© 2015
Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas 14 (5): 423 - 441
ISSN 0717 7917
www.blacpma.usach.cl

Revisión | Review

Medicinal value of the *Berberis* genus as hypoglycemic agent

[Valor medicinal del género *Berberis* como agente hipoglicemiante]

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Abstract: Type 2 diabetes mellitus (T2DM) is a common chronic disease whose prevalence is currently increasing worldwide. Nowadays, the main antidiabetic agent used is metformin. However, between 10 and 30% of patients undergoing metformin therapy have nonspecific gastric alterations as an undesired secondary effect. Therefore, the search for new therapeutic alternatives is especially useful, where plant-derived products emerge as an excellent phytochemical resource. The objective of this review is to present and discuss the state of the art of current research conducted on the *Berberis* gender with hypoglycemic activity, which is normally used in alternative medicine therapy for the treatment of T2DM, and its possible mechanisms of action described in literature.

Keywords: type 2 diabetes mellitus, hypoglycemic, berberine, *Berberis*.

Resumen: La diabetes mellitus tipo 2 (DM2) es una enfermedad crónica común, cuya prevalencia está actualmente aumentando en todo el mundo. Al presente, el principal fármaco antidiabético utilizado es la metformina. Sin embargo, entre un 10 y 30% de los pacientes tratados presentan como efecto no deseado de alteraciones gástricas inespecíficas. Por lo tanto, la búsqueda de nuevas alternativas terapéuticas es de gran utilidad, en donde los productos derivados de plantas emergen como un excelente recurso fitoquímico. El objetivo de esta revisión es presentar y discutir sobre el estado del arte de investigaciones realizadas en las especies del género *Berberis* con actividad hipoglicemiante, las cuales son normalmente utilizadas en medicina alternativa como terapia para el tratamiento de DM, y sus posibles mecanismos de acción descritos en la literatura.

Palabras clave: diabetes mellitus tipo 2, hipoglicemiante, berberina, *Berberis*.

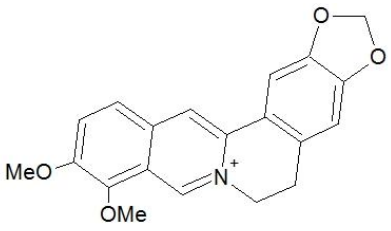
Recibido | Received: April 20, 2015
Aceptado | Accepted: May 25, 2015
Aceptado en versión corregida | Accepted in revised form: August 10, 2015
Publicado en línea | Published online: September 30, 2015
Declaración de intereses | Declaration of interests: María Cristina Furrianca was a National Doctorate fellow, Advanced Human Capital Formation Program, CONICYT-Chile (Nº 24121475).
Este artículo puede ser citado como / This article must be cited as: MC Furrianca, M Alvear, T Zambrano, L Barrientos, V Fajardo, LA Salazar. 2015. Medicinal value of the *Berberis* genus as hypoglycemic agent. **Bol Latinoam Caribe Plant Med Aromat** 14 (5): 423 – 441.

INTRODUCTION

Diabetes mellitus is a chronic disease that currently affects more than 6% of the world population, with a prevalence dramatically increasing worldwide (Shaw *et al.*, 2010). Type 2 Diabetes Mellitus (T2DM) is the most common clinical form of diabetes, accounting for approximately 90% of cases. Currently, it is considered a worldwide epidemic since its prevalence has tripled over the last 30 years (Chen *et al.*, 2011). Because of the complications and the increased mortality rate, T2DM is a considerably debilitating disease for patients, carrying also a high economic cost to society. In view of the prevalence and the rapid growth of this important health problem, T2DM-related investigation along with the pursuit of efficient and safe strategies for preventing and treating this disease are of great importance, both from an economic and an ethical point of view (Nolan *et al.*, 2011). Currently, metformin is widely used for the treatment of diabetes. However, 10-30% of treated patients have nonspecific gastrointestinal alterations (Olivera-González *et al.*, 2010). Therefore, the search for new compounds with anti-diabetic effect is highly required (Verspohl, 2002). Plants have always been a good source of drugs and many medications available today are derived directly or indirectly from them. Existing ethnobotanical information suggests that about 800 plants may possess anti-diabetic potential, evaluated by different experimental techniques (Patel *et al.*, 2012). Studies on *Berberis* species (Berberidaceae) have shown the importance of this genus and its potential application in the pharmacological field. The *Berberis* genus is composed globally of approximately 500 species, with nearly 300 species distributed in Eurasia and about 200 species in America (Ahrendt, 1961). This genus holds great value in traditional medicine, as it has been generally used as a herbal medicine for a long time (Potdar *et al.*, 2012), mainly by natives of Asian countries e.g. India, Pakistan and China. The objective of this review is to present and discuss the knowledge of the species of the *Berberis* genus with hypoglycemic activity, currently used as therapy for the treatment of diabetes and its possible mechanisms of action described in literature.

Berberis lycium Royle

B. lycium is an evergreen shrub that grows in the Himalayan region. Various parts of the plant (root, bark, stem, leaf and fruit) have been used by the natives of this area as a source of food, feed, fuel and medicine (Bano *et al.*, 2013). This plant is widely accepted as a medicine due to its therapeutic value in India´s Ayurvedic medicine (Sood *et al.*, 2013) (Shah *et al.*, 2012) and also as a medicinal plant in Pakistan (Ahmad *et al.*, 2009b; Ahmad *et al.*, 2011; Sharma & Devi, 2013) mainly used to prevent liver disorders, throat infections and asthma, among others (Ahmad *et al.*, 2011). Several studies support the function of *B. lycium* as a remedy for diabetes by traditional medicine in India and Pakistan (Arshad & Ahmad, 2005; Ur-Rehman, 2006; Rana *et al.*, 2010; Tiwari *et al.*, 2010; Joseph & Jini, 2011; Khan *et al.*, 2013; Gilani *et al.*, 2014). Folk´s medicine recipe for the treatment of this condition suggest that "the root powder (2.5 g) is given twice a day, early in the morning and evening after meals for three months" (Rana *et al.*, 2010) or that the "shredded bark is soaked into water and the resulting extract is drank in the morning" (Ahmed *et al.*, 2013). In recent years, pharmacological studies show that the extract of *B. lycium* reduces hyperglycemia, producing an insulin-like effect, which is suggested as a possible mechanism of the anti-diabetic activity of the extract (Shabbir *et al.*, 2012). Thus, its biological activity has been validated by using animal models, mainly normal and diabetic rabbits, showing that the use of the *B. lycium* extract reduces blood glucose concentration (Ahmad *et al.*, 2009a), as also in alloxan-induced diabetic rats (Gulfraz *et al.*, 2007; Mustafa *et al.*, 2011; Akram, 2013; Sharma & Sidhu, 2014). Using the same animal model, it was reported that both the fruit extract (Rahimi-Madiseh *et al.*, 2014), and the root extract (Mustafa *et al.*, 2011), improve the lipid profile and may be efficiently used as lipid-lowering therapy, especially in diabetic patients. In addition, existing reports indicate that the extract has anti-glycation and anti-oxidant properties, which would decelerate and reduce the aging rate and may have a potential role in the treatment of diabetes (Khan *et al.*, 2014). The major phytochemicals components of the *B. lycium* root are alkaloids, tannins and saponins (Rahaman *et al.*, 2013). Also, additional components have been isolated e.g. berberine (Figure 1a) berbamine (Figure 1b), karakoramine (Figure 1c), palmatine (Figure 1d), balauchistanamine (Figure 1e), gilgitine (Figure 1f), jhelumine (Figure 1g), punjabine (Figure 1h), sindamine (Figure 1i), maleic acid (Figure 1j) and ascorbic acid (Figure 1k) (Sood *et al.*, 2013).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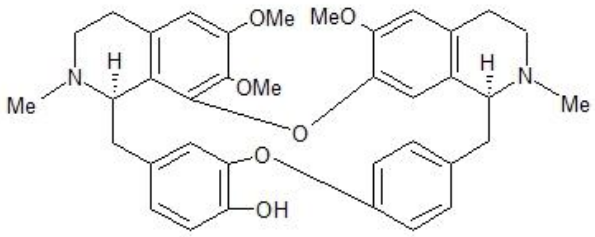
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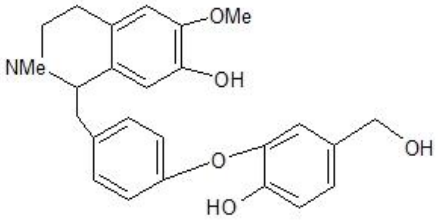
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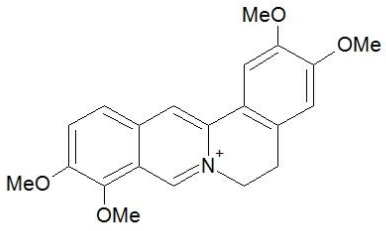
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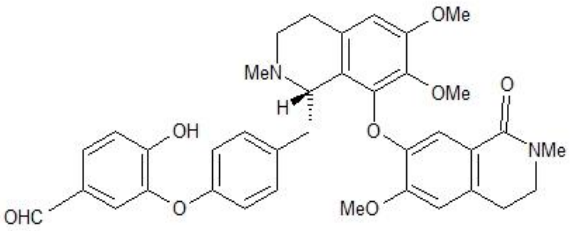
d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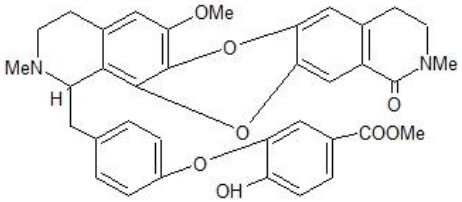
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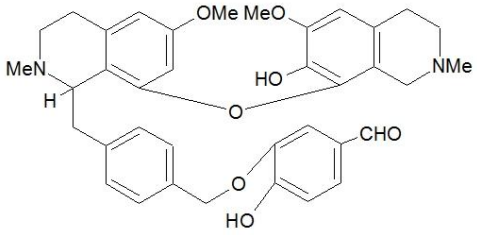
f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CHO
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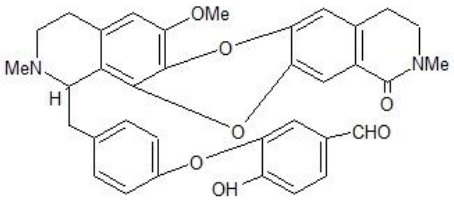
HO

g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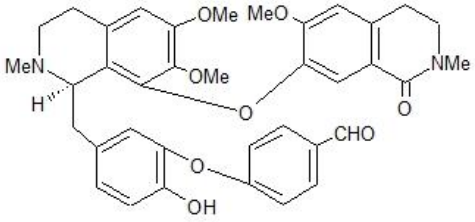
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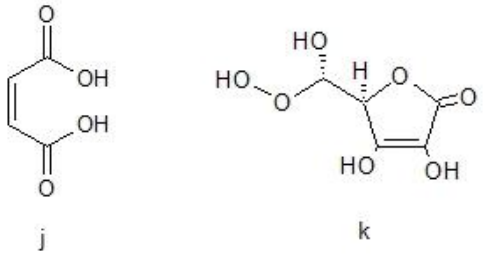


Figure 1
Chemical constituents isolated from *Berberis lycium*. a) Berberine, b) Berbamine, c) Karakoramine, d) Palmatine, e) Balauchistanamine, f) Gilgitine, g) Jhelumine, h) Punjabine, i) Sindamine, j) Maleic acid and k) Ascorbic acid.

Currently, berberine has shown to have antidiabetic properties (Lee *et al.*, 2006), principally in the root (Gulfraz *et al.*, 2006). However, *B. lycium* was comparable in efficacy to berberine, because the plant extract caused a significant reduction of blood glucose level and showed important and positive effects on glycated hemoglobin, glucose tolerance, lipid profile and body weight in alloxan-induced diabetic rats (Gulfraz *et al.*, 2008).

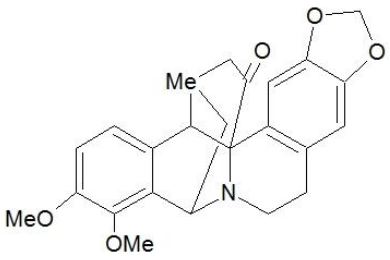
***Berberis aristata* DC.**

B. aristata is a native plant found in temperate regions of the northwest of the Himalayas, in the Nilgiri and Garhwal mountains and Parasnath hills, within an altitude of 1.800 to 2.400 m (Andola *et al.*, 2010). Several studies have reported this plant as a remedy for diabetes in traditional Indian medicine (Chauhan *et al.*, 2010; Malvi *et al.*, 2011; Pradhan, 2011; Kumar *et al.*, 2012; Saravanamuttu & Sudarsanam, 2012; Upadhyay *et al.*, 2012; Behera & Yadav, 2013; Gupta *et al.*, 2013; Peesa, 2013; Rathi *et al.*, 2013; Rawat *et al.*, 2013; Shafi & Tabassum, 2013; Gupta & Joshi, 2014; Tamilselvi *et al.*, 2014) and as part of ayurvedic polyherbal formulations (Yadav *et al.*, 2007; Sharma *et al.*, 2010; Kabilan *et al.*, 2013; Bordoloi & Dutta, 2014; Mittal *et al.*, 2014).

This plant has an old use as an antidiabetic agent by traditional healers of Sikkim (northeastern state of India) and the Himalayan Darjeeling region. In these tribal villages, bark extract is drank from the root of the plant (5-10 ml) twice a day for 1 or 2 weeks (Chhetri *et al.*, 2005). Moreover, scientific reports suggest that *B. aristata* is in fact an herbal remedy with a potent antidiabetic activity (Dixit & Mittal, 2013) significantly decreasing blood glucose in streptozotocin-induced diabetic rats, with results comparable to metformin (Rameshwar *et al.*, 2009; Pareek & Suthar, 2010). In the same animal model, besides producing an anti-diabetic effect, *B. aristata* extract also markedly decreased total cholesterol (TC) and increased high-density lipoproteins (HDL) when compared to diabetic controls (Ahamad *et al.*, 2012). Furthermore, in alloxan-induced diabetic rats, the extract of *B. aristata* has antidiabetic potential, reducing blood glucose levels by 60.4% and 75.46% using doses of 25 mg/kg and 50 mg/kg, respectively (Semwal *et al.*, 2008), as well as reducing TC and triglycerides in a dose-dependent manner using both bark (Gupta *et al.*, 2010; Ahmad *et al.*, 2012) and root extracts (Mittal *et al.*, 2012). Similarly, its hypoglycemic effect has been replicated in normal and diabetic rabbits, reducing blood glucose at 2, 4 and 8 hours following treatment with aqueous and methanolic extracts of *B. aristata* (Akhtar *et al.*, 2008). Effectiveness of *B. aristata* in regulating diabetes can be explained since this plant has the ability to inhibit the activity of dipeptidyl peptidase IV (DPP-IV), which is responsible for degrading the glucagon-like peptide 1 (GLP-1), which is the antidiabetic incretin (Chakrabarti *et al.*, 2011). It has also been reported that this extract improves glucose tolerance and homeostasis (Chan *et al.*, 2012), by activating antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase) being able to significantly reduce lipid peroxidation (41.6%) and protein carbonylation (30.15%). It also increases the activity of glucokinase and glucose-6-phosphate dehydrogenase besides reducing the activity of glucose 6-phosphatase, which

plays a critical role in glucose homeostasis in diabetic rats (Singh & Kakkar, 2009; Wang *et al.*, 2013).

The phytoconstituents present in the root of *B. aristata* are carbohydrates, alkaloids, tannins, phytosterols, flavonoids, volatile oils, oils and fats (Mittal *et al.*, 2012; Ranjan *et al.*, 2012). The compounds isolated from different parts of *B. aristata* correspond to alkaloids as palmatine (Figure 1d), karachine (2a) palmatine chloride (Figure 2b), tetrahydropalmatine (Figure 2c) pseudopalmatine chloride (Figure 2d), oxyberberine (Figure 2e), taxilamine (Figure 2f), pakistanine (Figure 2g), 1-O-Methyl pakistanine (Figure 2h), Oxycanthine (Figure 2i) berbamine (Figure 1b) and aromoline (Figure 2j). Flavonoids such as quercetin (Figure 2k), meratin (Figure 2l) and rutin (Figure 2m); and chlorogenic acid (Figure 2n) and (E)-caffeic acid (Figure 2o) (Potdar *et al.*, 2012). Among alkaloids with antidiabetic activity we can find berberine (Figure 1a), columbamine (Figure 2p) and jatrorrhizine (Figure 2q) (Osadebe *et al.*, 2014).



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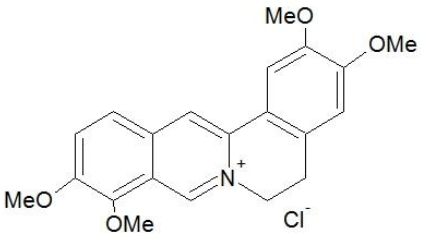

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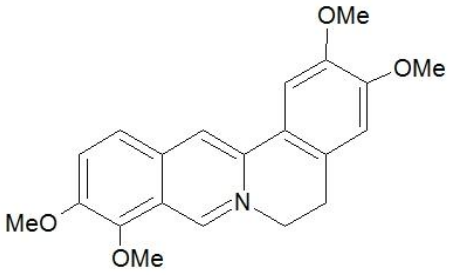

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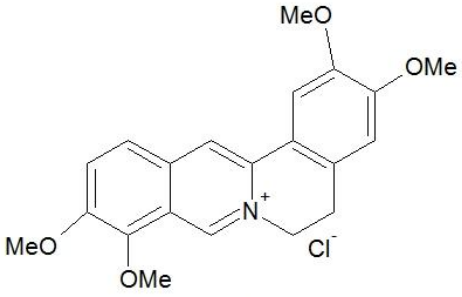

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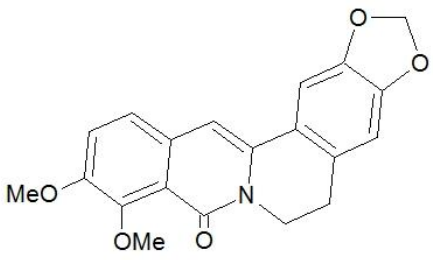

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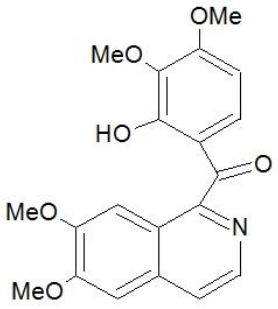

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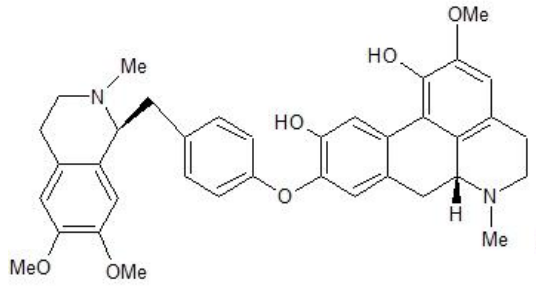
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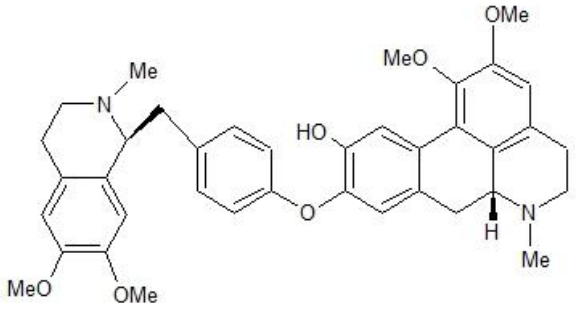
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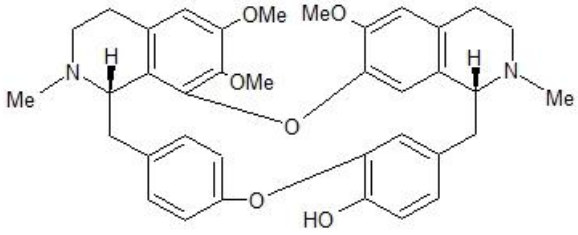
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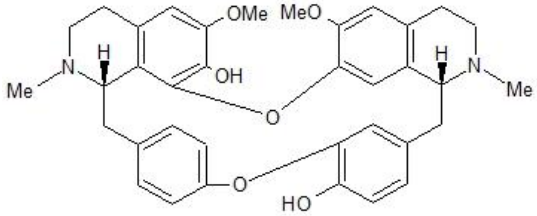
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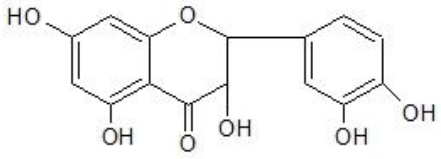
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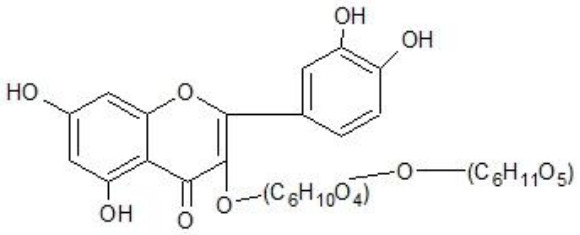
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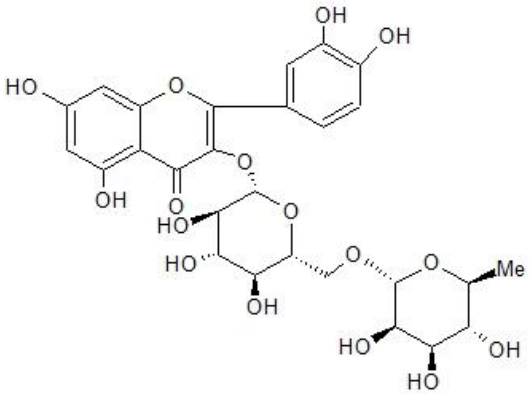
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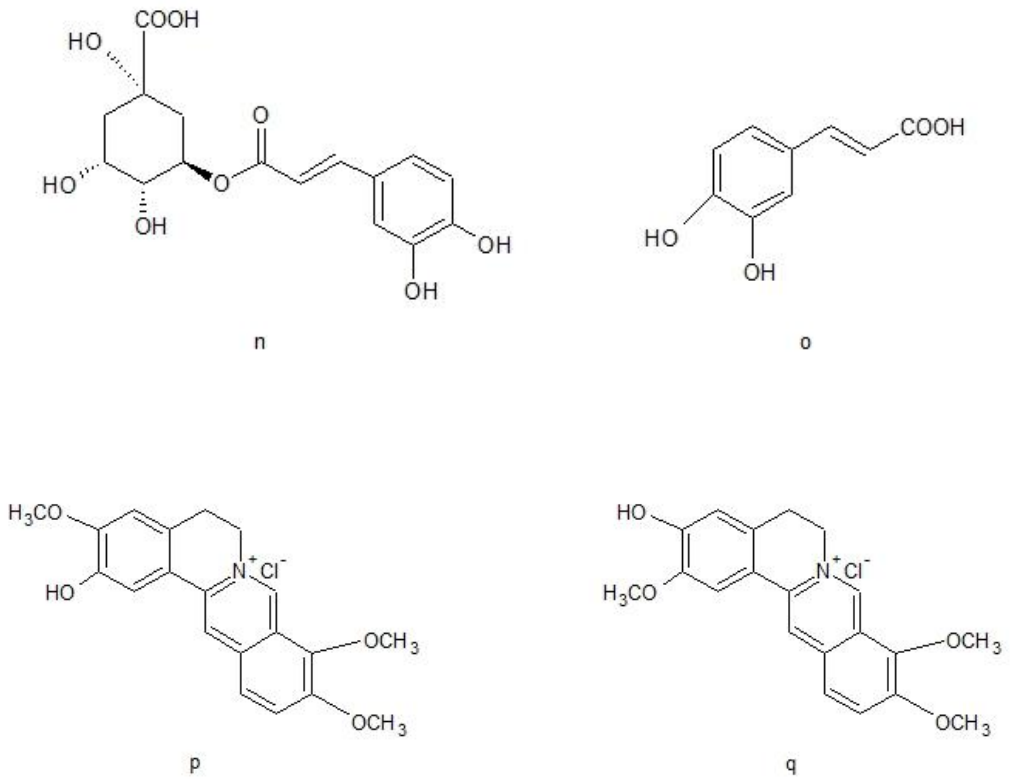


Figure 2
Chemical constituents isolated from *Berberis aristata.* a) Karachine, b) Palmatine chloride, c) Tetrahydropalmatine, d) Pseudopalmatine chloride, e) Oxyberberine, f) Taxilamine, g) Pakistanine, h) 1-o-methylpakistamine, i) Oxycanthine, j) Aromoline, k) Quercetin l) Meratin, m) Rutin, n) Chlorogenic acid, o) (E)-Caffeic acid, p) Columbamine and q) Jatrorrhizine.

***Berberis asiatica* Roxb. Ex. DC.**

B. asiatica is a thorny evergreen shrub reaching 1.8 to 2.4 m of height, and located at an altitude between 600-2550 m in the Himalayas (Patni *et al.*, 2012), used in traditional Indian medicine (Balami, 2004; Kala, 2005; Jain *et al.*, 2006; Joshi & Joshi, 2007; Kunwar *et al.*, 2008; Kunwar & Bussmann, 2009; Joshi *et al.*, 2010; Pala *et al.*, 2010; Joshi & Tyagi, 2011a; Joshi *et al.*, 2011b; Kumari *et al.*, 2011; Singh *et al.*, 2012; Thapa, 2012; Kunwar *et al.*, 2013; Radha *et al.*, 2013; Sigdel *et al.*, 2013) primarily for the treatment of muscle pain, toothache, stomach illness in animals, rheumatism and dental care (Shrestha & Dhillion, 2003) and also used as an antipyretic, anesthetic, antihypertensive and for the treatment of conjunctivitis (Uprety *et al.*, 2010). At present, it is used to combat some female pathologies such as menorrhagia and leucorrhea and as a special preparation for the treatment of poor lactation (Ghildiyal *et al.*, 2014). Moreover, in Bangladesh, Indian traditional medicine specialists are known for making up preparations from medicinal plants for the treatment of diabetes mellitus, including *B. asiatica* as a recognized alternative medicine product (Rahman *et al.*, 2009; Singh *et al.*, 2014). Research in rats indicate that the root extract of *B. asiatica* presents a very strong and even greater antidiabetic activity than obtained by glibenclamide (Singh & Jain, 2010b). Hypoglycemic activity in rats was also reported, however, at the studied concentration, no significant effect was observed when compared to *B. aristata*, suggesting that *B. asiatica* should be applied in higher doses (Upadhyay *et al.*, 2012). The phytochemical constituents that are part of the root and stem are tannins, flavonoids, alkaloids, steroids, saponins, phenols, carbohydrates, proteins and free

amino acids, while glycosides are absent in both structures (Patni *et al.*, 2012,).

From the root of *B. asiatica* have been isolated alkaloidal compounds such as berberine (Figure 1a), palmatine (Figure 1d), jatrorrihizine (Figure 2o), columbamine (Figure 2n), tetrahydropalmatine (Figure 2c), berbamine (Figure 1b), oxyberberine (Figure 2e) and oxycanthine (Figure2i) (Bhakuni *et al.*, 1968), being berberine the main compound to which has been attributed the pharmacological potential observed, and reporting that greater amounts are found in plants located at lower altitudes (Maithani *et al.*, 2014).

***Berberis vulgaris* Linn.**

B. vulgaris is a common shrub in Europe, Asia, Africa and some northeast regions of the United States. Its use in traditional medicine dates back more than 2.500 years in Ayurvedic and Chinese medicine as a treatment for fever and gastrointestinal disorders. In Iran, it is used as an antibacterial, antipyretic, antipruritic and antiarrhythmic agent (Brenyo & Aktas, 2014). In India, *B. vulgaris* is prescribed for patients suffering kidney and urinary problems and gallstones-related pain (Joshi & Joshi, 2013). In Turkey, the fruit is used to combat intestinal worms and for hepatoprotection (Tetik *et al.*, 2013) as well as to counteract diabetes mellitus (Altundag & Ozturk, 2011).

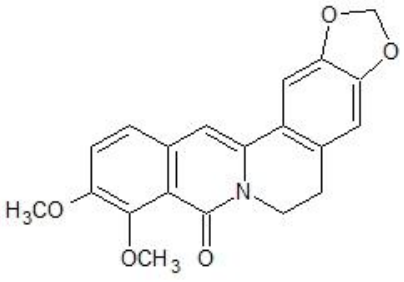
It has also been reported that the aqueous extract of the root and the crude saponin extract of this plant significantly reduce the concentration of blood glucose besides improving the lipid profile in streptozotocin-diabetic rats (Meliani *et al.*, 2011; Arumugam *et al.*, 2013). This hypoglycemic effect of the saponins from the *B. vulgaris* root may be due to the stimulating effect of the remaining beta cells (Saravanamuttu & Sudarsanam, 2012). Another possible mechanism that could explain the hypoglycemic effect could be because of the inhibition of the activity of the enzyme α-glucosidase, which would result in decreased carbohydrate absorption and the suppression of postprandial hyperglycemia, contributing to reduced hemoglobin A1c (HbA1c) (Abd El-Wahab *et al.*, 2013). It was also determined that the root extract of *B. vulgaris* was able to reduce alanine aminotransferase (Altundag & Ozturk., 2011) and alkaline phosphatase activities, reasons for which the extract would have important properties to improve hepatic function (Taheri *et al.*, 2012). However, despite all positive reports for diabetes treatment, at concentrations of 3.5% and 7.5% (v/v), the aqueous fruit extract of *B. vulgaris* do not possess hypoglycemic or hypolipidemic activity in streptozotocin-diabetic rats during a treatment period of 6 weeks (Hajzadeh *et al.*, 2011), which would pinpoint the necessity to continue further research in order to corroborate accurately the benefits of using this plant. The roots of *B. vulgaris* are formed by alkaloids, flavonoids, saponins, phenolic content, cardiac glycosides and terpenoids (El Sayed *et al.*, 2011; Meliani *et al.*, 2011; Abd El-Wahab *et al.*, 2013). In the root, chemical percentages are as follow: 2.6 to 4% alkaloids, 1.9 to 4.9% flavonoids and 0.3 to 0.35% saponins (El Sayed *et al.*, 2011; Abd El-Wahab *et al.*, 2013). Several alkaloids have been isolated from this plant, such as aromoline (Figure 2h), berbamine (Figure 1b), berberine (Figure 1a), berlambine (Figure 3a), columbamine (Figure 2n), hydroxycanthine (Figure 3b) isocorydine (Figure 3c), oxyberberine (Figure 2e), oxycanthine (Figure 2i), palmatine (Figure 1d), (-) - tejedine (Figure 3d) and jatrorrhizine (2o) (El Sayed *et al.*, 2011; Abd El-Wahab *et al.*, 2013; Mokhber-Dezfuli *et al.*, 2014), and only 2 compounds quercetin (Figure 2i) and rutin (Figure 2k)- are among the isolated flavonoids (El Sayed *et al.*, 2011; Abd El-Wahab *et al.*, 2013). The terpenoides, lupeol (Figure 3e) and oleanolic acid (Figure 3f) and the steroids stigmasterol (Figure 3g) and stigmasterol glucoside (3h) (Saied & Begum, 2004; Mokhber-Dezfuli *et al.*, 2014).

Regarding the active component concentration –berberine- it is mainly found in the bark (6%), followed by root (3.8%) and the lowest concentration is detected in leaves and fruits (1.29 and 1.18%, respectively) (Hadaruga *et al.*, 2010).

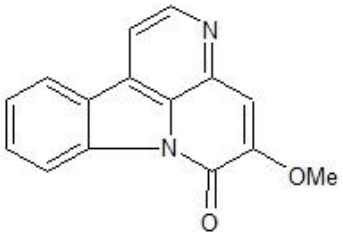
***Berberis integerrima* Bunge**

B. integerrima is an ethnobotanical species located in the Middle East (Rajaei & Mohamadi, 2012; Nasab & Khosravi, 2014). It is currently used as a medicinal plant in the region of Alamut (Ghazvin Province) northeast of Iran. Here, infusions or food preparations are meant to treat enteric fever, hyperlipidemia, diabetes and anemia (Ahvazi *et al.*, 2012). Likewise, it is used as nourishment in the villages of the Ilica district in Turkey (Özgen *et al.*, 2004) and to treat hemorrhoids (Özgen *et al.*, 2012). There have been several reports describing the hypoglycemic potential of the *B. integerrima* extract in streptozotocin-induced diabetic rats, where studies using the

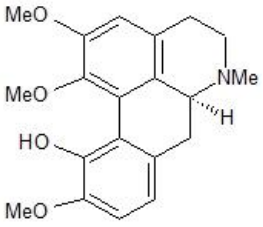
aqueous extract of the root have exhibited antihyperglycemic, antihyperlipidemic and antioxidant activities (Ashraf *et al.*, 2013c) by increasing insulin secretion and enhanced growth of the diameter and number of pancreatic islets of Langerhans (Ashraf *et al.*, 2013d). Therefore, B. integerrima possess a therapeutic and preventing role against diabetes mellitus (Ashraf *et al.*, 2012), along with the capability of protecting renal (Ashraf *et al.*, 2013b), and hepatic (Ashraf, 2014) tissues, and restoring diabetes-induced damage in testis along with improving testosterone levels (Ashraf *et al.*, 2013a). However, in a report made using the aqueous extract of the fruit, it is argued that this would not exercise any hypoglycemic or lipid-lowering effect, suggesting that the response to the extract is conditioned by both time and dose exposure (Ashraf *et al.*, 2014).



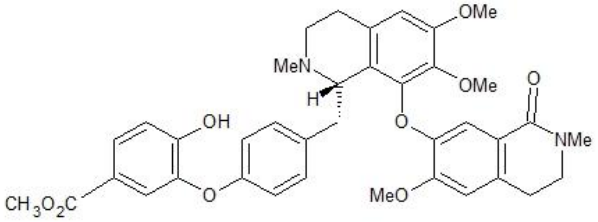
a



b



c



d

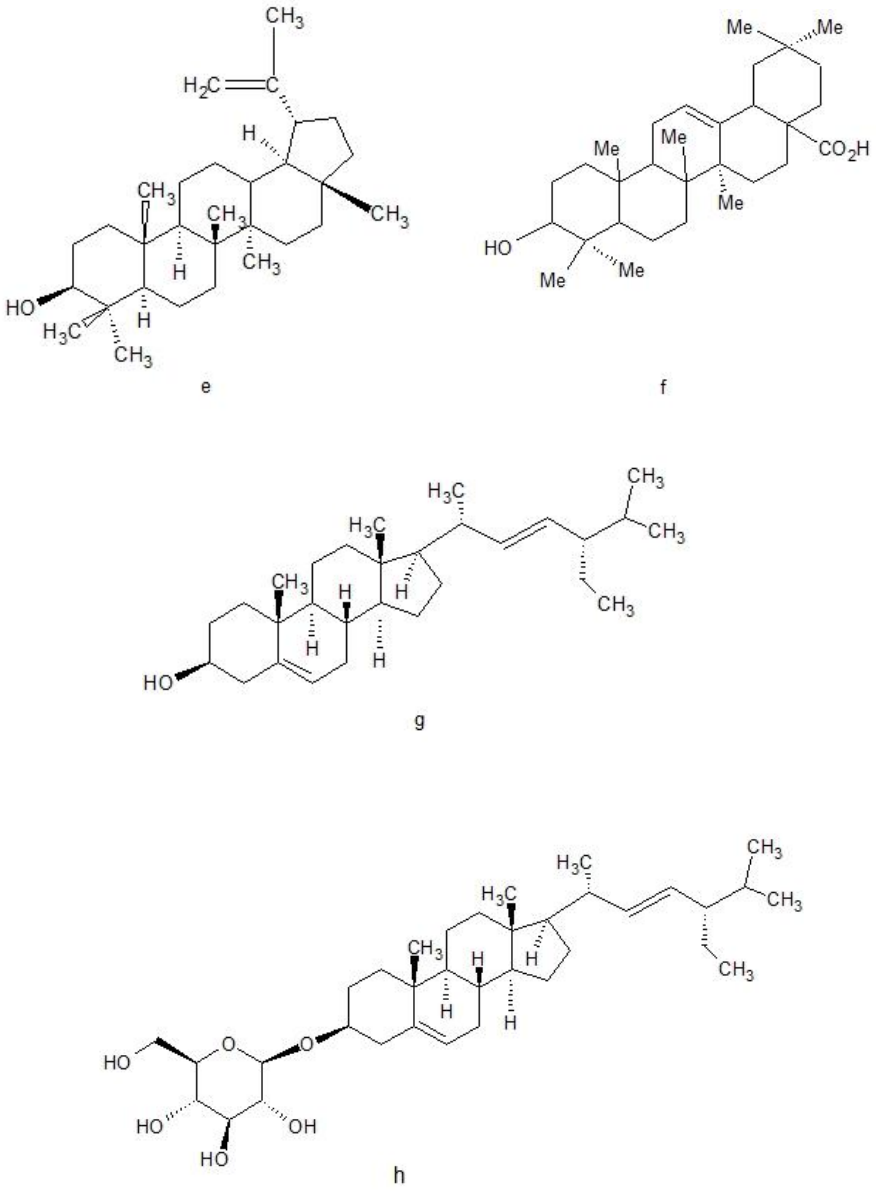


Figure 3
Chemical constituents from *Berberis vulgaris.* a) Berlambine, b) Hydroxycanthine, c) Isocorydine, d) (-) Tejedine, e) Lupeol, f) Oleanolic acid, g) Steroids stigmasterol and h) Stigmasterol glucoside.

***Berberis ceratophylla* G.**

B. ceratophylla is a species used as a natural medicine in the villages of the Middle East (Yavari & Shahgolzari, 2010) to treat diabetes and hepatitis (Ummara *et al.*, 2013). In India, it is also used as a antidiabetic treatment (Rani *et al.*, 2013). Nonetheless, poor information exists regarding its power as a hypoglycemic agent in current literature.

***Berberis moranensis* Schult. & Schult.**

At present, in Mexico there are more than 500 species being utilized in traditional medicine to counteract diabetes (Jarald *et al.*, 2008). Among these, *B. moranensis* is a prominently used hypoglycemic agent (Andrade-Cetto & Heinrich, 2005), but no further information was found regarding its glucose-lowering effect.

***Berberis crataegina* DC**

It is a traditional medicinal plant found in Turkey´s Middle East, presently used to treat diabetes (Karaman & Kocabas, 2001) by both the fruit and the root (Altundag & Ozturk, 2011). Among the alkaloids isolated from this plant, is highlighted the presence of berberine (Figure 1a) and palmatine (Figure 1e) which predominate in all organs excepting the seed (Petcu, 1968).

Alkaloids responsible for hypoglycemic activity

The high content of alkaloids present in the different species of *Berberis* would be responsible for exercising its hypoglycemic activity. In current literature, three alkaloidal compounds are emphasized to have this biological potential:

Berberine

Berberine has been defined as a potential drug because of its several pharmacological properties (Singh *et al.*, 2010a). Early studies with berberine arise from 1986. Since then, berberine was introduced as an alternative medicine for the treatment of diabetes in Asian countries (Yin *et al.*, 2012). At present, investigations have focused on determining the action mechanisms of berberine e.g. glucose and lipid metabolism, AMPK and mitochondrial function activation, liver, pancreas and intestine regulation and antioxidant activity (Yin *et al.*, 2012). Table one shows the main described mechanisms and study models used.

Table 1
Antidiabetic mechanisms described for berberine.

Study model	**Action mechanism**
DM2 patients	Decreased levels of free fatty acids in serum (Gu *et al.*, 2010).
Cell lines: CEM, HCT-116, HepG2.2.15, SW1990, HT1080 y 293T.	Increased gene expression of the insulin receptor (Zhang *et al.*, 2010).
Diabetic rats	Direct inhibition of liver gluconeogenesis (Xia *et al.*, 2011).
Cell line L929	Activation of GLUT 1 transporter (Cok *et al.*, 2011).
Cell lines 3T3-L1 y L6	Inhibition of the phosphatase activity of protein tyrosine phosphatase 1B (PTP1B), and increased IR and IRS1 phosphorylation (Chen *et al.*, 2010).
DM2 patients	AMPK pathway stimulation and insulin receptor expression induction (Di Pierro *et al.*, 2012).
Diabetic rats	Improved oxidant-antioxidant balance by increased mRNA expression of hepatic superoxide dismutase (Chatuphonprasert *et al.*, 2014).
Diabetic rats	Intestinal microbiome modulation (Han *et al.*, 2011).
Diabetic rats	Lipid metabolism regulation and increased elimination of free radicals (Tang *et al.*, 2006).
Diabetic rats	Down-regulation of lipogenic genes and up-regulation of genes involved in energy transfer in fatty and muscle tissues (Lee *et al.*, 2006).
Cell lines L6 and LKB1−/−	AMPK activation, by complex I inhibition of the mitochondrial transport chain (Turner *et al.*, 2008).
Diabetic rats	PPAR α/δ up-regulation and PPARδ repression in liver (Zhou *et al.*, 2008).
Non-obese diabetic rat	Regulation of MAPK activity to control the differentiation of Th17 and Th1 (Cui *et al.*, 2009).
Diabetic rats	Promotes secretion of glucagon-like peptide type I (Lu *et al.*, 2009).
Diabetic rats	Tyrosine phosphatase 1B activity inhibition and insulin-like effect (Chen *et al.*, 2010).

Cell line 3T3-L1	Decreased triglyceride accumulation by improving pIRS1-PI3K-pAkt, GLUT4 translocation and greater insulin tropic action by pCREB-pIRS2-pAkt (Ko *et al.*, 2005).
Diabetic hamster	Up-regulation of LXR y PPARα, and down-regulation of SREBPs (Liu *et al.*, 2009).
Cell line L6	Enhanced AMPK and p38 MAPK phosphorylation (Cheng *et al.*, 2006).
Cell line 3T3-L1	Regulation of PPARs and positive transcription elongation of factor b expression (Zhou & Zhou, 2010).
Diabetic rats	Decreased activity of intestinal disaccharidases and b-glucuronidases (Liu *et al.*, 2008).
Diabetic rats	Glucose metabolism modulation by GnRH-GLP-1 and MAPK pathway in the gut (Zhang *et al.*, 2014).
Cell lines HepG2 and C2C12	Enhanced glucose metabolism by glycolysis stimulation and mitochondrial respiratory chain inhibition (complex I) (Xu *et al.*, 2014).
Cell line HL-7702, normal human liver cell lines	LDLR up-regulation by AMPK-dependent Raf-1 activation (Li *et al.*, 2014).

Jatrorrihizine

Another alkaloid with important hypoglycemic activity is jatrorrihizine. This compound causes a pronounced decrease in blood glucose in both normal and hyperglycemic mice, which could be attributed to improved aerobic glycolysis (Yan *et al.*, 2005). However, when comparing the response obtained by jatrorrihizine vs. berberine in reducing blood glucose in mice, jatrorrihizine showed has a lower response to the same dose investigated (Fu *et al.*, 2005).

Palmatine

The hypoglycemic activity of palmatine has been explored since this compound lowers blood glucose concentration in normal rats (Patel & Mishra, 2011), and anti-diabetic activity may be mediated through insulin dependent pathway by the activation of IRTK and PI3K (Sangeetha *et al.*, 2013).

CONCLUSION

Different *Berberis* species exhibit hypoglycemic potential, being probably responsible for this activity the alkaloidal compounds, as they can modulate glucose metabolism through multiple mechanisms. However, we emphasize the need to continue further research along with performing toxicological tests, to avoid side effects risks associated to herbal medicine therapy. In addition, the *Berberis* genus presents a unique and great potential of study, not only as hypoglycemic agent but also as a diverse therapeutic product, generating the opportunity to explore different research lines related to the biological activity of this significant bio-resource.

ACKNOWLEDGMENTS

María Cristina Furrianca was a National Doctorate fellow, Advanced Human Capital Formation Program, CONICYT-Chile (No: 24121475).

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