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Revisión | Review

Pseudoxandra sclerocarpa Maas, Colombian medicinal plant: a review

[*Pseudoxandra sclerocarpa* Maas, planta medicinal colombiana: una revisión]

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Abstract: The Annonaceae family is one of the largest, with 130 genre and 2500 species, consisting of trees, shrubs and a few vines. Within this family, the *Pseudoxandra* genus of neotropical distribution is found. In Colombia, there are endemic and native species, distributed in the Amazon region and along the valley of the Magdalena River in the Chocó. Of the total of 22 species that form the genus in Colombia, *Pseudoxandra sclerocarpa* Maas is exclusive of the Antioquia region, receiving the common name of garrapato or frisolo. From this tree, bisbenzylisoquinolinic alkaloids like antioquine, medellline, obaberine, among others, has been isolated. Also neolignans: dieugenol and dehydro-1-O-methydehydrodieugenol. It is used in traditional medicine as an antiparasitic. From the pharmacological point of view, the alkaloids have shown activity against leishmaniasis and also have spasmolytic activity. Within the bisbenzylisoquinolinic alkaloids, antioquine has properties of being calcium antagonist.

Keywords: *Pseudoxandra sclerocarpa*, Colombia, bisbenzylisoquinoline alkaloid

Resumen: La familia Annonaceae es uno de los más grandes, con 130 géneros y 2.500 especies, que consiste en árboles, arbustos y algunos bejucos. Dentro de esta familia, el género *Pseudoxandra* es de distribución neotropical. En Colombia existen especies endémicas y nativas, distribuidas en la región del Amazonas ya lo largo del valle del río Magdalena en el Chocó. Del total de 22 especies que forman el género en Colombia, *Pseudoxandra sclerocarpa* es exclusiva de la región de Antioquia, recibiendo el nombre común de garrapato o frisolo. De este árbol se ha aislado alcaloides bisbencilisoquinolínicos como antioquina, medelllina, obaberina, entre otros. También neolignanos: dieugenol y dehidro-1-O-metil-dehidrodieugenol. Se utiliza en la medicina tradicional como un antiparasitario. Desde el punto de vista farmacológico, los alcaloides han mostrado actividad contra la leishmaniasis y también tienen actividad espasmolítica. Dentro de los alcaloides bisbencilisoquinolínicos, antioquina tiene propiedades de ser antagonista del calcio.

Palabras clave: *Pseudoxandra sclerocarpa*, Colombia, alcaloides bisbencilisoquinolínicos

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INTRODUCTION

The Annonaceae are a large, diverse and ecologically important family, especially in tropical systems. It has been studied since 1983 by researchers from the National Herbarium of Utrecht (Netherlands). It is widely distributed in the tropics and islands in the Pacific and northern Australia. In South America, are located in the Amazon region, Guyana, abundant biodiversity areas as Chocó of Colombia (Murillo, 2001; Pirie *et al.,* 2005; Maas *et al.,* 2007). The annonaceae family is an important food source in the Colombian amazonic region (Murillo, 2001). There have been several published studies on taxonomic keys to recognize genres Annonaceae, resulting in 34 neotropical genre, 40 in Africa and Madagascar, 42 in Asia and Australia, all based on vegetative characters and validated phylogenetically, there are in total of 2440 species and 109 genre reported so far (Chatrou *et al.,* 2012; Couvreur *et al.,* 2012).

Are trees, shrubs, rarely sub-shrubs or climbers, few vines, sometimes aromatic, characterized in that the outer bark peels off in strips so some species are used as ropes (Murillo, 2001; Maas & Westra, 2010) and the inner bark is crosslinked, the flowers may be solitary or in clusters called rápidios, axillary or not, most have bracts attached to the pedicels. It is covered in simple, stellate or scaly hairs garments; their leaves are long, alternate, in acuminated stipules (Maas *et al.,* 2001; Erkens *et al.,* 2006; Maas *et al.,* 2007; Maas & Westra, 2010; Couvreur *et al.,* 2012). The family is widely recognized for its long trimeric flowers with apical extension of the connective protecting the stamen and seed with endosperm.

In this diversity of genres, we found *Pseudoxandra*, first described by Robert E. Fries, 1937, as a plant whose leaves with primary veins, highlighted in the upper surface, with a present or not palpable marginal vein. Simple garments, bracts with two floral pairs, small, roughly globular in bud, imbricated petals somewhat rounded or concave, solitary axillary fruits are carpic or monocarpic, indehiscent with a shiny black seed, flattened in the equatorial groove (Maas & Westra, 2003; Maas & Westra, 2005; Maas *et al.,* 2007; Maas & Westra, 2010).

Other studies placed the genre *Pseudoxandra* within the family Annonaceae based on different anatomical characters:

- In 1971 Walker was based in treated pollen
- In 1992 Van House in the presence of the sepals and intertwined petals often ciliated, and a basal or lateral egg,
- While Koek Noorman and Van Setten used the fruit and seed, the carpels and

the only egg in apical or lateral position for *Pseudoxandra* and,

- Finally in 2000, Doyle by morphological and molecular analysis classifies the class Malmeoides within the family Annonaceae (Maas & Westra, 2003).

In 2003 it was reported by P. J. Maas, a taxonomic revision of the genus, which was initiated in 1990. 22 species are described, then in 2005 and 2010, two new species were reported to have at present 24 species belonging to the genus Pseudoxandra which have been validated by morphological, anatomical and phylogenetic studies (Maas & Westra, 2003; Maas & Westra, 2005; Erkens *et al.,* 2006; Chatrou *et al.,* 2012; Couvreur *et al.,* 2012).

This review of 2003, one of the most complete anatomical studies of the leaves was made by EJ Van Marle (Maas & Westra, 2003). It describes the presence of tiny warts in dry leaves, not detectable in the fresh leaf material. These correspond to the structures called osteoesclereidas, which are fibrous cells elongated with swollen ends, scattered in the mesophyll of species of this genus.

In turn, the polymorphism of the species of this genus is distinguishable through comprehensive analysis of specific features in their flowers. For example, in *Pseudoxandra polyphleba*, the flowers are small and glabrous, while in *Pseudoxandra lucida* these are bigger and hairy. Nevertheless, due to the fact that based in the leaf anatomical data, it is not possible to reach an undisputed classification of *Pseudoxandra*, the following taxonomic key for the genus, were established which have been subsequently confirmed:

- Leaves with distinct marginal vein palpable (except *Pseudoxandra spiritsantensis*); petals 4-15 mm long (Maas *et al.,* 1986; Maas & Westra, 2003; Maas & Westra, 2005; Maas & Westra, 2010; Couvreur *et al.,* 2012).

Within this review the species *Pseudoxandra sclerocarpa* is described, with an endemic Colombian distribution restricted to primary forests in the Municipality of San Luis, Antioquia, where he received the popular names of frisolo, garrapato, which leaves and bark are used in decoction, and different studies have established its alkaloid content

and neolignans (Cortes *et al.,* 1985; Cortes *et al.,* 1986a; Cortes *et al.,* 1986b; Cortes *et al.,* 1986c; Murillo, 2001; Instituto de Ciencias Naturales, 2015). It should be noted that this species was reported as *Pseudoxandra aff lucida* and later its taxonomic identity was verified as *sclerocarpa* by PJ Maas, being the same species reported and described in 1937 by Fries (Cortes *et al.,* 1986a).

Description

Distinguished by a relatively tall tree, reaching up to 28 meters high, with young glabrous branches, gray bark, yellow wood, fruits are drupes, ovoid or rounded, monocarpic, go to green to yellow when ripe and black when dry, shiny black or dark brown seeds 2 cm in diameter, ellipsoid or globose, oval leaves, oblong, leathery, sparsely warty surface is usually near the main vein, slightly dark at the top and bottom dark brown with scattered adpressed hairs 2 mm long, mostly near the main base of the acute to obtuse veins; often has angular shaped extensions in the form of secondary teeth, with acute acuminate long apex, secondary indistinct veins, lines on both sides of the primary veins, smallest marginal vein margin, between 1 and 2 mm distance. The axillary flowers are produced on leafless branches, rarely in a base of a lateral section, have adpressed hairs on the outer side, the petals are green in vivo, the margins ciliate, the outer part is elliptical-oval the internal part is slightly concave, the sepals are slightly depressed and triangular (Maas & Westra, 2003; Couvreur *et al.,* 2012; Instituto de Ciencias Naturales, 2015).

Taxonomic key

Monocarps with 2-3 mm wall thickness, base angular leaf blade with teeth-like projections on each side. They may present no or a marginal vein located 2 mm of the margin. Warts near the main vein (palpable dry, not fresh) a single seed, whitish flowers (Maas & Westra, 2001; Maas & Westra, 2003; Instituto de Ciencias Naturales, 2015).

Habitat

Pseudoxandra sclerocarpa is the restricted distribution, endemic, found within the trees of the tropical rain forests of the southeast, in the town of San Luis Antioquia, in the basin of the river course of Río Claro and Cocorná. The soils are of low fertility acids in most of the area. It grows at an altitude ranging between 350 and 700 meters, temperature between 23 and 27º C, an annual rainfall between 2000 and 2800 mm per year and a relative humidity of 78% (Hodge, 1947; Saez & Cortes, 1994; Murillo, 2001; Maas & Westra, 2003; Instituto de Ciencias Naturales, 2015).

The interest of gender Pseudoxandra is the presence of various derivatives of antioquines with different degrees of oxidation (Cave, 1985), so, the main aim of this article is to review the information published so far about Pseudoxandra sclerocarpa, a Colombian plant which is characterized by the presence of bisbenzylisoquinolinic alkaloids, which have been studied for being calcium antagonists.

Chemistry and Pharmacology

Antioquine

Studies of the phytochemical composition of *Pseudoxandra sclerocarpa*, reported alkaloids, mainly of the bisbenzylisoquinolinic type obtained from stems and leaves, of which there are five that are characterized by RS structures: antioquine (figure 1), obaberine (leaves and bark) (figure 2), medelline (figure 3), homoaromoline (homothalicrine)(figure 4), berbamunine (figure 5); luxandrine (figure 6)(Cortes *et al.,* 1986c); four minor alkaloids are characterized by the presence of a conjugated ketone in position α or α': oxandrine (figure 7), oxandrinine (figure 8), pseudoxandrine (figure 9), pseudoxandrinine (figure 10), found only in these species. Other alkaloids present: secantioquine (figure 11), secolucidine (figure 12), secoobaberine (figure 13), thaligrisine (figure 14) and one Hydroxy-7 aporphine type: ushinsunine (Cortes *et al.,* 1985; Schiff, 1987; Cortes *et al.,* 1986a; Cortes *et al.,* 1986b; Cortes *et al.,* 1986c; Schiff, 1991). Antioquine (figure 1) possess a significant the cytotoxic and antioxidant effect (Correche *et al.,* 2008). Antioquine was isolated later from other annonaceae *Guatteria boliviana* (Mahiou *et al.,* 2000).

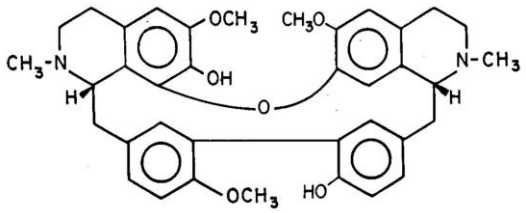

Figure 1: Antioquine

The synthesis of O-demethylrodiasine (antioquine = (synonyma: 7-O-Demethylrodiasine; (1α,1'α)-7-O-Demethylrodiasine) (Bentley, 1996), is rodiasine a cyclic bisbenzylisoquinoline alkaloid that was first isolated from the South American

greenheart tree *Chlorocardium rodiei* (Grundon & McGarvey, 1966).

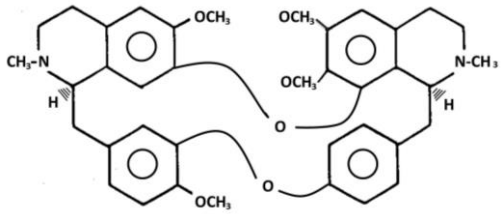

Figure 2: Obaberine

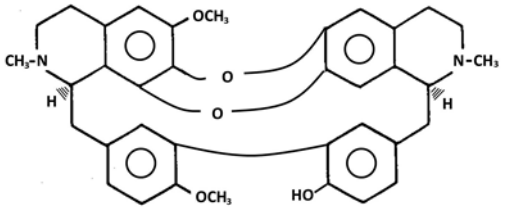

Figure 3: Medelline

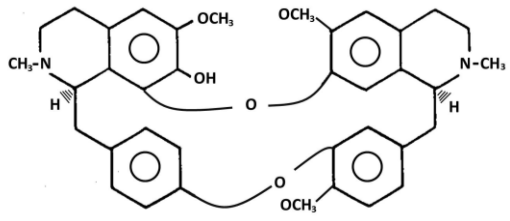

Figure 4: Homoaromoline

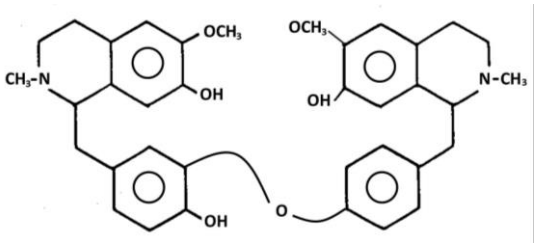

Figure 5: Berbamunine

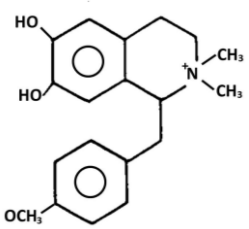

Figure 6: Luxandrine

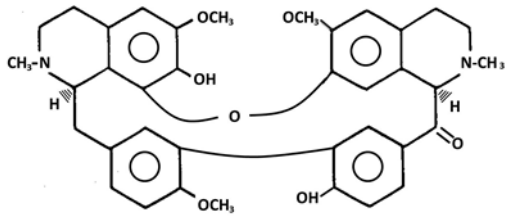

Figure 7: Oxandrine

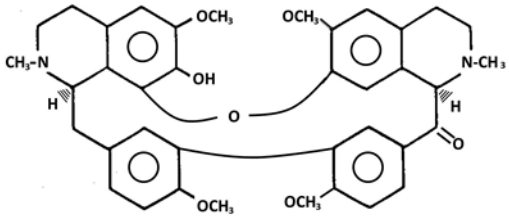

Figure 8: Oxandrinine

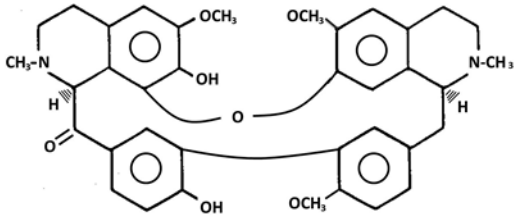

Figure 9: Pseudoxandrine

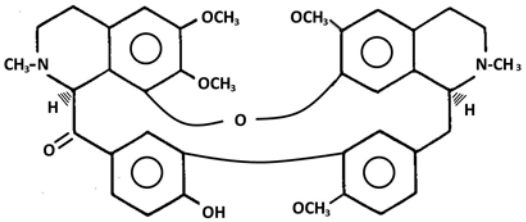

Figure 10: Pseudoxandrinine

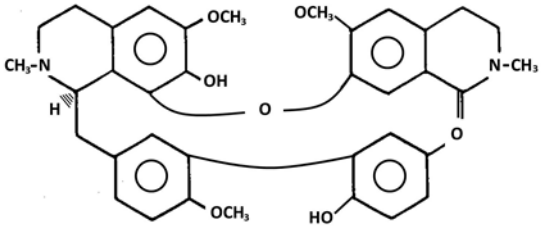

Figure 11: Secantioquine

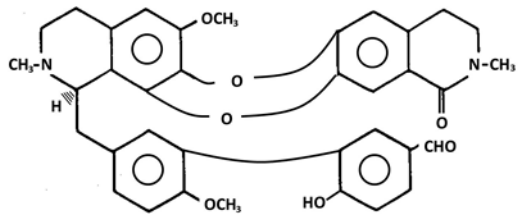

Figure 12: Secolucidine

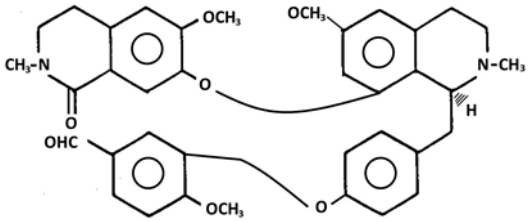

Figure 13: Secoobaberine

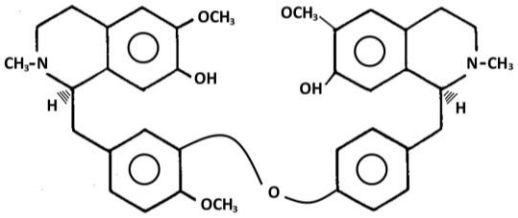

Figure 14: Thaligrisine

The preliminary pharmacological properties are described (Saez, 1994). Finally, the neolignans obtained in petroleum ether fractions from bark reported: dehidrodieugenol 1 and O-2 methyldehydrodieugenol (Saez & Cortes, 1994). It has been described extensively natural calcium antagonists (Schiff, 1987; Schiff, 1991; Pachaly, 1990; Martinez, 2003; Bhardwaj & Kaushik, 2013). The main alkaloid extracted from of *Pseudoxandra sclerocarpa*, antioquine (Cortes *et al.*, 1985) is well established (D'Ocon *et al.*, 1989; Liu *et al.*, 1991), showed its action in rat uterus preparation (D'Ocon *et al.*, 1989). Other studies, concluded that this alkaloid has a lower relaxant compared to papaverine (Candenas *et al.*, 1990). Ivorra *et al.*, (1993) showed the contractile dual-relaxing effect of antioquine on the rat aorta, all of which would be related to calcium channels. It has also been suggested for antioquine, antidepressant activity (Protais *et al.*, 1995).

Other bisbencilisoquinolinicos alkaloids have also been described as calcium antagonists of naturally occurring such as tetrandrine (figure 15) (Fang *et al.*, 1981; Fang & Jiang, 1986; Che *et al.*, 1994; Wang *et al.*, 2004), inhibited infection of Ebola virus in human (Sakurai *et al.*, 2015); Is calcium antagoism berbamine (figure 16) (Li *et al.*, 1986; Pachaly, 1990), isotetrandrine (figure 17) (D'Ocon *et al.*, 1992; Takemura *et al.*, 1996; Imoto *et al.*, 1997), hernandesine (figure 18) (Xu *et al.*, 1990: Low *et al.*, 1996), dauricine (figure 19)(Li *et al.*, 1984; Guo *et al.*, 1997); fangchinoline (figure 20) (Pan *et al.*, 1987; Choi *et al.*, 2000; Deng *et al.*, 2015), o-methylisothalicberine (figure 21) (Martinez *et al.*, 1997), 7-O-demethylisothalicberine (figure 22) (Torres *et al.*, 1979; Martinez, 1986; Morales *et al.*, 1989; Martinez *et al.*, 1992; Morales *et al.*, 1993).

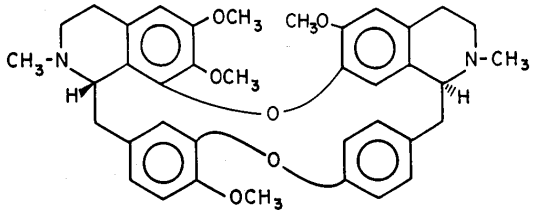

Figure 15: tetrandrine

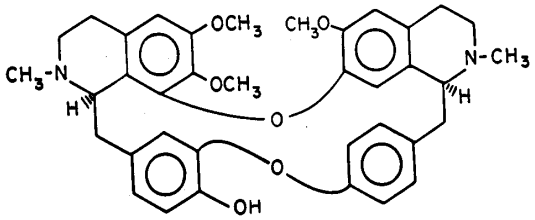

Figure 16: Berbamine

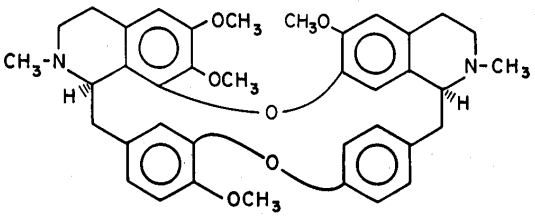

Figure 17: Isotetrandrine

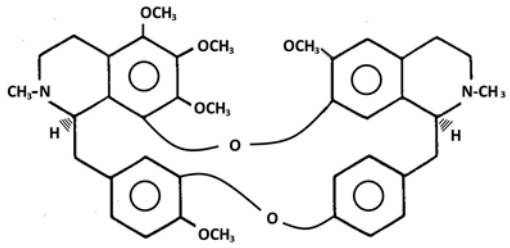

Figure 18 : Hernandezine

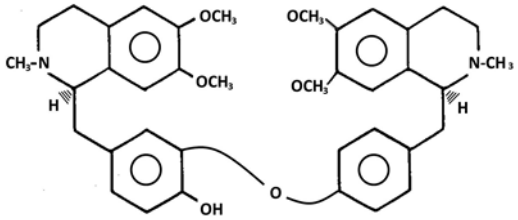

Figure 19 : Dauricine

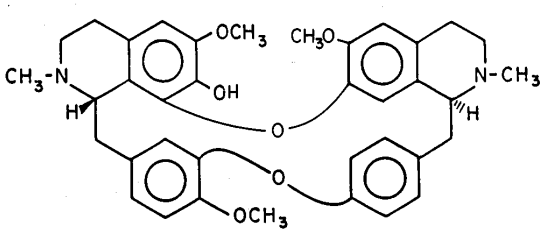

Figure 20: Fangchinoline

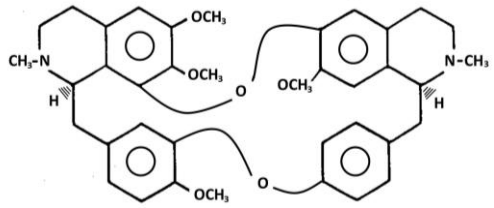

Figure 21: O-Methylisothalicberine (O-MI)

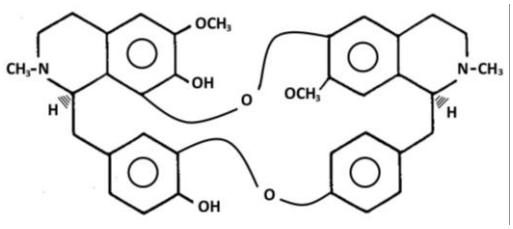

Figure 22: 7-O-demethilisothalicberine (7-O-Di)

Preliminary results of our group have shown that the Ca^{2+} blocking effect of antioquine on rat isolated aorta is higher than verapamil (Vargas-Rueda *et al.*, 2014).

Also, the bisbenzylisoquinolinic alkaloids are widely used in traditional medicine as antiparasitic (Chan-Bacab *et al.*, 2001) and are recognized for their strong activity against *L. donovani*, *L. braziliensis* and *L. amazonensis*, including obaberine (Ocampo & Ocampo, 2006) obtained from Pseudoxandra sclerocarpa. Also presents a IC_{100} anti lehismaniasis activity of ~ 50 ug / ml.

Studies of structure - activity relationships indicate that the number of bisbenzylisoquinolinic alkaloids have shown that the oxidation state and the type of substitution on the nitrogen atoms are crucial for the activity as well, alkaloids with methylated nitrogen are more active than unsubstituted aromatic nitrogens, and the quaternization of one or more nitrogen atoms, resulting in a loss of anti leishmaniasis activity (Osorio *et al.*, 2006; Mishra *et al.*, 2009). While the antioquina, presented good in vitro activity against the promastigotes form of Leishmania ssp. but showed activity against Lehismania amazonensis (pH = 8) in BALB/C pre infected mice with the parasite (Fournet *et al.*, 1993; Chan-Bacab *et al.*, 2001; Osorio *et al.*, 2006)

Another alkaloid of interest is thaligrisien: a bisbenzyltetrahydroisoquinolinic type was tested in several functional models and isolated aorta precontracted with noradrenaline or KCl, others with caffeine in the presence or absence of extracellular Ca^{+2} to evaluate the mechanisms of action. The resultant effect was the inhibition of the smooth muscle contractile response, concentration dependent, acting on α1-adrenoceptor antagonists and calcium channel blockers, suggesting a possible relaxing effect (Cortes *et al.*, 1986b; Tur *et al.*, 2000; Li *et al.*, 2011).

Regarding the neolignans, unique non alkaloidal compounds reported, it was suggested a probable antitumoral activity because they share similar structures possessing the same action, sucha as magnolol, honokiol and monoterpenilmagnolol, isolated from family magnoliaceaes (Cortes *et al.*, 1985).

Conclusion

Pseudoxandra sclerocarpa has been deeply characterized morpho-anatomically and from the botanical point of view. Pharmacological studies have been conducted with the isolated substances,

showing anti spasmodic activities, relaxing, antidepressants, anti leismaniasis. Further studies in the search of secondary metabolites are needed for disclose the fully pharmacological potential of this plant as a natural origin calcium antagonist.

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