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Review

Arbutus unedo L.: From traditional medicine to potential uses in modern pharmacotherapy

Sandra Morgado[a], Manuel Morgado[a,b,c,d,*,1], Ana I. Plácido[c,e], Fátima Roque[c,d,e], Ana Paula Duarte[b,d]

[a] Hospital Centre of Cova da Beira, E.P.E., Quinta do Alvito, 6200-251 Covilhã, Portugal
[b] University of Beira Interior, Faculty of Health Sciences, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal
[c] School of Health Sciences, Polytechnic Institute of Guarda, Avenida Rainha D. Amélia, S/N, 6300-749 Guarda, Portugal
[d] CICS-UBI – Health Sciences Research Centre, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal
[e] Research Unit for the Development of the Interior, Av[a] Dr. Francisco Sá Carneiro, no. 50, 6300-559 Guarda, Portugal

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ABSTRACT

Ethnopharmacological relevance: *Arbutus unedo* L., the strawberry tree (Ericaceae family) is of increasing interest because of its common traditional, industrial, chemical and pharmaceutical uses. The plant is a typical evergreen plant of the Mediterranean basin, as well as of other regions with hot summers and mild rainy winters. This review covers the studies relevant to *Arbutus unedo* L. utilization in the current pharmacological therapy.
Materials and methods: The available information on traditional uses, phytochemistry and biological activities of *Arbutus unedo* L. was collected from scientific databases through a search using the keywords '*Arbutus unedo* L.' and/or 'strawberry tree' in 'Google Scholar', 'Pubmed', 'Sciencedirect', 'SpringerLink', 'Web of Science - Clarivate Analytics' and 'Wiley'. Unpublished Ph.D. and M.Sc. dissertations were also consulted for chemical composition, biological activities and traditional uses of *Arbutus unedo* L. and for manual search of additional references.
Results: The fruits of the plant have been traditionally used as antiseptics, diuretics and laxatives in folk medicine, while the leaves have been used due to their diuretic, urinary antiseptic, antidiarrheal, astringent, depurative and antihypertensive properties. According to the scientific literature survey, different extracts obtained from *Arbutus unedo* L. have demonstrated a high pharmacological potential due to their *in vitro* and preclinical antibiotic, antifungal, antiparasitic, antiaggregant, antidiabetic, antihypertensive, anti-inflammatory, antitumoral, antioxidant, and spasmolytic properties.
Conclusion: This review suggests that *A. unedo* is a promising source of phytopharmaceutical products. The potential advantages of *Arbutus unedo* are related with the presence of polyphenolic compounds in its composition. However, further studies are needed to ascertain some profitable effects in humans. The beneficial effects associated with this shrub suggest that *Arbutus unedo* can be used for the development of new drugs to treat diseases such diabetes, hypertension, among others. Nonetheless, the safety of the *Arbutus unedo* compounds should also be examined.

1. Introduction

Many plant species could be used as sources of high value chemicals (such as bioactive compounds) for their secondary metabolites. *Arbutus unedo* L. (*A. unedo*, Ericaceae family), commonly known as the strawberry tree, is an evergreen shrub or small tree, normally between 1.5 m

Abbreviations: AAPH, 2,20-azobis(2-amidinopropane) dihydrochloride; ABTS, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid); A. unedo, Arbutus unedo L.; BrdU, 5-bromo-2´-deoxyuridine; COX-2, Cyclooxygenase-2; DPPH, 2,2-diphenyl-l-picrylhydrazyl; FRAP, Ferric ion reducing antioxidant power; GAE, Gallic acid equivalent; IL, Interleukin; IVGTT, Intravenous glucose tolerance test; L-NAME, N^G-nitro-L-arginine methyl-ester; MIC, Minimal inhibitory concentration; MMP, Matrix metalloproteinase; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NO, Nitric oxide; NOS, Nitric oxide synthase; OGTT, Oral glucose tolerance test; ORAC, Oxygen radical absorbance capacity; PUFA, Polyunsaturated fatty acids; ROS, Reactive oxygen species; SRB-, Sulforhodamine B; STAT, Signal transducer and activator of transcription; TBARS, Thiobarbituric acid reactive substances; TEAC, Trolox-equivalent antioxidant capacity; TNF, Tumor necrosis factor

* Corresponding author at: Hospital Centre of Cova da Beira, E.P.E., Quinta do Alvito, 6200-251 Covilhã, Portugal.
E-mail addresses: sandracristinamorgado@gmail.com (S. Morgado), mmorgado@fcsaude.ubi.pt (M. Morgado), aiplacido@gmail.com (A.I. Plácido), froque@ipg.pt (F. Roque), apduarte@fcsaude.ubi.pt (A.P. Duarte).
[1] www.fcsaude.ubi.pt.

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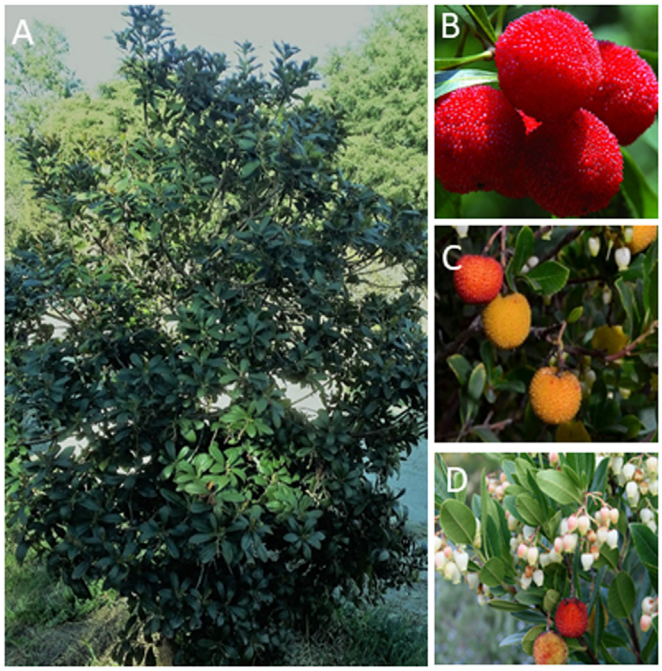

Fig. 1. *Arbutus unedo* tree (A); Ripe (B) and unripe fruits (C); *Arbutus unedo* flowers (D). *Adapted from* (Oliveira, 2010).

and 3 m tall (Fig. 1), native to the Mediterranean region, but also found in other regions characterized by hot summers and mild rainy winters (Fig. 2) (Celikel et al., 2008; Molina et al., 2016; Torres et al., 2002).

The trees show high resistance to hard environmental conditions like drought, low temperatures and heavy or poor soil conditions (Gomes and Canhoto, 2009). They also show rapid regeneration after forest fires (Arnan et al., 2013). The *A. unedo* tree's high resistance to harsh environmental conditions is particularly important with regard to fauna diversity and soil erosion prevention. From the ecological point of view, the resistance of *A. unedo* plays a pivotal role in forestation programs in southern European countries such as Greece, Italy, Portugal and Spain, where fires are common during the dry season (Schröter et al., 2005).

The ornamental, nutritional and medicinal value of *A. unedo* has been recognized since Greek times (Ruiz-Rodríguez et al., 2011). The production of red fruits and pinkish-white flowers, which appear during the winter, increase its crop value and ornamental uses (Males et al., 2006).

The fleshy edible fruit of *A. unedo* has been a part of the Mediterranean diet (Molina et al., 2011; Ortuño Moya, 2003; Ruiz-Rodríguez et al., 2011; Tardío et al., 2016). This fruit is usually consumed as jam or marmalade, or distilled into liquor (Rivera et al., 2006; Soufleros et al., 2005; Tardío et al., 2006). *A. unedo* fruits are a source of health, namely of vitamin C and dietary fibers, while also rated as a source of bioactive compounds for dietary supplements or functional foods (Ruiz-Rodríguez et al., 2011). This plant is traditionally referred as melliferous (Guzman Tirado, 1997) and strawberry-tree honey is very appreciated for its characteristic bitter taste and presumed biological properties, besides its remarkable economic importance (Tuberoso et al., 2013, 2010). *A. unedo* stems and leaves are used for hardening olives (Tardío et al., 2006).

Nonetheless, this plant remains largely underexploited and organizations such as Food and Agriculture Organization (FAO) are currently undertaking to increase the use of this species (FAO, 2010).

The different parts of this plant and strawberry-tree honey have been used in folk medicine to treat a large number of diseases (Kivçak and Mert, 2001; Morales et al., 2014; Spano et al., 2009; Tuberoso et al., 2010; Verde et al., 1998; Ziyyat et al., 2002).

A. unedo is generally regarded as a wild edible plant, but the significance and potential use for both medicinal and non-medicinal purposes, have led to the development of several ethnobotanical studies aiming to describe traditional uses, particularly in Iberian Peninsula (Carrió and Vallès, 2012; González et al., 2010; Guzman Tirado, 1997; Menendez-Baceta et al., 2012; Ocaña, 2000; Verde et al., 2006). Thus, besides the above mentioned uses as food or for liquors preparation, this plant is also described for animal feeding (Guzman Tirado, 1997; Ocaña, 2000). These ethnobotanical studies have demonstrated the ethnopharmacological importance of this species and several descriptions on the use of different parts of this plant in folk medicine, mainly in decoctions or infusions, are presented in Table 1.

The described medicinal characteristics are related to the contents of several pharmacotherapeutically active compounds in different parts of *A. unedo*. The plant contains a wide variety of antioxidant compounds (carotenoids, organic acids, phenolics, terpenoids, vitamins E and C) as well as compounds with antimicrobial, antiaggregant, antidiabetic, antihypertensive, anti-inflammatory and antitumoral properties (Carcache-Blanco et al., 2006; Tavares et al., 2010). The rationality of *A. unedo* uses in traditional medicine has been demonstrated by some reports, which will be discussed in later sections of this review. The phytochemical content of the different parts of the *A. unedo* tree (leaves, fruits, bark, wood/stalks and roots) have been the subject of several studies (Delgado-Pelayo et al., 2016; Erkekoglou et al., 2017; Fonseca

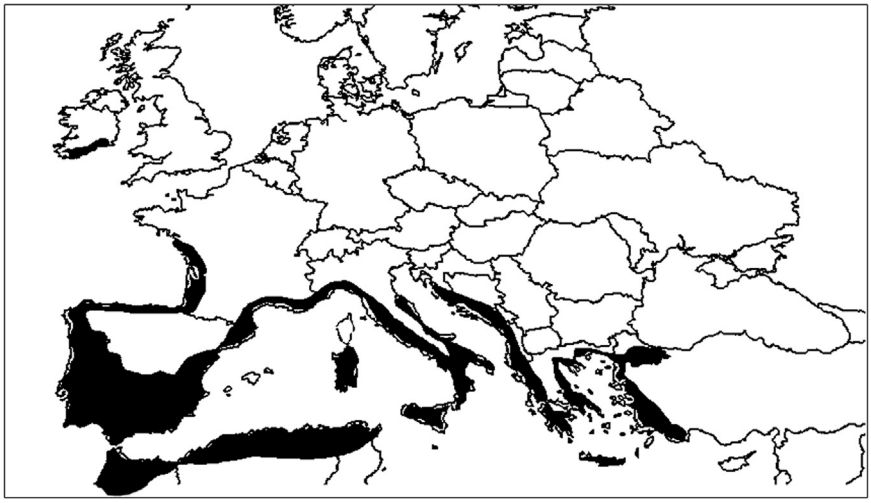

Fig. 2. Worldwide distribution of *A. unedo*. *Adapted from* (Oliveira, 2010).

Table 1
Folk medicinal uses of different parts of *Arbutus unedo* L. plant.

Part used	Medicinal indication
Leaves	Kidney diseases (El-Hilaly et al., 2003), antihaemorrhoidal (Cornara et al., 2009), gastrointestinal disorders (Leonti et al., 2009), diarrhea (Guzman Tirado, 1997), dermatologic diseases (Leonti et al., 2009), cardio-vascular application (Leonti et al., 2009), urological diseases (Leonti et al., 2009), diuretic (González et al., 2010), antidiabetic (Ziyyat et al., 1997), antihypertensive (Ziyyat et al., 1997), cardiac disease (Jouad et al., 2001), diabetes (Jouad et al., 2001), hypertension (Jouad et al., 2001), rheumatism (González et al., 2010; Guzman Tirado, 1997).
Fruits	Kidney diseases (El-Hilaly et al., 2003), gastritis (Cornara et al., 2009), gastrointestinal disorders (Leonti et al., 2009), diarrhea (Guzman Tirado, 1997), dermatologic diseases (Leonti et al., 2009), cardio-vascular application (Leonti et al., 2009), urological diseases (Leonti et al., 2009) diuretic (González et al., 2010).
Bark	Gastrointestinal disorders (Leonti et al., 2009), dermatologic diseases (Leonti et al., 2009), cardio-vascular application (Leonti et al., 2009), urological diseases (Leonti et al., 2009).
Roots	Gastrointestinal disorders (Leonti et al., 2009), dermatologic diseases (Leonti et al., 2009), cardio-vascular application (Leonti et al., 2009), urological diseases (Leonti et al., 2009), antidiabetic (Bnouham et al., 2002; Ziyyat et al., 1997), antihypertensive (Verde et al., 1998; Ziyyat et al., 1997), cardiotonic (Novais et al., 2004), abdominal pain (Novais et al., 2004), renal antispasmodic (Novais et al., 2004), bladder ailments (Novais et al., 2004), acne (Guzman Tirado, 1997), psoriasis (Guzman Tirado, 1997), abortive (Novais et al., 2004), antihypercholesterolaemic (Novais et al., 2004), blood depurative (Guzman Tirado, 1997; Novais et al., 2004), cardiac disease (Jouad et al., 2001), diabetes (Jouad et al., 2001), hypertension (Carrió and Vallès, 2012; Jouad et al., 2001; Ziyyat et al., 1997), vaginal infections (Verde et al., 2006).

et al., 2015; Guimarães et al., 2014; Karikas et al., 1987; Tuberoso et al., 2013). This review will focus on the pharmacological interest of the phytochemical content of *A. unedo* and on the different *in vitro* and preclinical studies conducted to date that provide evidence on the pharmacotherapeutic potential of this underexploited plant.

For this review, the pharmacological potential of *A. unedo*, as evidenced by previous studies, was searched using the terms "*Arbutus unedo* L.", "*Arbutus unedo*" and "*Arbutus*" on electronic databases, including 'Google Scholar', 'PubMed', 'ScienceDirect', 'SpringerLink', 'Web of Science - Clarivate Analytics', and 'Wiley'. Unpublished Ph.D. and M.Sc. dissertations were also consulted. This search was performed in January 2018 for records from January 1998 through December 2017. Articles would be included if they reported *in vitro*, preclinical or clinical studies about *A. unedo* or its utilization in folk medicine. A further criterion was the language of the article, which was limited to the following languages: English, Spanish, French and Portuguese. Additional studies were obtained through reading "pre-selected articles", in which case they were hand searched.

After a detailed analysis of *in vitro* and preclinical studies of extracts of different parts of the *A. unedo* plant, a total of 37 articles were selected to include this review. No clinical studies involving parts of this plant were found. All "selected articles" underline the role of *A. unedo* as an antibacterial, antifungal, antiparasitic, antiaggregant, antidiabetic, antihypertensive, antitumoral, antioxidant and anti-inflammatory agent. Twelve articles describe the use of *A. unedo* extracts in folk medicine for the treatment of kidney, gastrointestinal, dermatologic, urological, cardio-vascular and hypertensive diseases, and antidiabetic applications were also mentioned. Through the reading of 49 selected articles, 168 compounds of *A. unedo* have been identified.

2. Phytochemical content of Arbutus unedo L. with pharmacological potential

2.1. Phytochemical contents of leaves

Phytochemical studies showed that leaf extracts contain several phenolic compounds, essential oils (Bessah and Benyoussef, 2012; Erkekoglou et al., 2017; Jurica et al., 2015; Pavlović et al., 2009; Tavares et al., 2010) as well as α-tocopherol (Kivçak and Mert, 2001; Mosele et al., 2016). The phenolic fraction of the leaves contains a large diversity of compounds: tannins, flavonoids (catechin gallate, myricetin, rutin, afzelin, juglanin, avicularin), phenolic glycosides (quercitrin, isoquercitrin, hyperoside), and iridoid glucosides (Carcache-Blanco et al., 2006; Legssyer et al., 2004; Males et al., 2006). Several polyphenols have also been identified and quantified (Fiorentino et al., 2007): arbutin, ethyl gallate, *p*-hydroxybenzoyl arbutin, galloyl arbutin, gallocatechin, catechin, kaempferol 3-*O*-α-L-ramnopyranoside, quercetin 3-*O*-α-L-ramnopyranoside, myricetin 3-*O*-α-L-ramnopyranoside, kaempferol 3-*O*-β-D-arabinofuranoside, quercetin 3-*O*-β-D-arabinofuranoside and myricetin 3-*O*-β-D-arabinofuranoside. The major polyphenolic compounds in leaves were found to be arbutin (627 mg kg^{-1} of fresh leaves), followed by catechin (546 mg kg^{-1} of fresh leaves) and ethyl gallate (440 mg kg^{-1} of fresh leaves) (Fig. 3) (Fiorentino et al., 2007).

It has been suggested that the phytochemical content, as well as the chemical concentration and/or composition of compounds of *A. unedo* extracts, change seasonally and according to the geographical location of the sample. In leaf extracts from Croatia it was observed that the amount of hyperoside and quecitrin is higher in January than in June, July and October (Males et al., 2006; Maleš et al., 2013). Moreover, the analysis of chemical composition, by mass spectroscopy, of essential oils of leaf extracts from Algeria reports that the Algerian oil is characterized by a higher content of palmitic and linoleic acids, and the presence of heavy aliphatic hydrocarbons (Bessah and Benyoussef, 2012). This study observed that (*E*)-2-decenal, α-terpineol and (*E*)-geranyl acetone were present in low proportions (Bessah and Benyoussef, 2012). These observations are not in agreement with the results observed by a study performed in *A. unedo* extracts from Turkey. The analysis by TLC-densitometry assay of the essential oil of *A. unedo* extracts from Turkey revealed the presence of a significant amount of (*E*)-2-decenal, α-terpineol and (*E*)-geranyl acetone (Kivçak et al., 2001).

2.2. Phytochemical content of fruits

The chemical composition of *A. unedo* fruits has also been analyzed and reported in several studies (Ayaz et al., 2000; Barros et al., 2010; Delgado-Pelayo et al., 2016; Özcan and Haciseferogullan, 2007; Pallauf et al., 2008; Seker and Toplu, 2010). The most important constituents of the strawberry fruit, besides moisture (597.0 ± 26.7 g kg^{-1} of the fresh fruit), are carbohydrates (938.3 ± 4.1 g kg^{-1} of dry weight), which represents almost 40% of the total weight of the fresh fruit (Barros et al., 2010). In fact, these fruits are rich in different carbohydrates, either monosaccharides (fructose and glucose), disaccharides (sucrose), and polysaccharides (cellulose and starch) (Özcan and Haciseferogullan, 2007). The amount of saccharides present in fruits varies according to ripeness stages, sucrose being the major saccharide in the unripe fruit (208.0 ± 2.0 g kg^{-1} of dry weight) and fructose, the most abundant in the ripe fruits (87.7 ± 0.6 g kg^{-1} of dry weight) (Alarcão-E-Silva et al., 2001). Proteins are the second major macronutrient present in fruits (30.9 ± 0.8–33.6 ± 1.2 g kg^{-1} of dry weight) (Barros et al., 2010; Özcan and Haciseferogullan, 2007), followed by fatty acids. The major fatty acids present in the different maturation stages are α-linolenic acid (ranging from 36.90 ± 1.75 relative percent in unripe fruits to 43.07 ± 0.16 relative percent in ripe fruits), oleic acid (29.38 ± 1.82 and 26.75 ± 0.17 relative percent in unripe and ripe fruits, respectively), and linoleic acid (20.14 ± 0.64 and

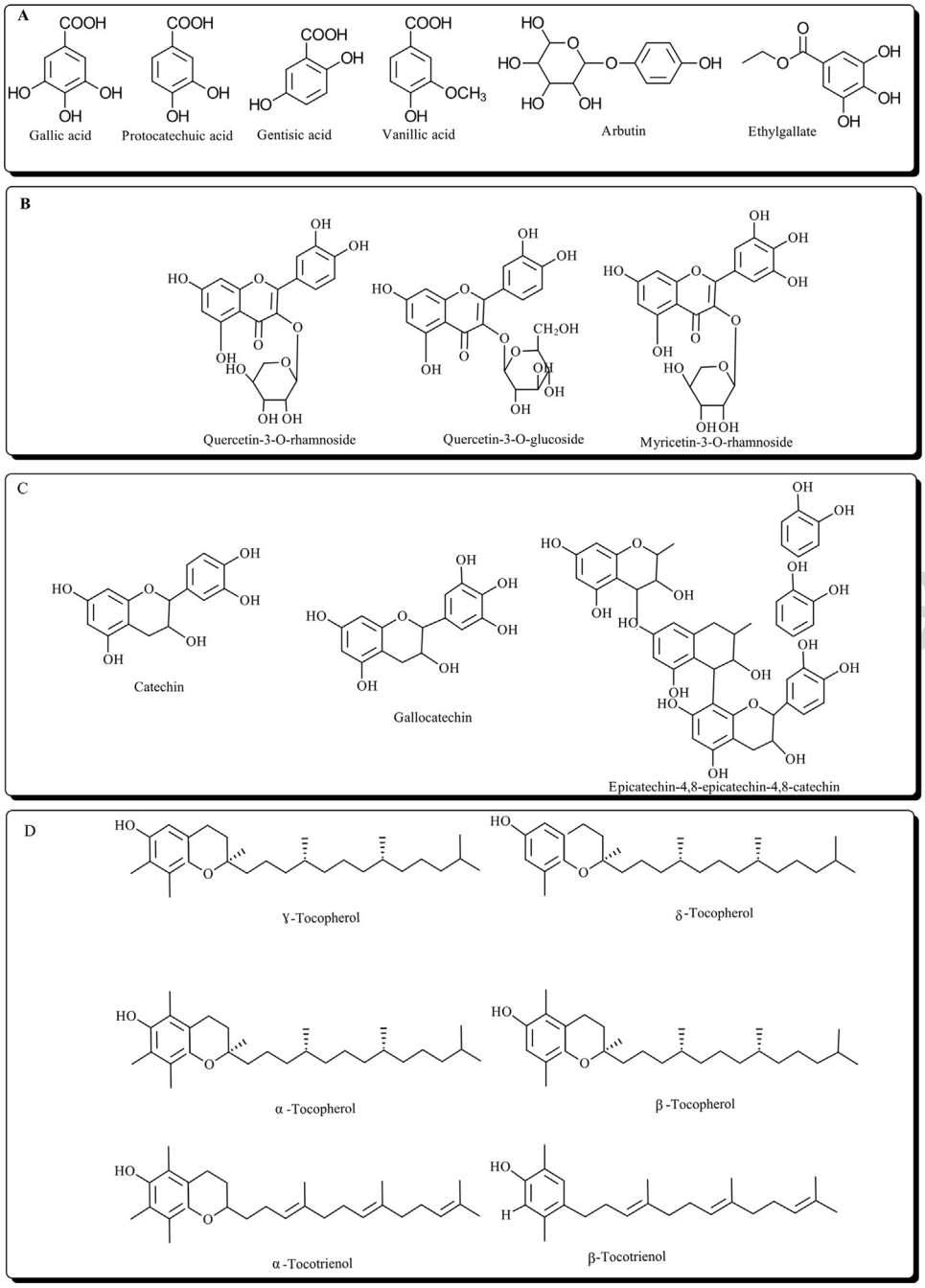

Fig. 3. Some chemical structures of compounds found in *A. Unedo.* ***A***- Main simple phenolic compounds; **B**- galloyl derivatives, tannins and flavonols; **C**- proanthocyanidins; **D**- Vitamins.

18.84 ± 0.11 relative percent in unripe and ripe fruits, respectively) (Oliveira et al., 2011). Polyunsaturated fatty acids (PUFA) represent as much as 60% of the total fatty acids (52.47 ± 4.26 and 62.01 ± 0.26 relative percent in unripe and ripe fruits, respectively), with a highly favorable ω3/ω6 ratio, due to the richness in α-linolenic acid. Among the vitamin E vitamers, γ-tocotrienol is the most abundant in different ripening stages of fruits (ranging from 1013.88 ± 90.33 mg kg^{-1} in unripe fruits to 498.96 ± 12.18 mg kg^{-1} in ripe fruits) (Oliveira et al., 2011). These results show that fruits of intermediate maturity can be considered important sources of biologically active compounds, with fatty acid content rich in ω-3 PUFA, properly supplemented with considerable vitamin E quantities (Oliveira et al., 2011). Minerals, phenolic compounds, organic acids, terpenoids, vitamins and carotenoids are also present in strawberry-tree fruits (Delgado-Pelayo et al., 2016; Guimarães et al., 2013). Potassium, calcium and phosphorus are the major minerals present in fruits (Özcan and Haciseferogullan, 2007). The phenolic compounds present in *A. unedo* fruits comprise several chemical classes, such as flavonoids (anthocyanins, proanthocyanidins and flavonols), tannins, and phenolics acids derivatives (ellagic acid and gallic acid derivatives). The total phenolics were quantified in several studies and ranged from 48.26 ± 4.49–126.83 ± 66.6 g of gallic acid equivalents (GAE) per kilogram of extract (Barros et al., 2010; Oliveira et al., 2011). Four anthocyanins were found: delphinidin-3-galactoside, cyanidin-3-glucoside, cyanidin-3-arabinoside and cyanidin-3-galactoside (Fortalezas et al., 2010; Pallauf et al., 2008). The amount of anthocyanins increase during maturation, from 0.25 ± 0.2 g kg^{-1} to 1.01 ± 0.1 g kg^{-1} of dry weight as the fruit becomes red mature (Alarcão-E-Silva et al., 2001). The most abundant

proanthocyanidins in fruits are epicatechin-4,8-epicatechin-4,8-catechin (Fig. 3), catechin and gallocatechin, and a total amount of proanthocyanidins of 274.6 ± 9.89 mg kg^{-1} of edible portion was obtained (Pallauf et al., 2008). The four flavonols quantitatively more abundant are quercetin-3-rutinoside, quercetin-3-xyloside, quercetin-3-rhamnoside (three quercetin derivatives), and myricetin-3-xyloside. A total of flavonols of 11.4 ± 3.46 mg kg^{-1} of edible portion was determined (Pallauf et al., 2008). The content of tannins decreased as the fruit became ripe, from 3.13 ± 0.06 g kg^{-1} to 1.75 ± 0.02 g kg^{-1} of dry weight (Alarcão-E-Silva et al., 2001). The bitter and astringent taste of unripe fruits can be attributed to the high content of tannins. Several organic acids (fumaric, malic, suberic, citric, quinic acids) and phenolic acids (gallic, gentisic, protocatechuic, *p*-hydroxybenzoic, vanilic, *m*-anisic acids) have been identified and quantified in the strawberry-tree (Alarcão-E-Silva et al., 2001; Ayaz et al., 2000). The terpenoids found in fruits are α-amyrin acetate, betulinic acid, and lupeol (Gaspar et al., 1997). Vitamin C and vitamin E (α-tocopherol, γ-tocopherol) are the predominant vitamins found. Carotenoids (in particular β-carotene) were also identified in very low quantities that are not dismissible (Alarcão-E-Silva et al., 2001; Barros et al., 2010; Delgado-Pelayo et al., 2016; Pallauf et al., 2008).

2.3. Phytochemical content of roots and stems

The phytochemical screening of roots of *A. unedo* revealed the presence of quinones, anthraquinones, anthocyanins, tannins, and flavonoids (Dib et al., 2013). Quantitative analysis showed that the roots were strongly dominated by anthocyanins compounds (3.65 mg g^{-1} of roots extract), followed by total flavonoids (0.56 mg g^{-1} of roots extract) and flavones and flavonols (0.17 mg g^{-1} of roots extract) (Dib et al., 2013). The dried stems of *A. unedo* revealed the presence of lupeol, ursolic acid, monotropein, unedoside, stilbericoside, geniposide, monotropein methyl ester, and betulinic acid (Karikas et al., 1987).

3. Potential pharmacotherapeutic applications of Arbutus unedo L

The different extracts obtained from A. unedo have been shown to possess a high pharmacological potential due to their antimicrobial, antiaggregant, antidiabetic, antihypertensive, anti-inflammatory, antitumoral, antioxidant, and spasmolytic properties (Afrin et al., 2017; El Haouari et al., 2007; Kivçak et al., 2009). In this section we will summarized the hypothetical pharmacotherapeutic applications of *A. unedo*.

Table 2
Antibacterial, antifungal and antiparasitic activities of *Arbutus unedo* L.

References	Part of plant	Type of study	Extract	Biological activity		
Ferreira et al., 2012	Entire plant: wood/ stalks, bark and leaves	Determination of growth inhibition zones by radial diffusion.	Ethanol 95% Methanol Acetone/water (60:40)	Bacteria Gram-positive *Bacillus cereus* *Enterococcus faecalis* *Clinical methicillin resistant Staphylococcus aureus*	Gram-negative *Klebsiella pneumoniae* *Helicobacter pylori*	Yeast *Candida tropicalis*
Malheiro et al., 2012	Leaves	Determination of growth inhibition zones by radial diffusion.	Water	Bacteria Gram-positive *Bacillus cereus* *Bacillus subtilis* *Staphylococcus epidermis* *Staphylococcus aureus*	Gram-negative *Pseudomonas aeruginosa* *Escherichia coli*	Yeast *Candida. albicans* *Candida krusei* *Candida parapsilosis* *Candida glabrata*
Dib et al., 2013	Roots	Determination of growth inhibition values by paper disc diffusion.	Water Methanol Phenolic fractions	Bacteria Gram-positive *Staphylococcus aureus*	Gram-negative *Escherichia coli* *Pseudomonas aeruginosa*	
Orak et al., 2011	Leaves	Determination of growth inhibition zones by disc diffusion.	Water	Bacteria Gram-positive *Staphylococcus aureus*	Fungi *Aspergillusparasiticus*	
Asmae et al., 2012	Leaves	Determination of growth inhibition values by paper disc.	Water Ethanol	Bacteria Gram-positive *Mycobacterium tuberculosis, Mycobacterium smegmatis* and *Mycobacterium aurum*		
Dib et al., 2010	Leaves and stems	Determination of MIC by the dilution agar method.	Light petroleum	Bacteria Gram-positive *Enterococcus faecalis*	Gram-negative Klebsiella pneumoniae	Yeast *Candida* albicans
Kahriman et al., 2010	Flower and fruit	Determination of MIC by dilution on broth media.	Essential oils	Bacteria Gram-positive *Listeria monocitogenes* *Enterococcus faecalis*		
Ertabaklar et al., 2009	Leaves	Analysis of antiproliferative activity by microscopic observation, based in the number, aspect and motility.	Sequential extraction with n-hexane, ethanol and ethyl acetate Water	*Trichomonas vaginalis* trophozoites		
Kivçak et al., 2009	Leaves	*In vitro* determination of the antileishmanial activity by microscope observation.	Ethanol n-Hexane Water	*Leishmania tropica* promastigotes		

MIC- Minimal inhibitory concentration.

3.1. Antibacterial, antifungal and antiparasitic activities of Arbutus unedo L

Table 2 presents nine *in vitro* studies providing evidence for the antibacterial, antifungal and antiparasitic activity of the different parts of *A. unedo*. The choice of solvents and extraction methods impacts on antimicrobial activity of the crude extracts (Dib et al., 2013; Ferreira et al., 2012; Kivçak et al., 2009). Some authors attributed these antimicrobial properties to tannins, flavonoids, and other phenolic components (Djipa et al., 2000; Esquenazi et al., 2002). The study of Dib et al. confirmed that the roots of *A. unedo* contain high amounts of polyphenol compounds (Dib et al., 2013). The phenolic compounds are commonly found in the plant kingdom, and they have been reported to have multiple biological effects, including antimicrobial activity.

The extract of leaves revealed antimicrobial activity against many gram-positive bacteria, including *Bacillus cereus*, *Enterococcus faecalis* and *clinical methicillin resistant Staphylococcus aureus* (Asmae et al., 2012; Ertabaklar et al., 2009; Ferreira et al., 2012; Kivçak et al., 2009; Malheiro et al., 2012; Orak et al., 2011). Research shows that leaf extracts of *A. unedo* only affect the activity of the gram-negative bacteria *Klebsiella pneumonia, Helicobacter pylori, Escherichia coli* and *Pseudomonas aeruginosa* (Ferreira et al., 2012; Malheiro et al., 2012). *A. unedo* leaf extracts also affect the activity of *Aspergillus parasiticus, Candida tropicalis* and *Candida albicans* (Dib et al., 2010; Orak et al., 2011). The ethanolic extract and the ethyl acetate extract of *A. unedo* leaves could become a promising antileishmanial and antitrichomonal agent, respectively (Ertabaklar et al., 2009; Kivçak et al., 2009). The antimicrobial properties of the unsaponifiable extracts of leaves, stems and roots were tested against several species of microorganisms and the monoterpene hydrocarbon contents of stems and leaves (21.9% and 30.7%, respectively) were considered partly responsible for their antibacterial activity as the root extract contained no monoterpene compounds and had no antibacterial activity (Dib et al., 2010). Research on the antimicrobial effect of monoterpenes suggests that they diffuse into and damage cell membrane structures (Sikkema et al., 1995). The essential oil from the aerial parts of *A. unedo* (flowers and fruits) showed moderated antibacterial activity against *Listeria monocitogenes* and *Enterococcus faecalis* (Kahriman et al., 2010). Further research on the purification of active compounds present in this species is needed in order to better understand the antimicrobial properties of the different parts of the plant.

3.2. Antiaggregant activity of Arbutus unedo L

Table 3 presents three *in vitro* studies providing evidence for antiaggregant activity of leaf and roots extracts of *A. unedo*. These extracts demonstrated *in vitro* antiaggregant effects in human and rat platelets (El Haouari et al., 2007). The beneficial effect of the extracts of *A. unedo* leaves in human platelets remains unclear. El Haouari et al., 2007 suggested the beneficial effect is related with the antioxidant activity of *A. unedo* extracts. It has been suggested that in human and rat platelets the antioxidant power of *A. unedo* extract might result in inhibition of protein tyrosine phosphorylation and Ca^{2+} influx (Redondo et al., 2005; Rosado et al., 2001). The tannins isolated from the methanol extract of leaves exhibited a strong antiplatelet effect and may constitute the major chemical compounds responsible for this action observed in rat platelets (Mekhfi et al., 2006). The antiaggregant effect of roots was attributed in part to the polyphenolic compounds present in their extracts (Mekhfi et al., 2004). Altogether, these results support the traditional use of this plant in the preventive or therapeutic treatment of platelet aggregation complications linked to arterial hypertension, inflammatory and cardiovascular diseases (El Haouari et al., 2007; Mekhfi et al., 2006, 2004). However, these results also emphasize the need to carry out phytochemical separation to identify the active principles responsible for the antiaggregant effect and elucidate their mechanisms of action.

Table 4
Antidiabetic activity of *Arbutus unedo* L.

References	Part of plant	Extract	Type of study	Biological effects
Bnouham et al. (2010)	Roots	Water	OGTT	Potentiate insulin activity. Improves the uptake of glucose.
Bnouham et al. (2007)	Roots	Water	OGTT and IVGTT	Decreased jejunal glucose absorption.

IVGTT - Intravenous glucose tolerance test; OGTT - Oral glucose tolerance test.

3.3. Antidiabetic activity of Arbutus unedo L

Table 4 presents two studies (involving one *in vitro* and two preclinical studies) providing evidence for antidiabetic activity of root extracts of *A. unedo*. The *in vitro* study of glucose utilization by isolated rat hemidiaphragm suggests that aqueous extracts of roots, in combination with insulin, potentiate its activity and enhance utilization of glucose (Bnouham et al., 2007). Preclinical studies conducted in Wistar rats suggest that these plants possess antidiabetic activity and could be beneficial in the prevention or treatment of both insulin resistance and type 2 diabetes mellitus (Bnouham et al., 2010, 2007). Moreover, they have provided a rational basis for the traditional use of these plants in the management of diabetes mellitus. The roots of *A. unedo* contain tannins and flavonoids. Some fractions contain polyphenol compounds, particularly epicatechin, catechin, catechin gallate, hyperoside, and gallic acid (Legssyer et al., 2004). *A. unedo* also contains arbutoside, quercetine, and ethyl gallate (Fiorentino et al., 2007). The antihyperglycemic activity of *A. unedo* is likely due to these compounds since several previous studies have shown that they had antidiabetic effect (Bone et al., 1985; Chakravarthy et al., 1982; Waltner-Law et al., 2002; Zarzuelo et al., 1990). Further experiments are warranted to identify the active compounds and the mechanism of action, which may involve, at least in part, a significant inhibition of jejunal glucose absorption as was revealed in the oral glucose tolerance test (OGTT)

Table 3
Antiaggregant actions of *Arbutus unedo* L.

References	Part of plant	extract	Type of study	Biological effects
El Haouari et al. (2007)	Leaves	Water Petroleum ether	*In vitro* platelet aggregation assessed by aggregometry.	Decreased Ca^{2+} mobilization. Decreased ROS production. Decreased protein tyrosine phosphorylation.
Mekhfi et al. (2006)	Leaves	Petroleum ether, dichloromethano11.18%, ethyl acetate 3.16%, methanol 7.57% and water 2.7%	*In vitro* measurement of platelet aggregation.	Inhibition of thrombin-induced platelet aggregation (probably due the presence of tannins).
Mekhfi et al. (2004)	Roots	Water	*In vitro* measurement of platelet aggregation.	Inhibition of thrombin-induced platelet aggregation.

Ca^{2+}- Calcium; ROS - Reactive oxygen species.

Table 5
Antihypertensive activity of *Arbutus unedo* L.

References	Part of plant	Extract	Type of study	Biological effects
Afkir et al., 2008	Leaves and Roots	Water	*In vivo* determination of both blood pressure and baroreflex sensitivity. *Ex vivo* analysis of vascular reactivity.	Reduces the development of increased systolic blood pressure. Ameliorates vascular reactivity and baroreflex sensitivity. Improves renal function. Reduces ventricular hypertrophy (root extracts).
Legssyer et al., 2004	Leaves	Water (for the aqueous extract) Hexane, Dichloromethane, Ethyl acetate, Methanol and Water (for the soxhlet extraction)	*In vitro* study of vasorelaxant effect.	Vasorelaxant activity due the presence of oligomeric condensed tannins and catechin gallate. This effect is endothelium-dependent and mediated by NO.
Ziyyat et al., 2002	Roots	Water	*In vitro* study of vasodilator effect and mechanisms of action.	Endothelium-dependent relaxation of the isolated rat aorta which may be mediated mainly by a stimulation of the endothelial NO synthase by mechanisms other than activation of muscarinic receptors.
Ziyyat and Boussairi, 1998	Roots	Water	*In vivo* study of hypertension.	Attenuation of the pressor responses to phenylephrine and angiotensin I. No effect in the final blood pressure and heart rate.

(Bnouham et al., 2007).

3.4. Antihypertensive activity of Arbutus unedo L

Table 5 summarizes the results of four studies that provided evidence for antihypertensive activity of leaves and roots of *A. unedo*. Afkir et al. demonstrated that chronic treatment of rats with *A. unedo* roots aqueous extract regress hypertension development, prevent myocardial hypertrophy, ameliorates vascular reactivity, and renal functional parameters caused by N^G-nitro-L-arginine methyl-ester (L-NAME) (Afkir et al., 2008). In addition, *A. unedo* root and leaf extracts also improved the sensitivity of the arterial baroreceptor controlling the heart rate to acute increases of arterial pressure (Afkir et al., 2008). In other preclinical study, the aqueous extract of the root attenuated the pressor responses to phenylephrine and angiotensin I (Ziyyat and Boussairi, 1998). Further studies are needed to assess whether these beneficial effects of *A. unedo* extract are entirely due to polyphenolic compounds, which are known to enhance endothelial nitric oxide synthase.

The aqueous extracts of leaves and roots also produced an endothelium dependent relaxation of rat aortic rings precontracted with noradrenaline (Legssyer et al., 2004; Ziyyat et al., 2002). When tannins (primarily condensed tannins) were precipitated from the methanolic extract of leaves, they showed a strong vasorelaxant activity, whereas the elimination of tannins from this extract significantly reduced its vasorelaxant activity (Legssyer et al., 2004). When the methanol extract was further separated semi-preparatively by reversed-phase high-performance liquid chromatography (RP-HPLC), the most active fractions in terms of vasorelaxation corresponded to polyphenol compounds. Analysis of one of the most active fractions indicated the presence of catechin gallate, a flavanol derivative (Legssyer et al., 2004). The vasorelaxant activity of *A. unedo* leaves was then attributed to polyphenol compounds, primarily oligomeric condensed tannins and catechin gallate (Legssyer et al., 2004). All together, these observations highlight the valuable therapeutic potential of *A. unedo* extracts in the treatment or prevention of hypertension, cardiovascular and renal diseases.

3.5. Cytotoxic and antitumoral actions of Arbutus unedo L

To the best of our knowledge, no *in vivo* study has been done to evaluate the cytotoxic effect of *A. unedo*-derivated products. Studies regarding the cytotoxicity of *A. unedo* are closely associated with an antitumoral effect. Cytotoxicity-related assays are useful to evaluate the ability of a compound to induce cell death. These assays are useful on a first screening for potential antitumor compounds. However, to infer about the antitumor effect of *A. Unedo* compounds, molecular studies elucidating the antitumor activity must be performed in the cells. Table 6 highlights eight studies that provide evidence for the antitumoral and cytotoxic actions of *A. unedo*.

Afrin et al. evaluated the phytochemical content and the cytotoxic properties of strawberry tree honey against human colon adenocarcinoma in HCT-116 and LoVo cell lines. The author observed that after the treatment of cells with different concentrations (0–60 mg mL^{-1}) of strawberry honey, a concentration- and a time-dependent decrease of cell viabillity occurred, when compared to untreated cells. These results suggest that strawberry honey has a chemoprotective effect and can be a useful tool against colon cancer (Afrin et al., 2017). Carcache-Blanco et al. conducted a phytochemical study of the petroleum ether and ethyl acetate extracts of the entire plant of *A. unedo* and the pomolic acid 3-acetate was found to be active in the JB6 cell transformation assay, with an IC_{50} value of 8.1 mg mL^{-1} (Carcache-Blanco et al., 2006).

Isolates evaluated for their potential to inhibit cyclooxygenase-2 (COX-2) showed that a C_{29} sterol derivative (7β-hydroxystigmast-4-en-3-one), a flavan [(-)-catechin] and three triterpenoids (α-amyrin acetate, betulinic acid, and lupeol) exhibited inhibitory activity with IC_{50} values of 93.2, 94.4, 10.2, 11.4, and 11.1 mg mL^{-1}, respectively (Carcache-Blanco et al., 2006). *In vitro* bioassays demonstrated that the inhibition of COX-2 enzyme represents major mechanisms of protection against tumor promotion (Chang et al., 2000; Cuendet and Pezzuto, 2000). Two independent studies (Guimarães et al., 2014; Schaffer et al., 2005), performed on ethanolic extracts of fruits, demonstrated that *A. unedo* could inhibit DNA synthesis and cellular proliferation in different cell lines of cancer (Kahriman et al., 2010; Oliveira et al., 2011; Schaffer et al., 2005). In neuroblastoma cell line, extracts of fruits in concentration > 125 μg gallic acid equivalent (GAE)/mL decreased cell viability (Fortalezas et al., 2010). No beneficial effect was observed in human platelets and in A549/8 cell line treated with leaves extracts of *A. unedo* (Mariotto et al., 2008b). However, in TPH-1 cells, concentrations of 29.6 μg mL^{-1} of leaf extracts led to a loss of 60% of cell viability (El Haouari et al., 2007; Mariotto et al., 2008b). An independent study conducted by Andrade and colleagues on a human fibroblast cell line concluded that *A. unedo* decreases cell viability, independently of the solvent used for extraction (Andrade et al., 2009). The ability of *A. unedo* extracts to decrease cell viability enhanced the potential therapeutic value of *A. unedo* for the prevention / treatment of

Table 6
Antitumoral action of *Arbutus unedo* L.

References	Part of plant	Extract	Type of study	Biological effects
Afrin et al. (2017)	[1]_____	Strawberry-tree honey	Cell viability and cell proliferation evaluated by MTT assay.	Inhibition of cell proliferation. Decreased cell viability.
Guimaraes *et al.*, 2014	Fruit	Methanol/water 80:20 (v/v)	Antitumoral potential by SRB assay.	Inhibition of tumor growth.
Fortalezas et al. (2010)	Fruits	Methanol/water 50:50 (v/v)	Cell viability evaluated using the CellTiter-Blue® Cell Viability Assay.	Decreased cell viability.
Andrade et al. (2009)	Entire plant (wood/stalks, bark and leaves)	Acetone/water 60:40 (v/v). Ethanol 95%.	Cell viability evaluated by MTT assay.	Decreased cell viability.
Mariotto et al. (2008b)	Leaves	Methanol	Cell viability evaluation based on the cleavage of the tetrazolium salt 4-[3-(4-iodophenyl)− 2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate WST-1 into formazan.	Concentrations of 29.6 μg/mL lead to a loss of 60% of TPH- 1 cells viability. No toxic effect was observed in A549/ 8 cell line.
El Haouari et al. (2007)	Leaves	Water	Cell viability evaluated using calcein and trypan blue.	Concentrations of 1.5 mg/mL lead to a loss of 4% of human platelets cell viability.
Carcache-Blanco et al. (2006)	Entire plant	Methanol and petroleum ether or ethyl acetate or water.	*In vitro* inhibition of carcinogenesis. *In vitro* inhibition of the COX-2 enzyme.	Activity in JB6 cell transformation assay was found for pomolic acid 3-acetate.
Schaffer et al. (2005)	Fruits	Ethanol 90%	*In vitro* assay measuring the anti-proliferation potential through BrdU assay.	Inhibition of DNA synthesis and cellular proliferation.

BrdU - 5-bromo-2´-deoxyuridine; COX-2 - cyclooxygenase-2; SRB- Sulforhodamine B; GAE - Gallic acid equivalent; IC_{50} - Concentration required for 50% inhibition of cell growth; MTT - 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.
[1] not applicable.

Table 7
Antioxidant actions of *Arbutus unedo* L.

References	Part of plant	Extract	Type of study	Antioxidant properties
Erkekoglou et al. (2017)	Leaves	Water	Antioxidant cell based-assays (DPPH$^{\bullet}$ and ABTS$^{\bullet+}$ and peroxyl radical scavenging).	Radical scavenging activity (DPPH$^{\bullet}$, ABTS$^{\bullet+}$, peroxyl).
			In vivo antioxidant assay.	Protective effect against antioxidant insults.
Orak et al. (2012)	Fruits	Ethanol	DPPH and scavenging activity and β-carotene bleaching activity.	Ability to act as free radical scavenger.
Mendes et al. (2011)	Leaves and fruits	Water	Evaluation of antioxidant activity.	High reducing power. Ability to act as free radical scavenger.
Pavloviç et al., 2011	Leaves	Ethanol (70%)	DPPH assay.	Decreased ileal basal tonus (reduction in contractile response to acetylcholine).
			Thiobarbituric acid test.	Inhibition of calcium channels.
			Determination of spasmolytic activity	Ability to act as free radical scavenger.
Barros et al. (2010)	Fruits	Methanol	Scavenging activity on DPPH radical. Inhibition of β-carotene bleaching. Inhibition of lipid peroxidation (TBARS).	Low antioxidant activity.
Fortalezas et al. (2010)	Fruits	Ethanol 50% (v/v)	Scavenging capacity for peroxyl radical (ORAC method).	The antioxidant activity is not necessarily correlated with biological significance.
Oliveira et al. (2011)	Fruits	Ethanol 96%(v/v)	Reducing power, scavenging effect on DPPH and superoxide radicals.	Antioxidant activity is dependent of the fruits ripening stage.
Sá et al. (2011)	Leaves	Aqueous	Reducing power and the scavenging effect of DPPH radicals.	Antioxidant activity depended on the geographic origin of leaves. Concentration-dependent antioxidant power.
Tavares et al. (2010)	Leaves and fruits	Ethanol/water 50% (v/v)	Peroxyl radical scavenging capacity by the ORAC method. MMP-9 inhibitory activity assay.	Antioxidant activity. MMP-9 inhibitory activity.
Andrade et al. (2009)	Entire plant (wood/stalks, bark and leaves)	Acetone/water 60:40 Ethanol 95%	Antioxidant activity evaluated by DPPH method	Ability to act as free radical scavenger.
Oliveira et al. (2009)	Leaves	Water, ethanol, methanol and diethyl-ether	Reducing power of iron (III)/ferricyanide complex assay. Scavenging effect on DPPH radicals.	Ability to act as free radical and superoxide radical scavenger.
			Scavenging effect on superoxide radicals by using the PMS-NADH-nitroblue tetrazolium system.	Concentration-dependent antioxidant power.
Pavlović et al., 2009	Leaves	Ethanol 70% (v/v)	FRAP (total antioxidant capacity) Lipid peroxidation DPPH free radical scavenging activity.	High scavenging activity. Ferric reducing antioxidant power. Inhibition of lipid peroxidation.
Schaffer et al. (2005)	Fruits	Ethanol 90% (v/v)	Determination of free radical scavenging activity by DPPH assay. Measurement of *A. unedo* effect on protection of peroxide-induced DNA damage.	High antioxidant activity. Moderated protection against peroxide-induced DNA damage.
Pabuçcuoğlu et al. (2003)	Leaves	Ethanol and methanol	Assay based on the decolorization of the radical monocation of ABTS.	Ability to act as free radical scavenger of ABTS$^{\bullet+}$.

ABTS - 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid); DPPH - 2,2-diphenyl-l-picrylhydrazyl; EC_n – Extract concentration providing n% antioxidant activity; FRAP - ferric ion reducing antioxidant power; MMP - Matrix metalloproteinase; ORAC - Oxygen radical absorbance capacity; TBARS - Thiobarbituric acid reactive substances.

different types of cancer. However, more studies are needed to clarify the biological targets of *A. unedo* compounds.

3.6. Antioxidant activity of Arbutus unedo L

Table 7 displays studies that offer wide evidence for the potent antioxidant activity of *A. unedo,* namely of leaves and fruits. Results showed leaves and fruits of *A. unedo* to possess a high scavenging effect against 2,2-diphenyl-l-picrylhydrazyl (DPPH) radical, as well as a high reducing power and potent effect in scavenging superoxide radical. The latter is one of the most important free radicals and precursor of several molecules associated with tissue damage through oxidation (Aruoma, 1996). By using human biological membranes for the first time, Mendes et al. demonstrated a potent antioxidant activity for aqueous extracts of leaves and fruits, although consistently higher in leaves (Mendes et al., 2011). Under the oxidative action of 2,20-azobis(2-amidinopropane) dihydrochloride (AAPH), *A. unedo* leaves and fruit extracts protected the erythrocyte membrane from hemolysis [IC_{50} (the inhibitory concentration 50%) of 0.062 ± 0.002 and 0.430 ± 0.091 mg mL^{-1}, respectively] and decreased the levels of malondialdehyde, a breakdown product of lipid peroxidation (IC_{50} of 0.075 ± 0.014 and 0.732 ± 0.452 mg mL^{-1}, respectively) (Mendes et al., 2011). In accordance with antioxidant activity, phenolic content was found to be significantly higher in leaf extracts (Mendes et al., 2011). The entire plant has also been subject to a study regarding its antioxidant capacity. Andrade et al. quantified the total phenolic content (mg of gallic acid equivalents / g of plant extract) and flavonoid content (mg of quercetin equivalents / g of plant extract), as well as the ability to scavenge DPPH radical, testing two different extraction solvents (ethanol and acetone) (Andrade et al., 2009). Results showed a high amount of both phenolics (255.19 ± 7.12 mg g^{-1}, in the ethanolic extract and 334.46 ± 31.83 mg g^{-1} for the acetone extract) and flavonoids (20.50 ± 0.77 mg g^{-1}, in the ethanolic extract and 23.37 ± 0.67 mg g^{-1} for the acetone extract) (Andrade et al., 2009). EC_{50} (extract concentration providing 50% antioxidant activity) values of extracts were considerably low, when compared with reference antioxidants, especially those obtained through ethanolic extraction (7.85 μg mL^{-1}), thus enhancing the potent antioxidant activity of this shrub (Andrade et al., 2009).

Antioxidant capacities reported in literature are difficult to compare due to differences in methodologies used. However, García-Alonso et al. determined the antioxidant activity of 28 different fruits, including strawberry tree and raspberry, and established a ranking [Trolox-Equivalent Antioxidant Capacity (TEAC) method]. Strawberry tree's antioxidant capacity was ranked fourth, slightly above raspberry (García-Alonso et al., 2004). The antioxidant activity of *A. unedo* has been attributed to the high flavonoid content (mainly comprised by proanthocyanidins, cyanidin and delphinidin glycosides), ellagic acid and its diglucoside derivative, vitamins C and E and carotenoids (Pallauf et al., 2008).

According to Pavlovic et al., positive effects of *A. unedo* leaf extracts against gastrointestinal complains are related to antioxidant compounds, such as tannins, arbutin and flavonoids (Pavloviç et al., 2011). In isolated tissues, ethanol extracts of leaves were found to decrease the ileal basal tonus (reduction in contractile response to acetylcholine, *i.e.,* spasmolytic properties), (Pavloviç et al., 2011). Antioxidant activity observed in these studies emphasizes a potential utilization of *A. unedo* extracts as supplement by the food and pharmaceutical industries.

3.7. Anti-inflammatory activity of Arbutus unedo L

Table 8 shows two studies that provide evidence for anti-inflammatory activity of *A. unedo*. Mariotto et al. conducted *in vitro* studies demonstrating that the aqueous extracts of *A. unedo* leaves are a promising source of compounds able to reduce inflammation (Mariotto et al., 2008a). Although the exact mode of action of the aqueous extracts still remains to be totally elucidated, the mechanisms of the anti-inflammatory effect appear to be correlated with the reduction of interleukin (IL)-6 production, the reduction of other pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-1, the decrease in the recruitment of neutrophils, and the decrease of expression of inducible nitric oxide synthase (iNOS) and COX-2 protein as well as activity, which finally may lead to the decrease of tissue injury (Mariotto et al., 2008a). Other studies also indicated that extracts of leaves are able to decrease the platelet hyperaggregability, which is an important factor in the pathogenesis of inflammatory diseases (El Haouari et al., 2007; Mekhfi et al., 2006). The anti-inflammatory effect of *A. unedo* extracts demonstrated by these studies should bring a potential valuable compound to the treatment of inflammatory diseases, in which STAT1 (signal transducer and activator of transcription) plays a critical role.

4. Concluding remarks

This literature review showed that almost all parts of the *A. unedo* shrub (leaves, fruits, bark, roots, as well as byproducts such as honey) have been used in traditional medicine for the treatment of many different diseases. Several *in vitro* and preclinical studies conducted with extracts of different parts of *A. unedo* support various popular uses in folk medicine, namely in the treatment of infections, cardiovascular diseases, hypertension, diabetes and inflammatory disease. Concerning the antioxidant power of *A. unedo* extracts, the majority of studies reported data based on total antioxidant activity evaluated by *in vitro*, non-specific and prone interference techniques, such as ORAC, DPPH and FRAP assays. Further research must be carried out in order to demonstrate both the biological significance of the antioxidant power and the mechanism of action of *A. unedo* compounds. However, these preliminary data suggest new potential indications of this plant in modern pharmacotherapy, especially for the development of new drugs to treat neurodegenerative and cancer diseases. The antioxidant properties of *A. unedo* leaves and fruits are recognizably linked to the polyphenolic profile of this plant, with potential application in diseases mediated by free radicals. Further research on the phytochemical purification of active compounds present in this plant must be carried out in order to identify the active principles responsible for the antimicrobial, anti-aggregant, antidiabetic, antihypertensive, anti-inflammatory properties of the different parts of the plant and to elucidate their mechanisms of action. Methodologies used in some studies for biological evaluation of

Table 8
Anti-inflammatory activity of *Arbutus unedo* L.

References	Part of plant	Extract	Type of study	Biological effects
Mariotto et al. (2008b)	Leaves	Methanol	Evaluation of inflammatory activation.	Down-regulate one of the initial factors of the inflammatory process on inflamed lungs, member of transcription factors, signal transducers and activators of transcription family (STAT's).
Mariotto et al. (2008a)	Leaves	Aqueous	*In vitro* evaluation of inhibition of STAT1 activation.	Inhibits STAT1 activation through activation of the protein tyrosine phosphatase SHP2.

STAT - Signal transducer and activator of transcription.

extracts are quite rudimentary (*e.g.,* disc diffusion assays for antimicrobial activity) and more advanced analyses of bioactivity are required for compliance with international standards [*e.g.,* Clinical and Laboratory Standards Institute (CLSI) broth microdilution susceptibility testing method]. It is also crucial to validate *in vitro* and preclinical studied bioactivities on different cell-based human-disease models assays and ultimately in the overall human organism, by conducting clinical trials. Cytotoxity-related assays were frequently used to evaluate a potential antitumor effect of *A. unedo* extracts. Although these assays are useful to screen for potential anticancer compounds, more studies must be carried out to understand the antineoplastic properties of A. unedo compounds. Toxicity tests performed in mice with plant extracts yielded high LD_{50} (lethal dose, 50%) values, which suggests the possibility to conduct clinical trials without the occurrence of significant adverse effects. It would also be useful to undertake studies to assess the bioaccessibility and bioavailability of the extract components, as well as the required dosage to ingest, by determining the dose-response curves of the extracts of different parts of *A. unedo* plant, to obtain the maximal benefits to human health with minimal undesirable effects.

Contribution of authors

SM conceptualized the review and drafted the initial version of the manuscript. MM undertook database search for the literature on *Arbutus unedo* L. uses in traditional medicine and its potential uses in current pharmacotherapy and has also contributed to the initial version of the manuscript. AIP and FR significantly contributed in collation of information and discussions of the manuscript. APD, who has extensive experience in medicinal plant research, led the discussions on topics and monitored the progress of the manuscript. All authors participated in the writing and gave feedback on the manuscript. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interests.

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