April 30, 2018

PharmacologyOnLine

Archives • 2018 • vol.1 • 58-67

BERBERIS CHILENSIS GILLIES EX HOOK: ALKALOIDS AND PHARMACOLOGICAL ACTIVITIES

José L. Martinez[1],*, Antonio Russo[2], Raul Vinet[3], Luisauris Jaimes[4], Luigi Russo[2] & Claudio Laurido[4]

[1]*Vicerrectoria de Investigación, Desarrollo e Innovación, Universidad de Santiago de Chile*

[2]*Departmento de Farmacia, Universidad de Salerno, Fisciano, Italia*

[3]*Facultad de Farmacia, Universidad de Valparaíso & CREAS, Valparaíso, Chile*

[4]*Facultad de Química y Biología, Universidad de Santiago de Chile*

joseluis.martinez@usach.cl

Abstract

Berberis chilensis Gillies ex Hook is an endemic Chilean plant not used in traditional medicine from which some chemical structures have been isolated. Bisenzylisoquinolinic alkaloids have been characterized as being calcium antagonists of natural origin; 7-O-Demethylisothalicberine, O-Methylisothalicberine, Berbamine, and isothalicberine have been isolated from this type of structures. Berbamina is an alkaloid that has also been isolated from a Chinese plant, which is used to prevent heart attack, along with 7-O-demethylisothalicberine are the two most important bisbenzylisoquinolinic alkaloids of this Chilean species. It shows the similarity between the chemical structures of this same family of alkaloids, where tetrandrine is perhaps the most studied structure and has been characterized as one of the most important calcium antagonists, isolated from the Chinese plant *Stephania tetrandra* which is used from about 500 years before Christ as a medicinal plant by the Chinese people.

Keywords: *Berberis chilensis, Chile, 7-O-Di, Calcium-antagonist*

Introduction

The genus *Berberis* (Fam. Berberidaceae) is widely distributed in Chile. It is known with the vernacular name of "Michay" or "Calafate" [1]. *Berberis chilensis* Gillies ex Hook, is an endemic plant of Central Valley of Chile (from Valparaíso to Talca), with the traditional name of "Michai", "Michay", "Richa" or "Palo Amarillo". Botanical characteristic is a flexous common shrub in the dry hill; inflorescence in a raceme of 3 - 3,5 cm of length, numerous flowers, yellowish, between September and November.

In Chile, *Berberis empetrifolia* (traditional name is "zarcilla"), small shrub, native environment in Chile (from Santiago to Magallanes) and Argentine with flowering between November and December; is the only Berberidaceae plant used in traditional medicine for mountain sickness [2,3] and with chemical studies [4].

PHYTOCHEMISTRY OF *Berberis chilensis*

Several bis benzylisoquinoline alkaloids have been isolated from *Berberis chilensis* (for a review of bis benzylisoquinoline alkaloids see [4,5,6,7,8]. In 1981, Torres [9] was a pioneer in published a chemical contribution to the determination of structure in two vegetals population from "Cajon del Maipo" and "Algarrobo", both small cities in the Central Valley of Chile. The Figure 1, 2 and 3, illustrates three alkaloids have been isolated and characterized from leaves and branches collected on the vegetal populations: O-methylisothalicberine (O-MI) (Figure 1), 7-O-demethylisothalicberine (7-O-DI) (Figure 2) and Isothalicberine (Figure 3) [9,10]. O-MI was previously isolated from Uruguayan species *Berberis laurina* [11], present also in Brazil and Argentine. 7-O-DI and Isothalicberine were isolated for the first time. This structures were classified according to the nomenclature described and complemented by Cassels and Shamma (1980)[12], and is the following: (R, S) 6,7,8*,11+,12-6*,7,12+. The biogenic way of the alkaloid derived of 1-bencyltetrahydroisoquinoline was demonstrated by Torres (1981 and 1988)[9,13]. The *Berberis chilensis* alkaloids, had been analyzed with RMN-C13, confirm the chemical structures. It is a natural source of a calcium antagonist.

Other bisbenzylisoquinoline alkaloid are also present in *Berberis chilensis*: Espinine, type (R,S)-6,7,11*,12-6,6,7,12* [14] and 12-O-demethyllauberine, type (R,S)-6,7*,11+,12-5*,6,7,12+ [15] (Figure 4). The late alkaloid was designed with the name Pavalamine [16].

Torres in 1979 published the isolation of Berbamine, type (R,S)-6,7,8*,11,12+-6,7*,12+ [17] from *Berberis chilensis* (Figure 5). This alkaloid was also isolated from the following plants: *Berberis aristata*, *Berberis lycium* [5], *Stephania cepharantha* [18], and in *Stephania tetrandra* [5,19] and majorities of Berberis species (*B. brandisiana*, *B. cretica*, *B. koreana*, *B. regeliana*, *B. wilsoniae* (see the review of Pachaly, 1990[6]) and *Mahonia aquifolium* [20]. Kashiwaba et al., (1995) [21] demonstrated that berbamine means of isomerization produce penduline. Methylation of this product with diazomethane gave tetrandrine. In a similar form in *Berberis chilensis*, isothalicberine by methylation with diazomethane gave O-methylisothalicberine [9].

PHARMACOLOGICAL ACTIVITIES OF *Berberis* ALKALOIDS

In Chile, the under graduate thesis of Martínez in 1986 [22] , was a pioneer in the pharmacological study of the 7-O-demethylisothalicberine (7-O-DI) alkaloid. This alkaloid showed antihypertensive action on cannulated femoral vein and artery Sprague Dawley rats. Their actions were to diminish the mean arterial pressure up to 45%. Negative chronotropic and inotropic effects, independently of their cholinergic, muscarinic and adrenergic mechanisms, were assayed in preliminary studies on guinea-pig atria [22,23,24]. The study of 7-O-DI was followed by studying the effects on the electrical activity of frog cardiac pacemaker cells [25]. The alkaloid induced a complete blockade of the action potential of the transitional cells, found also a similar effect between 7-O-DI and verapamil with respect to some action potential electrical parameters [25], like as been calcium channel blocker whose activity was similar to the other alkaloids like Antioquine (Figure 6) [26,27]; Berbamine [28,29]; Dauricine (Figure 7)[30,31]; Daurisoline (Figure 8)[32] and its derivative 0,0-bisacetyldaurisoline [33]; Hernandezine (Figure 9)[34,35]; Isotetrandrine (Figure 10) [36]; Oxyacanthine (Figure 11) [28]; Tetrandrine (Figure 12) [37,38,39,40,41,42,43,44,45,46]. O-MI in mean arterial pressure showed interesting effects; O-MI caused a notorious reduction of mean arterial pressure (MAP) in normotensive anesthetized rats. Doses of 1.0; 2.5; 5.0; 7.5 and 10.0 mg/Kg were administered via femoral vein. MAP was reduced by 5.8; 10.1; 35.6; 67.9 and 60.5 % respectively. The onset of hypotensive action was 5 sec after 5 mg/Kg i.v. and the effect lasted for about 120 sec. O-MI exhibited LD50 = 5 mg/ml towards brine shrimp (Artemia salina) [47].

The alkaloid Berbamine, isolated moreover of *Berberis chilensis* [17], have been extensively studied in China, isolated from other species. This alkaloid present hypotensive action in rats [48] and inhibited the force of contraction, prolonged the effective refractory period and attenuated adrenaline-induced automaticity in the isolated atria of guinea-pig and compared with verapamil showed similar effects; in addition, the alkaloid antagonize competitively the positive inotropic actions of isoproterenol in a noncompetitive manner, shifted the concentration-response curve of Ca^{2+} to the right in a

noncompetitive manner, in similar form to histamine or $CaCl_2$ [49]. Berbamine was studied in myocardium tissue isolated from humans and guinea pig [29]. Berbamine (5 mg/Kg i.v.) decreased the size of infarction induced by coronary artery ligation in both rabbits with acute myocardial infarction treated by this alkaloid were apparently less than that in rabbits treated with saline [29]. Berbamine inhibited the increase of free fatty acids after 4 hours. The number of Q wave was decreased in rabbits treated with berbamine after the coronary artery ligation [50] and prevent experimental arrhythmias [51] . With O-4-(ethoxylbutyl)berbamine (EBB), a derivative of bis benzylisoquinoline alkaloid (berbamine type) showed a powerful and specific calmodulin inhibitory properties. It inhibited calmodulin-stimulated Ca^{2+}-Mg^{2+}-ATPase in human erythrocyte membrane with an IC_{50} value of O.35 uM compared to that of 6O uM of Berbamine [52,53]. Compound E6 is another berbamine-derivative that inhibits the activity of calmodulin-dependent myosin light chain kinase and phosphodiesterase with IC50 values of 8 and 0.53 uM, respectively [54]. The experimental results showed that the inhibition of myosin light chain kinase activity plays a key role in the contraction of smooth muscle, was increased with increasing amount of E6 and was overcome completely by the addition of excessive calmodulin. E6 inhibited the stimulatory activity of myosin light chain kinase induced by calmodulin in form concentration-dependent with Ki = 0.95 uM [55]. Recently, Leung et al., (1996)[34], showed that berbamine was much less potent (IC_{50} = 200 uM) than tetrandrine and hernandezine (both IC_{50} = 25 uM) in inhibited Ca^{2+} entry activated by thapsigargin. However in 100 uM was much less effective that other two alkaloids in suppressing thapsigargin-induced Mg^{2+} entry. But, only berbamine was able to cause store depletion-activated Ca^{2+} entry upon Ca^{2+} readmission.

Berbamine possess other pharmacological properties, for instance anti-inflammatory [56], can reduce superoxide and hydroxyl radicals generated in human polymorphonuclear leukocytes [57], is useful in the prevention and treatment of radiation-induced leukopenia [58].

Other alkaloids from genus Thalictrum revelated hypotensive effect in dogs [59]. Recently studies with tetrandrine in deoxycorticosterone-acetate-salt hypertensive rats lowered systolic blood pressure, left ventricular weight, Ca^{2+} of mitochondria, and markedly decreased the density and total number of dihydropyridine binding sites in hypertrophic left ventricle; these authors concluded that tetrandrine decreased cardiac mass in this rats and may be associated with the density and the total number of dihydropyridine binding sites, Ca^{2+} and blood pressure control [60].

DISCUSSION

The biological activities of some plants had been known for centuries to peoples of many cultures, and there was never any question of their efficacy or their pharmacological effects [61,62].

The use of natural substances, particularly plants, to control the disease is a century old practice that as to the discovery of more than half of all "modern" pharmaceuticals [63]. Dioscorides in 78 AD wrote, "De Materia Medica" was pioneer in describing medicinal plants [64].

This article is a review of discuss of the bisbenzylisoquinoline alkaloids properties with very important biological activity present mainly in Berberis chilensis, an endemic Chilean plant without use in traditional medicine and other alkaloids with similar characteristics in chemical structure and action mechanisms as calcium antagonists.

ACKNOWLEDGMENTS

This work was supported partially by a grant from Dicyt-Usach N° 021643MS.

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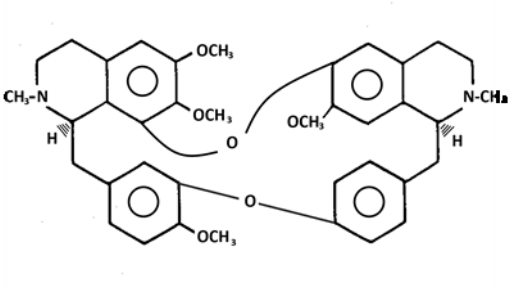
Figure 1



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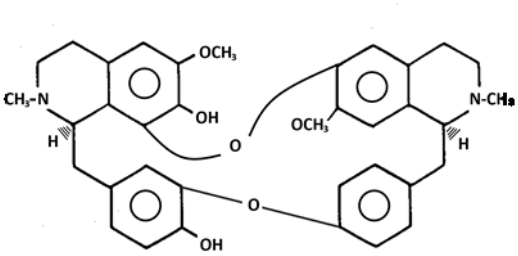

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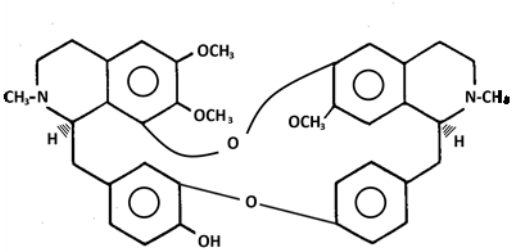

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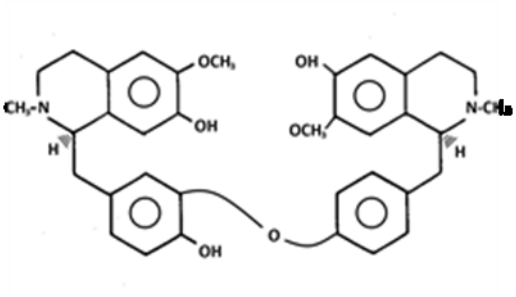

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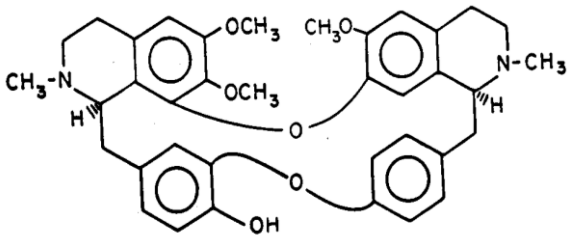

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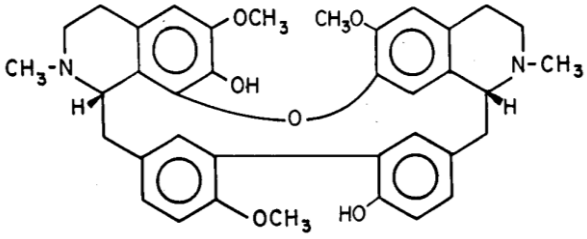

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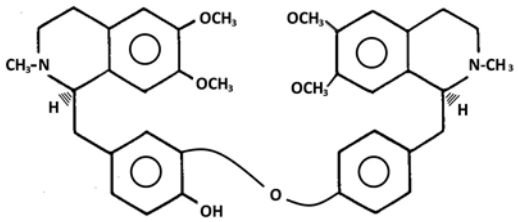

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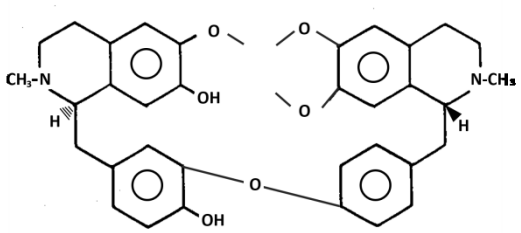

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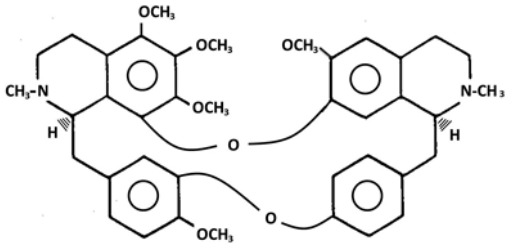

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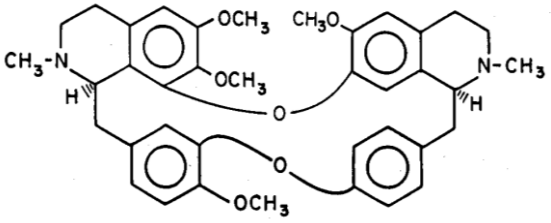

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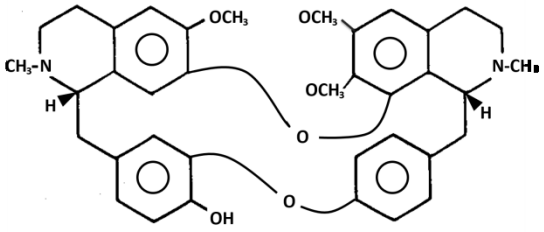

ISSN: 1820-8620

Figure 12