

REVISIONES

Endemic *Juniperus gracilior* varieties of the Hispaniola island, tree taxa of environmental and economic relevance and a valuable phytochemical source

Variedades de *Juniperus gracilior* endémicas de la Hispaniola, taxones con relevancia económica y ambiental y valiosas fuentes de fitoquímicos

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SUMMARY

The *Juniperus* genus has long been used and studied for the chemical components of its aerial parts (leaves, bark, twigs) and their bioactivity. Nevertheless, these studies and their compilation have been primarily focused on Europe and North America distributed taxa, leaving the knowledge and economic potential of the endangered Caribbean taxa highly underrepresented in the literature. Although, these conifers have been barely investigated for their bioactive compounds, bibliography does indicate the presence of potent antitumoral, anti-inflammatory and antimicrobial molecules such as deoxypodophyllotoxin, podophyllotoxin, amentoflavone and widdrol. Additional phytochemical potential can also be inferred from the systematical essential oil studies of the taxa, the only source of chemical composition information on most of them. These investigations can aid in the narrowing down of the possible bioactivities their lipidic extracts may possess, while also providing clues for the bioassays necessary to confirm them. This review aims to compile the known information on the usage, bioactivity and chemical composition of the Hispaniolian *J. gracilior* varieties and their phylogenetically proximal taxa (*J. gracilior* var. *saxicola*, *J. barbadensis* and *J. bermudiana*), to propitiate more holistic and in depth chemical studies on these potential phytochemical sources, in turn providing an economical incentive for their conservation.

Key words: bioactive compounds, conservation, metabolomics, Caribbean.

RESUMEN

El género *Juniperus* ha sido utilizado y estudiado a lo largo de los años por la bioactividad de los compuestos fitoquímicos encontrados en sus tejidos (hojas, corteza, ramas). Mayoritariamente, dichas investigaciones y las recopilaciones de estas se han centrado en taxones distribuidos en Europa y América del Norte, dejando de lado la investigación y potencial económico de otros, como los caribeños, que actualmente se encuentran en peligro de extinción. Aunque los compuestos bioactivos de los últimos apenas han sido estudiados, en la literatura se reportan potentes moléculas antitumorales, antiinflamatorias y antimicrobianas como la desoxipodofilotoxina, podofilotoxina, amentoflavona y el widdrol en su composición. De igual manera, investigaciones fitoquímicas realizadas a sus aceites esenciales con objetivo taxonómico, que en muchos casos representan la única fuente de información química de estos *Juniperus* del Caribe, permiten inferir propiedades bioactivas adicionales de los mismos, lo que resalta su posible potencial. Este trabajo tuvo como objetivo recopilar la información conocida sobre el uso, la bioactividad y la composición química de las variedades de *J. gracilior* endémicas de la Hispaniola y sus taxones filogenéticamente cercanos (*J. gracilior* var. *saxicola*, *J. barbadensis* y *J. bermudiana*), para propiciar futuros estudios holísticos y exhaustivos de los metabolitos encontrados en estas posibles fuentes de compuestos fitoquímicos, proporcionando así un incentivo económico para su conservación.

Palabras clave: compuestos bioactivos, conservación, metabolómica, Caribe.

INTRODUCTION

The *Juniperus* genus, commonly referred to as “cedars” in English and “enebro” or “sabina” in Spanish, comprises 67 species and 37 varieties (Adams 2014). From Tibetan mountains to tropical islands, juniper trees and shrubs are distributed in all continents except Antarctica. Of the 114 taxa, seven are localized in the Caribbean archipelago: *J. gracilior* var. *gracilior* (Pilger), *J. gracilior* var. *ekmanii* (Florin) R. P. Adams and *J. gracilior* var. *urbaniana* (Pilger et Ekman), endemic to Hispaniola island, *J. gracilior* var. *saxicola* (Britton et P. Wilson), endemic to Cuba, *J. barbadensis* var. *barbadensis* (Linnaeus), endemic to St. Lucia, *J. barbadensis* var. *lucayana* (Britton) R. P. Adams, found in Cuba, Bahamas and Jamaica, and *J. bermudiana* (Linnaeus), endemic to Bermuda (Adams 2014).

Species within the *Juniperus* genus have long been used for therapeutic purposes and known for their pharmacological properties (Seca et al. 2015). Their chemical components have also been utilized in food production as flavoring (Falasca et al. 2013) and could be used as food preservatives (Lesjak et al. 2017). Additionally, polyphenols and other compounds of the genre provide an essence potentially used in the cosmetic (Rangel et al. 2018), while also being interesting for pharmaceutical industries, with individual bioactive compounds being potential leads for new drug development (Kwon et al. 2010, Tavares and Seca 2018). Although these investigations have been gathered by review articles such as those written by Seca and Silva (2006), Seca and collaborators (2015) and Tavares and Seca (2018), the economic value and potential of the critically endangered *J. gracilior* (Pilger) Hispaniolan varieties have not been described (García et al. 2016). This review aims to emphasize the current and potential use of bioactive chemical components from *J. gracilior* by compiling pertinent information of phylogenetically proximal taxa (*J. gracilior* var. *saxicola*, *J. barbadensis* var. *barbadensis*, *J. barbadensis* var. *lucayana* and *J. bermudiana*). Information available in Dominican governmental reports and overall bibliography was consulted to provide a comprehensive review for *J. gracilior* chemical components and to highlight its economic potential as a way of guaranteeing this species conservation (Newton 2008).

JUNIPERS IN THE HISPANIOLA ISLAND, ENVIRONMENTAL SITUATION AND ECONOMIC IMPORTANCE

The Hispaniola is a Caribbean island comprised of two countries, the Dominican Republic and Haiti. The forest cover of the island is reported to be ~2 % on the west side (Haiti) and ~41 % on the east (Dominican Republic) (Posner et al. 2010, MIMARENA 2019). These habitats have a biodiverse flora with an array of endemic species, being especially true in the mountainous territory, which holds pine forests and hundreds of endemic species, including

its most representative conifer species *Pinus occidentalis* (Swartz), *Podocarpus hispaniolensis* (Laubenfels) and *J. gracilior* (Posner et al. 2010, Cano-Ortiz et al. 2016, MIMARENA 2019). The islands' juniper (*Juniperus*) varieties (figure 1) inhabit elevations between 1,000 and 2,550 meters above sea level, with locations (figure 2) differing among varieties. *J. gracilior* var. *gracilior* inhabits Dominican mountainous ranges such as Sierra Martín García, Cordillera Central, Sierra de Bahoruco (Zanoni and Mejía 1986) and Sierra de Neiba (Familia et al. 2019), while *J. gracilior* var. *ekmanii* is found in the Haitian Massif de la Selle, Massif du Nord (Adams 1983) and the Dominican Sierra de Bahoruco (Adams 2014), and *J. gracilior* var. *urbaniana* occupies Haitian Massif de la Selle and Dominican Sierra de Bahoruco (Adams 2014).

Although these forests represent an environmental and economic benefit for the island, since colonial times, unsustainable depletion of their vegetation has resulted in significant forest reduction and in the critical endangerment of many endemic taxa (Posner et al. 2010, García et al. 2016). The three *J. gracilior* varieties have been jeopardized due to this anthropic intervention. Mainly, as a result of continuous community and farmland establishment in and tree logging, which locals undertake to economically sustain themselves and supply the demand of the fragrant *ekmanii* and *gracilior* wood, coveted in the territory (Adams 1983, Peguero and Clase 2015). Since in the 1980s, reforestation efforts have been made on the island, however, the endemic junipers have not taken a significant role in this rehabilitation (Williams 2011, MIMARENA 2019). Two organizations, Dominican National Botanical Garden [2007 - ongoing] and Arche aux Plantes [2013 - 2018], have in recent times, undertaken projects which aim to conserve and propagate seeds of the species (Conservatoire Botanique National de Brest 2017, Mattana et al. 2017). Nevertheless, these have not sufficed to augment populations enough to reduce extinction risk.

BIOACTIVE PREPARATIONS AND EXTRACTS FROM CARIBBEAN JUNIPERS

Juniperus species have been used in traditional or folk medicine even when the scientific bases of their mode of action and the chemicals behind their bioactivity are unknown. Within the genus, *J. oxycedrus* and *J. communis* are the most studied in terms of their pharmacological and therapeutic effects (Tavares and Seca 2018). The list of referenced properties pertaining the extracts of their aerial parts is ample, including antifungal (Ortiz et al. 2004), insect repellent (Jacobson 2018), antitussive (Carpenter et al. 2012), antihypertensive (Usmanghani et al. 1997), diuretic (Öztürk et al. 2011), antiseptic (Khare 2007), anti-inflammatory (Khare 2007, Jazayeri et al. 2014), carminative (Usmanghani et al. 1997, Khan et al. 2012) hypoglycemic (Orhan et al. 2012), antioxidant (Jazayeri et al. 2014) and abortive (Öztürk et al. 2011), while also being

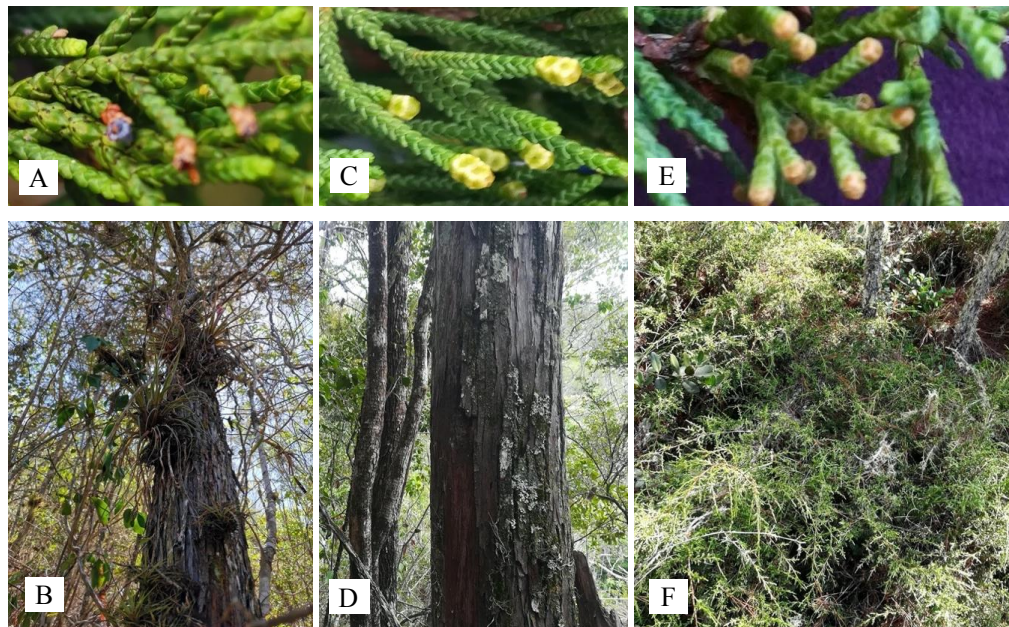


Figure 1. Morphology of the three endemic *J. gracilior* varieties. A) Leaves and berry (purple structure), *gracilior* variety; B) *gracilior* variety tree; C) Leaves and cones (yellow structures), *ekmanii* variety; D) Trunk, *ekmanii* variety; E) Leaves and cones (yellowish structures) *urbaniana* variety; F) *urbaniana* variety shrub. Photo credits: Carolina Juncá (A, B) and Amelia Mateo (C, D, E, F).

Morfología de las tres variedades endémicas de *J. gracilior*. A) Hojas y fruto (estructura morada), variedad *gracilior*; B) Árbol, variedad *gracilior*; C) Hojas y conos (estructuras amarillas), variedad *ekmanii*; D) Tronco, variedad *ekmanii*; E) Hojas y conos (estructuras amarillas), variedad *urbaniana*; F) Arbusto, variedad *urbaniana*. Fotografías tomadas por Carolina Juncá (A, B) y Amelia Mateo (C, D, E, F).

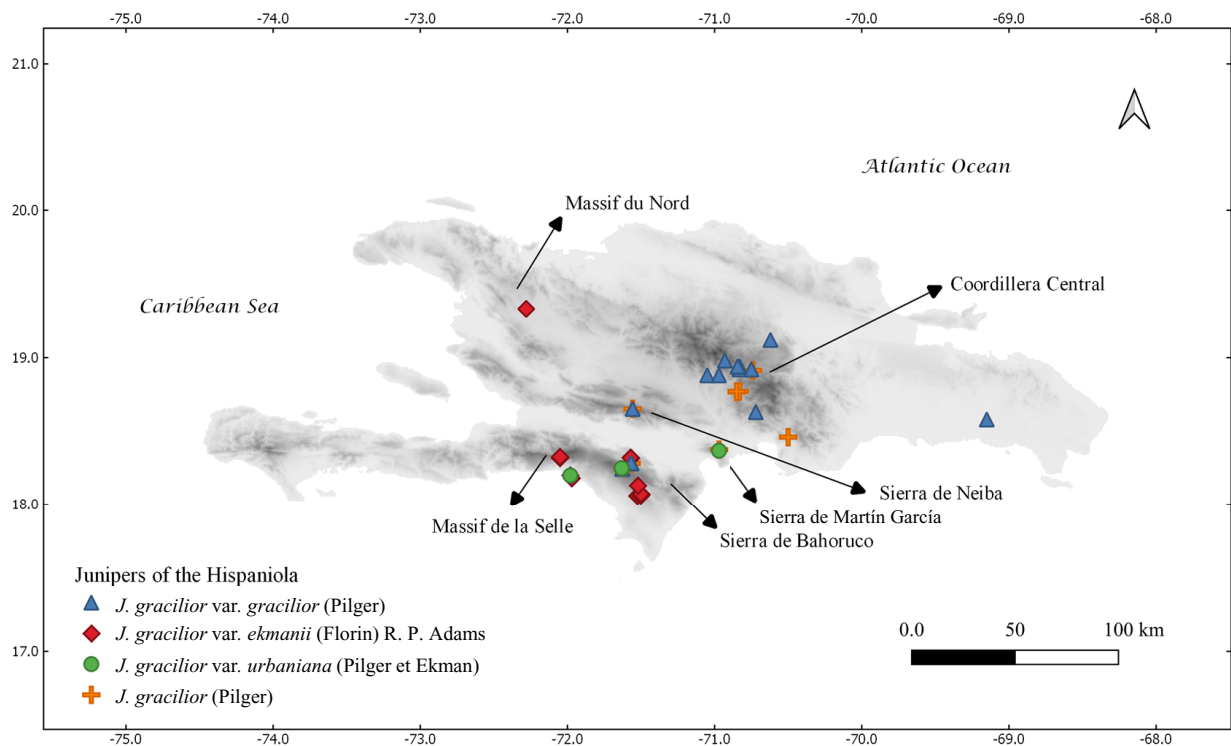


Figure 2. Distribution of *J. gracilior* in Hispaniola Island. Sightings obtained from GBIF (GBIFab) and field trips organized by the Instituto Tecnológico de Santo Domingo (INTEC) between 2018 and 2019 (unpublished data).

Distribución de las variedades de *J. gracilior* en la isla de la Hispaniola. Avistamientos obtenidos de GBIF (GBIFab) y de viajes de campo organizados por el Instituto Tecnológico de Santo Domingo (INTEC) entre 2018 y 2019 (datos no publicados).

used as remedies for urinary infection (Grosourdy 1864), cold, bronchitis (Öztürk *et al.* 2011) diabetes (Orhan *et al.* 2012, Carpenter *et al.* 2012), asthma (Khan *et al.* 2012), urticaria, dysentery, leucorrhoea (But *et al.* 1997), haemorrhoids (Öztürk *et al.* 2011) and tuberculosis (Omari *et al.* 2019).

Although a vast array of information can be found for taxa in territories outside the Caribbean, for the four species that do inhabit these islands, historical uses bibliography is scarce. Only *J. bermudiana* preparations have been reported to be utilized in precolonial times for medicinal and culinary purposes (Wolsak 2017). Nevertheless, studies have reported that Caribbean junipers have been employed in treating urinary infections and have also presented cytotoxic, antioxidant, antibacterial and pest repellency properties (Fitzgerald *et al.* 1957, Grosourdy 1864, Martínez *et al.* 1996, Jacobson 2018). A list of the bioactivities attributed to Caribbean juniper preparations can be found in table 1.

JUNIPERS AS A SOURCE OF PHYTOCHEMICALS AND BIOACTIVE COMPOUNDS

Besides the interest shown for its bioactive preparations, *Juniperus* genus has been investigated for phytochemicals such as abietatriene derivatives, widdrol, deoxypodophyllotoxin, amentoflavone, dehydroabietic acid and limonene, whose properties could aid in new drug and product development (Kwon *et al.* 2010, Seca *et al.* 2015, Tavares and Seca 2018, Mukhtar *et al.* 2018). Among these taxa, those from the Caribbean are known to possess potent antitumor molecules against human cancer cell lines. For instance, in these taxa, researchers have been able to identify deoxypodophyllotoxin (Tammami *et al.* 1977), considered to be one of the most cytotoxic metabolites in the genus (Tavares and Seca 2018), and its biosynthetic product podophyllotoxin (Renouard *et al.* 2011), whose

concentrations in Caribbean taxa have made *J. bermudiana* its second most important producer (Bazaldúa *et al.* 2019). Chemical studies have also led to the detection of other useful compounds such as amentoflavone (Gadek and Quinn 1985), a flavonoid with properties such as antitumoral (Chen *et al.* 2015) antimicrobial (Coulerie *et al.* 2013), antioxidant (Li *et al.* 2014), anti-inflammatory (Abdallah *et al.* 2015), antidiabetic (Laishram *et al.* 2015) and diuretic (Aguilar *et al.* 2015, Tavares and Seca 2018). Additionally, widdrol has been found, a lignin reported to be antiproliferative against adenocarcinoma HT29 cells (Kwon *et al.* 2010), lipolysis inducer in mice adipocytes (Jeong *et al.* 2015) and inhibitor of *B. cinerea* growth (Ortiz *et al.* 2005). Moreover, other compounds with antifungal activity against *B. cinerea* have been identified and evaluated, including 15-hydroxy- α -pseudowiddrene, cedrol, 3-hydroxypseudowiddran-6(7)-en-4-ol, 12-hydroxywiddrol, sandaracopimaric acid and α -bisabolol (Ortiz *et al.* 2004, 2005).

Besides the aforementioned compounds, which have been uncovered and bioassayed, other molecules have been reported as part of the essential oil characterization of Caribbean junipers. A list summarizing reported compounds can be found in table 2. Said characterization of foliar terpenes was used to determine the systematic relationship among the taxa utilizing gas chromatography coupled with mass spectrometry (GC-MS) (Adams 1983, 2000). These studies revealed that in Hispaniolan varieties, bornyl acetate accounts for more than 30 % of their essential oil terpene content, followed by terpinen-4-ol, sabinene, limonene in *J. gracilior* var. *gracilior*, limonene and sabinene in *J. gracilior* var. *ekmanii*, and sabinene, limonene and terpinen-4-ol in *J. gracilior* var. *urbaniana* (Adams 1983, 2000). Junipers found in Caribbean territories other than this island do not possess bornyl acetate as their major essential oil component. Perhaps the best example is the Cuban *J. gracilior* variety, *saxicola*, which

Table 1. Reported bioactivities of Caribbean taxa extracts.

Bioactividades reportadas para los extractos de los taxones caribeños.

Taxa	Extract (organ)	Bioactivity	Reference
<i>J. bermudiana</i>	Ethanollic extract (twigs and leaves)	Inhibitory activity toward the P-388 lymphocytic leukemia (PS) cell line and cytotoxic activity toward human epidermoid carcinoma of the nasopharynx (KB)	Tammami <i>et al.</i> 1977
<i>J. barbadensis</i> var. <i>lucayana</i>	Acetone extract (wood)	Inhibition of the fungus <i>Botrytis cinerea</i> growth	Ortiz <i>et al.</i> 2004
<i>J. barbadensis</i> var. <i>lucayana</i>	Ethanollic extract (wood)	Inhibition of the fungus <i>B. cinerea</i> growth	Ortiz <i>et al.</i> 2004
<i>J. barbadensis</i> var. <i>lucayana</i>	Aqueous extract (stem)	Antimicrobial activity against <i>Staphylococcus aureus</i>	Martínez <i>et al.</i> 1996
<i>J. barbadensis</i> var. <i>barbadensis</i>	Aqueous extract (shoots)	Treats urinary system pathologies	Grosourdy 1864

Table 2. Summary of identified metabolites in Caribbean taxa.
 Resumen de los metabolitos identificados en taxones caribeños.

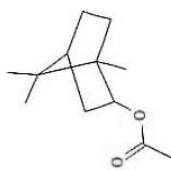
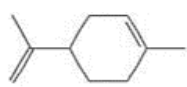
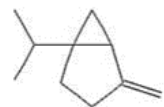

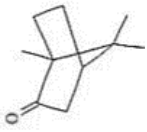
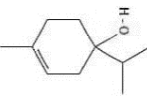
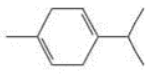
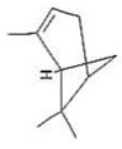
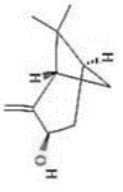
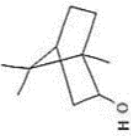

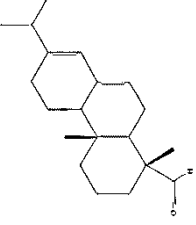
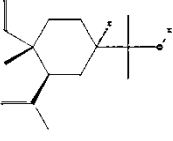
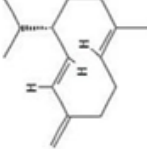
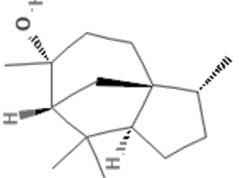
Compound (PubChem ID) method	Structure	Chemical Type	Taxa	Organ (solvent)	Identification	References
Bornyl acetate (6448)		Monoterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 1983
Limonene (22311)		Monoterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 1983
Sabinene (18818)		Monoterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 1983
Myrcene (31253)		Monoterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 2000

Table 2 Continued

Camphor (2537)		Monoterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>urbaniiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>urbaniiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
Terpene-4-ol (11230)		Monoterpene	<i>J. gracilior</i> var. <i>urbaniiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>urbaniiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
γ -Terpinene (7461)		Monoterpene	<i>J. gracilior</i> var. <i>urbaniiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 1983
α -Pinene (6654)		Monoterpene	<i>J. gracilior</i> var. <i>urbaniiana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
Trans-pinocarveol (1201530)		Monoterpene	<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 2000

Continue

Table 2 Continued

Borneol (64685)		Monoterpene	<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 2000
δ -2-Carene (78249)		Monoterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 1983
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 2000
4-Epi-Abietal (6427962)		Diterpene	<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
Elemol (92138)		Sesquiterpene	<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 2000
Germacrene D (5317570)		Sesquiterpene	<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 2000
Cubebol (11276107)		Sesquiterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>ekmanii</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>barbadensis</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	GC-MS	Adams 2000
			<i>J. bermudiana</i>	Leaves (water)	GC-MS	Adams 2000

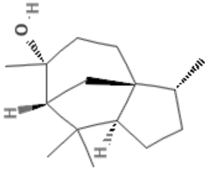
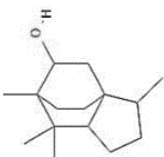
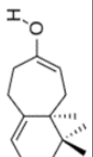
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Table 2 Continued

β-Eudesmol (91457)		Sesquiterpene	<i>J. gracilior</i> var. <i>gracilior</i>	Leaves (water)	GC-MS	Adams 2000
	<i>J. gracilior</i> var. <i>ekmanii</i>		Leaves (water)	GC-MS	Adams 2000	
	<i>J. gracilior</i> var. <i>urbaniana</i>		Leaves (water)	GC-MS	Adams 2000	
α-Eudesmol (92762)		Sesquiterpene	<i>J. gracilior</i> var. <i>saxicola</i>	Leaves (water)	GC-MS	Adams 2000
	<i>J. gracilior</i> var. <i>gracilior</i>		Leaves (water)	GC-MS	Adams 2000	
	<i>J. gracilior</i> var. <i>ekmanii</i>		Leaves (water)	GC-MS	Adams 2000	
Methyl eugenol (7127)		Cinnamate	<i>J. gracilior</i> var. <i>urbaniana</i>	Leaves (water)	GC-MS	Adams 2000
	<i>J. gracilior</i> var. <i>urbaniana</i>		Leaves (water)	GC-MS	Adams 2000	
	<i>J. bermudiana</i>		Leaves (water)	GC-MS	Adams 2000	
Sandaracopimaric acid (221580)		Diterpene	<i>J. bermudiana</i>	Leaves (*)	CC, TLC, IR, H-NMR	Khan 1989
	<i>J. bermudiana</i>		Leaves (*)	CC, TLC, IR, H-NMR	Khan 1989	
Hydroxypseudowiddran-6(7)-en-4-ol** (+)		Sesquiterpene	<i>J. barbadiensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007
	<i>J. barbadiensis</i> var. <i>lucayana</i>		Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007	
15-Hydroxyallo-cedrol** (+)		Sesquiterpene	<i>J. barbadiensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007
	<i>J. barbadiensis</i> var. <i>lucayana</i>		Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007	
12-Hydroxywiddrol** (+)		Sesquiterpene	<i>J. barbadiensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007
	<i>J. barbadiensis</i> var. <i>lucayana</i>		Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007	
β-Chamigrenic acid (13648247)		Sesquiterpene	<i>J. barbadiensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007
	<i>J. barbadiensis</i> var. <i>lucayana</i>		Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Núñez <i>et al.</i> 2007	

Continue

Table 2 Continued

α -Bisabolol (442343)		Sesquiterpene	<i>J. barbadensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, HPLC, spectroscopy	Ortiz <i>et al.</i> 2005
Cedrol (65575)		Sesquiterpene	<i>J. barbadensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, HPLC, spectroscopy	Ortiz <i>et al.</i> 2005
allo-Cedrol (527227)		Sesquiterpene	<i>J. barbadensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, HPLC, spectroscopy	Ortiz <i>et al.</i> 2005
Widdrol (94334)		Sesquiterpene	<i>J. barbadensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, HPLC, spectroscopy	Ortiz <i>et al.</i> 2005
15-Hidroxy- α -pseudowiddrene** (+)		Sesquiterpene	<i>J. barbadensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, HPLC, spectroscopy	Ortiz <i>et al.</i> 2005
Robustiflavone (5281694)		Flavonoid	<i>J. bermudiana</i>	Leaves and small branchlets (70 % ethanol and petrol)	HPLC-UV	Gadek and Quinn 1985
7,4-dimethylamentoflavone (5271805)		Flavonoid	<i>J. bermudiana</i>	Leaves and small branchlets (70 % ethanol and petrol)	HPLC-UV	Gadek and Quinn 1985



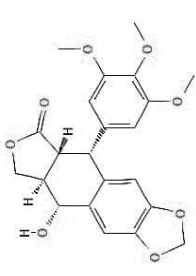
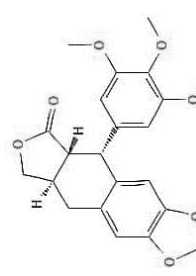
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Table 2 Continued

Amentoflavone (5281600)		Flavonoid	<i>J. bermudiana</i>	Leaves and small branchlets (70 % etanol and petrol)	HPLC-UV	Gadek and Quinn 1985
Quercetin-3-O- α -L- rhamnopyranoside (40486293)		Flavonoid	<i>J. bermudiana</i>	Leaves (water and then ethyl acetate)	CC, TLC, IR, H-NMR	Khan 1989
Cupressuflavone (5281609)		Flavonoid	<i>J. bermudiana</i>	Leaves and small branchlets (70 % etanol and petrol)	HPLC-UV	Gadek and Quinn 1985
Hinokiflavone (5281627)		Flavonoid	<i>J. bermudiana</i>	Leaves and small branchlets (70 % etanol and petrol)	HPLC-UV	Gadek and Quinn 1985
Naringenin (932)		Flavonoid	<i>J. barbadensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Nuñez <i>et al.</i> 2007
Aromadendrin (122850)		Flavonoid	<i>J. barbadensis</i> var. <i>lucayana</i>	Wood (ethanol)	CC, TLC, HPLC, H NMR, C NMR, 2D NMR, MS, IR	Nuñez <i>et al.</i> 2007

Continue

Table 2 Continued

1-Nonacosanol (243696)		Fatty alcohol	<i>J. bermudiana</i>	Leaves (*)	CC, TLC, IR, H-NMR	Khan 1989
Nonacosane (12409)		Hydrocarbon	<i>J. bermudiana</i>	Leaves (*)	CC, TLC, IR, H-NMR	Khan 1989
Podophyllotoxin (10607)		Lignan	<i>J. barbadensis</i> var. <i>lucayana</i>	Leaves (water)	CC, IR, NMR	Fitzgerald <i>et al.</i> 1957
Deoxypodophyllotoxin (345501)		Lignan	<i>J. bermudiana</i>	Twigs and leaves (ethanol)	CC, TLC, IR, NMR	Tammami <i>et al.</i> 1977

+: compound not found in PubChem, structure taken from reference; x: unspecified; *: acetone extraction treated with petroleum ether and benzene; **: a novel compound found in the taxa; CC: column chromatography; TLC: thin layer chromatography; IR: infrared spectroscopy; H-NMR: proton nuclear magnetic resonance; GC: gas chromatography coupled to mass spectrometry; HPLC: high-performance liquid chromatography; MS: mass spectrometry; C-NMR: carbon nuclear magnetic resonance; UV: ultraviolet spectroscopy; 2D NMR: two-dimensional nuclear magnetic resonance spectroscopy.

has 4-epi-abietal, elemol and sabinene as its majoritary terpenes, only having 0.3 % bornyl acetate in its oil (Adams 2000). As for the remaining Caribbean junipers: *J. barbadensis* var. *barbadensis* has limonene, sabinene, terpinen-4-ol, and α -pinene, while *J. bermudiana*, has limonene, α -pinene and camphor, and *Juniperus barbadensis* var. *lucayana* α -pinene, limonene and sabinene as their major essential oil terpenes (Adams 2000). The bioactive potential of the pure form of some of these majority essential oil compounds can be consulted in table 3.

In general, literature describing the chemical composition and usage of the Caribbean taxa is concentrated on *J. bermudiana* and *J. barbadensis* var. *lucayana* (Fitzgerald *et al.* 1957, Tammami *et al.* 1977, Gadek and Quinn 1985, Khan 1989, Martínez 1996, Ortiz *et al.* 2004, 2005, Nuñez *et al.* 2007, Renouard *et al.* 2011, Wolsak 2017). The other taxa are only mentioned in studies about insect repellency and are not reported their traditional usage and medicine bibliography in their respective countries (Jacobson 2018). Studies involving a holistic chemical characterization of these taxa with subsequent bioactivity assays need to be conducted to elucidate the phytochemical composition and potential usage of these conifers. The mentioned pure form bioactivities of these essential oil terpenes, although not accounting for their synergistic or antagonistic interactions with other compounds, might present a lead for future bioactivity assays of the taxa.

FUTURE DIRECTION IN INVESTIGATING JUNIPERS PHYTOCHEMICALS, THE METABOLOMICS APPROACH

As mentioned above, the full phytochemical composition of endemic Caribbean *Juniperus* spp. is widely understudied. This information, being of pivotal importance for

botanical, conservation, and pharmacological purposes, is crucial for bioprospecting studies of the species to increase its protection locally. Currently, among the characterization of living organisms, metabolomics is playing a key role, either alone or in combination with guided biological activity assays (Wishart 2016). Metabolomics is the systematic study, identification and quantification, of the metabolites in an organism at a specific moment in time (metabolome) (Tugizimana *et al.* 2013). And while phylogenetic lineages can help select new taxon targets for bioactivity studies, metabolomics can help identify structurally related metabolites conserved throughout evolution that might be of interest to the investigator (Mawalagedera *et al.* 2019).

In a broad sense, the steps of a metabolomics study (figure 3) are as follows: material sampling and extraction, extract analyses or data acquisition, statistical analyses and metabolite identification (Choi and Verpoorte 2014). How these steps are performed ultimately depends on the investigator's objective and approach (targeted or untargeted). A targeted approach identifies and quantifies a few known and predetermined metabolites, while an untargeted one aims to study all the known and unknown metabolites present in a sample (Tugizimana *et al.* 2013).

For metabolite identification and quantification, different extraction solvents and methodologies can be employed. According to the analytical platform used, metabolomic studies mainly belong to two groups, MS- and RMN- based. These can be utilized in parallel or combination to other classic protocols of thin layer, liquid or gas chromatography, spectrometry and spectroscopy (Nuñez *et al.* 2007). The platforms employed in the identification of chemical components of the *Juniperus* Caribbean clade can be found in table 2. As a whole, this genus has had compounds from leaf, wood and berry extract characterized, with most of these investigations being designed with

Table 3. Essential oil majority terpenes of Hispaniolian junipers and their pure form bioactivities.

Bioactividades de las formas puras de los terpenoides mayoritarios en el aceite esencial de los *Juniperus* de la Hispaniola.

Terpene	Bioactivities	References
Bornyl acetate	Antioxidant and anti-inflammatory. Acaricidal against <i>Dermaphagoides farinae</i> , <i>D. pteronyssinus</i> and <i>Tyrophagus putrescentiae</i> . Strong fumigant with contact toxicity against <i>Liposcelis bostrychophila</i> and <i>Tribolium castaneum</i> .	Lee <i>et al.</i> 2009, Chen <i>et al.</i> 2014, Yang <i>et al.</i> 2014, Feng <i>et al.</i> 2019
Terpinen-4-ol	Anti-demodectic and antimicrobial against <i>Streptococcus mutans</i> and <i>Lactobacillus acidophilus</i> . Significant growth inhibitor of colorectal, pancreatic, prostate and gastric cancer cells.	Shapira <i>et al.</i> 2016, Bordini <i>et al.</i> 2018, Cheung <i>et al.</i> 2018
Sabinene	Strong antioxidant activity and antibacterial activity against <i>Escherichia coli</i> .	Sharma <i>et al.</i> 2019
Limonene	Antiviral, anti-inflammatory, and antibacterial. Antitumor capabilities for gastric lung, pancreatic, mammary, liver and colon tumor models.	Stayrook <i>et al.</i> 1997, Yoon <i>et al.</i> 2010, Jia <i>et al.</i> 2013, Astani and Schnitzler 2014, Zhang <i>et al.</i> 2014, Miller <i>et al.</i> 2015, Yu <i>et al.</i> 2018, Hafidh <i>et al.</i> 2018, Han <i>et al.</i> 2019

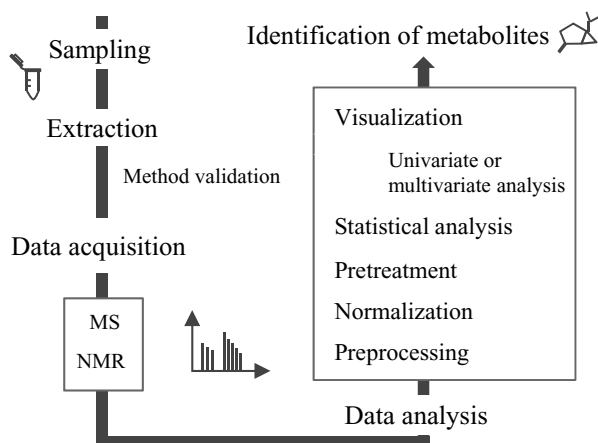


Figure 3. General metabolomics workflow.

Flujo de trabajo general para un experimento de metabolómica.

a targeted approach to specific chemical groups (Adams 2000, Renouard *et al.* 2011, Falasca *et al.* 2013, Rangel *et al.* 2018). For the identification of novel and/or useful bioactive compounds of *J. gracilior* and other Caribbean junipers, an untargeted approach focused on a larger range of metabolites including uninvestigated chemical groups such as polyphenols, known antioxidants, anti-mutagenic and antitumor compounds (Rangel *et al.* 2018), might need to be used.

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