Buddleja globosa Hope

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Buddleja globosa leaves. Chillán, Región de Ñuble, Chile. (Photos: E Pastene, October, 2019)

Abstract *Buddleja globosa* Hope (Buddlejaceae) is a native species cultivated in Chile, Peru and Argentina. In folk medicine, this plant is frequently used for the treatment of different wounds (internal and external), as well as intestinal and liver diseases. There is growing scientific evidence on the growing conditions for *Buddleja globosa* and how its cultivation could be optimized. Methods for its vegetative propagation have also been successfully elaborated. The leaves contain phenylpropanoids,

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iridoids, terpenes and flavonoids. Ethnopharmacological validation studies suggest that phenylpropanoids and flavonoids are the main and most important compounds in defining the therapeutic activity of *Buddleja globosa*. This chemical composition explains its pharmacological activity as antioxidant, anti-inflammatory, antimicrobial and, in particular, its wound healing effects. Due to its undeniable potential as a domesticated, cultivated medicinal plant and its remarkable chemical composition, it is still necessary to develop its properly standardized, clinically validated phytopharmaceutical products.

Keywords "Matico" · Phenylpropanoids · Verbascoside · Wound healing

1 Introduction

Buddleja globosa Hope ("matico") has multiple uses in traditional medicine, such as healing stomach ulcers, colitis, and to improve cicatrization of cutaneous wounds. Plants with wound healing properties are not very abundant. Furthermore, in few cases the pharmacological mechanisms of action are known. Among these species, *Centella asiatica, Curcuma longa, Calendula officinalis*, and *Paeonia suffruticosa* can be mentioned. Remarkably, the chemical composition of these species is different from that of *B. globosa*. Recently, data suggest the possibility that chemical constituents of this species could act jointly on different overlapping events in the wound healing process. So, the effects upon proliferation/migration properties can be added to its antimicrobial, anti-inflammatory and antioxidant properties. It is an important advantage of its utilization that its agronomic aspects are already known and this could contribute to the scaling of its production for pharmaceutical purposes.

2 Taxonomic Characteristics

Buddleja is a generic name given in honor of Adam Buddle, a botanist and rector in Essex, England. "*globose"* is a Latin epithet meaning "spherical, shaped like a balloon". *Buddleja globosa* Hope: This species was described by John Hope (The Plant List 2020). It can be found in Argentina, Bolivia, Chile and Peru.

B. globosa is widely grown as an ornamental in parks and gardens in the United Kingdom. Its decorative globose heads of golden-yellow flowers attract large numbers of honeybees in early summer. In Spanish, *B. globosa* is known as "matico" and as "palñín" or "pañil" in the native tongue of Mapuche (indigenous inhabitants of central Chile). In Quechua's native tongue this plant is known as "palguín" (Malaret 1970; Colmeiro 1871).

Synonyms *Buddleja capitata* Jacq., *Buddleja connata* Ruiz & Pav., *Buddleja globifera* Duhamel (The Plant List 2020).

Photo 1 *Buddleja globosa.* Powdered drug. (Photo: E Pastene, October, 2019)

3 Crude Drug Used

Dried and powdered leaves (Photo 1) are used to prepare infusions, while fresh crushed leaves are used to make poultices that are applied to wounds.

4 Major Chemical Constituents and Bioactive Compounds

The iridoids aucubin, catalpol, and *O*-methyl catalpol (the first two isolated as 7-*p*-methoxycinnamoyl derivatives) are the most important and representative chemical compounds of the Buddlejaceae family. A second group of compounds consists of flavonoids whose main representative is scutellarin. The third group is composed of phenylpropanoids, among them, verbascoside (Pardo et al. 1993), linarine and echinacoside (Muñoz et al. 1999). Backhouse et al. (2008a) extracted "matico" leaves with solvents of increasing polarity to obtain different fractions. In these fractions, verbascoside, luteolin 7-*O*-glucoside and apigenin 7-*O*-glucoside were isolated and identified. In another study of the same group, beta-sitosterol, stigmasterol, stigmastenol, stigmastanol, campesterol and beta-sitosterol-glycoside were isolated (Goity 2007).

The roots of plants in this family produce sesquiterpenoids with caryophyllene skeleton. Several of these compounds were isolated from *Buddleja davidii* Franch and named buddledins A, B, C and E (Yoshida et al. 1976, 1978). Buddledins A, B and C also were isolated from *B. globosa* along with the presence of dehydrobuddledin, zerumbone, buddledone-A and buddledone-B. Moreover, the following constituents have been isolated from *B. globosa:* diterpenes buddlejone, deoxybuddlejone, hydroxybuddlejone and the bisditerpene maytenone (Liao et al. 1999; López et al. 1979). Lupeol and α-amyrin were isolated from the leaves and flowers of *B. globosa* (Marín et al. 1979; López et al. 1979).

5 Morphological Description

Buddleja globosa is an evergreen shrub of 1.5–3 m height, with yellowish sumptuous stems. Opposite leaves, 3–15 cm long by 1–5 cm wide, oval-lanceolate, rough, whitish on the underside, sharp at the tip. Orange, yellow and red flowers arranged in globose heads of 1–2 cm. Fruit in capsule of 3 mm in diameter. Numerous seeds, polyhedral, less than 1 mm long. *Buddleja globosa* is a dioecious shrub attaining 4 m in height which is common in the central and southern regions of Chile. The plant has tomentose branches with subsessile leaves, with conspicuous stipulation, lanceolate or elliptic, subcoriaceous to membranoceous, glabrescent, and decurrent to the base. Flowers are clustered in pairs in pedunculated heads. The tubular calyx is tomentose outside, with acute lobes. The corolla glabrous on the outside and with yellow-orange color. Stamens are sessile, ovary is tomentose in the upper half with a claviform style. The fruit is an ellipsoidal capsule, tomentose and glandular, with septicidal dehiscence and rounded valves (Norman and Ariza Epinar 1995).

6 Geographical Distribution

The plants grow at low elevations in interior valleys. In the Chilean coastal mountain range, this plant grows at 500–2000 m.a.s.l. In Chile, *B. globosa* could be found from Valparaíso, Región Metropolitana de Santiago, O'Higgins, Maule, Biobío, Ñuble, Araucanía, Los Ríos and Los Lagos.

Doll et al. (2003), studied different experimental conditions to achieve vegetative propagation of "matico". These authors reported that *B. globosa* is an easy-rooting species, reaching rooting rates of about 80%. The treatments with 1000–2000 ppm of indole butyric acid (IBA) applied at the base of the cuttings improve rooting process. The authors also found that cuttings from the apical portion of the mother-branch displayed better rooting rates. A mixture (1:1) of perlite and vermiculite resulted to be the most favorable rooting media. Wilckens et al. (2013), determined the growth cycle of *B. globosa* and created a regeneration model in order to establish productive management and sustainable use of this plant. These authors also quantified the growth dynamics of biomass regeneration and identified the effects of harvest methods. In this study, the final average biomass was 2.51 g per branch in the Cordillera, and 18.3 g per branch in the Valley area. The growth rates were significantly lower in the Cordillera than in the Valley. Similar results were obtained also in basal pruning treatments. In the control treatments, the plants in the Cordillera reached growth rates of 4.0% in relation to those of 6.7% in the Valley. In the treatments, the mean pruning reached a regeneration rate of 1.97% in the Cordillera and 10.7% in the Valley, while values for the basal pruning were 0.95% and 8.42%, respectively. The decrement rates of mean and basal pruning showed, significantly higher decrement rates in the Valley than in the Cordillera. According to these authors, December was the month for optimal harvest period for the control, apical and medium pruning. It is in this period when biomass maximization occurs in Cordillera. On the other hand, in the Valleys area, biomass maximization occurred in February only for control treatment, while in the medium and apical treatments the maximum was measured in January. These results suggest an anticipated period of biomass maximization in the Cordillera in relation to the basal pruning.

7 Ecological Requirements

This species grows in areas with permanent rainfall. The plants can withstand short periods of drought, but not beyond one month. The plant grows in water or extends its roots within permanent watercourse. It is common to find this plant in meadows, water courses, lakes edges and swamps. It requires some shade and protection against the sunlight, by low dense vegetation and rocks that help to filter approx. 20–40% of the sunlight. Such conditions can be found also in steep slopes with southern exposure, deep ravines, or under the protection by dense layer of vegetation beneath large trees with a 40–80% sunlight filtration.

In Chile, it can be found from Copiapó to the isle of Chiloé; growing in dry and moist forests, from near sea level to 2000 m, associated with native trees such as *Nothofagus dombeyi, Drimys winteri*, and *Populus pyramidalis*.

8 Traditional Use (Part(s) Used) and Common Knowledge

Buddleja species from Central America, Southern Africa and Eastern Asia have common traditional uses (Houghton and Manby 1985). For instance, “Mi-meng-hua”, is a preparation made with the flowers of *B. officinalis* Maxim, which is a traditional herb from Chinese medicine used for the treatment of conjunctival congestion (Chinese Pharmacopoeia Committee 2015). On another hand, the roots of *Buddleja asiatica* Lour. (Dog tail; “Qi-li-xiang”) are used as anti-inflammatory (Houghton 1984). Similar use is reported for *B. globosa* Hope from Chile, where leaves and flowers were used to wash wounds and treat gastric ulcers (Houghton and Manby 1985).

B. globosa was official drug included in the first Chilean Pharmacopeia published in 1886. The drug (whole or powdered leaves) is used as an herbal tea for washing wounds. Powdered dried leaves or crushed fresh plant preparation are used to help cicatrization of wounds and skin bruises (Houghton 1984; Houghton and

Manby 1985). Herbal tea is used to treat dysentery, hemorrhoids, hepatitis and catarrh. The juice squeezed from the leaves was also used to treat warts and callous ulcers (Houghton 1984).

9 Modern Medicine Based on Its Traditional Medicine Uses

"Matico" leaves contain phenylpropanoids, iridoids, terpenes and flavonoids (Montes and Wilkomirsky 1985, 1992; Mensah et al. 2000) and show antihepatotoxic, bactericidal, antioxidant, anti-inflammatory, wound healing and analgesic activities (Pardo et al. 1997; Mensah et al. 1998; Liao et al. 1999; Backhouse et al. 2008a, b). Also, diuretic, wound-healing and anti-inflammatory properties have been associated with the presence of tannins (5.7%) and flavonoid glycosides (Varillas and TTito 2018). This medicinal plant presents iridoids with antibacterial activity and phenylpropanoids with analgesic, antibacterial and antihypertensive properties (Recio et al. 1994). In other study, high concentrations from 0.5–1 mM (expressed as gallic acid equivalents) of *B. globosa* leaf extract protect erythrocytes from HClO damage (Suwalsky et al. 2017). Also, using a *Drosophila melanogaster* wing-spot mutagenic model, Carmona et al. (2016) reported that *B. globosa* show desmutagenic effects. This author states that verbascoside and luteolin are bioactive components responsible of this antimutagenic effect. Debenedetti et al. (2002) reported that a methanol extract of *B. globosa* showed antiplasmodial activity with IC_{50} of 6.2μg/ml.

Regarding wound-healing activity, an aqueous extract of *B. globosa* leaves displayed growth-promotive and antioxidant activities upon fibroblasts treated with hydrogen peroxide. Low concentrations of the extract gave an increase in fibroblast growth that was non-significant. Nevertheless, cytotoxicity was observed at concentrations greater than 50 mg/ml (Mensah et al. 2001). In this study, the extract showed a strong antioxidant effect, and further chromatographic fractionation led to the isolation of three flavonoids and two caffeic acid derivatives. All these compounds showed antioxidant effect at concentrations below 10 mg/ml. These activities contribute to wound healing properties (Mensah et al. 2001). Some *in vitro* tests demonstrated antibacterial activity against Gram (+) and (−) germs, which is mainly due to the presence of diterpenes and triterpenes mainly (Alonso 2004). It should be noted that certain compounds, like catalposide and aucubin, described in *B. globosa* and other species an anti-inflammatory effect, which contributes to the wound-healing process (Kim et al. 2004; Park and Chang 2004). In addition, angaroside A is most likely the molecule responsible for antibacterial activity against *Staphylococcus aureus* (Hoffmann et al. 1992; Muñoz et al. 1999). *B. globosa* presents terpenes with antifungal activity against *Trichophyton rubrum*, *Trichophyton interdigitale* and *Epidermophyton floccosum* (Mensah et al. 2000). On the other hand, it is well-known that catalposide -one of the iridoids isolated from *B. globosa*- inhibits NO synthase, an enzyme involved in the pro-inflammatory response (Oh et al. 2002). In line with the effects of catalposide, iridoids such as aucubin, have also been shown to have anti-inflammatory effects that could help the cicatrization process (Recio et al. 1994).

There is a patent (WO2012100365A; US8852654B2): "Use of a standardized dry extract of *Buddleja globosa* leaves, BG-126, for the treatment and prevention of gastrointestinal disorders caused by treatment with nitrofurantoin and other antimicrobials". This invention relates to the use of a composition containing extracts of *Buddleja globosa* ("matico") and pharmacologically accepted additives for the treatment or prevention of various gastrointestinal disorders, in particular those associated with patients treated with nitrofurantoin as a therapy against *Escherichia coli* (Letelier et al. 2014).

In another study, an aqueous extract of *B. globosa* leaves (1 mg/ml) protected hepatocytes treated with carbon tetrachloride, galactosamine and complement-mediated cytotoxic medium (CMC) (Houghton and Hikino 1989). After bioassay-guided fractionation, the main compounds responsible for this effect were iridoids, flavonoids (linarin) and phenylpropanoid glycosides (verbascoside and echinacoside). Linarin (1 mg/ml) was the most active compound giving a 40% reduction of the released glutamic-pyruvic transaminase (GPT) in CCl_4 treated hepatocytes, whereas the reduction reaches 75% in those cells challenged with galactosamine. Isolated echinacoside was also active giving 45% and 66% reduction at the same tested concentrations. This protection in hepatocytes probably could be ascribed to the antioxidant properties common to these molecules. The sesquiterpenes buddledins A–C inhibit both cyclooxygenase and 5-lipoxygenase (5-LOX) at 50 mg/ml, *in vivo*. Among the tested compounds, buddledin A showed the greatest inhibition against COX achieving 89%. In addition, the inhibition against 5-LOX reaches 98% (Mensah et al. 1999).

Antioxidant (DPPH assay) and antiproliferative activity of *B. globosa* aqueous extract (5 mg/ml) have been assessed in T84 (tumoral) and HTR-8/SVneo (non-tumoral) cell lines. The effect was dependent on the cellular context since cytotoxicity was observed mainly in HTR-8/SVneo cells (Gastaldi et al. 2018).

The *in vivo* wound healing properties have been assessed using Sprague-Dawley rats treated with *B. globosa* orally administered for 12 days. Also, the extract was topically administered. The results have shown an improvement in the wound-healing process associated with anti-inflammatory and antioxidant effects. Hence, COX-2 levels and Ki-67 (proliferation biomarker) (Letelier et al. 2012).

Recent work demonstrated that *B. globosa* extracts are able to prevent collagen-induced platelet activation (Fuentes et al. 2017). In this study, *B. globosa* inhibits the phosphorylation of PLC-γ2 and PKC-β2 in human platelets. These kinases are involved in pathways related to collagen induced platelet activation. Considering this mechanism, the author stated that *B. globosa* may be useful in cardiovascular disease (CVD) because platelet hyperreactivity is closely associated with thrombosis related diseases.

Regarding clinical trials, there is only one report of a study that is currently being carried out. However, at the time of the elaboration of this chapter, the results are not yet available (Bustamante et al. 2014, 2015).

10 Conclusions

B. globosa is a medicinal shrub with an important body of scientific evidence including agronomic, phytochemical and experimental and molecular pharmacology studies. Some preclinical studies support the use of this species as a wound healing agent, although the underlying molecular mechanisms are not yet fully elucidated. Many of these studies were carried out in the previous decade, therefore they need to be revisited in order to improve the validation of the ethnomedical uses of this species. On the other hand, it is striking that recent phytochemical studies have not used advanced analytical technology in the identification process of chemical composition of *B. globosa*. Much of the pharmacological properties of this species are attributed to components already isolated from other sources and which, by extrapolation, have been assigned to *B. globosa*. Even to date, there is a lack of properly designed clinical studies. None of the available results appear to categorically support the traditional use of the "matico", therefore the study of this species in the future is guaranteed.

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