

LYCHNOPHORINAE (ASTERACEAE): A SURVEY OF ITS CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES[#]**Larissa Costa Keles, Nathalya Isabel de Melo, Gabriela de Paula Aguiar, Kamila Akemi Lima Wakabayashi, Carlos Eduardo de Carvalho, Wilson Roberto Cunha e Antônio Eduardo Miller Crotti**

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LYCHNOPHORINAE (ASTERACEAE): A SURVEY OF ITS CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES.

This work reviews the current literature about the chemical constituents and the biological activities of the subtribe Lychnophorinae (Vernoniae, Asteraceae). The notable secondary metabolites are sesquiterpene lactones of furanoheliangolide (goyzensolide and eremantholide types) and flavonoids. Some of its most investigated activities include its anti-inflammatory, analgesic, antimicrobial and cytotoxic activities, specially for the *Lychnophora* and *Eremanthus* species. The data presented on this paper not only displayed the role played by the Lychnophorinae species as a source of bioactive compounds, but also reinforced the need of further studies involving the species of such subtribe.

Keywords: Lychnophorinae; *Lychnophora*; sesquiterpene lactones.**INTRODUCTION**

The subtribe Lychnophorinae belongs to the tribe Vernoniae of Asteraceae (Compositae). Most of its genera is found on the Brazilian's rupestrian vegetation (Table 1), which is present on the top of mountain chains on the Central and Southeastern regions of Brazil, especially in Minas Gerais, Bahia and Goiás, all presenting many species¹ with a high degree of endemism.

Due to the taxonomic complexity of the Lychnophorinae, the genera of this subtribe have received considerable attention and several previous classification had to be changed.²⁻⁴ In the most recent literature review of Lychnophorinae, Robinson³ considered the following ten genera: *Anteremanthus* H. Robinson, *Chronopappus* DC, *Eremanthus* Less. (syn. *Sphaerophora* Schultz-Bip = *Paralychnophora* MacLeish), *Vanillosmopsis* Schultz-Bip, *Lychnophora* Mart. (syn. *Haplostephium* Mart.), *Lychnophoriopsis* Schultz-Bip. (syn. *Episcothamnus* H. Robinson), *Minasia* H. Robinson, *Piptolepis* Schultz-Bip, *Pithecoseris* Mart., and *Proteopsis* Mart & Zucc. ex Schultz-Bip.

The terpenoid chemistry of this subtribe is mainly formed by furanoheliangolide sesquiterpene lactones (STL).⁴ The biological activities of these compounds were extensively investigated in the literature. Some species of the subtribe Lychnophorinae have also been employed in Brazilian traditional medicine. For example, the *Lychnophora* species, popularly known as “arnica da serra” or “falsa arnica” are used as analgesic and anti-inflammatory agents.⁵ Some species also have an economic importance, such as *Eremanthus erythropappa*, popularly known as “candeia” in Portuguese, whose essential oil is rich in α -bisabolol and it is used in several cosmetic preparations.⁶

Based on the economical and social importance of the subtribe Lychnophorinae, the goal of this work is to present a current literature review on the secondary metabolites and biological activities of the species of such subtribe in order to provide a basis for several

different research areas such as botanic, pharmaceutical, medical and chemical fields.

SECONDARY METABOLITES OF LYCHNOPHORINAE

The chemical composition of *Eremanthus* and *Lychnophora*, the two most numerous genera of Lychnophorinae have been extensively investigated, as clearly seen by the number of papers dealing with this matter. On the other hand, some genera of this subtribe (i.e., *Anteremanthus*, *Chronopappus* and *Pithecoseris*) have not been submitted to phytochemical studies yet. Previous studies have been mostly focused on the investigation of extracts from the aerial parts or leaves of this subtribe, although a number of studies on roots have also been reported.⁷⁻¹⁶ The secondary metabolites mentioned earlier were usually identified and/or isolated from extracts obtained by maceration with non-polar (*n*-hexane or petroleum ether) or moderately polar solvents (i.e., dichloromethane, chloroform, and ethyl acetate). Nevertheless, more recent studies have focused on the chemical composition of alcoholic and hydroalcoholic extracts.^{11,12,17,18} Alternative extraction methods, such as glandular trichomes microsampling¹⁹ and sonication-assisted extraction²⁰ have also been investigated.

Figure 1 shows the main groups of secondary metabolites that have been described for the Lychnophorinae species, and their structures are shown in Figures 5-21. Terpenoids (70.2%) and flavonoids (16.9%) are the notable secondary metabolites of Lychnophorinae, although acetylene derivatives (2.6%), quinic acid derivatives (5.0%), benzoic acid derivatives (0.4%), phenylpropanoids (1.4%), and lignans (1.2%) have also been reported. It must be mentioned that the lack of data on the chemical composition of polar fractions and hydroalcoholic and aqueous extracts have direct influence on the number of occurrences of such metabolite groups in literature.

Among the terpenoids, there is a predominance of sesquiterpenes (65.8%), which are reported to be present in each species of the subtribe, as shown in Figure 2. Triterpenes (26.9%), steroids (2.9%), saponins (0.3%) and monoterpenes (3.7%) have also been noted, whereas diterpenes (0.2%) were found only in *Lychnophora*

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[#]This paper is dedicated to Prof. Hans Vierthler

Table 1. Chemical constituents isolated and/or identified from species of the subtribe *Lychnophorinae**

Species	Chemical constituents	Ref.
<i>Eremanthus arboreus</i> (Gardner) MacLeish [= <i>Vanillosmopsis arborea</i> (Gardner) Baker]	19 ^w -EO, 25 ^w -EO, 27 ^w -EO/w-Hex, 28 ^w -Hex, 37 ^w -EO, 39 ^w -EO, 40 ^w -EO, 75 ^w -EO, 77 ^w -EO, 80 ^w -EO, 126 ^{ap} -EtOAc, 127 ^{ap} -EtOAc, 137 ^{ap} -EtOAc, 235 ^w -EO, 236 ^w -EtOH, 237 ^w -EtOH, 266 ^{ap} -EtOAc	46
<i>E. argenteus</i> McLeish & H. Schumacher	94 ^{ils} -CHCl ₃ , 96 ^{ils} -CHCl ₃ , 135 ^{ils} -CHCl ₃ , 136 ^{ils} -CHCl ₃ , 276 ^{ils} -CHCl ₃ , 291 ^{ils} -CHCl ₃ , 296 ^{ils} -CHCl ₃	47
<i>E. bicolor</i> (DC.) Baker	83 ^{ap} -PE, 88 ^{ap} -PE, 102 ^{ap} -PE, 104 ^{ap} -PE, 116 ^{ap} -PE, 119 ^{ap} -PE, 121 ^{ap} -PE, 139 ^{ap} -PE, 141 ^{ap} -PE, 146 ^{ap} -PE, 147 ^r -PE, 179 ^r -PE, 184 ^r -PE, 185 ^r -PE, 186 ^r -PE, 202 ^{ap} -PE, 203 ^r -PE/ap-PE, 225 ^r -PE, 229 ^r -PE, 230 ^r -PE, 231 ^r -PE	8
<i>E. brasiliensis</i> (Gardner) MacLeish [= <i>Vanillosmopsis brasiliensis</i> (Gardner) Sch. Bip.]	34 ^{ap} -PE, 69 ^{ap} -PE, 84 ^{ap} -PE, 113 ^{ap} -PE, 179 ^{ap} -PE, 201 ^{ap} -PE, 202 ^{ap} -PE, 203 ^{ap} -PE, 230 ^{ap} -PE, 231 ^{ap} -PE, 289 ^{ap} -PE	16
<i>E. cinctus</i> Baker	190 ^t -CHCl ₃ , 203 ^{is} -CHCl ₃ , 216 ^{is} -CHCl ₃ , 219 ^{is} -CHCl ₃ , 221 ^{is} -CHCl ₃ , 224 ^{is} -CHCl ₃ , 226 ^{es} -CHCl ₃ , 234 ^l -MeOH, 257 ^l -MeOH, 272 ^{es} -MeOH, 319 ^l -MeOH/l-MeOH	48
<i>E. crotonoides</i> (DC.) Sch. Bip.	34 ^{ap} -PE, 45 ^{ap} -PE, 52 ^{ap} -PE, 69 ^{ap} -PE, 83 ^{ap} -PE, 86 ^{ap} -PE, 88 ^{ap} -PE, 91 ^{ap} -PE, 104 ^{ap} -PE, 105 ^{ap} -PE, 116 ^{ap} -PE, 119 ^{ap} -PE, 121 ^{ap} -PE, 135 ^{ap} -PE, 200 ^{ap} -PE, 202 ^{ap} -PE, 203 ^{ap} -PE, 215 ^{ap} -PE, 216 ^{ap} -PE	49
<i>E. elaeagnus</i> (Mart. ex. DC.) Sch. Bip.	27 ^l -MeOH, 83 ^l -MeOH, 84 ^l -MeOH, 101 ^l -MeOH, 102 ^l -MeOH, 106 ^l -MeOH, 107 ^l -MeOH, 116 ^l -MeOH/s-MeOH:H ₂ O, 119 ^l -MeOH/s-MeOH:H ₂ O, 125 ^l -MeOH/s-MeOH:H ₂ O, 141 ^l -MeOH, 149 ^l -EtOAc/l-MeOH, 150 ^l -EtOAc, 151 ^l -EtOAc, 152 ^l -EtOAc, 179 ^w -Hex/ap-DCM, 199 ^s -PE, 202 ^s -PE, 203 ^s -PE, 215 ^l -MeOH, 220 ^l -MeOH, 223 ^l -MeOH, 224 ^l -MeOH, 226 ^s -PE, 227 ^s -PE, 256 ^l -MeOH, 262 ^l -EtOAc, 268 ^s -MeOH:H ₂ O, 269 ^s -MeOH:H ₂ O, 274 ^l -MeOH, 282 ^l -MeOH, 283 ^w -MeOH:H ₂ O, 291 ^l -EtOAc	24, 50-52
<i>E. erythropappus</i> (DC.) MacLeish [<i>Vanillosmopsis erythropappa</i> (DC.) Sch. Bip.]	1 ^l -EO, 2 ^l -EO, 3 ^l -EO, 5 ^l -EO, 7 ^l -EO, 8 ^l -EO, 9 ^l -EO, 13 ^l -EO, 14 ^l -EO, 15 ^l -EO, 19 ^l -EO, 20 ^l -EO, 27 ^w -EtOAc, 34 ^l -EO, 35 ^l -EO, 36 ^l -EO, 37 ^l -EO, 38 ^l -EO, 42 ^l -EO, 45 ^l -EO, 52 ^l -EO, 58 ^l -EO, 69 ^l -EO, 71 ^l -EO, 73 ^l -EO, 76 ^l -EO, 79 ^l -EO, 83 ^{ap} -Hex/w-EtOAc, 84 ^w -EtOAc, 91 ^w -EtOAc, 95 ^w -EtOH, 136 ^w -EtOH, 139 ^w -EtOH, 143 ^w -EtOH, 147 ^w -EtOAc, 173 ^w -EtOH, 174 ^w -EtOH, 175 ^w -EtOH, 176 ^w -EtOH, 177 ^w -EtOH, 178 ^w -EtOH, 179 ^w -EtOH, 180 ^w -EtOH, 182 ^w -EtOH, 184 ^w -EtOH, 191 ^w -EtOH, 193 ^w -EtOH, 195 ^w -EtOH, 196 ^w -EtOH	53, 54
<i>E. eriopus</i> Sch. Bip. ex Baker	92 ^{ap} -CHCl ₃ , 161 ^{ap} -CHCl ₃ , 272 ^{ap} -CHCl ₃ , 295 ^{ap} -CHCl ₃	55
<i>E. glomerulatus</i> Less.	34 ^{ap} -PE, 40 ^{ap} -PE, 52 ^{ap} -PE, 60 ^{ap} -PE, 70 ^{ap} -PE, 80 ^{ap} -PE, 94 ^{ap} -PE, 95 ^{ap} -PE, 98 ^{ap} -PE, 111 ^{ap} -PE, 116 ^r -PE/t-Hex:EtOAc, 117 ^t -Hex:EtOAc, 122 ^{ap} -PE, 123 ^{ap} -PE, 124 ^{ap} -PE, 128 ^t -Hex:EtOAc, 129 ^t -Hex:EtOAc, 131 ^t -Hex:EtOAc, 132 ^t -Hex:EtOAc, 134 ^t -Hex:EtOAc, 135 ^{ap} -PE, 147 ^r -PE, 155 ^{ap} -PE, 161 ^{ap} -PE/t-Hex:EtOAc, 163 ^{ap} -PE/t-Hex:EtOAc, 164 ^{ap} -PE, 165 ^t -Hex:EtOAc, 191 ^{ap} -PE, 200 ^r -PE, 202 ^{ap} -PE, 203 ^{ap} -PE/t-PE, 204 ^{ap} -PE, 209 ^r -PE, 212 ^r -PE, 231 ^{ap} -PE, 293 ^{ap} -PE	8, 49, 50, 56, 57
<i>E. goyazensis</i> (Gardner) Sch. Bip.	84 ^{ap} -EtOAc/ap-CHCl ₃ , 106 ^{ap} -EtOAc, 107 ^{ap} -EtOAc, 116 ^{ap} -EtOAc, 117 ^{ap} -EtOAc, 139 ^{ap} -EtOAc, 142 ^{ap} -EtOAc, 182 ^w -EtOH, 183 ^w -EtOH, 282 ^{ap} -EtOAc	53, 58
<i>E. incanus</i> (Less.) Less.	27 ^{ap} -PE, 119 ^{ap} -PE, 147 ^{ap} -PE, 179 ^{ap} -PE, 189 ^{ap} -PE, 202 ^{ap} -PE, 203 ^{ap} -PE, 242 ^{ap} -PE	8, 41, 59
<i>E. mattogrossensis</i> Kuntze	84 ^{ap} -CHCl ₃ , 113 ^{ap} -CHCl ₃ , 302 ^{ap} -CHCl ₃	55
<i>E. mollis</i> Sch. Bip.	34 ^{ap} -PE, 52 ^{ap} -PE, 69 ^{ap} -PE, 74 ^{ap} -PE, 84 ^{ap} -PE, 92 ^{ap} -PE, 202 ^{ap} -PE, 203 ^{ap} -PE/t-PE, 239 ^{ap} -PE, 243 ^{ap} -PE, 244 ^{ap} -PE, 289 ^{ap} -PE, 293 ^{ap} -PE	56
<i>E. polhii</i> (Baker) MacLeish [<i>Vanillosmopsis pohlii</i> Baker]	3 ^l -EO, 5 ^l -EO, 13 ^l -EO, 15 ^l -EO, 19 ^w -EO, 27 ^w -EO, 34 ^{ap} -PE, 35 ^l -EO, 36 ^l -EO, 45 ^w -EO/l-EO, 52 ^l -EO, 69 ^{ap} -PE, 73 ^l -EO, 84 ^{ap} -PE, 113 ^{ap} -PE, 202 ^{ap} -PE, 203 ^{ap} -PE, 204 ^{ap} -PE, 212 ^{ap} -PE, 214 ^{ap} -PE, 215 ^{ap} -PE, 216 ^{ap} -PE, 230 ^{ap} -PE, 231 ^{ap} -PE	16, 60
<i>E. seidelii</i> MacLeish & H. Schumacher	102 ^{ap} -EtOAc, 105 ^{ap} -EtOAc, 106 ^{ap} -EtOAc, 107 ^{ap} -EtOAc/l-EtOH, 139 ^{ap} -EtOAc, 141 ^{ap} -EtOAc, 142 ^{ap} -EtOAc, 282 ^{ap} -EtOAc	53, 61
<i>E. uniflorus</i> MacLeish & H. Schumacher	84 ^t -CHCl ₃ , 200 ^t -CHCl ₃ , 202 ^t -CHCl ₃ , 203 ^t -CHCl ₃ , 205 ^t -CHCl ₃ , 215 ^t -CHCl ₃ , 216 ^t -CHCl ₃ , 218 ^t -CHCl ₃ , 219 ^t -CHCl ₃ , 220 ^t -CHCl ₃ , 221 ^t -CHCl ₃ , 224 ^t -CHCl ₃ , 233 ^t -CHCl ₃ , 234 ^t -CHCl ₃ , 240 ^t -CHCl ₃ , 262 ^t -MeOH, 264 ^t -CHCl ₃ , 272 ^t -CHCl ₃ , 276 ^t -CHCl ₃ , 289 ^t -CHCl ₃ , 292 ^t -CHCl ₃ , 297 ^t -CHCl ₃	48
<i>E. veadeiroensis</i> H. Rob.	56 ^{ap} -CHCl ₃ , 179 ^s -Hex:EtOAc, 192 ^s -Hex:EtOAc, 200 ^s -Hex:EtOAc/s-EtOH, 202 ^s -EtOH, 205 ^s -Hex:EtOAc, 206 ^s -Hex:EtOAc, 215 ^s -EtOH, 218 ^s -EtOH, 220 ^s -EtOH, 223 ^s -EtOH, 226 ^s -EtOH, 227 ^s -Hex:EtOAc/s-EtOH, 257 ^{ap} -EtOH, 272 ^{ap} -CHCl ₃ , 274 ^{ap} -CHCl ₃ , 276 ^{ap} -CHCl ₃ /ap-EtOH, 319 ^{ap} -CHCl ₃ /ap-EtOH	48, 62
<i>Lychnophora affinis</i> Gardner	46 ^{ap} -EtOH, 47 ^{ap} -EtOH, 90 ^{ap} -EtOH, 92 ^{ap} -EtOH, 116 ^{ap} -EtOH, 121 ^{ap} -EtOH, 129 ^{ap} -EtOH, 130 ^{ap} -EtOH, 132 ^{ap} -EtOH, 133 ^{ap} -EtOH, 217 ^{ap} -EtOH, 271 ^{ap} -EtOH, 273 ^{ap} -EtOH, 274 ^{ap} -EtOH, 275 ^{ap} -EtOH, 276 ^{ap} -EtOH, 277 ^{ap} -EtOH, 294 ^{ap} -EtOH, 297 ^{ap} -EtOH, 298 ^{ap} -EtOH	9, 42, 63
<i>L. antillana</i> Urb.	153 ^{sl} -DCM-MeOH, 154 ^{sl} -DCM-MeOH, 205 ^{sl} -DCM-MeOH, 222 ^{sl} -DCM-MeOH	10
<i>L. bahiensis</i> Mattf.	83 ^r -PE/ap-PE, 91 ^{ap} -PE/r-PE, 92 ^{ap} -PE, 128 ^{ap} -PE, 131 ^{ap} -PE, 134 ^{ap} -PE, 179 ^r -PE, 184 ^r -PE, 200 ^{ap} -PE, 202 ^{ap} -PE/r-PE, 203 ^r -PE/ap-PE, 204 ^r -PE/ap-PE, 230 ^r -PE/ap-PE	21
<i>L. blanchetti</i> Sch. Bip.	41 ^r -PE, 71 ^r -PE, 83 ^{ap} -PE, 91 ^r -PE, 147 ^r -PE, 148 ^r -PE, 157 ^{ap} -PE, 158 ^{ap} -PE, 159 ^{ap} -PE, 160 ^{ap} -PE, 162 ^{ap} -PE, 165 ^{ap} -PE, 179 ^r -PE/ap-PE, 188 ^r -PE, 190 ^r -PE, 193 ^r -PE, 202 ^{ap} -PE, 203 ^r -PE, 230 ^r -PE/ap-PE, 242 ^r -PE	21, 64
<i>L. brunoides</i> Mart.	179 ^{ap} -EtOAc, 279 ^{ap} -EtOAc, 280 ^{ap} -EtOAc, 301 ^{ap} -EtOAc, 305 ^{ap} -EtOAc, 311 ^{ap} -EtOAc, 312 ^{ap} -EtOAc, 313 ^{ap} -EtOAc	65
<i>L. columnaris</i> Mattf.	52 ^{ap} -PE, 53 ^{ap} -PE, 54 ^{ap} -PE, 55 ^{ap} -PE, 56 ^{ap} -PE, 62 ^{ap} -PE, 63 ^{ap} -PE, 64 ^{ap} -PE, 65 ^{ap} -PE, 66 ^{ap} -PE, 67 ^{ap} -PE, 68 ^{ap} -PE, 91 ^{ap} -PE, 179 ^{ap} -PE, 181 ^r -PE, 183 ^r -PE, 200 ^{ap} -PE, 202 ^{ap} -PE/r-PE, 203 ^{ap} -PE/r-PE, 230 ^r -PE, 231 ^r -PE	66
<i>L. crispa</i> Mattf.	88 ^{ap} -PE, 91 ^{ap} -PE, 108 ^{ap} -PE, 110 ^{ap} -PE, 128 ^{ap} -PE, 131 ^{ap} -PE, 145 ^{ap} -PE, 179 ^r -PE, 202 ^r -PE/ap-PE, 203 ^r -PE/ap-PE, 230 ^r -PE/ap-PE	21
<i>L. diamantina</i> Coile & S. B. Jones	84 ^{ap} -EtOAc, 85 ^{ap} -EtOAc, 92 ^{ap} -EtOAc, 93 ^{ap} -EtOAc, 282 ^{ap} -EtOAc, 301 ^{ap} -EtOAc, 311 ^{ap} -EtOAc	67

Table 1. continuation

Species	Chemical constituents	Ref.
<i>L. ericoides</i> Mart.	4 ^l -EO, 5 ^l -EO, 6 ^l -EO, 7 ^l -EO, 8 ^l -EO, 10 ^l -EO, 11 ^l -EO, 12 ^l -EO, 13 ^l -EO, 16 ^l -EO, 17 ^l -EO, 18 ^l -EO, 19 ^l -EO, 21 ^l -EO, 22 ^l -EO, 23 ^l -EO, 26 ^l -EO, 27 ^l -EO, 30 ^l -EO, 37 ^l -EO, 45 ^l -EO, 72 ^l -EO, 81 ^l -EO, 82 ^l -EO, 83 ^l -MeOH, 84 ^l -DCM, 91 ^l -DCM/l-MeOH, 92 ^l -DCM/ap-DCM/l-MeOH, 95 ^l -DCM, 102 ^l -DCM/l-MeOH, 103 ^l -DCM/l-MeOH, 108 ^l -MeOH, 109 ^l -DCM, 110 ^l -DCM/l-MeOH, 115 ^l -MeOH, 116 ^l -DCM, 119 ^{ap} -Hex/l-DCM, 128 ^l -DCM/l-MeOH, 131 ^l -MeOH, 138 ^l -DCM/l-MeOH, 139 ^l -DCM/l-MeOH, 140 ^{ap} -EtOAc, 141 ^{ap} -Hex, 143 ^l -DCM, 144 ^l -DCM, 145 ^l -DCM/l-MeOH, 146 ^l -MeOH, 198 ^{ap} -Hex, 200 ^{ap} -Hex, 202 ^l -DCM/ap-Hex/l-MeOH, 220 ^l -DCM, 223 ^l -DCM, 225 ^l -DCM/ap-Hex, 227 ^{ap} -Hex, 245 ^r -DCM, 246 ^r -DCM, 247 ^r -DCM, 248 ^r -DCM, 249 ^r -DCM, 250 ^r -DCM, 251 ^r -DCM, 252 ^r -DCM, 253 ^r -DCM, 254 ^r -DCM, 256 ^l -MeOH, 257 ^l -MeOH, 258 ^l -MeOH, 259 ^l -MeOH, 262 ^{ap} -EtOAc/l-MeOH, 263 ^l -MeOH, 266 ^l -MeOH, 281 ^{ap} -EtOAc, 291 ^l -MeOH, 301 ^l -DCM/l-MeOH, 305 ^l -DCM/l-MeOH, 311 ^l -DCM/ap-DCM/l-MeOH, 314 ^l -MeOH, 315 ^l -MeOH, 316 ^l -MeOH, 317 ^l -MeOH, 318 ^l -MeOH, 319 ^l -MeOH, 320 ^l -MeOH, 322 ^l -MeOH, 323 ^l -MeOH, 324 ^l -MeOH, 325 ^l -MeOH, 326 ^l -MeOH, 327 ^l -MeOH, 328 ^l -MeOH, 330 ^l -MeOH, 331 ^l -MeOH, 332 ^r -MeOH/l-MeOH, 333 ^r -MeOH/l-MeOH, 334 ^r -MeOH/l-MeOH, 336 ^l -MeOH, 337 ^l -MeOH, 338 ^l -MeOH	11, 12, 18, 19, 27, 68-70
<i>L. gramogolensis</i> (Duarte) D. J. N. Hind	84 ^{li} -EtOAc, 90 ^{li} -EtOAc, 92 ^{li} -EtOAc, 264 ^{li} -EtOAc, 270 ^{li} -EtOAc, 286 ^{li} -EtOAc, 303 ^{li} -EtOAc, 304 ^{li} -EtOAc, 307 ^{li} -EtOAc, 313 ^{li} -EtOAc	31
<i>L. hakeaefolia</i> Mart.	91 ^{ap} /PE, 147 ^r -PE, 179 ^r -PE, 202 ^r -PE/ap-PE, 203 ^r -PE/ap-PE, 229 ^r -PE, 230 ^r -PE	13
<i>L. markgravi</i> Gardner	83 ^r -DCM, 88 ^r -DCM, 179 ^r -DCM, 199 ^r -DCM, 200 ^r -DCM, 202 ^r -DCM, 215 ^r -DCM, 218 ^r -DCM, 220 ^r -DCM, 223 ^r -DCM, 226 ^r -DCM, 267 ^{ap} -DCM, 288 ^{ap} -DCM, 301 ^{ap} -DCM, 305 ^{ap} -DCM, 319 ^{ap} -EtOH	71
<i>L. martiana</i> Gardner	49 ^{ap} -Hex:EtOAc, 51 ^{ap} -Hex:EtOAc	72
<i>L. passerina</i> (Mart. ex DC.) Gardner	52 ^{ap} -PE, 83 ^l -EtOH, 84 ^{ap} -EtOH/l-EtOH/ap-PE, 147 ^r -PE, 179 ^r -PE/ap-PE, 181 ^r -PE, 182 ^r -PE/ap-PE, 183 ^r -PE/ap-PE, 184 ^r -PE/ap-PE, 187 ^r -PE, 200 ^r -PE/ap-PE, 202 ^r -PE/ap-PE, 203 ^r -PE/ap-PE, 215 ^r -PE, 212 ^r -PE, 216 ^r -PE/ap-PE, 217 ^{ap} -PE, 223 ^r -PE/ap-PE, 224 ^r -PE/ap-PE, 257 ^l -EtOH, 262 ^l -EtOH, 280 ^l -EtOH, 281 ^l -EtOH, 319 ^l -EtOH, 321 ^l -MeOH	14, 17, 37
<i>L. phlycaefolia</i> DC.	45 ^{ap} -PE, 179 ^r -PE/ap-PE, 202 ^r -PE/ap-PE, 203 ^r -PE/ap-PE, 210 ^{ap} -PE, 229 ^r -PE, 230 ^r -PE, 308 ^{ap} -PE	13
<i>L. pinaster</i> Mart.	46 ^{ap} -Hex, 57 ^{ap} -Hex, 83 ^{ap} -DCM, 202 ^{ap} -Hex, 220 ^{ap} -Hex, 223 ^{ap} -Hex, 227 ^{ap} -Hex, 238 ^{ap} -EtOH:H ₂ O, 241 ^{ap} -EtOH:H ₂ O, 261 ^{ap} -EtOH:H ₂ O, 281 ^{ap} -DCM, 311 ^{ap} -EtOH:H ₂ O, 328 ^{ap} -EtOH:H ₂ O, 335 ^{li} -H ₂ O:MeOH	37, 73
<i>L. pohlii</i> Sch. Bip.	83 ^{li} -DCM, 84 ^{li} -DCM, 86 ^{li} -DCM, 91 ^{li} -DCM, 92 ^{li} -DCM/l-MeOH:H ₂ O, 241 ^{li} -MeOH, 258 ^{li} -MeOH/l-MeOH:H ₂ O, 260 ^{li} -MeOH:H ₂ O, 262 ^{li} -MeOH, 267 ^{li} -MeOH, 269 ^{li} -H ₂ O:MeOH, 274 ^{li} -DCM, 279 ^{li} -DCM, 282 ^{li} -H ₂ O:MeOH/l-MeOH:H ₂ O, 288 ^{li} -DCM, 300 ^{li} -MeOH:H ₂ O, 301 ^{li} -H ₂ O:MeOH/l-MeOH:H ₂ O, 311 ^{li} -DCM, 314 ^{li} -DCM, 320 ^{li} -H ₂ O:MeOH/l-MeOH:H ₂ O, 322 ^{li} -MeOH:H ₂ O, 323 ^l -MeOH:H ₂ O, 324 ^l -MeOH:H ₂ O, 325 ^l -MeOH:H ₂ O, 332 ^l -MeOH:H ₂ O, 333 ^l -MeOH:H ₂ O, 335 ^{li} -H ₂ O:MeOH	28, 70, 74
<i>L. pseudovillosissima</i> Semir & Leitão	83 ^{li} -EtOAc/ap-EtOAc, 87 ^{ap} -EtOAc, 91 ^{ap} -EtOAc/l-MeOH:H ₂ O, 166 ^{li} -EtOAc, 167 ^{li} -EtOAc, 168 ^{li} -EtOAc, 169 ^{li} -EtOAc, 170 ^{li} -EtOAc, 171 ^{li} -EtOAc, 172 ^{li} -EtOAc, 200 ^{ap} -EtOAc, 202 ^{ap} -EtOAc, 207 ^{ap} -EtOAc, 208 ^{ap} -EtOAc, 258 ^l -MeOH:H ₂ O, 260 ^l -MeOH:H ₂ O, 282 ^l -MeOH:H ₂ O, 300 ^l -MeOH:H ₂ O, 319 ^l -MeOH:H ₂ O, 320 ^l -MeOH:H ₂ O, 322 ^l -MeOH:H ₂ O, 323 ^l -MeOH:H ₂ O, 324 ^l -MeOH:H ₂ O, 325 ^l -MeOH:H ₂ O, 332 ^l -MeOH:H ₂ O, 333 ^l -MeOH:H ₂ O	28, 68, 70
<i>L. reticulata</i> Gardner	83 ^l -MeOH, 202 ^l -MeOH, 203 ^l -MeOH, 204 ^l -MeOH, 215 ^l -MeOH, 216 ^l -MeOH, 219 ^l -MeOH, 221 ^l -MeOH, 223 ^l -MeOH, 224 ^l -MeOH, 226 ^l -MeOH, 227 ^l -MeOH, 302 ^l -MeOH, 305 ^l -MeOH	75
<i>L. rupestris</i> Semir & Leitão	91 ^{li} -AcOEt, 116 ^{li} -EtOAc, 117 ^{li} -EtOAc, 118 ^{li} -EtOAc, 128 ^{li} -EtOAc, 131 ^{li} -EtOAc, 179 ^s -EtOAc, 180 ^s -EtOAc, 202 ^{li} -HEX, 207 ^{li} -HEX, 208 ^{li} -HEX, 223 ^{li} -HEX, 225 ^{li} -HEX, 265 ^{li} -EtOH, 300 ^{li} -EtOH, 332 ^s -MeOH	76, 77
<i>L. salicifolia</i> Mart.	43 ^{ap} -PE, 44 ^{ap} -PE, 45 ^{ap} -PE, 46 ^{ap} -PE, 48 ^{ap} -PE, 49 ^s -EtOH/li-EtOAc/ap-PE, 51 ^{li} -EtOAc/li-EtOH, 59 ^{ap} -PE, 60 ^{ap} -PE, 61 ^{ap} -PE, 147 ^{ap} -PE, 179 ^r -PE/ap-PE, 202 ^l -EtOH/ap-PE/li-EtOAc, 203 ^r -PE/ap-PE, 212 ^r -PE, 216 ^r -PE, 223 ^{ap} -PE, 224 ^{ap} -PE/r-PE, 230 ^r -PE/ap-PE, 231 ^{ap} -PE/r-PE, 276 ^{li} -EtOAc, 287 ^{li} -EtOAc, 297 ^{li} -EtOAc	13, 14, 32, 78, 79
<i>L. sellowii</i> Sch. Bip.	31 ^{ap} -PE, 32 ^{ap} -PE, 33 ^{ap} -PE, 91 ^{ap} -PE, 92 ^{ap} -PE, 114 ^{ap} -PE, 115 ^{ap} -PE, 179 ^{ap} -PE, 197 ^{ap} -PE, 202 ^{ap} -PE, 203 ^{ap} -PE, 230 ^{ap} -PE	21
<i>L. staavioides</i> Mart.	255 ^l -MeOH, 258 ^l -MeOH, 264 ^l -MeOH, 267 ^l -MeOH, 288 ^l -MeOH, 291 ^l -MeOH, 301 ^l -MeOH, 305 ^l -MeOH, 311 ^l -MeOH, 314 ^l -MeOH, 332 ^s -MeOH	39, 77
<i>L. trichocarpha</i> (Spreng.) Spreng.	91 ^{ap} -EtOH, 116 ^{ap} -EtOH, 199 ^{ap} -EtOH, 200 ^{ap} -EtOH, 202 ^{ap} -EtOH, 220 ^{ap} -EtOH, 223 ^{ap} -EtOH, 227 ^{ap} -EtOH	80, 81
<i>L. uniflora</i> Sch. Bip.	59 ^{ap} -PE, 91 ^{ap} -PE/r-PE, 116 ^{ap} -PE, 128 ^{ap} -PE, 179 ^r -PE, 200 ^{ap} -PE, 202 ^{ap} -PE/r-PE, 203 ^{ap} -PE/r-PE, 204 ^{ap} -PE/r-PE, 208 ^{ap} -PE, 210 ^{ap} -PE, 212 ^{ap} -PE/r-PE, 216 ^{ap} -PE, 223 ^{ap} -PE, 224 ^{ap} -PE	14
<i>L. villosissima</i> Mart.	83 ^{ap} -EtOH, 255 ^{ap} -EtOH, 258 ^{ap} -EtOH/l-MeOH:H ₂ O, 260 ^l -MeOH:H ₂ O, 262 ^{ap} -EtOH, 265 ^l -DCM, 279 ^l -DCM, 299 ^l -MeOH:H ₂ O, 320 ^l -MeOH:H ₂ O, 322 ^{ap} -EtOH/l-MeOH:H ₂ O, 323 ^l -MeOH:H ₂ O/ap-EtOH, 324 ^{ap} -EtOH/l-MeOH:H ₂ O, 325 ^l -MeOH:H ₂ O, 328 ^l -MeOH:H ₂ O, 332 ^{ap} -EtOH, 333 ^{ap} -EtOH/l-MeOH:H ₂ O	28, 70, 82
<i>Lychnophoriopsis candelabrum</i> (Sch. Bip.) H. Rob.	92 ^l -MeOH:H ₂ O, 209 ^l -DCM, 220 ^l -DCM, 223 ^l -DCM, 232 ^l -DCM, 258 ^l -MeOH:H ₂ O, 260 ^l -MeOH:H ₂ O, 265 ^l -DCM, 279 ^l -DCM, 282 ^l -MeOH:H ₂ O, 284 ^l -DCM, 285 ^l -DCM, 299 ^l -MeOH:H ₂ O, 301 ^l -MeOH:H ₂ O, 320 ^l -MeOH:H ₂ O, 322 ^l -MeOH:H ₂ O, 323 ^l -MeOH:H ₂ O, 324 ^l -MeOH:H ₂ O, 325 ^l -MeOH:H ₂ O, 327 ^l -MeOH:H ₂ O, 328 ^l -MeOH:H ₂ O, 333 ^l -MeOH:H ₂ O	15, 28
<i>Minasia alpestris</i> (Gardner) H. Robinson	83 ^l -DCM/r-DCM, 84 ^l -DCM, 86 ^l -DCM, 87 ^l -DCM, 88 ^l -DCM, 98 ^l -DCM, 99 ^l -DCM, 100 ^l -DCM, 116 ^l -DCM, 202 ^l -DCM, 215 ^l -DCM, 218 ^l -DCM, 220 ^l -DCM, 221 ^l -DCM	7, 83
<i>Piptolepis ericoides</i> (Less.) Sch. Bip.	110 ^r -PE, 164 ^r -PE, 202 ^r -PE, 203 ^r -PE, 204 ^{ap} -PE/r-PE, 229 ^{ap} -PE/r-PE, 230 ^r -PE	16
<i>P. leptospermoides</i> (Mart. ex DC.) Sch. Bip.	24 ^{ap} -PE, 34 ^{ap} -PE, 52 ^{ap} -PE, 91 ^{ap} -PE, 97 ^{ap} -PE, 116 ^{ap} -PE, 117 ^{ap} -PE, 128 ^{ap} -PE, 156 ^{ap} -PE, 179 ^r -PE, 201 ^{ap} -PE, 203 ^{ap} -PE/r-PE, 204 ^{ap} -PE/r-PE, 216 ^r -PE, 217 ^r -PE, 229 ^{ap} -PE	84
<i>P. argentea</i> Mart. & Zucc. ex Sch. Bip.	91 ^{ap} -PE/r-PE, 94 ^{ap} -PE/r-PE, 128 ^{ap} -PE/r-PE, 135 ^{ap} -PE/r-PE, 202 ^{ap} -PE/r-PE, 203 ^{ap} -PE/r-PE, 204 ^{ap} -PE, 212 ^{ap} -PE/r-PE, 214 ^r -PE, 229 ^r -PE, 230 ^{ap} -PE/r-PE, 231 ^{ap} -PE/r-PE	85
<i>P. furnensis</i> Semir & Leitão Filho	91 ^{ap} -EtOAc, 82 ^{ap} -EtOAc	86

* The superscripts following the number of the compound indicates the part of the plant and the extract from which each compound was isolated. **w**: wood; **ap**: aerial parts; **r**: roots; **i**: inflorescences; **is**: internal part of stem; **es**: external part of stem; **l**: leaves; **t**: total plant; **li**: leaves and inflorescences; **EO**: essential oil; **Hex**: hexane; **EtOAc**: ethyl acetate; **PE**: petroleum ether; **DCM**: dichloromethane; **EtOH**: ethanol; **MeOH**: methanol.

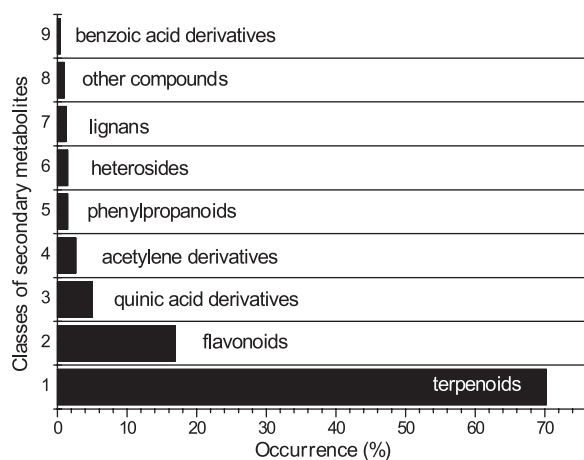


Figure 1. Percentage of secondary metabolites occurrence in Lychnophorinae (percentage was calculated in relation to the total hit number)

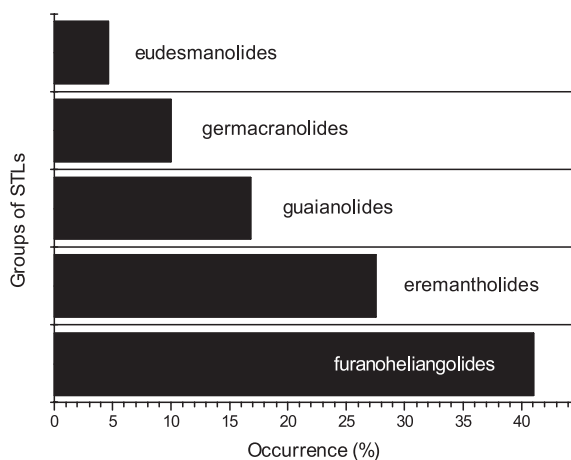


Figure 2. Occurrence of sesquiterpene lactones (STLs) in Lychnophorinae (percentage was calculated in relation to the total hit number)

selowii.²¹ Regarding the sesquiterpenes, sesquiterpene lactones (STL) are reported to be isolated and/or identified in 90% of the species investigated. This class of secondary metabolites is divided into groups (i.e., germacranolides, eudesmanolides, guaianolides, furanoheliangolides, among others) according to their structural diversity, which results of enzyme-catalyzed and eventually selective oxidations, cyclizations, condensations and rearrangements of their common biosynthetic precursor (farnesylpyrophosphate, FPP).²² Because of their number of occurrence and structural diversity, STLs have been used as chemotaxonomic markers of various *taxa* of Asteraceae,²³ including the subtribe Lychnophorinae.^{4,22}

Furanoheliangolides from the goyazensolide and eremantholide types are the most common STLs in Lychnophorinae, as shown in Figure 3. They have been reported to be the major STL of all the investigated species, except for *Lychnophoriopsis candelabrum*, *Lychnophora pseudovillosissima* and *L. reticulata*, in which the predominance of guaianolides and eudesmanolides were observed. Furanoheliangolides of the eremantholide type has been proposed to be biosynthesized from a goyazensolide type of STL by means of a Michael-type addition to the exocyclic double bond conjugated with the lactone carbonyl (Figure 3).^{22,24} The conversion of goyazensolide-type into eremantholide in laboratory was recently achieved by making use of Striker's reagent.²⁵ Most of the furanoheliangolides from goyazensolide type occurring in Lychnophorinae have the same structural core, but they differ on the degree of oxidation and

substituents at C-8. The majority mostly exhibit exocyclic double bond between C-11 and C-13 (94.8%) and an oxygenated group (a hydroxyl or an acyloxy group) bounded at C-8 (100%), followed by common methacryloxy (52.2%), angeloxy (36.5%), tigloxy (11.3%) or their derivatives. In contrast, oxygenated groups at C-15 (26.9%) and double bonds between C-4 and C-5 (74.8%) are less common. The oxygenated groups at C-8 from mostly of the STL of Lychnophorinae are usually α -orientated in relation to the mean plane of the ring, as reported for other subtribes of Vernoniae.²² Differently, the furanoheliangolides of the eremantholide type mostly shows double bond between C-4 and C-5 (72.7%) and hydroxyl at C-1' (93.5%), whereas oxygenated groups at C-15 are rarely found (20.8%).

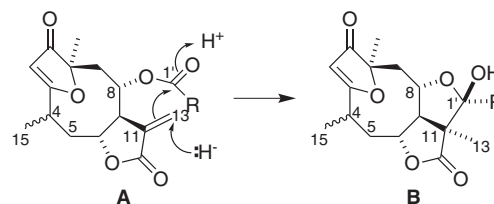


Figure 3. Biogenesis of eremantholides (B) from goyazensolide-type of furanoheliangolides (A)²⁴

Flavonoids also have a widespread occurrence in the subtribe Lychnophorinae. Flavonols (37.4%) and flavones (38.7%) have higher percentages of occurrence than dihydroflavones (12.9%), dihydroflavonols (9.7%) and chalcones (1.3%). Methoxyl (53.3%) and glycosyl (25.0%) are the most common substituent groups in flavones. The glycosyl groups are often bounded at C-6 and C-8 or at C-8 solely. In the case of flavonols, only 37.9% exhibit free hydroxyl group at C-3 (B ring), once this group is the precursor of methoxyl (32.8%), glycosyl (8.6%) and heteroside groups (20.7%). Chalcones have been identified only in *Lychnophora ericoides*.²⁶

Opposed to terpenoids and flavonoids, whose occurrence is widespread in Lychnophorinae, some classes of secondary metabolites have been restricted to some species. Lignans were isolated only from roots of *Lychnophora ericoides*,¹¹ and quinic acid derivatives have been found only in some *Lychnophora* species (*L. ericoides*,^{12,27} *L. pinaster*,²⁸ *L. pohli*²⁸ and *L. vilosissima*²⁸) and *Lychnophoriopsis candelabrum*.²⁸

BIOLOGICAL ACTIVITIES OF LYCHNOPHORINAE

Although fifty species of Lychnophorinae have been submitted to phytochemical studies, up to now only twenty-eight species were investigated regarding their biological activities, as shown in Table 2. Several biological activities from the species of the Lychnophorinae subtribe have been evaluated, and their mostly common reported activities are antimicrobial, anti-inflammatory, tripanocidal, toxicity, analgesic and antinociceptive (Figure 4).

Extracts from the *Lychnophora* species have been used in the Brazilian folk medicine as analgesic and anti-inflammatory. For this reason, a number of studies have focused on the evaluation of crude extracts and pure compounds for their analgesic and anti-inflammatory potential. Guzzo and co-workers²⁹ investigated the antinociceptive activity of the ethanol aerial parts extracts of five *Lychnophora* species using hot-plate and writhing tests. They reported that the *Lychnophora pinaster* (0.75 g/kg) and *Lychnophora ericoides* (1.50 g/kg) extracts significantly increased the time for paw licking in mice. By using the dose of 0.75g/kg for *Lychnophora passerina*, *Lychnophoriopsis candelabrum* and *Lychnophora pinaster*, and doses of 0.75 and 1.50 g/kg for both *Lychnophora ericoides* and *Lychnophora trichocarpha* it was observed a significant reduction on the number

Table 2. Biological activities of species of the subtribe Lychnophorinae

Species	Tested biological activities	Ref.
<i>Eremanthus arboreus</i>	Antiinflammatory activity of 15-hydroxyeremantholide B (126) and 15-acetoxyeremantholide B (127)	87
	Gastroprotective effect of the bark essential oil	88
	Anticholinesterase activity of dichloromethane:methanol and dichloromethane extracts	89
<i>E. elaeagnus</i>	Antitumoral activity of the ethanolic extract from stems and eremantholide A (119)	24,52
	Antiinflammatory activity of 15-deoxygoyazensolide (83)	87
	Citotoxicity of lychnopholide (91)	90
	Clastogenicity of eremanthin (179) and lychnopholide (91)	90,91
	Genotoxicity of eremanthin (179)	91
	Immunomodulatory activity of eremanthin (179)	92
	Schistosomicidal activity of eremanthin (179), costunolide (147) and α -bisabolol (27) against <i>Schistosoma mansoni</i>	92,93
<i>E. erythropappus</i>	Antimicrobial activity of the essential oil of leaves and β -bisabolene (25)	35,45,94
	Toxicity of extracts and essential oil of leaves	44,45
	Antifungal activity of essential oil, extracts and α -bisabolol (27)	95,96
	Moluscidal activity of the aerial parts ethanol extract against <i>Biomphalaria glabrata</i>	97
	Antiedematogenic activity of the essential oil of leaves	98
	Antinociceptive and antiinflammatory activities of the essential oil of leaves	36,95,99
	Antiulcerogenic activity of the essential oil of leaves and α -bisabolol (27)	100
<i>E. glomerulatus</i>	Moluscidal activity of the aerial parts ethanol extract against <i>Biomphalaria glabrata</i>	57,97
<i>E. goyazensis</i>	Citotoxicity and schistosomicidal activity of goyazensolide (84) against <i>Schistosoma mansoni</i>	101
<i>E. incanus</i>	Cytotoxic activity of eregoyazin (182)	41
<i>E. mattogrossensis</i>	Antiinflammatory activity of goyazensolide (84) and isogoyazensolide (112)	87
<i>E. pohlii</i>	Insecticidal activity of the essential oil against <i>Bemisia argentifolii</i>	60
<i>E. sphaerocephalus</i>	Moluscidal activity of the ethanol extract from the aerial parts against <i>Biomphalaria glabrata</i>	97
<i>Lychnophora affinis</i>	Antineoplastic activity and citotoxicity of flavonoids (255-321), lychnophorolide A (92) and lychnopholic acid (46)	9,40,42
<i>L. antillana</i>	Antineoplastic activity of crude ethanolic extract, lychnostatin 1 (153) and 2 (154)	10
<i>L. brunioides</i>	Moluscidal and tripanocidal activity of flavonoids isolated from the ethyl acetate extract of leaves	65,102
<i>L. diamantinana</i>	Antinociceptive and anticonvulsant effects of stems methanol extracts	77
<i>L. ericoides</i>	Analgesic activity of the crude lyophilized aqueous extracts from stem and leaves	5
	Analgesic activity of di-caffeoyquinic acids (325 , 332 and 333) isolated from roots methanolic extracts	12
	Analgesic and antioxidant activities of di-C-glucosylflavones isolated from hydromethanolic extract of leaves	18
	Anti-inflammatory, antipyretic and antiedematogenic activities of lignans (245-254) isolated from the dichloromethane extract of roots	11
	<i>In vitro</i> anti-inflammatory activity of centratherin (92) and goyazensolide (84)	33
	Antinociceptive and anti-inflammatory activity of ethanol extract from the aerial parts	29
	Antiproliferative activity of goyazensolide (84) isolated from cell culture	103
<i>L. gardneri</i>	Genotoxicity of 15-deoxygoyazensolide (83)	43
	Inhibitory activity of flavonoids 264 , 281 , 283 and 303 on generation of reactive oxygen species	104
	Xantine oxidase inhibitory activity of the ethanolic extract of the aerial parts	105
	Tripanocidal activity of crude extracts, flavonoids (255-321) and lychnopholic acid (46)	37
	Tripanocidal and analgesic activities of the crude hexane, ethyl acetate and ethanol extracts from the aerial parts and centratherin (92); goyazensolide (84), lychnophorolide B (90) and the flavonoid 303	31
	Antimicrobial activity of crude extracts from the aerial parts and flavonoids (255-321) against <i>Streptococcus sp</i>	106
	Leishmanicidal activity of flavonoids 267 and 305 , against <i>Leishmania amazonensis</i>	106
<i>L. passerina</i>	Tripanocidal activity of the hydroalcoholic extract of aerial parts and goyazensolide (84)	37,107
	Antinociceptive and antiinflammatory activities of the ethanolic extract from the aerial parts	29
	Inhibitory activity of flavonoids 264 , 281 , 283 and 303 on generation of reactive oxygen species	104
	Antioxidant activity of methanolic extracts from leaves, and quercetin (281), kaempferol (280) and tiliroside (319)	17
	Xantine oxidase inhibitory activity of the ethanolic extract of the aerial parts	105
<i>L. pinaster</i>	Antinociceptive and antiinflammatory activities of the ethanolic extract from the aerial parts	29
	Moluscidal activity of the ethanolic extract of the aerial parts against <i>Biomphalaria glabrata</i>	97
	Tripanocidal activity of the aqueous and hexane extracts of the aerial parts and lychnopholic acid (46)	37,108
	Xantine oxidase inhibitory activity of the ethanolic extract of the aerial parts	97

Table 2. continuation

Species	Tested biological activities	Ref.
<i>L. pohlii</i>	Tripanocidal activity of the n-hexane, dichlorometane and methanol extracts of leaves and inflorescences, and lychnopholide (91), centratherin (92), goyazensolide (84), 15-deoxygoyazensolide (83), caffeic acid (241), luteolin (262) and vicenin-2 (258)	74
	Inhibitory activity of flavonoids 264 , 281 , 283 and 303 on generation of reactive oxygen species	104
<i>L. pseudovilosissima</i>	Moluscicidal activity of the ethanol extract from the aerial parts against <i>Biomphalaria glabrata</i>	97
<i>L. rupestris</i>	Antinociceptive and anticonvulsant effects of polar extracts and 4,5-di-O-[E]-caffeoylquinic acid (331)	77
<i>L. salicifolia</i>	Antifungal activity of crude extract and sesquiterpene lactones	109
	Tripanocidal and antinociceptive activity of ethyl acetate extracts from leaves and inflorescences, lychnopholic acid (46) and quercetin-7,3',4'-trimethyl ether	32
	Antimicrobial activity of lupeol (202), lychnopholic acid (46) and its acetate (51) against <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Candida albicans</i> , <i>C. tropicalis</i> , <i>Tricophyton rubrum</i> , <i>Aspergillus flavus</i> , <i>Penicillium</i> and <i>Rhodotura rubra</i>	78,109
<i>L. staavioides</i>	Tripanocidal activity of the flavonoid 282	39
	Antinociceptive and anticonvulsant effects of polar extracts and 4,5-di-O-[E]-caffeoylquinic acid (332)	77
	Xantine oxidase inhibitory activity of the ethanolic extract of the aerial parts	91
<i>L. trichocarpa</i>	Tripanocidal activity of the ethanol extract of the aerial parts; lychnopholide (91) and eremantholide C (116)	37,38
	Antimicrobial activity of lychnopholide (91), eremantholide C (116) and Five synthetic derivatives against <i>Enterococcus faecalis</i> , <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Salmonella typhimurium</i> , <i>Escherichia coli</i> and <i>Proteus</i> sp	80
	Xantine oxidase inhibitory activity of the aerial parts ethanol extract	91
	Antinociceptive and antiinflammatory activities of the aerial parts ethanol extract	29
<i>L. villosissima</i>	Tripanocidal activity of 15-deoxygoyazensolide (83)	38,82
<i>Lychnophoriopsis candelabrum</i>	Xantine oxidase inhibitory activity of the aerial parts ethanol extract	91
	Antinociceptive and antiinflammatory activities of the aerial parts ethanol extract	29
<i>Proteopsis furnensis</i>	Antiinflammatory activity of centratherin (92)	87

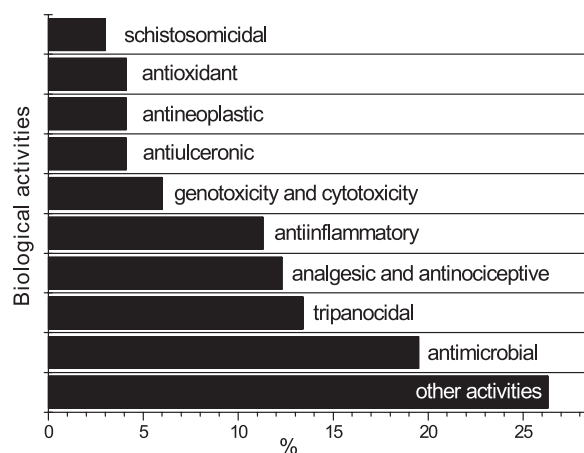


Figure 4. Biological activities of species of the subtribe Lychnophorinae reported in the literature. Percentage was calculated in relation to the total number of hits

of writhes induced by acetic acid. This activity was initially proposed due to the presence of sesquiterpene lactones.³⁰ However, Graef and co-workers³¹ reported that extracts of the aerial parts of *Lychnophora granmongolense* showed no analgesic activity in the writhing model of pain, even though the STLs goyazensolide (**84**) and centratherin (**92**) were isolated from those extracts. These results, in combination with those obtained for the *L. salicifolia* extracts,³² suggested that not all the *Lychnophora* species could exhibit analgesic activity correlated to the accumulation of sesquiterpene lactones. Differently, lignans¹¹ and di-caffeoylquinic acid derivatives,¹² isolated from roots of *Lychnophora ericoides* exhibited interesting analgesic activity. More recently, di-caffeoylquinic acid derivatives were also identified in the leaves of *L. ericoides*,²⁶ thus indicating that these compounds

can be responsible for the analgesic activity of the hydroalcoholic extracts used by the Brazilian population.

Rungeler and co-workers³³ investigated the anti-inflammatory activity of 28 sesquiterpene lactones (STL), which are commonly found in leaves and aerial parts of extracts of *Lychnophora* and other species from the subtribe Lychnophorinae. These compounds are known to inhibit the transcription factor NF- κ B by selectively alkylating its p65 sub-unit probably by reacting with cysteine residues.³⁰ The authors proposed that the α -methylene- γ -lactone and α,β -unsaturated carbonyl can alkylate the cysteine residue (Cys 38) in the DNA binding loop 1 (L1) and a further cysteine (Cys 120) in the nearby E' region. This cross link alters the position of tyrosine 36 and additional amino acids in such a way that their specific interactions with the DNA become impossible.³³ However, Gobbo-Neto and co-workers¹⁸ recently reported that vicenin-2 (**258**), isolated from the methanol extract of the leaves of *Lychnophora ericoides* showed significant anti-inflammatory activity in the carrageenan-induced rat paw edema, thus indicating that this compound is responsible for the anti-inflammatory activity. More recently, Dos Santos and co-workers³⁴ demonstrated that vicenin-2 (**257**) exhibits no effect on tumor necrosis factor (TNF)- α production, but inhibits, in a dose-dependent manner, the production of prostaglandin (PG) E2 without altering the expression of cyclooxygenase (COX)-2 protein. Also, the authors reported that 3,5-dicafeoylquinic acid (**333**) and 4,5-dicafeoylquinic acid (**332**), at lower concentrations, had small but significant effects on reducing PGE2 levels; at higher doses these compounds stimulated PGE2 and also TNF- α production by the cells. Both compounds **333** and **332**, in a dose-dependent manner, were able to inhibit monocyte chemoattractant protein-3 synthesis/release, with compound **332** being the most potent at the highest tested concentration. These results strongly suggested that the anti-inflammatory effect of hydroalcoholic extracts of *L. ericoides* are due to the presence of compounds **332** and **333**, rather than sesquiterpene

lactones. In addition, Guzzo and co-workers²⁹ investigated the ethanolic extracts of the aerial parts of five *Lychnophora* species for their anti-inflammatory and antinociceptive activities. They reported that administration of *Lychnophora pinaster* and *Lychnophora trichocarpa* ointments, in both evaluated concentrations (5 and 10%, w/w), and *Lychnophora passerina* and *Lychnophoriopsis candelabrum*, in the concentration of 10%, significantly reduced the paw edema measured 3 h after carrageenan administration, suggesting, for the first time, an anti-inflammatory activity upon topical administration of these species. However, the authors did not report the chemical composition of those extracts.

Despite the fact that sesquiterpene lactones have a widespread occurrence in the *Eremanthus* species, most of the biological activities of this genus are due to their essential oils from the leaves and stems. Nascimento and co-workers³⁵ investigated the activity of *Eremanthus erythropappus* oil and some of its compounds and their potential synergistic interaction with ampicillin against different strains of *Staphylococcus aureus*. They identified β -bisabolene as the main active constituent and reported its potential to restore the effectiveness of ampicillin against the resistant *S. aureus*.

Recently, the antimicrobial activity of this oil against *Candida albicans* and *Salmonella* ssp was also reported, but the major constituents were β -pinene and β -caryophyllene instead of β -bisabolene.⁶ More recently, the essential oil of *E. erythropappus* was also investigated for its antinociceptive and anti-inflammatory activities.³⁶ The authors found that doses of 200 and 400 mg/kg inhibited 10.69% and 27.06% of acetic-acid-induced writhing in mice, respectively. In the formalin-induced nociception test in mice, the essential oil inhibited the first phase of paw licking by 29.13% (400 mg/kg) and the second phase by 32.74% (200 mg/kg) and 37.55% (400 mg/kg). In the hot-plate test in mice, doses of 200 and 400 mg/kg significantly increased the reaction time after 30, 60 and 90 min of treatment. Doses of 200 and 400 mg/kg inhibited carrageenan-induced paw edema in rats by 15.18 and 36.61%, respectively. Doses of 200 and 400 mg/kg administered 4 h before intra-pleural injection of carrageenan significantly reduced exudation volume (by 20.20 and 48.70%, respectively) and leucocyte mobilization (by 5.88 and 17.29%, respectively).

The trypanocidal activity of the *Lychnophora* species has been extensively investigated in the literature. In this case, however, these studies are part of an intensive search for active compounds against *Trypanosoma cruzi*, the etiology agent of Chaga's disease, therefore, they are not correlated with the use of species from the subtribe Lychnophorinae in traditional medicine. The bioguided fractionation of the crude extracts of *L. passerina*, *L. pinaster* and *L. trichocarpa* resulted in the isolation of the bioactive sesquiterpene lactones goyazensolide (**84**), eremantholide C (**116**), lychnopholide (**91**), and lychnophoic acid (**57**).³⁷ Goyazensolide and eremantholide C were 100% active at concentrations of 240 and 3600 $\mu\text{g/mL}$, whereas lychnopholide inhibited 50% of the grown of trypanomastigote forms at concentration of 150 $\mu\text{g/mL}$.³⁸ Besides goyazensolide, centratherin (**92**) and the flavonoid eridictyol (**303**), isolated from *L. grammongolense* were also found to be active against *T. cruzi*.³¹ Quercetin 3-methyl ether (**291**), isolated from *L. staavioides* showed also significant trypanocidal activity.³⁹

Flavonoids and sesquiterpene lactones have also been investigated for their cytotoxicity⁴⁰⁻⁴² and genotoxicity.⁴³ Recent studies performed by Vasconcellos and co-workers⁴³ demonstrated that 15-deoxygoyazensolide (**83**) is mutagenic in *Saccharomyces cerevisiae* due to the possible intercalation effect, in addition to the pro-oxidant status that exacerbates oxidative DNA damage. Studies on the toxicity of the essential oil of *Eremanthus erythropappus* have also been reported.^{44,45}

CONCLUDING REMARKS

In this literature review, information concerning the occurrence and pharmacological activities of secondary metabolites isolated from species of the subtribe Lychnophorinae were collected. Sesquiterpene lactones of furanoheliangolide (goyazensolide and eremantholide types) and flavonoids are the distinguished secondary metabolites. Anti-inflammatory, analgesic, antimicrobial and cytotoxic properties are amongst the most investigated activities in the literature, mainly for the *Lychnophora* and *Eremanthus* species. However, a number of species of Lychnophorinae has not been submitted to phytochemical or pharmacological studies yet. Furthermore, although vicenin-2 and di-caffeoylquinic acids have been reported responsible for the anti-inflammatory and analgesic activities of the hydroalcoholic extracts of *Lychnophora ericoides* used in the medicine folk, a number of other species of Lychnophorinae used by the Brazilian population for medicinal purposes remains unknown until now. In this context, data presented herein demonstrated not only the role played by species of Lychnophorinae as source of bioactive compounds, but also reinforce the need of further studies involving species of such subtribe.

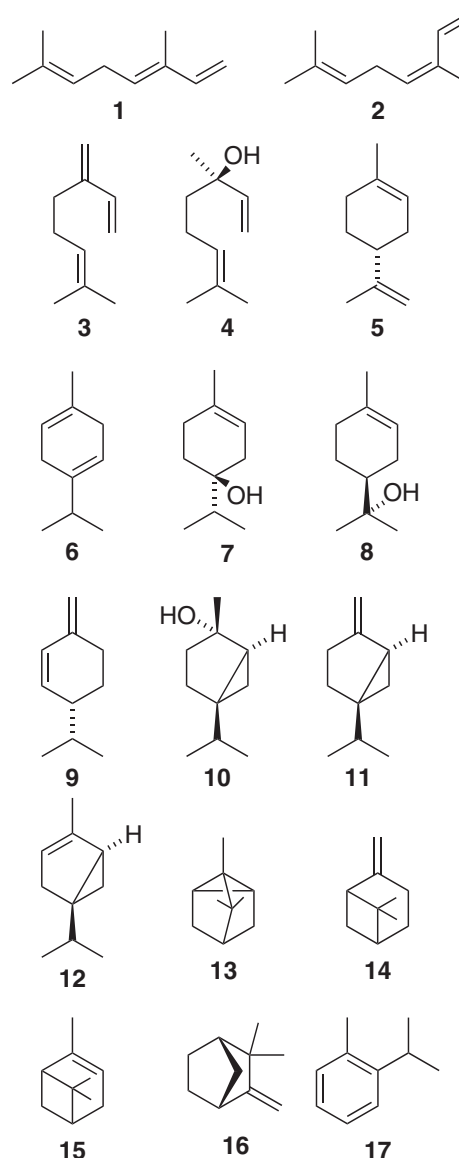


Figure 5. Monoterpenes isolated and/or identified in species of the subtribe Lychnophorinae

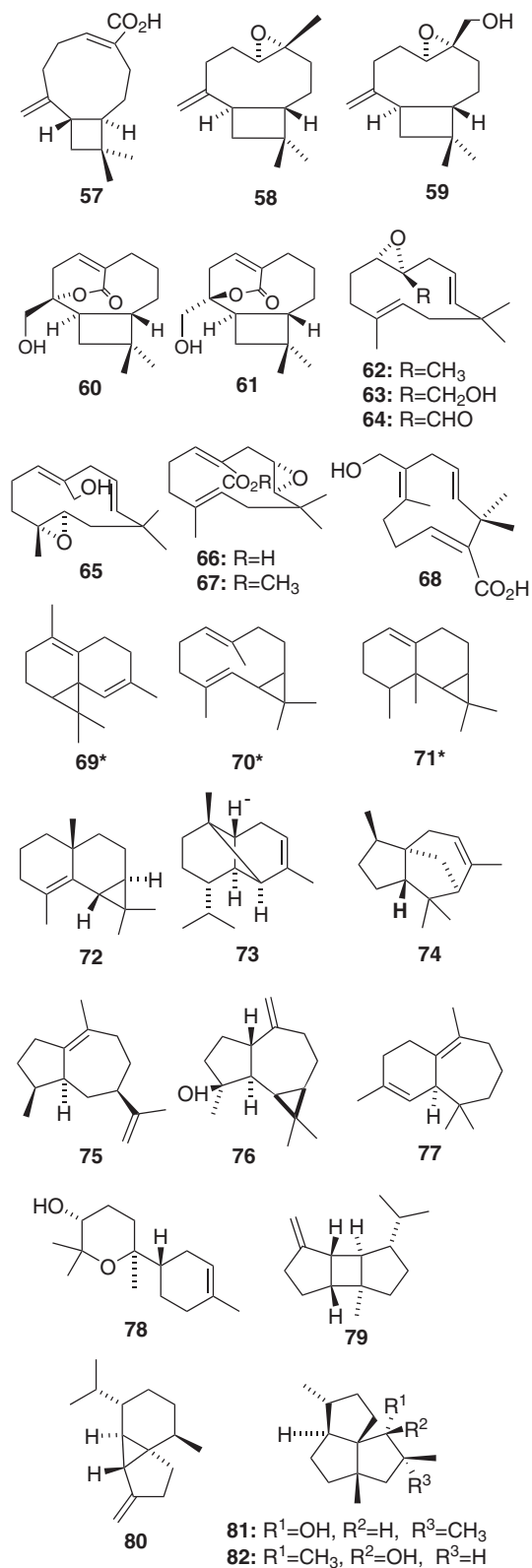
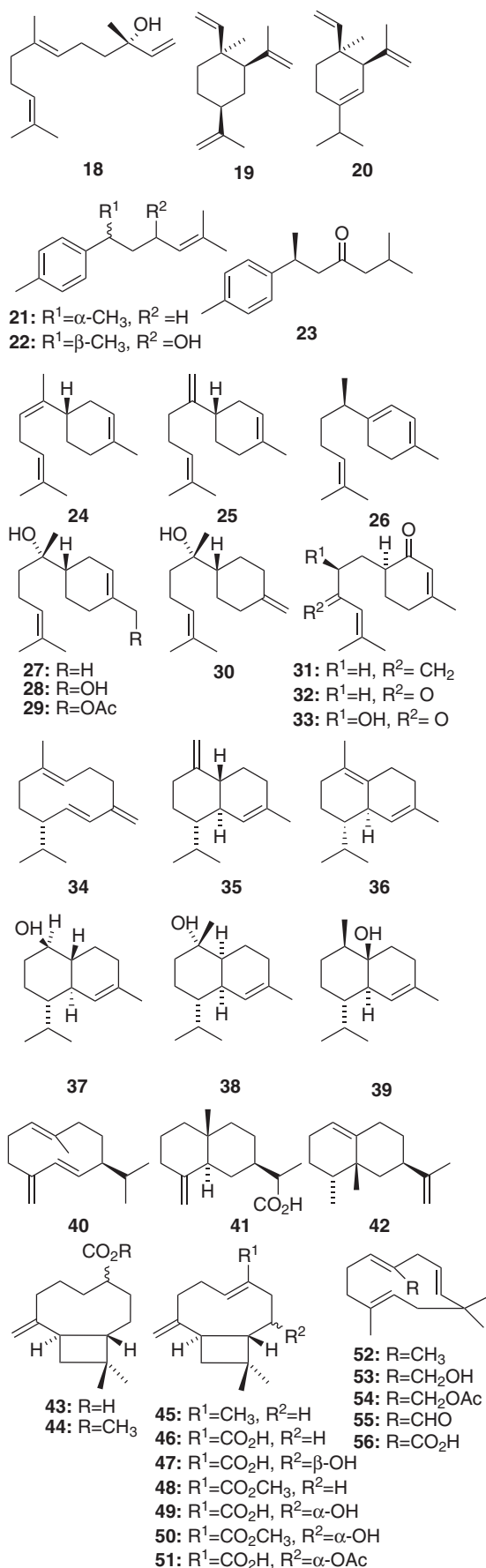


Figure 7. Sesquiterpenes isolated and/or identified in species of the subtribe *Lychnophorinae*. *Configurations of the stereocenters were not shown in the original papers

Figure 6. Sesquiterpenes isolated and/or identified in species of the subtribe *Lychnophorinae*

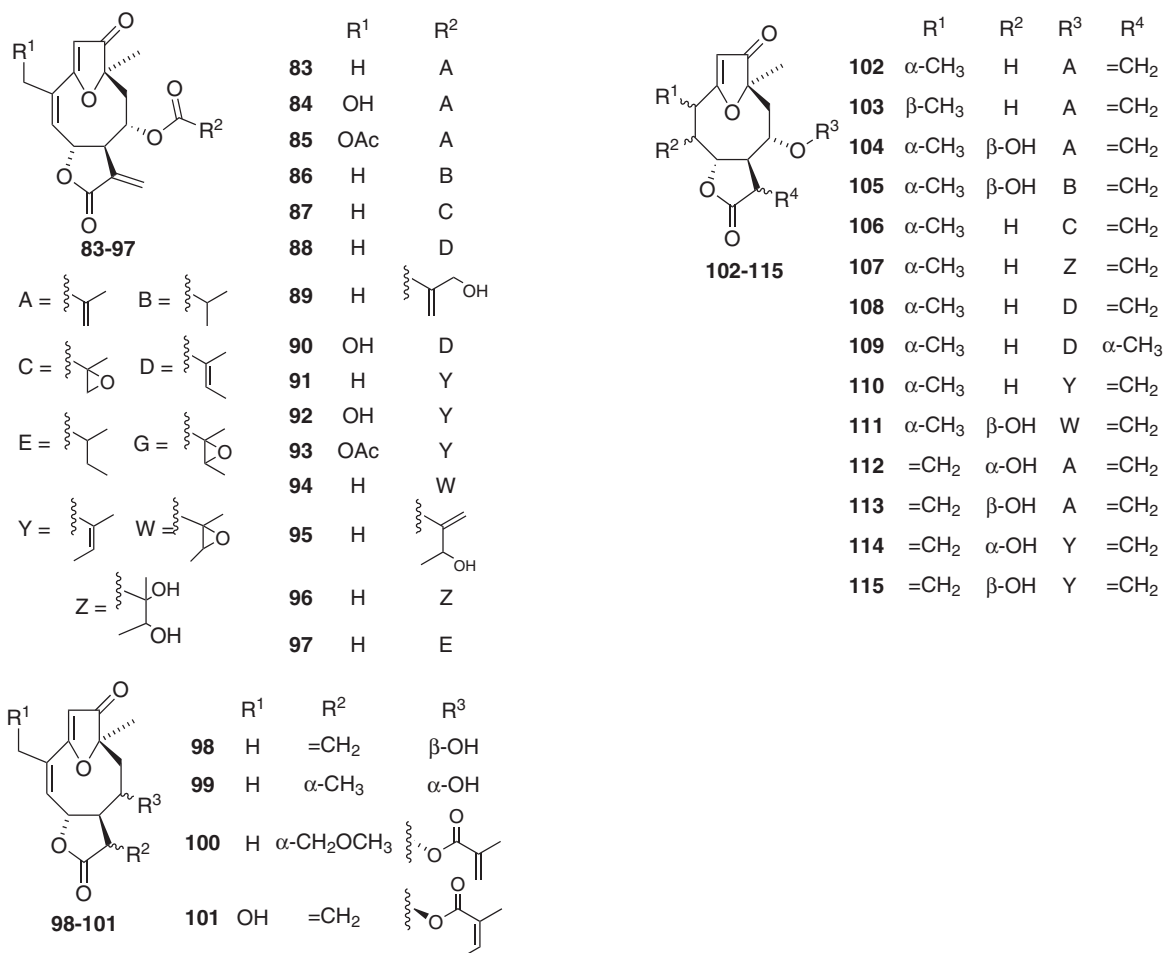


Figure 8. Furanoeliangolides of the goyazensolide type isolated and/or identified from species of the subtribe Lychnophorinae

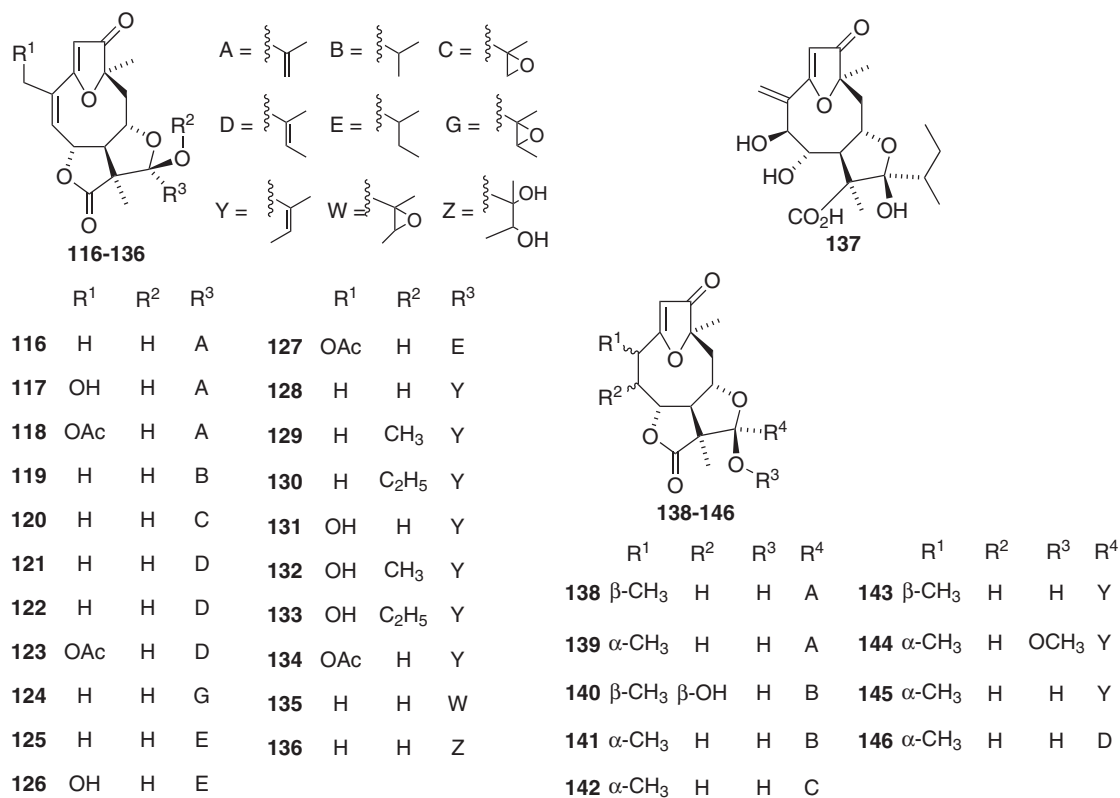


Figure 9. Furanoheliangolides of eremantholide type isolated and/or identified from species of subtribe Lychnophorinae

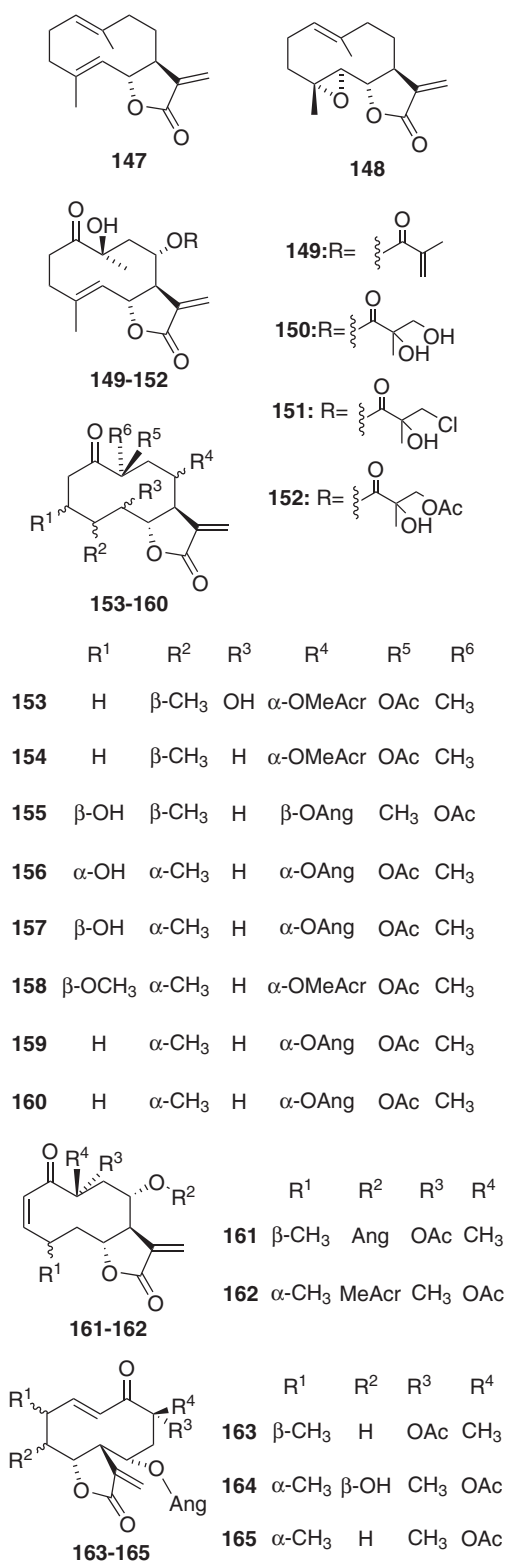


Figure 10. Germacranolides isolated and/or identified from species of subtribe *Lychnophorinae*

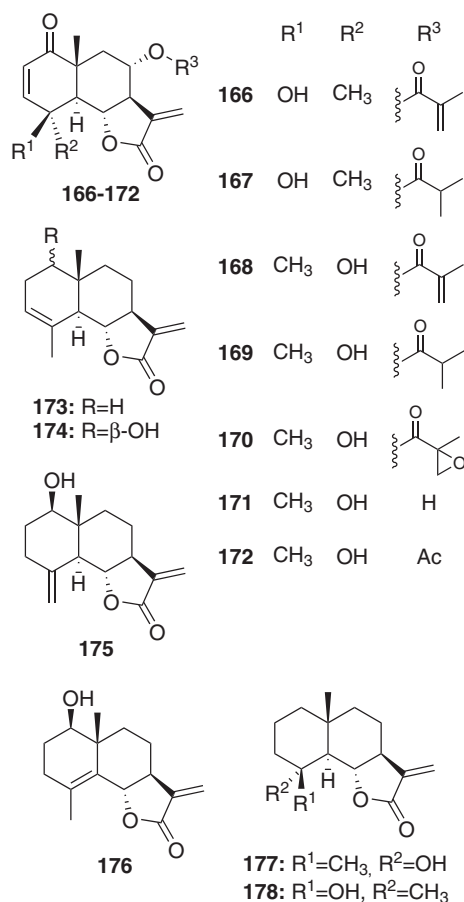


Figure 11. Eudesmanolides isolated and/or identified from species of subtribe *Lychnophorinae*

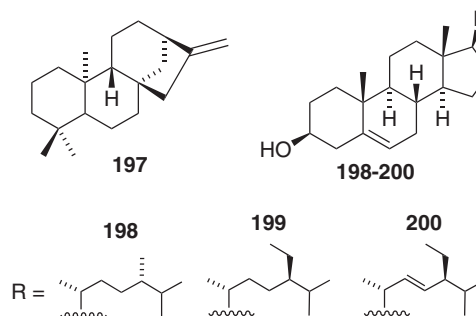


Figure 13. Steroids isolated and/or identified in species of the subtribe *Lychnophorinae*

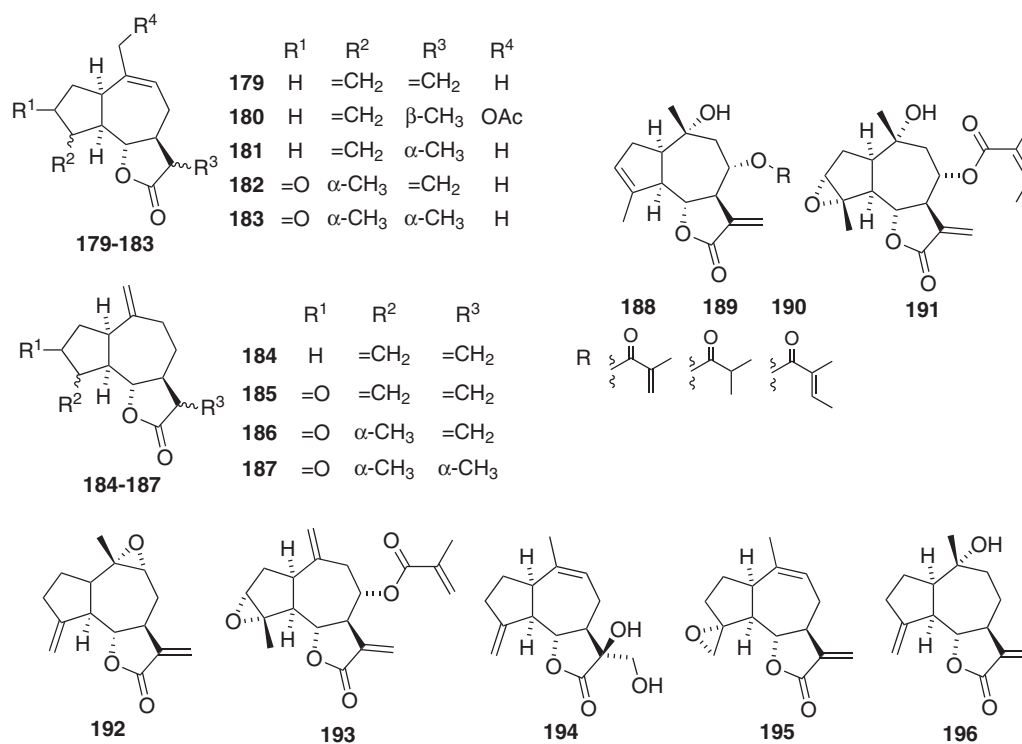


Figure 12. Guaianolides isolated and/or identified in species of the subtribe Lychnophorinae

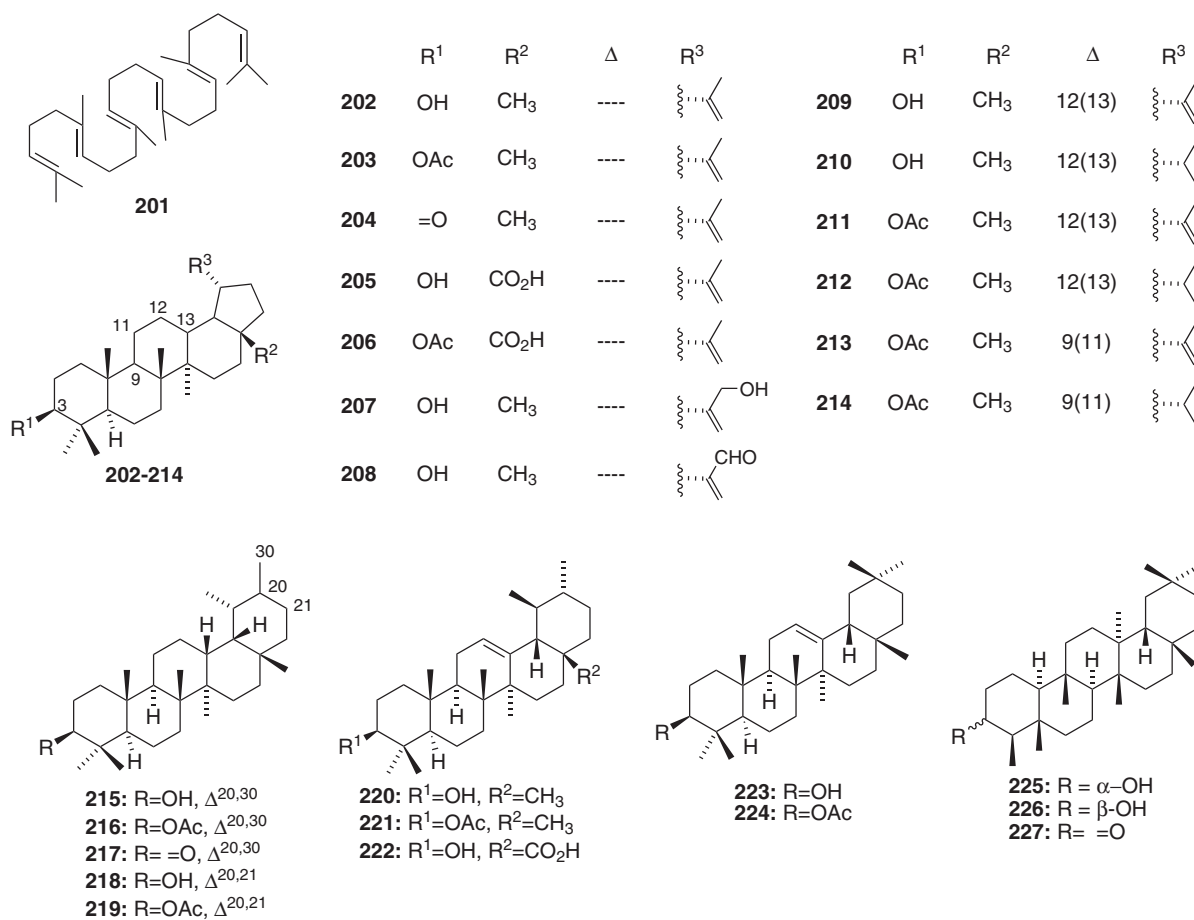


Figure 14. Triterpenes isolated and/or identified in species of the subtribe Lychnophorinae

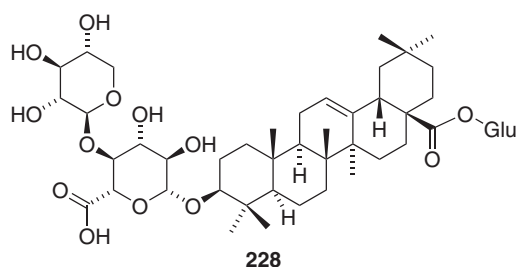


Figure 15. Triterpene saponin isolated and/or identified in species of the subtribe Lychnophorinae

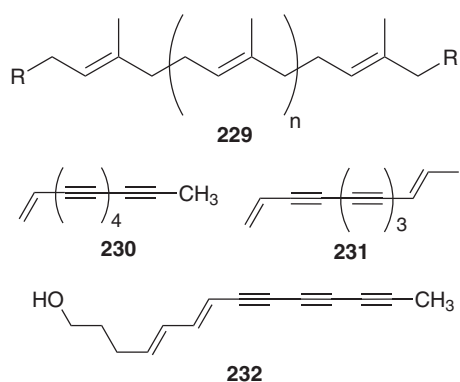


Figure 16. Polyisoprene and acetylene derivatives isolated and/or identified in species of the subtribe Lychnophorinae

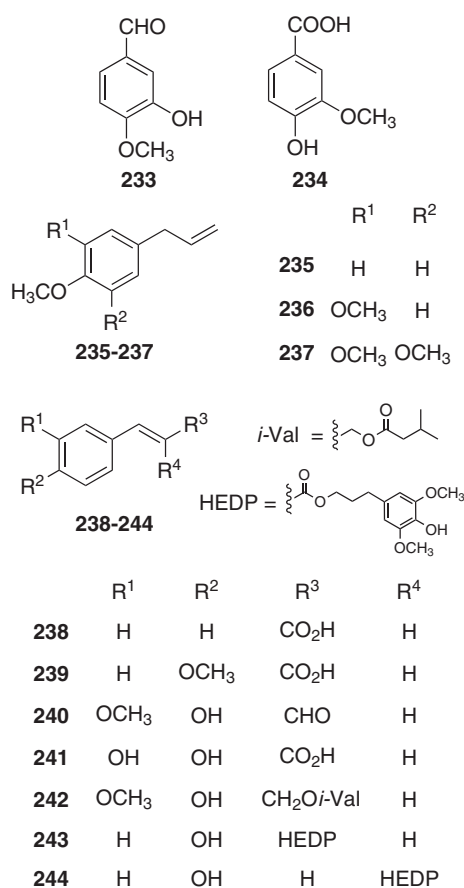


Figure 17. Benzoic acid derivatives (233 and 234) and Phenylpropanoids (235 to 244) isolated and/or identified in species of the subtribe Lychnophorinae

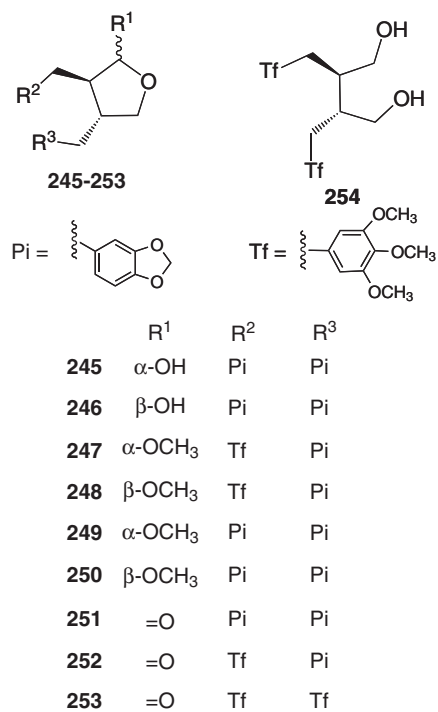
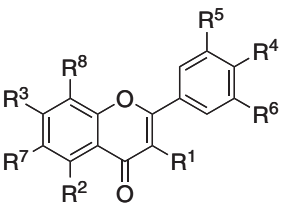
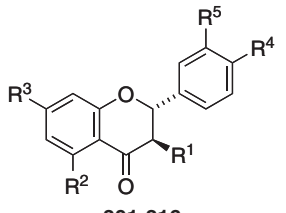


Figure 18. Lignans isolated and/or identified in species of the subtribe Lychnophorinae



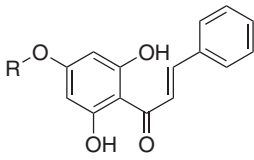
255-300

	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
255	H	OH	OH	H	H	H	H	H
256	H	OH	OH	H	H	H	Glu	Glu
257	H	OH	OH	OH	H	H	H	H
258	H	OH	OH	OH	H	H	Glu	Glu
259	H	OH	OH	OH	H	OH	Glu	Glu
260	H	OH	OH	OH	H	H	Glu	H
261	H	OH	OH	OH	H	H	H	Glu
262	H	OH	OH	OH	OH	H	H	H
263	H	OH	OH	OH	OH	H	Glu	Glu
264	H	OH	OH	OH	OCH ₃	H	H	H
265	H	OH	OH	OCH ₃	H	H	H	H
266	H	OH	OH	OCH ₃	OCH ₃	H	H	H
267	H	OH	OCH ₃	H	H	H	H	H
268	H	OH	OCH ₃	OH	H	H	H	H
269	H	OH	OCH ₃	OH	OH	H	H	H
270	H	OH	OCH ₃	OH	OCH ₃	H	H	H
271	H	OH	OCH ₃	OH	OCH ₃	H	H	OCH ₃
272	H	OH	OCH ₃	OCH ₃	H	H	H	H
273	H	OH	OCH ₃	OCH ₃	H	OCH ₃	H	OCH ₃
274	H	OH	OCH ₃	OCH ₃	OH	H	H	H
275	H	OH	OCH ₃	OCH ₃	OH	H	H	H
276	H	OH	OCH ₃	OCH ₃	OCH ₃	H	H	H
277	H	OH	OCH ₃	OCH ₃	OCH ₃	H	H	OCH ₃
278	OH	H	OH	OH	H	H	H	H
279	OH	OH	OH	H	H	H	H	H
280	OH	OH	OH	OH	H	H	H	H
281	OH	OH	OH	OH	OH	H	H	H
282	OH	OH	OH	OH	OCH ₃	H	H	H
283	OH	OH	OH	OCH ₃	OH	H	H	H
284	OH	OH	OCH ₃	H	H	H	H	H
285	OH	OH	OCH ₃	OH	H	H	H	H
286	OH	OH	OCH ₃	OH	OCH ₃	H	H	H
287	OH	OH	OCH ₃	OCH ₃	OCH ₃	H	H	H
288	OCH ₃	OH	OH	H	H	H	H	H
289	OCH ₃	OH	OH	OH	H	H	H	H
290	OCH ₃	OH	OH	OH	H	OH	H	OH
291	OCH ₃	OH	OH	OH	OH	H	H	H
292	OCH ₃	OH	OH	OCH ₃	H	H	H	H
293	OCH ₃	OH	OCH ₃	OH	H	H	H	H
294	OCH ₃	OH	OCH ₃	OH	OCH ₃	H	H	H
295	OCH ₃	OH	OCH ₃	OCH ₃	H	H	H	H
296	OCH ₃	OH	OCH ₃	OCH ₃	OH	H	H	H
297	OCH ₃	OH	OCH ₃	OCH ₃	OCH ₃	H	H	H
298	OCH ₃	OH	OCH ₃	OCH ₃	OH	OCH ₃	H	H
299	OGlu	OH	OH	OH	OH	H	H	H
300	OGlu	OH	OH	OH	OCH ₃	H	H	H

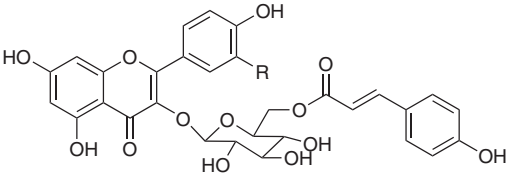


301-316

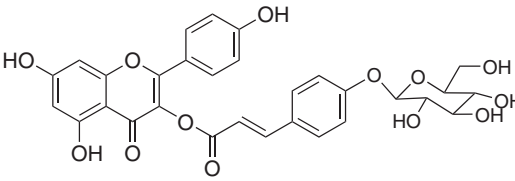
	R ¹	R ²	R ³	R ⁴	R ⁵
301	H	OH	OH	H	H
302	H	OH	OH	OH	H
303	H	OH	OH	OH	OH
304	H	OH	OH	OH	OCH ₃
305	H	OH	OCH ₃	H	H
306	H	OH	OCH ₃	OH	H
307	H	OH	OCH ₃	OH	OCH ₃
308	H	OH	OCH ₃	OCH ₃	OH
309	H	H	OH	OCH ₃	H
310	OH	H	OH	OH	H
311	OH	OH	OH	H	H
312	OH	OH	OCH ₃	H	H
313	OH	OH	OH	OH	OCH ₃
314	OAc	OH	OH	H	H
315	OAc	OH	OCH ₃	H	H
316	OCOC ₂ H ₅	OH	OCH ₃	H	H



317: R = H
318: R = CH₃



319: R = H
320: R = OCH₃



321

Figure 20. Diidroflavones (**301 to 309**), diidroflavonols (**310 to 316**), chalcones (**317 and 318**) and heteroside flavonoids (**319 to 321**) identified in species of the subtribe Lychnophorinae

Figure 19. Flavones (**254 to 276**) and flavonols (**277 to 300**) identified in species of the subtribe Lychnophorinae

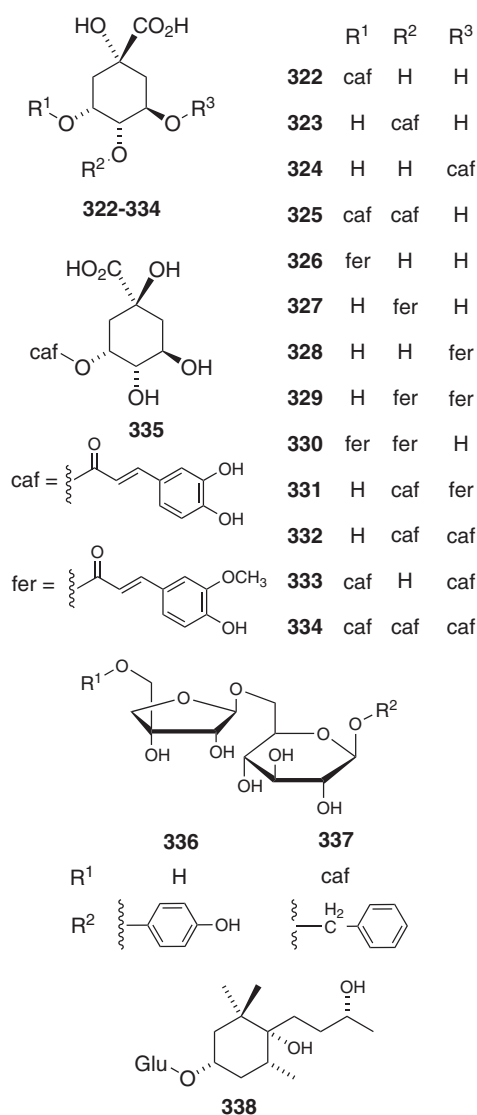


Figure 21. Quinic acid derivatives (322 to 335) and other heterosides (336 to 338) isolated and/or identified in species of the subtribe *Lychnophorinae*

REFERENCES

- Mansanares, M. E.; Forni-Martins, E. R.; Semir, J.; *Caryologia* **2002**, *55*, 367.
- Robinson, H.; *P. Biol. Soc. Wash.* **1992**, *105*, 640.
- Robinson, H.; *Smithson. Contrib. Bot.* **1999**, *I-IV*, 1.
- Herz, W. In *Compositae: Systematics. Proceedings of the International Compositae Conference*, Kew; Hind, D. J. N.; Beentje, H. J., eds.; Kew, 1996, chap. 17.
- Bastos, M.; Cerqueira, S.; Souza, J. T.; Júnior, R. A.; Peixoto, A. B. F.; *Cienc. Cult.* **1987**, *39*, 551.
- Sousa, O. V.; Dutra, R. C.; Yamamoto, C. H.; Pimenta, D. S.; *Rev. Bras. Farm.* **2008**, *89*, 113.
- Keles, L. C.; Gianasi, F. M.; Souza, R. C.; Brito, B. L.; Schaab, E. H.; Souza, M. G. M.; Carvalho, T. C.; Martins, C. H. G.; Veneziani, R. C. S.; Cunha, W. R.; Crotti, A. E. M.; *Nat. Prod. Res.* **2011**, *25*, doi: 10.1080/14786410903533612.
- Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H.; *Phytochemistry* **1980**, *19*, 2663.
- Lequesne, P. W.; Menachery, M. D.; Pastore, M. P.; Kelley, C. J.; Brennan, T. F.; Onan, K. D.; Raffauf, R. F.; Weeks, C. M.; *J. Org. Chem.* **1982**, *47*, 1519.
- Pettit, G. R.; Herald, D. L.; Cragg, G. M.; Rideout, J. A.; Brown, P.; *J. Nat. Prod.* **1990**, *53*, 382.
- Borsato, M. L. C.; Graef, C. F. F.; Souza, G. E. P.; Lopes, N. P.; *Phytochemistry* **2000**, *55*, 809.
- Dos Santos, M. D.; Gobbo-Neto, L.; Albarella, L.; de Souza, G. E. P.; Lopes, N. P.; *J. Ethnopharmacol.* **2005**, *96*, 545.
- Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M.; *Phytochemistry* **1980**, *19*, 2381.
- Bohlmann, F.; Muller, L.; King, R. M.; Robinson, H.; *Phytochemistry* **1981**, *20*, 1149.
- Dos Santos, P. A.; Lopes, J. L. C.; Lopes, N. P.; *Biochem. Syst. Ecol.* **2004**, *32*, 509.
- Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M.; *Phytochemistry* **1981**, *20*, 731.
- Chicaro, P.; Pinto, E.; Colepicolo, P.; Lopes, J. L. C.; Lopes, N. P.; *Biochem. Syst. Ecol.* **2004**, *32*, 239.
- Gobbo-Neto, L.; Santos, M. D.; Kanashiro, A.; Almeida, M. C.; Lucisano-Valim, Y. M.; Lopes, J. L. C.; Souza, G. E. P.; Lopes, N. P.; *Planta Med.* **2005**, *71*, 3.
- Sakamoto, H. T.; Flausino, D.; Castellano, E. E.; Stark, C. B. W.; Gates, P. J.; Lopes, N. P.; *J. Nat. Prod.* **2003**, *66*, 693.
- Sargent, S. R.; Vichnewski, W.; *Phytochem. Anal.* **2000**, *11*, 69.
- Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M.; *Phytochemistry* **1982**, *21*, 1087.
- Bohlmann, F.; Jakupovic, J.; *Plant Syst. Evol.* **1990**, *4* (suppl.), 3.
- Emerenciano, V. P.; Ferreira, Z. S.; Kaplan, M. A. C.; Gottlieb, O. R.; *Phytochemistry* **1987**, *26*, 3103; Da Costa, F. B.; Terfloth, L.; Gasteiger, J.; *Phytochemistry* **2005**, *66*, 345.
- Lequesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F.; *J. Chem. Soc. Perkin Trans. 1* **1978**, 1572.
- Sass, D. C.; Heleno, V. C. G.; Lopes, J. L. C.; Constantino, M. G.; *Tetrahedron Lett.* **2008**, *49*, 3877.
- Gobbo-Neto, L.; Lopes, N. P.; *J. Agr. Food Chem.* **2008**, *56*, 1193.
- Gobbo-Neto, L.; dos Santos, M. D.; Albarella, L.; Zollo, F.; Pizza, C.; Lopes, N. P.; *Biochem. Syst. Ecol.* **2008**, *36*, 473.
- Moraes, S. L.; Gregorio, L. E.; Tomaz, J. C.; Lopes, N. P.; *Chromatographia* **2009**, *69* (suppl. 2), S157.
- Guzzo, L. S.; Saude-Guimaraes, D. A.; Silva, A. C. A.; Lombardi, J. A.; Guimaraes, H. N.; Grabe-Guimaraes, A.; *J. Ethnopharmacol.* **2008**, *116*, 120.
- Schmidt, T. J.; *Bioorgan. Med. Chem.* **1997**, *5*, 645.
- Graef, C. F. F.; Vichnewski, W.; de Souza, G. E. P.; Lopes, J. L. C.; Albuquerque, S.; Cunha, W. R.; *Phytother. Res.* **2000**, *14*, 203.
- Jordao, C. O.; Vichnewski, W.; De Souza, G. E. P.; Albuquerque, S.; Lopes, J. L. C.; *Phytother. Res.* **2004**, *18*, 332.
- Rungeler, P.; Castro, V.; Mora, G.; Goren, N.; Vichewski, W.; Pahl, H. L.; Merfort, I.; Schmidt, T. J.; *Bioorgan. Med. Chem.* **1999**, *7*, 2343.
- Dos Santos, M. D.; Chen, G.; Almeida, M. C.; Soares, D. M.; Souza, G. E. P.; Lopes, N. P.; Lantz, R. C.; *Nat. Prod. Comm.* **2010**, *5*, 733.
- Nascimento, A. M. A.; Brandao, M. G. L.; Oliveira, G. B.; Fortes, I. C. P.; Chartone-Souza, E.; *Anton. Leeuw. Int. J. G.* **2007**, *92*, 95.
- Sousa, O. V.; Silverio, M. S.; Del-Vechio-Vieira, G.; Matheus, F. C.; Yamamoto, C. H.; Alves, M. S.; *J. Pharm. Pharmacol.* **2008**, *60*, 771.
- Oliveira, A. B.; Saude, D. A.; Perry, K. S. P.; Duarte, D. S.; Raslan, D. S.; Boaventura, M. A. D.; Chiari, E.; *Phytother. Res.* **1996**, *10*, 292.
- Saúde-Guimarães, D. A.; Faria, A. R.; *Rev. Bras. Farmacogn.* **2007**, *17*, 455.
- Takeara, R.; Albuquerque, S.; Lopes, N. P.; Lopes, J. L. C.; *Phytomedicine* **2003**, *10*, 490.
- Edwards, J. M.; Raffauf, R. F.; Le Quesne, P. W.; *J. Nat. Prod.* **1979**, *42*, 85.
- Herz, W.; Kumar, N.; Vichnewski, W.; Blount, J. F.; *J. Org. Chem.* **1980**, *45*, 2503.

42. Lequesne, P. W.; Pastore, M. P.; Raffauf, R. F.; *Lloydia* **1976**, *39*, 391.
43. Vasconcellos, M. C.; Rosa, R. M.; Machado, M. S.; Villela, I. V.; Crotti, A. E. M.; Lopes, J. L. C.; Pessoa, C.; Moraes, M. O.; Lopes, N. P.; Costa-Lotufu, L. V.; Saffi, J.; Henriques, J. A. P.; *Mutat. Res.* **2007**, *631*, 16.
44. Silvério, M. S.; Souza, O. V.; Leite, M. N.; *Eur. J. Pharm. Sci.* **2001**, *13*, 103.
45. Ferraz, S. O.; Dutra, R. C.; Yamamoto, C. H.; Pimenta, D. S.; Souza, O. V.; *Abstracts, XII Meeting of Scientific Initiation*, Juiz de Fora, Brazil, 2006.
46. Vichnewski, W.; Skrochy, C. A.; Maria, A.; Nasi, T. T.; Lopes, J. L. C.; Herz, W.; *Phytochemistry* **1999**, *50*, 317; Matos, M. E. O.; de Souza, M. P.; Matos, F. J. A.; Craveiro, A. A.; *J. Nat. Prod.* **1988**, *51*, 780.
47. Heleno, V. C. G.; Sakamoto, H. T.; Crotti, A. E. M.; Lopes, N. P.; Vichnewski, W.; Lopes, J. L. C.; *Nat. Prod. Comm.* **2010**, *5*, 681.
48. Sacilotto, A. C. B. C.; *Doctoral Thesis*, University of São Paulo, Brazil, 2000.
49. Bohlmann, F.; Singh, P.; Zdero, C.; Ruhe, A.; King, R. M.; Robinson, H.; *Phytochemistry* **1982**, *21*, 1669.
50. Sakamoto, H. T.; *Doctoral Thesis*, University of São Paulo, Brazil, 2004.
51. Mauro, M. R. V.; Tucci, A. M.; Nasi, A. M.; Nasi, T. T.; *J. Braz. Chem. Soc.* **1993**, *4*, 30; Vichnewski, W.; Gilbert, B.; *Phytochemistry* **1972**, *11*, 2563.
52. Raffauf, R. F.; Huang, P. C.; Le Quesne, P. W.; Levery, S. B.; Brennan, T. F.; *J. Am. Chem. Soc.* **1975**, *97*, 6884.
53. Vichnewski, W.; Takahashi, A. M.; Nasi, A. M. T.; Goncalves, D.; Dias, D. A.; Lopes, J. N. C.; Goedken, V. L.; Gutierrez, A. B.; Herz, W.; *Phytochemistry* **1989**, *28*, 1441.
54. Galdino, A. P. P.; Brito, J. O.; Garcia, R. F.; Scolforo, J. R. S.; *Rev. Bras. Plant. Med.* **2006**, *8*, 44; Vichnewski, W.; Lopes, J. L. C.; Dos Santos-Filho, D.; Herz, W.; *Phytochemistry* **1976**, *15*, 1775; Lima, P. D. D. B.; Garcia, M.; Rabi, J. A.; *J. Nat. Prod.* **1985**, *48*, 986.
55. Lunardello, M. A.; Tomaz, J. C.; Vichnewski, W.; Lopes, J. L. C.; Gutierrez, A. B.; Diaz, J. G.; Herz, W.; *J. Braz. Chem. Soc.* **1995**, *6*, 307.
56. Bohlmann, F.; Gupta, R. K.; Jakupovic, J.; Robinson, H.; King, R. M.; *Phytochemistry* **1981**, *20*, 1609.
57. Barros, D. A. D.; Lopes, J. L. C.; Vichnewski, W.; Lopes, J. N. C.; Kulanthaivel, P.; Herz, W.; *Planta Med.* **1985**, *51*, 38.
58. Vichnewski, W.; Welbancide, F.; Machado, L.; Rabi, J. A.; Murari, R.; Herz, W.; *J. Org. Chem.* **1977**, *42*, 3910; Vichnewski, W.; Sarti, S. J.; Gilbert, B.; Herz, W.; *Phytochemistry* **1976**, *15*, 191.
59. Asakawa, Y.; Taira, Z.; Toyota, M.; Takemoto, T.; *J. Org. Chem.* **1981**, *46*, 4602.
60. Andrade, I. L.; Bezerra, J. N. S.; Lima, M. A. A.; De Faria, R. A. P. G.; Lima, M. A. S.; Andrade-Neto, M.; *J. Agr. Food Chem.* **2004**, *52*, 5879.
61. Sakamoto, H. T.; Gobbo-Neto, L.; Cavalheiro, A. J.; Lopes, N. P.; Lopes, J. L. C.; *J. Braz. Chem. Soc.* **2005**, *16*, 1396.
62. Sacilotto, A. C. B. C.; Sartori, F. T.; Vichnewski, W.; *Biochem. Syst. Ecol.* **2002**, *30*, 897.
63. Lequesne, P. W.; Menachery, M. D.; Raffauf, R. F.; *J. Nat. Prod.* **1979**, *42*, 320; Raffauf, R. F.; Pastore, M. P.; Kelley, C. J.; Le Quesne, P. W.; Miura, I.; Nakanishi, K.; Finer, J.; Clardy, J.; *J. Am. Chem. Soc.* **1978**, *100*, 7437.
64. Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H.; *Phytochemistry* **1980**, *19*, 2669.
65. Bazon, J. N.; Lopes, J. L. C.; Vichewski, W.; Lopes, J. L. C.; *Fitoterapia* **1997**, *LXVIII*, 92.
66. Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M.; *Phytochemistry* **1982**, *21*, 685.
67. Da Costa, F. B.; Dias, D. A.; Lopes, J. L. C.; Vichnewski, W.; *Phytochemistry* **1993**, *34*, 261.
68. Borella, J. C.; Lopes, J. L. C.; Vichnewski, W.; Cunha, W. R.; Herz, W.; *Biochem. Syst. Ecol.* **1998**, *26*, 671.
69. Gobbo-Neto, L.; *Doctoral Thesis*, University of São Paulo, Brazil, 2007; Curado, M. A.; Oliveira, C. B. A.; Jesus, J. G.; Santos, S. C.; Seraphin, J. C.; Ferri, P. H.; *Phytochemistry* **2006**, *67*, 2363; Moraes, S. L.; Tomaz, J. C.; Lopes, N. P.; *Biomed. Chromatogr.* **2007**, *21*, 925; Lopes, N. P.; *Biológico* **2003**, *65*, 67; Da Costa, M. A. C.; Jesus, J. G.; Farias, J. G.; Nogueira, J. C. M.; Oliveira, A. L. R.; Ferri, P. H.; *Rev. Biol. Neotrop.* **2008**, *5*, 53; Lyra, C.; Vieira, R. F.; de Oliveira, C. B. A.; Santos, S. C.; Seraphin, J. C.; Ferri, P. H.; *J. Braz. Chem. Soc.* **2008**, *19*, 842.
70. Moraes, S. L.; Carollo, C. A.; Tomaz, J. C.; Lopes, N. P.; *Anal. Chem. Indian J.* **2007**, *4*, 54.
71. Sartori, F. T.; Barrachia, A. C.; Sacilotto, C.; Lopes, J. L. C.; Lopes, N. P.; Vichnewski, W.; *Biochem. Syst. Ecol.* **2002**, *30*, 609.
72. Vichnewski, W.; Lins, A. P.; Herz, W.; Murari, R.; *Phytochemistry* **1980**, *19*, 685.
73. Silveira, D.; de Souza Filho, J. D.; de Oliveira, A. D.; Raslan, D. S.; *Eclética Quím.* **2005**, *30*, 37.
74. Grael, C. F. F.; Albuquerque, S.; Lopes, J. L. C.; *Fitoterapia* **2005**, *76*, 73.
75. Alves, K. C. M.; Gobbo-Neto, L.; Lopes, N. P.; *Biochem. Syst. Ecol.* **2008**, *36*, 434.
76. Cunha, W. R.; Lopes, J. L. C.; Vichnewski, W.; Diaz, J. G.; Herz, W.; *Phytochemistry* **1995**, *39*, 387.
77. Taleb-Contini, S. H.; Santos, W. F.; Mortari, M. R.; Lopes, N. P.; Lopes, J. L. C.; *Basic Clin. Pharmacol.* **2008**, *102*, 281.
78. Miguel, O. G.; Lima, E. O.; Morais, V. M. F.; Gomes, S. T. A.; DelleMonache, F.; Cruz, A. B.; Cruz, R. C. B.; Cechinel, V.; *Phytother. Res.* **1996**, *10*, 694.
79. Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H.; *Liebigs Ann. Chem.* **1983**, *8*, 1455.
80. Saúde, D. A.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Raslan, D. S.; Silva, E. A.; *Rev. Bras. Farmacogn.* **2002**, *12*, 7.
81. Saude, D. A.; Rasland, D. S.; De Souza, J. D.; De Oliveira, A. B.; *Fitoterapia* **1998**, *69*, 90.
82. Tavares, K. G.; *Doctoral Thesis*, Federal University of Minas Gerais, 1990.
83. Crotti, A. E. M.; Cunha, W. R.; Lopes, N. P.; Lopes, J. L. C.; *J. Braz. Chem. Soc.* **2005**, *16*, 677; Crotti, A. E. M.; Do Sim, P. C.; Lopes, N. P.; Lopes, J. L. C.; *Abstracts, 25th Annual Meeting of the Brazilian Chemical Society*, Poços de Caldas, Brazil, 2002.
84. Bohlmann, F.; Wallmeyer, M.; King, R. M.; Robinson, H.; *Phytochemistry* **1982**, *21*, 1439.
85. Zdero, C.; Bohlmann, F.; Robinson, H.; King, R. M.; *Phytochemistry* **1981**, *20*, 739.
86. Vichnewski, W.; Semir, J.; Leitão-Filho, H. F.; Nakashima, C.; Lunardello, M. A.; Gutierrez, A. B.; Herz, W.; *Rev. Latinoam. Quím.* **1990**, *21*, 28.
87. Siedle, B.; Garcia-Piñeres, A. J.; Murillo, R.; Schulte-Monting, J.; Castro, V.; Rungeler, P.; Klaas, C. A.; Da Costa, F. B.; Kisiel, W.; Merfort, I.; *J. Med. Chem.* **2004**, *18*, 6042.
88. Leite, G. O.; Rosangela da Penha, A.; Fernandes, C. N.; Souza, H. H. F.; da Costa, J. G. M.; Campos, A. R.; *Fitoterapia* **2009**, *80*, 77.
89. Trevisan, M. T. S.; Macedo, F. V. V.; Van de Meent, M.; Rhee, I. K.; Verpoorte, R.; *Quim. Nova* **2003**, *26*, 301.
90. Canalle, R.; Burim, R. V.; Lopes, J. L. C.; Takahashi, C. S.; *Cancer Detect. Prev.* **2001**, *25*, 93.
91. Dias, F. D.; Takahashi, C. S.; Sakamoto-Hojo, E. T.; Vichnewski, W.; Sarti, S. J.; *Environ. Mol. Mutagen.* **1995**, *26*, 338.
92. Yuuya, S.; Hagiwara, H.; Suzuki, T.; Ando, M.; Yamada, A.; Suda, K.; Kataoka, T.; Nagai, K.; *J. Nat. Prod.* **1999**, *62*, 22.
93. Baker, P. M.; Fortes, C. C.; Fortes, E. G.; Gazzineli, G.; Gilbert, B.; Lopes, J. N. C.; Pellegrino, J.; Tomassini, T. C.; Vichnewski, W.; *J. Pharm. Pharmacol.* **1972**, *24*, 853.

94. Souza, O. V.; Silvério, M. S.; Oliveira, I. C. M.; Mattos, M. C.; Benchetrit, L. C.; Kaplan, M. A. C.; *Abstracts, 4th International Congress of Pharmaceutical Sciences*, Ribeirão Preto, Brazil, 2003; Silvério, M. S.; Rabello, S. V.; do Carmo, M. I.; Sousa, O. V.; Oliveira, I. C. M.; Mattos, M. C.; Benchetrit, L. C.; Figueiredo, M. R.; Heringer, A. P.; Kaplan, M. A. C.; *Rev. Bras. Farmacogn.* **2003**, *39*, 248; Sousa, O. V.; Silvério, M. S.; Oliveira, I. C. M.; Mattos, M. C.; Benchetrit, L. C.; Kaplan, M. A. C.; *Abstracts, III Brazilian Symposium of Pharmacognosy*, Curitiba, Brazil, 2001; Silvério, M. S.; *Master Dissertation*, Federal University of Rio de Janeiro, Brazil, 2004; Oliveira, G. B.; Chartone-Souza, E.; Nascimento, A. M. A.; *Abstracts, XXI Brazilian Congress of Microbiology*, Foz do Iguaçu, Brazil, 2001; Oliveira, G. B.; Brandão, M. G. L.; Chartone-Souza, E.; Nascimento, A. M. A.; *Anais da XI Semana de Iniciação Científica da Universidade Federal de Minas Gerais*, Belo Horizonte, Brasil, 2002; Chartone-Souza, E.; *Abstracts, Brazilian Symposium of Medicinal Plants*, Manaus, Brazil, 2004.
95. Sousa, O. V.; Moreira, F. O.; Silvério, M. S.; Pinto, P. F.; Barros, R. A. M.; Kaplan, M. A. C.; *Resumos do Congresso Íbero-Americano de Plantas Mediciniais*, Angra dos Reis, Brasil, 2004.
96. Moreira, F.; *Master Dissertation*, Federal University of Minas Gerais, Brazil, 2005.
97. Mendes, N. M.; Queiroz, R. O.; Grandi, T. S. M.; dos Anjos, A. M. G.; de Oliveira, A. B.; Zani, C. L.; *Mem. I. Oswaldo Cruz* **1999**, *94*, 411.
98. Frighetto, N.; Carvalho, J. E.; Antônio, M. A.; Dias, P. C.; Oliveira, J. G.; Kohn, L. K.; *Resumos da XI Reunião Anual da Federação de Sociedade de Biologia Experimental*, Caxambu, Brasil, 1996.
99. Tavares, C. Z.; Dutra, R. C.; Ferraz, S. O.; Sousa, O. V.; *Abstracts, XII Meeting of Scientific Investigation*, Juiz de Fora, Brazil, 2006; Sousa, O. V.; Tavares, C. Z.; Soares Júnior, D. T.; Dutra, R. C.; Ferraz, S. O.; Ferraz, S. O.; Campos, A. C.; *Abstracts, XI Meeting of Scientific Initiation*, Juiz de Fora, Brazil, 2004; Soares Júnior, D. T.; Dutra, R. C.; Ferraz, S. O.; Campos, A. C.; Silvério, M. S.; Sousa, O. V.; *Abstract, XI Congress of Clinical Analysis of Minas Gerais*, Juiz de Fora, Brazil, 2004.
100. Sousa, O. V.; Domingues, E. C.; Moreira, F. O.; *Resumos da I Mostra de Trabalhos de Graduação da Universidade Federal de Juiz de Fora*, Juiz de Fora, Brasil, 2003; Frighetto, N.; Oliveira, J. G.; Carvalho, J. E.; Nogueira, D. C. F.; Dias, P. C.; Mendonça, C. J. S.; Antônio, M. A.; *Abstracts, XI Annual Meeting of the Federation of Societies of Experimental Biology*, Caxambú, Brazil, 1996; Frighetto, N.; Oliveira, J. G.; Carvalho, J. E.; Possenti, A.; Dias, P. C.; Nogueira, D. C. F.; *Abstract, III Paulista Congress of Medicinal Plants*, Campinas, Brazil, 1997; Frighetto, N.; Oliveira, J. G.; Carvalho, J. E.; Possenti, A.; Mendonça, C. J. S.; Dias, P. C.; Nogueira, D. C. F.; *Abstracts, XIII Annual Meeting of the Federation of Societies of Experimental Biology*, Caxambú, Brazil, 1998.
101. Barth, L. R.; Fernandes, A. P. M.; Ribeiro Paes, J. T.; Rodrigues, V.; *Mem. I. Oswaldo Cruz* **1997**, *92*, 427.
102. Bazon, J. N.; *Master Dissertation*, University of São Paulo, Brazil, 1997.
103. Dos Santos, P. A.; Amarante, M. F. C.; Pereira, A. M. S.; Bertoni, B.; Franca, S. C.; Pessoa, C.; de Moraes, M. O.; Costa-Lotufo, L. V.; Pereira, M. R. P.; Lopes, N. P.; *Chem. Pharm. Bull.* **2004**, *52*, 1433.
104. Kanashiro, A.; Kabeya, L. M.; Polizello, A. C. M.; Lopes, N. P.; Lopes, J. L. C.; Lucisano-Valim, Y. M.; *Phytother. Res.* **2004**, *18*, 61.
105. Filha, Z. S. F.; Vitolo, I. F.; Fietto, L. G.; Lombardi, J. A.; Saude-Guimaraes, D. A.; *J. Ethnopharmacol.* **2006**, *107*, 79.
106. Salvador, M. J.; Sartori, F. T.; Sacilotto, A.; Pral, E. M. F.; Alfieri, S. C.; Vichnewski, W.; *Z. Naturforsch. C* **2009**, *64*, 509.
107. Chiari, E.; Duarte, D. S.; Raslan, D. S.; Saúde, D. A.; Perry, K. G.; *Phytother. Res.* **1996**, *10*, 636.
108. Silveira, D.; Wagner, H.; Chiari, E.; Lombardi, J. A.; Assunção, A. C.; Oliveira, A. B.; Raslan, D. S.; *Rev. Bras. Farmacogn.* **2005**, *15*, 294.
109. Silva, M. Q. O. R.; Guedes, V. R.; Young, C. M.; Martins, D.; *Abstracts, 22nd Annual Meeting of the Brazilian Chemical Society*, Poços de Caldas, Brazil, 1999.