Diabetes and Medicinal Plants in Portugal

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ABSTRACT

Due to western lifestyles generalization and consequent increase in childhood and adult obesity, type 2 diabetes has become an epidemic on global scale. According to the World Health Organization, type 2 diabetes mellitus is the most common endocrine disorder, currently affecting more than 173 million people around the world and about 9 per cent of global mortality is closely related to diabetes mellitus.

Currently, the use of anti-diabetic oral drugs (ADOs) to control hyperglycaemia does not promote a satisfactory goal for most diabetic patients.

In recent years, and despite the advances in the diagnosis and treatment of diabetes in the western medicine, an increasing interest in traditional anti-diabetic plants has been observed. Indeed, medicinal plants seem to be a useful alternative to synthetic drugs used in diabetes therapy and several active compounds of some of these synthetic drugs (such as metformin or

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guanidine) are extracted from plants or have similar effects. In Portugal where the prevalence of diabetes is also increasing, there has been a remarkable quest for anti-diabetic medicinal plants to be used alone or in combination with prescribed medication. In this narrative review, we describe and characterize aromatic and medicinal plants as, for instance, Artium minus Bernh., Cistus ladanifer L., Cytisus multiflorus Sweet, Geranium robertianum L., Hypericum androsaemum L., Lupinus albus L., Pterospartum tridentatum (L.) Willk, Salvia officinallis L. and Vaccinium myrtillus L., used in Portuguese folk medicine for type 2 diabetes treatments.

Keywords: Medicinal plants, Type 2 diabetes mellitus, Phytotherapy.

Abreviations

ADO: Antidiabetic oral drug

NO: Nitric oxide

PPAR-γ: Peroxisome proliferator-activated receptor γ

ROS: reactive oxidation species.

Introduction

Plants have been used since times immemorial for treatment of human complaints. However, in the last century, due to the pharmaceutical progress, herbal medicine in the developed countries have been relegated to a lesser position and, often, patients who still employed medicinal plants were connoted with ignorant and witchcraft practices.

Nevertheless, this situation has been reversed in the last few decades and an increasing demand for herbal medicine as a complement for traditional therapy occurred (Izzo and Ernst, 2009). Simultaneously, there has been an exponential growth in aromatic and medicinal plant(s) research. Actually, medicinal plants are a good source of supply for pharmaceutical industry and many popular medicines in use, as the common aspirin, or the antiadiabetic oral drug metformin are derived from plants.

Medicinal plants seem to be an important and useful alternative (or complementation) to the synthetic drugs used in type 2 diabetes' therapy. In fact, several of these synthetic drugs, such as metformin or guanidine, are based in active compounds previously extracted from medicinal plants (Petlevski *et al.*, 2001; Mueller and Jungbauer, 2009). Despite the increasing use of medicinal plants in the treatment of diabetes mellitus (Halestrap *et al.,* 2000; Ryan *et al.,* 2001), there is still little knowledge of the mechanism of action and the therapeutic effects of several of these plants with attributed anti-diabetic action by folk medicine (Naga Raju *et al.,* 2006).

In Portugal, it was also observed an increasing interest of phytotherapy treatments as a complement for diabetes traditional therapy (oral anti-diabetic medication or insulin) in order to reach normal glycemic levels and prevent later complications (Barata, 2008).

The current review focuses on herbal drug preparations and plants used in Portugal since ancient times for the treatment of diabetes mellitus.

Diabetes and Significance

Diabetes mellitus is a complex and a multifarious group of disorders that disturbs the metabolism of carbohydrates, fat and protein, with one common manifestation – hyperglycemia (WHO, 1980). While type 1 diabetes is caused by an abolishment of insulin production, type 2 diabetes, the most common form, and accounting for 85-90 per cent of the occurrences, is caused by hepatic and peripheral tissue insulin resistance and pancreatic beta-cell dysfunction (William and Pickup, 2003). Due to western lifestyles of developing countries and to the consequent increasing rates of childhood and adult obesity, type 2 diabetes mellitus has become an epidemiologic problem (WHO, 2006).

Hyperglycaemia, as a result of uncontrolled glucose regulation, promotes oxidative stress and causes severe diabetic complications, such as nephropathy, retinopathy, neuropathy and cardiovascular diseases, which severely impairs diabetic patients' life quality (Engelgau and Geiss, 2000; Nuorooz-Zadeh, 2000; Yorek, 2003). Therefore, the major goal of diabetes therapy is to maintain normal glycaemia levels (Agius, 2007; Yu *et al.*, 2010). Nevertheless, this target usually remains unreachable using regular therapies and chemical anti-hyperglycaemic agents.

Medicinal plants are being rediscovered for the treatment of chronic diseases, including diabetes. As a matter of fact, many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin illustrates an efficacious oral glucose-lowering agent. Its development was based on the use of *Galega officinalis*, which is rich in guanidine, a hypoglycemic component. Nevertheless, as guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s (Dey *et al.*, 2002). Despite its properties, their use was discontinued after insulin became more readily available. Nevertheless, the experience with guanidine and biguanides prompted the development of metformin (Dey *et al.*, 2002). To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy (Modak *et al.*, 2007). Even so, the hypoglycemic effect of some herbal extracts has been corroborated in humans or in type 2 diabetes animal models (Shukia *et al.*, 2000).

The World Health Organization Expert Committee on Diabetes has recommended traditional medicinal herbs to be further investigated (Day, 1989; Dey *et al.*, 2002). In the last two decades innumerous scientific works were published reporting the effectiveness and promising effects of several plants and their chemical constituents in diabetes mellitus therapy.

List of Medicinal and Aromatic Plants Focused in this Chapter

1. Family Asteraceae
   (*a*) *Arctium minus* (Hill) Bernh

2. Family Cistaceae
   (*a*) *Cistus ladanifer* L.
3. Family Clusiaceae
   (*a*) *Hypericum androsaemum* L.
4. Family Ericaceae
   (*a*) *Vaccinium myrtillus* L.
5. Family Fabacea
   (*a*) *Cytisus multiflorus* (L' Hér.) Sweet
   (*b*) *Lupinus albus* L.
   (*c*) *Pterospartum tridentatum* (L.) Willk. subsp. *tridentatum*
6. Family Gentianaceae
   (*a*) *Centaurium erythraea* RAFN
7. Family Geraneaceae
   (*a*) *Geranium robertianum* L.
8. Family Lamiaceae
   (*a*) *Rosmarinus officinalis* L.
   (*b*) *Salvia officinalis* L.

1. Family Asteraceae

(*a*) *Arctium minus* (Hill) Bernh

Arctium minus (Hill) Bernh (lesser burdock or common burdock), is a species of the genus *Arctium*, tribe *Cynareae*, family *Asteracea*. This genus comprises some other species such as *A. lappa*, *A. pubens* and *A. tomentosum*, the species *A. lappa* being the mostly used in phytotherapy.

A. minus, a Portuguese autochthonous plant, is locally known as "*pegamasso*", "*pegamaço*" or "*bardana*". Lesser burdock is a biennial thistle spontaneous plant, found mainly in country paths edges and uncultivated grounds. *A. minus* is native to Europe (alternatively to *A. lappa*, usual in eastern countries); however, nowadays it is widespread throughout most of the United States, as a common weed. It can grow up to 1.5 meters tall and forms multiple branches. Flowers are prickly and pink to lavender in colour. Flower heads are about 2 cm wide. The plant flowering season is from July through October. Leaves are long and ovate. It grows an extremely deep taproot, and roots attain up to 30 cm.

A. minus roots decoctions are commonly used in Portugal to treat type 2 diabetes mellitus (Cunha *et al.*, 2006). In fact, *Arctium* roots contain inulin, a fructan compound, indigestible in the upper gastro-intestinal tract, with inhibitory action over the absorption of substances in small intestine and leading to intestinal microflora improvement. Therefore, *A. minus*' roots are used by diabetic patients to slow carbohydrate digestion, to reduce the absorption and control glucose intolerance (Kardosová *et al.*, 2003; Li *et al.*, 2008; Lou *et al.*, 2009).

Some controversial results were found about the antihyperglycemiant activity of *A. minus* roots in animal models. Cavalli and collaborators found that *A. minus* leaves and roots reduce alloxan-treated rats' plasmatic glucose level, in a similar way to the ADO glibenclamide (Cavalli *et al.*, 2007). These authors suggest that these extracts increase both insulin production and insulin cells sensitivity. However, using Goto-Kakizaki (GK) rats, we did not observe an improvement in hyperglycaemia control (Ferreira *et al.*, 2010a). Indeed the plant extract prepared from *A. minus* available in Portuguese herb shops, contained nickel (Ni) and cadmium (Cd) that could inhibit insulin release (Dormer *et al.*, 1974; Gupta *et al.*, 2000; Lei *et al.*, 2007) and possess toxic effects (Wang *et al.*, 2004; Ferreira *et al.*, 2010a). Nevertheless, as most aromatic and medicinal plants have the ability to bioaccumulate several heavy metals (Broadley *et al.*, 2001), the variations observed in both studies may be attributed both to the different animal models of diabetes and to the different chemotypes studied.

Arctium roots also contain arctiin, a lignane glucoside compound (Yakhontova and Kibal'chich, 1971), with anticarcinogenic activity (Wang *et al.*, 2005). Furthermore, ethanolic and aqueous extracts from *A. minus* leaves were found to possess antioxidant and anti-inflammatory properties, being relevant to diabetic patients in order to decrease oxidative stress and common low-grade of inflammation associated to the disease (Erdemoglu *et al.*, 2009).

2. Cistaceae Family

(*a*) *Cistus ladanifer* L.

Roots and aerial parts of *Cistaceae* plants have been used since ancient times in the Mediterranean cultures for its medicinal properties. The species *Cistus ladanifer* L. (rock-rose or gum rockrose), is an indigenous plant of the western Mediterranean region, being widely distributed over western Iberia and northwest Africa (Sosa *et al.*, 2005; Belmokhtar *et al.*, 2009). It is a shrub growing 1-2.5 m tall and wide. The leaves are evergreen, dark green above and paler underneath, lanceolate, with dimensions varying from 3-10 cm long and 1-2 cm broad. The flowers are 5-8 cm diameter, with 5 papery white petals, usually with a red to maroon spot at the base, surrounding the yellow stamens and pistils. The whole plant is covered with the sticky exudates of a fragrant resin known as labdanum gum, being particularly appreciated for their therapeutic applications as well as for their balsamic odour and their fixative properties (Teixeira *et al.*, 2007; Barrajón-Catalán *et al.*, 2010).

In Portugal, *C. ladanifer* L., locally known as "esteva das cinco chagas" or simply "esteva", is widely distributed, being one of the most abundant species in the southern part of the country, occurring in large areas as pure dense stands. This shrub colonizes degraded areas and inhibits the growth of other plants (Dias and Moreira, 2002), either by restricting aerial growth of plants or by inhibiting germination of other species, due to its phytotoxicity over other plants and soil, a phenomenon known as allelopathy (Chaves *et al.*, 2001; Alías *et al.*, 2006). *Cistus* genus easily adapts to wildfires that destroy large forest areas, as their seeds resist fire and rapidly repopulate in the following season (Ferrandis *et al.*, 1999). This could explain why *C. ladanifer* is very abundant along the Portuguese forest and landscape, and their overgrowth is becoming an environmental problem.

In Portugal, rock-rose is used for diabetes, for respiratory and rheumatic problems, among other applications (Castro, 1998; Camejo-Rodrigues, 2001; Carvalho, 2005). In fact, *C. ladanifer* is used as a panacea or "a remedy for all diseases" (Carvalho, 2005). Fruits and aerial parts (harvested before flowering season) infusions are usually used in therapeutic applications in Portugal (Castro, 1998; Camejo-Rodrigues, 2001; Carvalho, 2005; Andrade *et al.,* 2009). Nevertheless, in Morocco, the use of leaf infusions or decoctions (Bnouham *et al.,* 2002), seed infusions are also used in diabetes therapy (Merzouki *et al.,* 2003).

Despite its widespread use, at the present time, no scientific reports concerning the effectiveness of *C. ladanifer* water extracts on diabetes mellitus were found. In recent years, several publications noticing high antioxidant power either in water and ethanol extracts and essential oils from *C. ladanifer* were achieved (Andrade *et al.,* 2009; Barrajón-Catalán *et al.,* 2010; Guimarães *et al.,* 2010). Actually, exudates from this plant present characteristic aglycone flavonoid compounds, such as apigenin (and derivatives), several kaempferol derivatives, quercetins and ellagitannins (Chaves *et al.,* 1998; Barrajón-Catalán *et al.,* 2010). Phenolic content of *C. ladanifer* water extract was higher than that of other aqueous extracts previously reported (Dudonne? *et al.,* 2009; Barrajón-Catalán *et al.,* 2010) and almost similar to ethanolic *C. ladanifer* extracts contents (Andrade *et al.,* 2009; Barrajón-Catalán *et al.,* 2010). As the inhibition of reactive oxygen species (ROS) is associated with a positive impact on human health, throughout pathogenesis modulation of many diseases associated to oxidative stress, such as atherosclerosis, hypertension, cardiovascular disease, ischemia/reperfusion injury, diabetes mellitus, cancer and neurodegenerative diseases (Ceriello, 2003; Valko *et al.,* 2006; Seifried, 2007; Valko *et al.,* 2007; Barrajón-Catalán *et al.,* 2010), the high antioxidant activity of *C. ladanifer* is probably associated with the widespread therapeutic utilization of this plant.

C. ladanifer extract also demonstrated to possess anticancer activity against several tumour cell lines (Barrajón-Catalán *et al.,* 2010), namely breast and pancreas tumour cells. This anticarcinogenic potential is probably related to the combination of elligitannins present in the extract. Moreover, this plant showed antihypertensive effects (Belmokhtar *et al.,* 2009), improving vascular reactivity and induced an endothelium- and NO-dependent relaxation of vascular smooth muscle.

In conclusion, *C. ladanifer* extracts possess a significant amount and variety of polyphenolic compounds with an important antioxidant activity, being worthy to prevent or reduce the development of diabetic complications.

3. Family Clusiaceae

(*a*) *Hypericum androsaemum* L.

Hypericum androsaemum L., commonly known as tutsan, is a *Clusiaceae* (or *Guttiferea*) plant, native on open woods and hillsides in Europe and Near West. Usually requires shadowy places to grow (Cunha *et al.,* 2009). In Portugal, it is usually known as "Hipericão do Gerês", "androsemo" or "erva-da-pedra", and is a common plant in northern and central areas of the country, mainly in the highest altitudes of Minho, Beiras and Estremadura (Valentão, 2002; Cunha *et al.,* 2009). *H. androsaemum* is a perennial shrub, between 30-120 centimetres in height. Branches are separated in two longitudinal lines, with oval and green leaves. It flowers from June to September, and flowers are small (2 cm) and yellow (Coutinho, 1939). The berries turn from white/green, to red and to black during the maturation process.

Infusions (or decoctions) of aerial parts of *H. androsaemum* are traditionally used in folk medicine, being one of the most consumed medicinal plants in Portugal (Valentão, 2002; Cunha *et al.,* 2009). The common name tutsan appears to be a corruption of "*toute saine*", literally meaning all healthy and probably in reference to its healing properties. Usually, dry aerial parts, harvested just before or during flowering season are used for treating kidney and liver ailments and as diuretic (Valentão, 2002; Novais *et al.,* 2004; Cunha *et al.,* 2009). Further, leaves are applied topically to wounds or burns, due to its healing properties (Lavagna *et al.,* 2001; Valentão, 2002; Cunha *et al.,* 2009). Information collected in several ethnobotanical studies, confirms also the use of *H. androsaemum* as sedative, antidepressant, antihypertensive and for digestive ailments treatment (Novais *et al.,* 2004; Carvalho, 2005) as well for diabetes treatment (Castro, 1998).

Chemically, *H. androsaemum* contain many polyphenolic compounds, namely flavonoids and phenolic acids (Valentão *et al.,* 2002; Valentão, 2002), that show seasonal variations (Guedes *et al.,* 2004) and chemical polymorphism (Valentão *et al.,* 2003). The compounds mainly described are caffeic acid, chlorogenic acid, luteolin, kaemferol, quercetins and several xanthones ((Valentão, 2002) and references therein). However, rutin (quercetin-3-rutinoside) and hypericin, an anthraquinone-derivative, present in other *Hypericum* species (*H. perforatum, H. undulatum*), are absent in *H. androsaemum*.

H. androsaemum extracts present high antioxidant potential, against hypochlorous acid and oxygen and nitrogen free radicals (Valentão *et al.,* 2002; Valentão *et al.,* 2004; Almeida *et al.,* 2009), probably due to the presence of several quercetin glycosides in the tutsan extract (Valentão *et al.,* 2002). The important antioxidant capacity, *in vitro*, seems to be responsible, in part, for the hepatoprotective properties attributed to this plant, in hepatocytes submitted to oxidative stress (Valentão *et al.,* 2004). Nevertheless, *in vivo* studies demonstrate that *H. androsaemum* water extract increase hepatotoxicity induced by tert-butyl hydroperoxide (t-BHP) (Valentão *et al.,* 2004). t-BHP is metabolized into free radical intermediates by cytochrome P450 in hepatocytes, which initiate lipid peroxidation, glutathione depletion and cell damage. Histopathological evaluation of the mice livers revealed that *H. androsaemum* infusion raised the incidence of liver lesions induced by t-BHP. Hence, this study, involving cytochrome P450 activity, does not corroborate the effectiveness of *H. androsaemum* infusion as hepatoprotector, but rather its effect as hepatotoxicity potentiator (Valentão *et al.,* 2004).

H. androsaemum is commonly referred as a species in which xanthonoids biosynthesis play an important role (Schmidt and Beerhues, 1997; Schmidt *et al.,* 2000), mainly 1,3,5,6 and 1,3,6,7 oxygenated xanthones (Dias *et al.,* 2000).

Concerning to *H. androsaemum* employment as an antihyperglycemiant plant (Castro, 1998), mangiferin (1,3,6,7-tetrahydroxy-2-[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]xanthen-9-one), one of the modified xanthones present in *H. androsaemum,* is of major importance. Indeed, this glucosylxanthone shows antihyperglycemic activity (Miura *et al.*, 2001; Muruganandan *et al.*, 2005) and also presents important antiatherogenic properties (Muruganandan *et al.*, 2005), preventing diabetic nephropathy progression in streptozotocin-induced diabetic rats, improving renal function in diabetic rats (Li *et al.*, 2010) and presents a high antioxidant activity (Prabhu *et al.*, 2006), counteracting oxidative stress associated to diabetes. Furthermore, luteolin, a flavone present in *H. androsaemum*, also displays antidiabetic activity (Zarzuelo *et al.*, 1996), increasing insulin sensitivity in adipocytes (Ding *et al.*, 2009), presents an important antioxidant power (Torel *et al.*, 1986; Miean and Mohamed, 2001) and an significant anti-inflammatory action (Chen *et al.*, 2007), reducing the impairment of endothelium-dependent relaxation in rat aorta, common in diabetic patients, by reducing oxidative stress (Qian *et al.*, 2010). Together with the potential antidiabetic activity, *H. androsaemum* possesses an elevated antioxidant activity and undoubtedly plays an important role in avoiding (or decreasing) diabetic complications.

4. Family Ericaceae

(*a*) *Vaccinium myrtillus* L.

Vaccinium myrtillus L. (bilberry or European blueberry), is an *Ericaceae*. This genus is widespread over the world and comprises over 200 species of evergreen woody plants varying from dwarf shrubs to trees (Jaakola, 2003). *V. myrtillus* is a shrubby perennial plant that can be found in mountains and forests both in Europe and in the northern United States. In fact, bilberry is found in very acidic and nutrient-poor soils, throughout the temperate and subarctic regions of the world. In Portugal, bilberry (*V. myrtillus*) is commonly known as "mirtilo","mirtilho","arando" or "uva-do-monte".

Bilberries produce single or paired dark berries on the bush, instead of clusters. Berries are dark, near black, with a slight shade of blue. The bilberry fruit is smaller than the blueberry one, but with a fuller taste. While the blueberry's fruit pulp is light green, the bilberry's is red or purple, heavily staining the fingers and lips of consumers eating the raw fruit.

V. myrtillus is extremely difficult to grow being seldom cultivated in Portugal. However, both due to its high economic value and growing demand in the last years, the agriculture of several counties close to Vouga River, namely Sever do Vouga, deeply depend on bilberry production. Indeed, this province possesses the climatic requisites to produce high quality berries and this activity is partially supported by Portuguese Agricultural Ministry. Grândola, in the southern Portuguese seacoast, is another region where the bilberry production became a significant economic activity (Sousa *et al.*, 2007). In addition to the cultivated bilberry, we can also find wild bilberries in the northern Portugal, mainly in Trás-os-Montes (Neves *et al.*, 2009) and Alto Minho.

Actually, coupled to its utilization in food industry, mainly in jams, pies or yogurt and ice-creams preparation, this plant is widely used since ancient times in folk medicine, due to its therapeutic properties (Canter and Ernst, 2004; Valentová *et al.*, 2007; Bao *et al.*, 2008). Bilberry's history of medicinal use dates back to the medieval times, but it did not become widely known to herbalists until the 16th century, when it was used for treating biliary disorders, bladder stones, scurvy, coughs and lung tuberculosis. Lately, bilberry fruit extracts have also been used for the treatment of diarrhea, dysentery and mouth and throat inflammations (Anonymous, 2001, Valentová *et al.*, 2007).

V. myrtillus berries contain a large amount of anthocyanines and quercetins (and also pectins and fibers; conversely, present a low amount of glucides) (Häkkinen *et al.*, 1999; Erlund *et al.*, 2003; Sousa *et al.*, 2007). Nevertheless, the amount of phenolic compounds in berries largely depends upon the tissue analysed, the cultivar type and the edaphoclimatic conditions (Häkkinen and Törrönen, 2000; Witzell *et al.*, 2003). Usually, wild bilberry content of anthocyanins is substantially higher than the cultivated one (Kraus *et al.*, 2010).

Hence, owing its high content in antioxidant compounds, namely flavonoids and phenolic acids, bilberry fruit is commonly used in folk medicine for micro-and-macrovascular system protection (Valentová *et al.*, 2007; Bao *et al.*, 2008). In fact, bilberry fruit extract is freely available in the market as a pharmaceutical preparation for the treatment of vascular diseases and diabetic retinopathy (Kalt and Dufour, 1997; Fraunfelder, 2004; Bao *et al.*, 2008). Furthermore, there is an increasing use of pure flavonoids to treat many important common diseases, due to their proven ability to inhibit specific enzymes, to simulate some hormones and neurotransmitters and to scavenge free radicals (Prior *et al.*, 1998; Martín-Aragón *et al.*, 1999; Havsteen, 2002).

Bilberry leaf decoctions and infusions are used by Portuguese people both in the treatment of diabetes mellitus (Castro, 1998) and hypercholesterolemia (Neves *et al.*, 2009). Indeed, all over the world, *V. myrtillus* leaf tea is used due to their antihyperglycemic properties (Cignarella *et al.*, 1996; Jaric *et al.*, 2007), sometimes in herbal mixtures (Petlevski *et al.*, 2001). Neomyrtillin, a glucoside compound found in *V. myrtillus* leaves, also known as "plant insulin" (Edgars, 1936; Bever, 1980), is associated to the attributed antidiabetic properties of bilberry leaf tea. Nevertheless, the decrease in blood glucose levels promoted by this neomyrtillin has no consensual opinions (Helmstädter and Schuster, 2010). Our results show that diabetic Goto-Kakizaki rats treated during 4 weeks with *V. myrtillus* leaf decoction lead to a slight decrease of occasional glycaemia and an improved intraperitoneal glucose tolerance test, mainly during the initial 60 minutes (Ferreira *et al.*, 2010b). Moreover, metal ions analysis showed that *V. myrtillus* extracts have an appreciable content of chromium (Cr) (Castro, 1998; Ferreira *et al.*, 2010c), an ion known to be altered in the diabetic state (Kim *et al.*, 2004; Zhao *et al.*, 2009). In effect, Cr has been described as a potential therapy of insulin resistance, a feature of type 2 diabetes (Kim *et al.*, 2004).

Furthermore, leaves also possess a large amount of flavonoid compounds, mainly procyanidins and the flavonols quercetin and kaempferol (Jaakola, 2003). This high antioxidant capacity, due to presence of flavonoids, is responsible for *V. myrtillus* health-promoting effects. In fact, it is well known that oxidative stress in diabetic patients leads to multiple cellular dysfunctions and chronic complications associated to the disease (Baynes and Thorpe, 1999; 2000; Ceriello, 2003). In consequence, an enhancement in dietary antioxidants possesses advantageous effects to diabetic patients (Prior *et al.,* 1998; Catoni *et al.,* 2008). Indeed, previous studies report cytoprotective effects of bilberry anthocyanins against oxidative damage in hepathocytes (Valentová *et al.,* 2007; Bao *et al.,* 2008). Further, protective effects of *V. myrtillus* anthocyanin rich extracts against mitochondrial dysfunction were described (Yao and Vieira, 2007; Ferreira *et al.,* 2010b), probably correlated to the great content of quercetins that can improve mitochondrial biogenesis (Davis *et al.,* 2009). Also, a decrease of potential neurotoxic activity with an improvement of neuronal and cognitive brain functions was also reported (Yao and Vieira, 2007; Zafra-Stone *et al.,* 2007). In fact, berries as a potential source of natural anthocyanins, have demonstrated a broad spectrum of biomedical functions, in cardiovascular disorders, advancing age-induced oxidative stress, inflammatory responses and diverse degenerative diseases (Zafra-Stone *et al.,* 2007). Berry anthocyanins also protect genomic DNA integrity and, in fact, the intake of these flavonoid compounds seems to be correlated with the growth suppressing-effect observed in several types of cancer cells (Madhavi *et al.,* 1998; Cooke *et al.,* 2005; Zafra-Stone *et al.,* 2007; Nandakumar *et al.,* 2008; Milbury, 2009; Kraus *et al.,* 2010). The chemopreventive effects of flavonoid compounds in tumoral cells are undoubtedly important for diabetic patients, since it is widely proved the relationship between cancer and diabetes (Psarakis, 2006; Giovannucci *et al.,* 2010).

Dyslipidaemia is usually correlated to diabetic condition. Previous studies showed that bilberry leaf and fruit flavonoid compounds exhibited either a dose-dependent lipid-lowering activity in genetically hyperlipidemic Yoshida rats (Cignarella *et al.,* 1996) and an antihypercholesterolemic activity in hamsters, thus preventing atherosclerosis (Zafra-Stone *et al.,* 2007; Rouanet *et al.,* 2010). Additional, there are some reports showing that anthocyanines prevent angiogenesis and are also responsible for collagen stabilization (Roy *et al.,* 2002; Matsunaga *et al.,* 2009). Moreover, some studies reveal that bilberry fruit extracts present antibacterial properties (Rauha *et al.,* 2000; Puupponen-Pimiä *et al.,* 2008).

For all the stated reasons, *V. myrtillus* is usually considered as a nutraceutical (Espín *et al.,* 2007; Garzón *et al.,* 2010) or a functional food (Katsube *et al.,* 2002). Additionally to lowering blood glucose levels ability of bilberry leaf teas, the valuable effects of anthocyanins against cellular damage induced by hyperglycaemic condition associated with high antimicrobial activity, makes this plant a worthy food supplement to consider for diabetic patients.

5. Family Fabacea

(*a*) *Cytisus multiflorus* (L' Hér.) Sweet

Cytisus multiflorus (L' Hér.) Sweet (white Spanish Broom) is a species of the genus *Cytisus*, locally known as "giesta branca" (or "gesta branca") and widely spread in Portugal, where it invades a wide range of fertile soils. This plant can fix nitrogen and form a dense scrub layer that outcompetes with native species and becoming an environmental problem. White Spanish broom is native to Portugal, Spain and France and it has been introduced as an ornamental plant in India, Australia, Italy, United States, New Zealand and Argentina (Weed Management Guide, 2003).

This is a shrub growing up to 3 or 4 meters in sprawling height with leaves appearing mainly on lower branches, each of them made up of three leaflets. Some leaves grow on the upper branches, generally made up of a single leaflet. Each leaflet is under a centimetre-long and may have a shape varying from linear to oblong. The white, pea-like flower is up to a centimetre long. The fruit is a hairy legume pod up to 3 centimetres long. The pods turn black when mature and release explosively their four to six seeds away from the parent plant (Guide, 2003).

In Portugal, *C. multiflorus* flowers are usually used in popular medicine (sometimes in herbal mixtures) for the treatment of type 2 diabetes, headaches or for controlling hypertension and hypercholesterolemia (Castro, 1998; Camejo-Rodrigues, 2001; Camejo-Rodrigues *et al.*, 2003; Carvalho, 2005).

Some recent studies suggest the validity of ethnical use of *C. multiflorus* in hyperglycaemia control. The effect of aqueous extracts of *C. multiflorus* was studied in the third inbreeding generation of (Wistar) rodents, showing abnormal glucose tolerance and following oral glucose tolerance test, female glucose intolerant rats were selected. A significant dose-dependent decrease of the postprandial blood glucose levels was observed, in response to treatment with the plant extract, possibly due to an increase of insulin release, while fasting glycaemia was not significantly altered in treated rats (Areias *et al.*, 2008; Vieira *et al.*, 2010). Furthermore, the maximum effect of the plant extract was similar to the glycazide treated group of the experimental assay (Areias *et al.*, 2008; Antunes *et al.*, 2009).

The enhanced insulin secretion can be due to the presence of spartein, an alkaloid present in *Cytisus* genus, that blocks K_{ATP} channels and decreases β-cell K^+ permeability (García López *et al.*, 2004). Nevertheless, some intoxication cases are related to the ingestion of *Cytisus* genus plants prepared infusions (Nunes, 1999), due to the presence of spartein.

Despite the chemical characterization available for *C. multiflorus* is far from being complete, water extract from this plant contain a great amount of alkaloids, hydrolysed tannins and triterpenes (or steroids) and flavonoids (Antunes *et al.*, 2009).

This plant also possesses an elevated antioxidant activity, due to its high content in flavonoids and, therefore, plays an important role in preventing or reducing the development of diabetic complications (Gião *et al.*, 2007).

(*b*) *Lupinus albus* L.

White lupin (*Lupinus albus* L.) is a species of the genus *Lupinus*, tribe *Luppineae*, family *Fabacea*. Four species of this genus (*L. albus, L. angustifolius, L. luteus* and *L. mutabilis*) are cultivated in the world with three main uses: human consumption, green manure and as forage (Huyghe, 1997). *L. albus* is an annual, endemic, traditional and widespread legume in Portugal, commonly used as a snack. The white lupin is an annual, more or less pubescent plant, with 30 - 120 cm high, and exists in many distinct forms, as a result of adaptation to different edaphoclimatic (soil and climate) conditions, throughout the country (Carmali *et al.*, 2010; Vaz *et al.*, 2004). The plant has a single tap root system with threadlike portions reaching down to 70 cm and owns its name to the flower colour (white). Each plant can produce primary, secondary, and tertiary pods with each pod containing 3 to 7 seeds. Seeds with high protein content (around 30-35 per cent) and rich in dietary fibers, present a bitter taste due to the presence of quinolizdone alkaloids, and therefore, for consumption these alkaloids must be previously separated (Carmali *et al.,* 2010). It has been previously described that the architecture and behaviour of the plants changes from the north (where tall and late flowering types are common) to the south of Portugal (with short and early flowering types predominant), reflecting diversity in plants phylogenetic origin (Martins, 1994; Vaz *et al.,* 2004). Moreover, the alkaloid composition also varies due to genetic and environmental differences (Carmali *et al.,* 2010).

In Portugal (as well as in other Mediterranean countries) *L. albus*, locally known as "tremoço", is used in folk medicine due to its hypoglycemiant action (Pereira *et al.,* 2001; Eddouks *et al.,* 2002; Sheweita *et al.,* 2002). Traditionally, *L. albus* wastewaters, containing high amounts of alkaloids, mainly lupanine, are used intending to control blood glycaemia (Camejo-Rodrigues, 2001). In fact, scientific studies showed that lupanine (as well as 13-α-lupanine and 17-oxo-lupanine) stimulate insulin secretion in a glucose-dependent manner (only at high glucose concentrations, ? 7 mM) (Pereira *et al.,* 2001; García López *et al.,* 2004). Spartein, another lupine alkaloid, showed similar effect, blocking K_{ATP} channels, decreasing β-cell K^+ permeability (García López *et al.,* 2004). Moreover, alkaloids, due to their phenolic nature, also have antioxidant activity, worthy in diabetes mellitus therapy (Tsaliki *et al.,* 1999).

Likewise, in certain Portuguese regions, *L. albus* debittered seeds are also used to counteract type 2 diabetes (Pereira *et al.,* 2001). In fact, white lupine seeds contain a large amount of conglutin-γ (around 2 per cent of dry weight), a glycoprotein composed of two disulfide bridges subunits (Mr ~ 47 kDa) (Magni *et al.,* 2004). Conglutin-γ displays unique features, as an unusual primary structure, with high resistance to *in vitro* proteolysis, and the ability of binding divalent ions, such as Zn^{2+} and Ni^{2+} (Magni *et al.,* 2004), and articles therein). This globular glycoprotein also mimetizes insulin action in myoblasts, playing an important role in vesicular transport of glucose carrier (GLUT 4), influencing cell differentiation and controlling muscle growth (Terruzzi *et al.,* 2010).

L. albus seeds also have antioxidant activity, being important in counteracting oxidative stress induced by hyperglycaemia (Tsaliki *et al.,* 1999). *L. albus* is also used in traditional medicine in some diseases associated with diabetes mellitus, such as dyslipidemia, hypercholesterolemia and hypertension (Camejo-Rodrigues, 2001; Sirtori *et al.,* 2009). It has been proven that white lupin alkaloids, 13-α-lupanine and 17-oxo-lupanine, reduce blood pressure (Yovo *et al.,* 1984). Moreover, white lupin seeds significantly decrease blood pressure in diabetic and hypertensive rats (Pilvi *et al.,* 2006). This is a possible consequence of their high content in arginine, leading to an increase in NO production (Duke, 1992; Sirtori *et al.,* 2009). Several scientific reports indicate a substantial reduction of hypercholesterolemia induced by lupin seed proteins and moderate changes in triglycerides (Sirtori *et al.,* 2004), that appears to depend on a down regulation of liver SREBP-1c (sterol regulatory element-binding protein), a transcription factor that regulates the expression on lipogenic enzymes (Spielmann *et al.*, 2007).

Concerning to toxicological studies, main alkaloid compounds (lupanine and ehydroxilupanine (Duke, 1992)) do not pose a health problem for man, since LD_{50} values for oral administration are elevated (around 1500 mg/Kg), being rapidly cleared from the body (Petterson *et al.*, 1987). Spartein, another alkaloid found in *Lupinus* genus, with low LD_{50}, is classified as antiarrhythmic agent and sodium channel blocker (Yovo *et al.*, 1984; Pothier *et al.*, 1988). Some anticholinergic effects of lupine alkaloids have also been observed in rodents (Pothier *et al.*, 1988) and there are two case reports in humans associated with *L. albus* ingestion, due to sparteine intoxication (Tsiodras *et al.*, 1999; Litkey and Dailey, 2007). Moreover, during a 3 months lasting study with rodents, lupin alkaloids ingestion (500mg/kg/day) produced nonlethal hematological effects (Butler *et al.*, 1996).

(*c*) ***Pterospartum tridentatum*** **(L.) Willk. subsp.** ***tridentatum***

Pterospartum tridentatum (L.) Willk., known as "prickled broom" (and previously known as *Chamaespartum tridentatum*) is an autochthonous plant, found commonly in Portuguese territory. In fact, *P. tridentatum* is usual in the Norwest part of Iberian Peninsula and in Morocco. *P. tridentatum*, locally known as "carqueja" or "carqueija", grows in acidic soils, in brushwood's, thickets and is a shrub, with characteristic yellow flowers with a typical odour, that are traditionally harvested in Spring (from March to June). The yellow flowers are used in popular medicine (sometimes in herbal mixtures) for the treatment of throat irritation conditions, diabetes (Castro, 1998; Vitor *et al.*, 2004; Grosso *et al.*, 2007) or for controlling hypertension and hypercholesterolemia (Camejo-Rodrigues, 2001; Carvalho, 2005). In fact, the *P. tridentatum* flowers tea is used as a panacea, being a potential cure for all illnesses of the body (Camejo-Rodrigues, 2001; Carvalho, 2005). The leaves (steams) are normally used in culinary applications, to flavour rice, roast meat or hunting animals (Carvalho, 2005).

Complete chemical characterization of the plant is not yet available in literature, since only in the last decade this plant became a subject of scientific research. However, a recent study in *P. tridentatum* essential oils showed that chemical composition of the analyzed oils are less a consequence of climatic factors in different years than due to differences in genetic heritage and/or other environmental factors (Grosso *et al.*, 2007).

Despite the information collected in several ethnobotanical studies, confirming the use of *P. tridentatum* extracts in diabetes therapy (Camejo-Rodrigues, 2001; Carvalho, 2005), at the present time, there is only one scientific report concerning the effects of *P. tridentatum* water extracts on the blood glucose levels (Paulo *et al.*, 2008). In this work, normal Wistar rats' glycaemia was investigated in a situation of oral glucose challenge. Water extract (300 mg/kg) showed an antihyperglycaemic effect in the initial 30 min after glucose challenge, but then the blood glucose levels rose above those of the control group, indicating the presence of compounds with different effects on glucose tolerance. Probably, these opposite effects were due to the presence of two different compounds: the isoflavone sissotrin and the flavonol derivative isoquercitrin. Isoquercitrin (100 mg/kg) showed time-dependent anti-hyperglycaemic activity by delaying the post-oral glucose load glycaemia peak at 30 min, similarly to phloridzin (100 mg/kg), a sodium-dependent glucose transporters inhibitor (Paulo *et al.*, 2008). In contrast, sissotrin (100 mg/kg) showed an opposite effect, impairing glucose tolerance (Paulo *et al.*, 2008).

Water extracts prepared from *P. tridentatum* aerial parts possess a strong antioxidant activity, with a high content of phenolic compounds and flavonoids (Luís *et al.,* 2009). Ethanolic extracts prepared from the same plant samples own lower antioxidant activity, despite having higher flavonoid content; even so, its antioxidant activity is similar to the standard antioxidant BHT (2,6-bis(1,1-dimethylethyl)-4-methylphenol or butylated hydroxytoluene) (Luís *et al.,* 2009). Indeed, Vitor and collaborators (Vitor *et al.*, 2004) suggested that flavonoids present in *P. tridentatum* water extracts exhibit endothelial protection against oxidative injury and, thus, may prevent or reduce the development of diabetic vascular complications.

6. Gentianaceae Family

(*a*) *Centaurium erythraea* RAFN

Centaurium erythraea RAFN, previously known as *Erythraea centaurium*, *Centaurium minus* and *Centaurium umbellatum*, belongs to the *Gentianaceae* family and is usually known as "common centaury" or "European centaury". In Portugal, it is known as "centáurea-menor" (or commonly "fel-da-terra", due to its bitter taste) (Cunha *et al.*, 2009). This is an erect annual or biennial herb, reaching half a meter in height.

C. erythraea inflorescences contain many small pinkish-lavender flowers, of about a centimeter across, flat-faced with yellow anthers and usually flowers from June to September. The fruit is a cylindrical capsule. *C. erythraea* is a widespread plant of Europe, western Asia and northern Africa. It has also been introduced in parts of North America and throughout eastern Australia.

Infusions (and decoctions) of aerial parts of common centaury are traditionally used in folk medicine either in mild dyspeptic and/or gastrointestinal disorders and in temporary loss of appetite (Bnouham *et al.*, 2002; El-Hilaly *et al.*, 2003; Jaric *et al.*, 2007; CMHP 2009; Cunha *et al.*, 2009). This usage was approved by the "Committee on herbal medicinal products" of European Medicines Agency (Ref.: EMEA/HMPC/105535/2008) (CMHP 2009; Cunha *et al.*, 2009). In Portugal, *C. erythraea* is also used, as antipyretic, in hypercholesterolemia, hepatobiliary problems and diabetes mellitus therapy and as vermifuge (Camejo-Rodrigues *et al.*, 2003; Carvalho, 2005; Cunha *et al.*, 2009; Neves *et al.*, 2009). Besides, in some provinces of Morocco, *C. erythraea* is used for kidney disorders treatment (El-Hilaly *et al.*, 2003) and as diuretic (Haloui *et al.*, 2000). Reduction of blood pressure and a decrease in smooth muscle spasms of the gastrointestinal tract and sedative action over the central nervous system have also been reported (Loizzo *et al.*, 2008; Cunha *et al.*, 2009). *C. erythraea* utilization is discouraged both in young people and in the presence of peptic ulcers (CMHP 2009; Cunha *et al.*, 2009). Due to its bitter constituents, common centaury should also be avoided by lactating women (Cunha *et al.*, 2009).

C. erythraea is widely used in folk medicine due to its antihyperglycemiant properties (Bnouham *et al.,* 2002; Cunha *et al.,* 2009; Hamza *et al.,* 2010), sometimes in herbal mixtures (Petlevski *et al.,* 2001).

Common centaury presents a high xanthone 6-hydroxylase activity, leading to 1,3,5-trihydroxyxanthone intramolecular cyclization (Schmidt *et al.,* 2000). The aerial parts of this plant possess a large content and variety of methoxylated xanthone derivatives (Schimmer and Mauthner, 1996; Valentão *et al.,* 2000; Valentão *et al.,* 2002; Valentão *et al.,* 2003). These xanthones, which contain a distinctive polyphenolic structure, show many pharmacological effects (Singh, 2008; Shekarchi *et al.,* 2010), such as antioxidant (Valentão *et al.,* 2001), antitumor (Schimmer and Mauthner, 1996), anti-diabetes (Petlevski *et al.,* 2001; Hamza *et al.,* 2010), bactericidal (Kumarasamy *et al.,* 2003) and hepatoprotective properties (Jaishree and Badami, 2010). Monotherpenes, β-sitosterol and some flavonoids are also present (Loizzo *et al.,* 2008; Cunha *et al.,* 2009). The gentianaceae plants also present secoiridoid glycosides, responsible for the characteristic bitter taste (Singh, 2008; Cunha *et al.,* 2009).

Recently interest among medicinal potential gentianaceae plants has been revived and phytochemicals, like swerchirin and swertiamarin have been rediscovered (Singh, 2008). Swerchirin (1,8-dihydroxy-3,5-dimethoxyxanthone) decreased high blood glucose, by stimulating insulin release in streptozotocin-induced type 2 diabetes rats (35 mg/kg i.v.) (Saxena *et al.,* 1991; 1993). Furthermore, *C. erythraea* hydroethanolic extract exhibited an antihyperglycemiant effect, decreased insulin resistance and triglycerides. These studies were conducted with C57BL mice with standardized high fat diet induced type 2 diabetes and no weight or caloric differences were noticed, when compared to controls (Hamza *et al.,* 2010). Swertiamarin is another important constituent, to which several medicinal properties are also attributed. Swertiamarin is a bitter secoiridoid glycoside, with high antimicrobial activity (Kumarasamy *et al.,* 2003) and both with high antioxidant and hepatoprotective potential (Jaishree and Badami, 2010). Swertiamarin metabolites also present anti-inflammatory properties (Jun *et al.,* 2008).

In summary, *C. erythraea* extracts stimulate pancreatic β-cells insulin release and decrease insulin resistance. Moreover, common centaury extracts possess a large content and variety of xanthones with uncommon polyphenolic structures, presenting a significant antioxidant and anti-inflammatory activities and therefore may prevent (or diminish) the development of diabetic chronic complications.

7. Geraniaceae Family

(*a*) *Geranium robertianum* L.

The genus *Geranium* encompasses more than 400 different species of flowering plants.

G. robertianum, a Geraniaceae commonly known as Herb Robert or Red Robin, is a common species found in Europe, Asia, North Africa, and introduced in North America (Cunha *et al.,* 2009). In Portugal, it is commonly known as "erva de S. Roberto" or "erva roberta". It can grow in shadowy and wet lands, as an annual or biennial plant, and are common at altitudes of up to 1,500 meters. *G. robertianum* produces small, pink, five-petalled flowers, from April until the autumn. The leaves are fern-like, sometimes resembling parsley, turn red at the end of the flowering season, the stems often reddish and possess little roots structure.

In Portugal, there is some confusion concerning to "erva de S. Roberto". Indeed, several etnobotanical studies show that different species from the genus *Geranium*, as *G. dissectum* L. (Carvalho, 2005), *G. lucidum* L. (Carvalho, 2005), *G. purpureum* Vill. (Camejo-Rodrigues *et al.*, 2003; Novais *et al.*, 2004) and *G. molle* L. (Neves *et al.*, 2009) also share the same popular name.

Infusions (and decoctions) of aerial parts of Herb Robert are traditionally used in herbal medicine with several applications: stop bleeding (as nose bleeding) and, thus, are used topically in wounds, accelerating the healing process (Cunha *et al.*, 2009). Further, it is employed in folk medicine either due to its anti-inflammatory properties and anti-cancer potential activity (Amaral *et al.*, 2009). In Lebanon, *G. robertianum* is also used due to their anti-rheumatic properties (Marc *et al.*, 2008).

An infusion made from the aerial parts is usually used for its diuretic and tonic effects and as a remedy for dysentery and digestive problems (Carvalho, 2005; Cunha *et al.*, 2009). *G. robertianum* is also used in Portugal due to its anti-diabetic (Castro, 1998; Braga and Pontes, 2005; Cunha *et al.*, 2009) and antihypertensive properties (Braga and Pontes, 2005).

Despite the common use of *G. robertianum* as antihyperglycemiant, as well as some other *Geranium* species (Rodriguez *et al.*, 1994), specialized literature regarding the specific effects of this plant is not easy to achieve. In a previous study, we observed a significant decrease in occasional glycaemia of diabetic Goto-Kakizaki rats, treated during 4 weeks with a *G. robertianum* decoction (Nunes *et al.*, 2006; Ferreira *et al.*, 2010d). Furthermore, a decrease in the blood glucose values was observed in the intraperitoneal glucose tolerance test (Nunes *et al.*, 2006). However, this was a preliminary investigation and several studies are still required in order to clarify the mechanisms of action of *G. robertianum* water extract.

Regarding its chemical composition, *G. robertianum* possesses a high content of polyphenols and flavones (Amaral *et al.*, 2009; Neagu *et al.*, 2010). Among these bioactive components were 3,4-dimethoxyflavone, homoeriodictyol and kaempferol. Kaempferol is known to be an excellent antioxidant, since it exhibits the 3-OH and 5-OH groups with the 4-oxo group in the C-ring and the C2–C3 double bond, despite having just one OH group in the B-ring (Amaral *et al.*, 2009). In vitro studies suggest that this compound, in association with quercetin, can improve glucose uptake in 3T3-L1 cells. Thus, kaempferol potentially acts at multiple targets to ameliorate hyperglycemia, including by acting as partial agonist of PPAR-γ (Fang *et al.*, 2008).

Moreover, kaempferol also show an important activity as anti-inflammatory agent (Mahat *et al.*, 2010) and, together with quercetin, possesses an important inhibitory effect in the osteoclast bone reabsorption (Wattel *et al.*, 2003). Furthermore, several studies point the kaempferol proapoptotic effect in tumoural cells (Leung *et al.*, 2007; Yoshida *et al.*, 2008; Kang *et al.*, 2009). Hence, the high content of this polyphenolic compound seems to be correlated to several medicinal properties attributed to this plant.

Syringic acid, acetovanillion, ferulic methyl ester and ferulic ethyl ester were also identified. The ferulic acid derivatives also possess a high antioxidant activity and can explain the anti-cancer potential and the anti-inflammatory properties of the plant (Amaral *et al.,* 2009), ferulic acid also decrease diabetic complications. Accordingly to the exposed, *G. robertianum* seem to be a very promising medicinal plant; nevertheless, further studies are required, in order to determine both the bioactive compounds responsible for its health effects and the underlying biological mechanisms of action.

8. Lamiaceae Family

(*a*) *Rosmarinus officinalis* L.

Rosemary or *Rosmarinus officinalis* L. is a woody, perennial herb with fragrant evergreen needle-like leaves (green above and white below) with dense short woolly hair, native to the Mediterranean region. Flowers are terminal and usually blue-coloured, and bloom in summer in the north; nevertheless, *R. officinalis* can be everblooming in warm-winter climates, as in Portugal, where it is commonly known as "alecrim". This lamiaceae possesses a very strong and pleasant odor, being widely used in culinary and perfumery applications. Frequently, in Portugal, bee hives are placed close to rosemary lands and honey show an exquisite and appreciated flavor (Carvalho, 2005).

R. officinalis is used since ancient times in herbal medicine in Portugal and other Mediterranean countries. Indeed, it is often one of the medicinal plants with wide use and different therapeutic applications include treatment of respiratory problems, headaches, hypercholesterolemia, hypertension (Camejo-Rodrigues, 2001; Carvalho, 2005; Neves *et al.,* 2009), rheumatism (Carvalho, 2005; Neves *et al.,* 2009), digestive problems, anxiety, as antipyretic (Camejo-Rodrigues, 2001; Neves *et al.,* 2009) and heal wounds and burns (Camejo-Rodrigues, 2001; Neves *et al.,* 2009; Abu-Al-Basal, 2010), and also showing a high antimicrobial activity (Rasooli *et al.,* 2008). Furthermore, is used due to its diuretic (Haloui *et al.,* 2000; Camejo-Rodrigues, 2001; Neves *et al.,* 2009) and anti-diabetic properties (Castro, 2001; Tahraoui *et al.,* 2007; BakIrel *et al.,* 2008) and also due to hepatoprotective properties (Amin and Hamza, 2005). Usually, aerial parts are therapeutically used dried or green, as a decoction (or infusion) or externally as an ointment (Camejo-Rodrigues, 2001; Carvalho, 2005) or ethanolic extract. Essential oils usage is also reported (BakIrel *et al.,* 2008), as well as other applications (Camejo-Rodrigues, 2001; Neves *et al.,* 2009) and sometimes is also used in herbal mixtures (Camejo-Rodrigues, 2001).

Chemically, rosemary plant extracts contain several phenolic compounds, as caffeic acid and its derivative, rosemarinic acid. Carnosic acid and carnosol are also important chemical constituents (Duke 1992; Moreno *et al.,* 2006; Pe?rez-Fons *et al.,* 2009). Essential oils present α-pinene, 1,8-cineole, camphor, verbenone and borneol, that constitute around 80 per cent of the total oil (Atti-Santos *et al.,* 2005; Santoyo *et al.,* 2005), despite the variations due to different environmental conditions and harvesting time.

Concerning type 2 diabetes therapy, *R. officinalis* water extracts (at doses of 100 or 200 mg/kg) can decrease hyperglicaemia in alloxan-treated rabbits (BakIrel *et al.,* 2008), in a dose-dependent way and similarly to glibenclamide. The observed lower glycaemia can be either produced by a diuretic higher activity (Haloui *et al.,* 2000) and a decrease in pancreatic amylase promoted by rosmarinic acid (McCue and Shetty, 2004), among other features. In fact, this anti-diabetic activity of rosemary water extracts also seem to be related to PPAR-γ activation, induced by carnosol and carnosic acid (Rau *et al.,* 2006).

A different study referred that essential oil administration decreased insulin production and increased hyperglycaemia in alloxan-treated rabbits during the intraperitoneal glucose tolerance test (Al-Hader *et al.,* 1994). Nevertheless, a recent study showed that alloxan-treated rats' occasional glycaemia presented a decrease after an ingestion of rosemary essential oil during 7 days (Benkhayal *et al.,* 2009). Moreover, after a period of 21 days, the ingestion of *R. officinalis* essential oil (0.1 ml/kg body weight) led to normal glycaemias, compared to control non-diabetic group (Benkhayal *et al.,* 2009). These results, apparently contradictory, probably reflect a *R. officinalis* specific effect in carbohydrate absorption or metabolization.

Several scientific studies point out the high antioxidant capacity of *R. officinalis* water and ethanolic extracts, and are usually referred as one of the most antioxidant aromatic plants (Inatani *et al.,* 1983; Celiktas *et al.,* 2007; Gachkar *et al.,* 2007; Erkan *et al.,* 2008). This high antioxidant capacity is of major importance to counteract oxidative impairments that attain all cells in diabetic patents.

(*b*) ***Salvia officinalis*** **L.**

Salvia officinalis L. (common sage or sage) is native to the Mediterranean region, though nowadays it is widely widespread throughout the world. *S. officinalis* is a small perennial evergreen small shrub that plant flowers in late spring or summer. The leaves are oblong, ranging in size up to 6 long by 2.5 cm wide. Leaves are grey-green, rough on the upper side, and nearly white underneath due to the many short soft hairs or trichoma.

Sage has a long history of medicinal and culinary use, and in modern times also as an ornamental garden plant. In Portugal is typically known as "sálvia" or "salva", and commonly leaves (fresh or dried) are used in folk medicine (sometimes also in herbal mixtures) for the treatment of throat irritation (amygdalitis, laryngitis) and respiratory problems (asthma and bronchitis), as an oral antiseptic (against aphthas and ulcers), for blood pressure increase, for digestive problems treatments (as gases, diarrhea, indigestion or stomach aches), against animal bites, as sweat inhibitor, for inhibiting lactation and for diabetes mellitus therapy (Castro, 1998; Carvalho, 2005; Lima *et al.,* 2006; Neves *et al.,* 2009).

This plant is chemically well characterized, even considering some chemotypes or seasonal variations (Duke, 1992; Chalchat *et al.,* 1998; Kintzios, 2000; Lu and Yeap Foo, 2000; Lu and Yeap Foo, 2002; Dob *et al.,* 2007; Glisic *et al.,* 2010). The major leaf active constituents are tannic acid, oleic acid, ursonic acid, ursolic acid, caffeic acid, thujones, niacin, nicotinamide, flavones and flavonoid glycosides. Probably, due to the toxicity of thujones (Scientific Committee on Food, 2003), this plant is stated as "abortive", and according folk medicine, should be avoided by pregnant woman (Carvalho, 2005).

S. officinalis leaf water extracts (and essential oils) have a great antioxidant activity, due to the presence of large amounts of flavonoids and phenolic compounds (Lu and Yeap Foo, 2001; Miura *et al.,* 2002; Glisic *et al.,* 2010). In fact, ingestion of sage infusions improves glutathione-S-transferase and/or glutathione reductase status in (Wistar) rats and in (Balb/c) mice (Lima *et al.,* 2005) and thus protect from liver damage (Amin and Hamza, 2005; Lima *et al.,* 2005).

Regarding diabetes therapy, there are several reports confirming *S. officinalis* beverages hypoglycemiant effects on alloxan- or streptozotocin-induced diabetic animal models (Alarcon-Aguilar *et al.,* 2002; Eidi *et al.,* 2005; Lima *et al.,* 2006). Alarcon-Aguilar and collaborators (Alarcon-Aguilar *et al.,* 2002) found that ethanolic extracts of *S. officinalis* significantly reduced blood glucose levels in fasting normal mice 120 and 240 min (15.7 per cent and 30.2 per cent, respectively) following intraperitoneal administration. It also, significantly diminished hyperglycaemia in mildly alloxan-induced diabetic mice 240 min after glucose load (32.6 per cent and 22.7 per cent, respectively). These results seemed to indicate an enhanced insulin release in the presence of sage extract and have good correlation with some other recent studies.

Eidi and collaborators studied the effects of methanolic sage extracts and essential oils on streptozotocin-induced diabetic rats. They found that, in the presence of methanolic extracts, blood glucose concentration only decreased in streptozotocin-induced diabetic fasted rats, but not in healthy fasted rats (Eidi *et al.,* 2005). However, the extract did not affect insulin release from the pancreas of both animal groups. In this work, intraperitoneal administration of sage essential oil did not change serum glucose (Eidi *et al.,* 2005). Conversely, Lima and co-workers, using the same animal model - streptozotocin-induced diabetic rats, demonstrated that sage water extracts and essential oil affected liver glucose uptake and gluconeogenesis (Lima *et al.,* 2006). In this work, primary cultures of hepatocytes from healthy, sage-tea-drinking rats showed, after stimulation, a high glucose liver uptake capacity and decreased gluconeogenesis in response to glucagon. Moreover, sage essential oil both increased hepatocyte sensitivity to insulin and inhibited gluconeogenesis. The authors suggest that these sage effects are similar to metformin, a known inhibitor of gluconeogenesis used in the treatment and prevention of type 2 diabetes mellitus. Nevertheless, in primary cultures of rat hepatocytes isolated from streptozotocin (STZ)-induced diabetic rats, none of these activities was observed. This was probably because STZ-induced diabetic rats used in both research works were not a type 2 diabetes animal model but a type 1 diabetes model (Sitasawad *et al.,* 2001). Indeed, the stimulation of insulin release requires some functional pancreatic beta-cells that are commonly completely destroyed with a dose of 50 mg STZ/kg (or higher) used in both studies. We performed some preliminary experiments in young Goto-Kakizaki (GK) rats, a good animal model for the initial stages of type 2 diabetes mellitus (Goto and Kakizaki, 1981; Portha *et al.,* 2009). We observed that GK rats drinking *S. officinalis* water extracts during 4 weeks showed an improved response in glucose tolerance tests (Nunes *et al.,* 2006). Conversely, comparing sage effects between GK and STZ rats, we did not observe any hypoglycemiant effect in STZ rats (Nunes *et al.,* 2004).

However, there is no major information about the molecular mechanisms of action of sage extract over insulin release. Concerning this point, our results showed that sage decoction used in this study contained a large amount of some insulinotropic agents, namely amino acids (Nunes *et al.*, 2006). Indeed, our sage extract contained mainly alanine and arginine (Milner, 1969; Robert *et al.*, 1982; Sener and Malaisse, 2002; Nunes *et al.*, 2006). Smaller amounts of other insulinotropic amino acids - lysine and leucine – were also found (Milner, 1969; Robert *et al.*, 1982; Welsh *et al.*, 1982; Nunes *et al.*, 2006).

Moreover, the anti-diabetic activity of sage water extracts also seem to be related to PPAR-γ activation, induced by carnosol and carnosic acid (Rau *et al.*, 2006).

Consequently, fasting glucose levels decrease in normal animals and its metformin-like effects on rat hepatocytes suggest that *S. officinalis* may be useful as a food supplement in the prevention of type 2 diabetes mellitus by lowering the plasma glucose of individuals at risk (Lima *et al.*, 2006). This research team has also performed a pilot trial (non-randomized crossover trial) with six healthy female volunteers (aged 40-50) demonstrating the beneficial properties of sage tea consumption on lipid profile and transaminase activity in humans (Sá *et al.*, 2009). Although not demonstrating positive effects on glucose regulation in human healthy individuals, this study corroborate both the beneficial use of S. officinalis extracts in diabetic patients (since lipid profile is usually altered in type 2 diabetic patients). However, further studies seem to be necessary to elucidate the sage extracts molecular mechanisms of action in diabetes.

Some other useful properties of *S. officinalis* may be interesting for diabetic patients. In fact, many scientific works since ancient times describe the antimicrobial activities of common sage (Dobrynin *et al.*, 1976; Horiuchi *et al.*, 2007; Longaray Delamare *et al.*, 2007; Pinto *et al.*, 2007; Bouaziz *et al.*, 2009). Furthermore, anti-inflammatory activity is attributed to ursodecolic acid, present in sage extracts (Baricevic *et al.*, 2001).

In conclusion, *S. officinalis* extracts seem to inhibit gluconeogenesis and stimulate insulin release. Moreover, sage extracts possess a large content and variety of polyphenolic compounds with significant antioxidant activity against ROS and therefore may prevent or reduce the development of chronic complications associated with the disease.

Conclusion

This review clearly indicates that for almost all aromatic and medicinal plants used in Portugal for (type 2) diabetes mellitus therapy there are some scientific evidences pointing to anti-hyperglycemiant attributes and antioxidant power, which prevent or delays the onset of associated diseases to diabetes. Nonetheless, for most aromatic and medicinal plants cited, the mechanisms of action or the active chemical compounds remain unclear and further studies are still required.

Furthermore, we can't forget that usually, and unlike synthetic drugs, different chemical constituents that despite their lower amounts act in a synergistic manner potentiate the effectiveness of medicinal plants.

Therefore, the secondary effects are usually reduced, as compared to synthetic drugs. Even so, long lasting treatments to a single medicinal plant should be avoided, since conversely to the popular knowledge that "medicinal plants" are safe, long-lasting treatments with aromatic plants are prone to induce also several pathological conditions.

Moreover, different abiotic conditions lead to different chemotypes in the same species and thus a chemical characterization concerning both the active constituents and noxious components of commercialized aromatic and medicinal plants are of major importance but usually is absent. Besides, it should be noticed that phenolic compounds undergo chemical modifications *in vivo*, which may change some of their biological effects, including the antioxidant properties. Thus, further studies concerning these modifications are also of major importance.

In conclusion, medicinal plants commonly used in Portuguese folk medicine for diabetes treatment seem to have scientific support and, thus, seem feasible to be used together with synthetic oral anti-diabetic drugs, not only due to their anti-hyperglycemiant properties but also due to their ability to prevent several pathologies associated to diabetes and as a result, to improve diabetic patients daily life.

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