The majority of in vitro and in vivo studies conducted so far have attributed the protective effect of bioactive polyphenols to their chemical reactivity toward free radicals and their capacity to prevent the oxidation of important intracellular components. However, observations from our and other laboratories, reveal a potential novel aspect in the mode of action of polyphenols, that is the activation of Nrf2 transcription factor, and by this, the upregulation of inducible genes characterized by antioxidant responsive element (ARE) in their promoter region. Unprecedented data from our laboratory have shown that maqui berries extract Delphinol®, strongly induce heme-oxygenase-1 (HO-1) expression and activity in endothelial cells via the activation of Nrf2 pathway (unpublished data). Many studies clearly demonstrate that activation of Nrf2 target genes, and particularly HO-1, is strongly protective against inflammation, oxidative damage, and cell death.

Antioxidant activity has been also proposed as one of the possible mechanism of the strong neuroprotective activity of maqui anthocyanions, in hippocampal cultured neurons exposed to soluble oligomers of beta-amyloid 1-40 (8).

In vivo studies have also confirmed the ability of maqui berry to reduce oxidative stress in different tissues. Orally administered maqui berry extracts (MBE) suppress reactive oxygen species formation from lacrimal gland tissue, preserve and restore tear secretion capacity in dry eye. This effect is associated with the modulation of the lacrimal gland secretory system stimulated by MBE containing the anthocyanin delphinidin 3,5-O-diglucoside (9).

We have recently investigated the effects of oral administration of Maqui Berry extract, titled in delphinidin, Delphinol®, on lipid peroxidation in healthy smokers subjects, aged 50-70 years (10). A randomized placebo-controlled, double-blind study (n=43) was conducted, during which anthocyanins from Maqui Berry (~300 mg/day) or placebo were orally administered to 43 healthy smokers.
subjects once daily for 4 weeks. Basic biochemical and hematological parameters were determined throughout the trial. Oxidative damage to lipids was assessed by measuring plasma-circulating oxidized LDL (immunoenzymatic assay) urine total F2-isoprostanes (HPLC with tandem MS). Efficacy was defined as the change from baseline and after oral administration of berry anthocyanins, oxidative stress indicators in the supplemented group were better than in the placebo. Indeed, a statistically significant reduction in oxidised LDL and total F2-isoprostanes, was observed.

**Anti-inflammatory effect**

The anti-inflammatory effect of anthocyanins was evaluated using mouse macrophage cells (RAW 264.7). Upon addition of LPS (lipopolysaccharides, inflammation inducer) to macrophage cells RAW264.7, the expression of cyclo-oxygenase-2 (COX-2) markedly up-regulated in response to activation of inflammatory cascades. However, in sample treated with delphinidin, up-regulation of COX-2 is inhibited. Meanwhile, the expression of COX-1 is not affected indicating that delphinidin is a COX-2 selective anti-inflammatory agent. COX-1 is important in the healthy maintenance of physiological functions. Upon UVB-irradiation on the skin, inflammatory cascade is activated with up-regulation of COX-2 and release of pro-inflammatory prostaglandins E2 (PGE2) (11, 12).

Dichloromethane and methanol extracts, from both leaves and fruits of *Aristotelia chilensis*, show similar effects against 12-deoxyphorbol-13-decanoate (TPA)-induced inflammation (63.9 and 66.0%, respectively). On the other hand, aqueous extract show an high effect (56.2%) against arachidonic acid induced inflammation, more than the reference drug nimesulide, reaching almost double the effect exhibit for hexane and dichloromethane extracts (30.0 and 31.5%, respectively). The topical anti-inflammatory effect of methanol extract (20%) is not significant. Tests carried out with a mixture of alkaloids extracted from the same plant allow to exclude the possibility that these are the cause of these effects (13, 14).

The topical anti-inflammatory effect in the TPA and arachidonic acid assays and the analgesic activity of dichloromethane extract may be partly caused by the mixture of the pentacyclic triterpenoids, ursolic acid and friedelin, with quercetin 5,3'-O-dimethyl ether. This flavonoid has greater anti-inflammatory activity than the positive control mafenamic acid. Reports suggest that the topical anti-inflammatory activity of plant extracts is due to the presence of these compounds, mostly to the high content of ursolic acid. Quercetin 3-O-D-glucoside and kaempferol in methanol extract show an high effect against arachidonic acid induced inflammation, more than the reference drug nimesulide, reaching almost double the effect exhibit for hexane and dichloromethane extracts (30.0 and 31.5%, respectively). The topical anti-inflammatory effect of methanol extract (20%) is not significant. Tests carried out with a mixture of alkaloids extracted from the same plant allow to exclude the possibility that these are the cause of these effects (13, 14).

Considering the good bioavailability and the human nutritional efficacy demonstrated in clinical studies (15), we should consider maqui extract, with high levels of
delphinidin, a promising helpful dietary complement to counteract alterations in cellular redox status, in several physiological and pathologic conditions, included skin ageing and photo carcinogenesis.

DELPHINIDIN FOR THE MAINTENANCE OF SKIN HEALTH.

Exposure of solar UV radiation, particularly its UVB component, to humans causes many adverse effects that include erythema, hyperpigmentation, hyperplasia, immune suppression, photaging, and skin cancer. UVB exposure to skin cells results in several types of DNA damage such as the formation of cyclobutane pyrimidine dimers (CPDs), pyrimidine (6-4) pyrimidone. These effects of UVB radiation resulting in damaged DNA can initiate photocarcinogenesis. Experimental and epidemiologic studies have suggested that polyphenols protect the skin from the adverse effects of UV radiation, and they have gained considerable attention as photochemopreventive agents for human use. Among the phytochemicals with antioxidant/anti-inflammatory potent activity, delphinidin deserves particular consideration. The low molecular size of delphinidin, the high bioavailability and the expected good skin tissue distribution makes this anthocyanidin a promising candidate for skin-ageing protection (16).

First evidences for delphinidin ability to protect skin cells from UVB-mediated, have been demonstrated by an in vitro model using cultured human keratinocytes (HaCaT cells) (17). This study have shown that pretreatment of cells with delphinidin inhibited UVB-mediated apoptosis as determined by flow cytometry, confocal microscopy, and PARP cleavage. Delphinidin treatment of HaCaT cells prior to UVB irradiation resulted in a significant decrease in Bax with concomitant increase in Bcl-2 resulting in a shift in Bax/Bcl-2 ratio that does not favor apoptosis. Moreover, it has been found that topical application of delphinidin (both pretreatment and post-treatment) inhibited UVB-induced apoptosis in SKH-1 hairless mouse skin. Another study, conducted on both in vitro and in vivo model, has highlighted the strong antinflammatory effects of delphinidin against UVB induced inflammation (18). Treatment of JB6 P++ mouse epidermal cells with delphinidin suppressed UVB induced COX-2 expression and PGE2 production, and this was also shown in vivo on mouse skin exposed to UVB. This activity has been associated with the suppression of AP-1 and NF-κB transcriptional activities, and the phosphorylation of JNKs, p38 and Akt. The study also revealed that delphinidin binds directly with MAPKK4 and PI3K in an adenosine triphosphate-competitive manner. In another study, delphinidin treatment significantly inhibited UVB-induced MMP-1 expression in primary cultured human dermal fibroblasts (HDF), and significantly inhibited UVB-induced ROS production and NOX activity (19).

Delphinidin has been also shown to induces differentiation in human epidermal keratinocytes both in submerged cultures and 3D EEs model resulting in increased expression in caspase-14 expression, a protease tightly regulated during keratinization and down-regulated in hyperproliferative skin disorders including psoriasis (20). In another study, appli-
cilation of delphinidin to flaky skin mice abrogated the histological characteristics of psoriasisiform lesions and greatly reduced infiltration of inflammatory cells such as neutrophils and macrophages (21).

Accordingly with the previous evidences, the positive effect of maqui berry, containing high amounts of delphinidin, has been demonstrated. Maqui extract has been experimented in fibroblasts cells exposed to UVB-irradiation. Results showed that maqui effectively inhibit UVB-induced cell damage of fibroblasts cells. Furthermore, MMP-1 gene up-regulation by UV, is actively downregulated by maqui, that offered a protection the degradation of collagen (22).

These promising biological effects coupled with the relatively low cost and toxicity of natural agents makes maqui and delphinidin, promising agents for the treatment of photo-aging and also inflammatory skin disorders such as psoriasis (23).

CONCLUSIONS

Growing evidence shows that nutrition through the intake of fruits and vegetable can contribute to prevent and to treat almost all diseases including early aging. Indeed fruits and vegetables contain several active molecules like anthocianins that are able to dial directly with DNA by genetic and/or epigenetic mechanisms. On this background delphinidin from maqui berry (Aristotelia chilensis), a super-fruit indigenous to Chile, showed powerful antioxidant and anti-inflammatory properties either in vitro or in vivo that can be very useful in aesthetic medicine and in dermatology.

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