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Review Article

Phytochemistry, Pharmacology and Botanical Aspects of *Hortia* Species in the Search for Molecules with Bioactive Potential – A Review

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ABSTRACT

Hortia Vand. is a Neotropical genus of *Rutaceae*. Ten species occurs in South America in Atlantic forests, in Brazilian Savannah (Cerrado) and especially in the Amazon. Among these species, *H. brasiliana* is used to treat fevers, malaria, diarrhea, vomiting and liver diseases. *H. oreadica* is popularly use as antipyretic, substitute for quina, as tonic and stomach. This paper aims to give an overview of the *Hortia* genus, focusing on morphological, phytochemical and biological activities to stimulate new studies about these species. The main substances and derivatives isolated from *Hortia* species include dictamnine, γ-fagarine, skimmianine, robustine, flindersine, N-methyl-flindersine, rutaecarpine, hortiamine, hortiacine, seselin, 5-methoxy-seselin, scoparon, guianin, limonin and nerolidol. These substances present properties such as antimicrobial, antifungal, anti-inflammatory, spasmolytic, anti-diabetic, anti-atherosclerotic, antiulcerogenic, anticancer, hepatoprotective, neuroprotective, immunosuppressive, anti-malarial, acaricidal, larvicidal and antifeed. Several of these activities could justify the popular uses of the *Hortia* species.

Key words: Active compounds, Biological activity, Brazilian Cerrado, Medicinal plants, *Rutaceae*, Taxonomy

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INTRODUCTION

The cerrado is one of the largest biomes in Brazil, occupying the second position that includes Federal District, Goiás, Tocantins, Maranhão, Mato Grosso do Sul, Minas Gerais and transition zones of six other states. It presents a high aquifer potential with the source of the three South American basins: Amazon/Tocantins, São Francisco and Prata, which contributes to a wide biodiversity.[1-3]Approximately half of the two million square kilometers of the Cerrado are use for planted pastures, agricultural and industrial activities, urbanization and other types of use. It is estimate that the annual deforestation rate is 22,000 and 30,000 km².[4-7]

The changes in the Cerrado have caused serious environmental damage as extinction of biodiversity, soil erosion, climate change, invasion of atypical species and pollution of aquifers. As much as the Cerrado is adapted to the fire, the fires used for regrowth of the pastures generate losses of nutrients and alterations of the soils, which can cause the loss of important species for research.[6,8-10] The reduction of the impact caused by the extensive exploration of the Cerrado can happen in joint actions of the fiscalization agencies and studies of the fauna and flora, for valorization of the threatened biodiversity.[7]

The search for new active compounds of plants attends to interests that, in principle, seem conflicting, since on the one hand the environmental sciences seek knowledge as an instrument of understanding of reality for preservation/conservation[11,12] and the other side, chemical, pharmaceutical, medical and agrarian sciences that place knowledge at the service of pharmacochemistry and agribusiness for the production of new drugs and inputs,[13] which can implement the exploitation of natural resources in a predatory manner.

The *Rutaceae* family possess about 150 genera with more than 1500 species, some quite aromatic,[14] relevant in horticulture (*Citrus*,[15] forestry (*Chloroxilon, Flindersia, Zanthoxilum*) and for therapeutic purposes (*Pilocarpus, Agathosma*). Rutaceae species are rich in alkaloids, coumarins, flavonoids and limonoids. Among the various genus in this family, *Hortia* species can be highlighted due its importance to obtain active molecules. Species of *Hortia* are composed mainly by trees up to 38 m high, but *H. oreadica* a shrub with well developed subterranean stem.[16-19]

Phytochemical and biological studies on the *Hortia* have been performed since 1960[20-22] and more frequently in the last 20 years.[23-28] A taxonomic review of *Hortia* was carried out by Groppo and Pirani,[19] based on the analysis of specimens deposited in herbaria in Brazil and in other countries,

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as well as in field work, resulted in the update of botanical classification and nomenclature for ten species of *Hortia* in South America, nine of them occurring in Brazil.

The aim of this study was to review the literature on *Hortia* genus, focusing on morphological aspects, phytochemicals and biological activities, highlighting the potential of these species as sources of new bioactive molecules, to stimulate new studies about these species.

MATERIALS AND METHODS

The literature review of *Hortia* species was based on databases: PUBMED (National Library of Medicine National Institutes of Health), SCOPUS, Web Collection of Science, Science Direct, CAPES jornals, Google Scholar and SciELO databases. The search used uniterms in English and Portuguese using scientific and popular names of species including synonyms and heteronyms, associated with other terms such as "botanical, chemical, phytochemical, activity, components, isolated." 329 documents were found, 59 articles were selected, 22 which focused on botanical and ethnobotanical aspects, 18 on chemical isolation and 19 on chemical isolation and biological activity.

The inclusion criteria used in the files selection were scientific articles with editorial staff of *Hortia* species focusing on morphological description, ethnobotanical aspects and biological activities *in vivo*, *in vitro* from extracts, fractions, isolated substances and chemical isolation. Non-scientific articles, reports, non-scientific opinion articles, abstracts, theses, monographs, anatomical studies, planting, phenology were excluded.

Data were extracted in two standardized data collection instruments: biological activities (year, author, genus, species studied, current nomenclature, plant part, extract, fraction, isolated substance, biological activity, action, test organism and strain, active concentration, positive control and potential value); phytochemical studies (year, author, genus, species studied, current species nomenclature, plant part, extraction method, liquid extractor, fraction, class, substance and molecular structure).

After cataloging phytochemical data and biological activities, substances that were identified or isolated in at least two species of *Hortia,* or in different parts from the same species, were evaluated by *in silico* prediction according to the "Lipinski Five's Rule" and the bibliographic survey for these substances was expanded. 37 articles were selected involving biological activities, occurrence in species of other botanical genera, molecular and/or biological relevance and presentation of the molecular structure.[29-31]

RESULTS AND DISCUSSION

Taxonomy, distribution and popular use of *Hortia*

Vandelli (1788) described the genus *Hortia* and Candolle (1824) described the Brazilian Hortia Vand. ex DC. for the first time.[16-18,32-37]

Ten *Hortia* species were described in South America and are distributed from Panama to Brazil: eight of them in the Amazon rainforest; one species is found in forest formations of Atlantic Forest: coastal vegetation, mesophilic and submontane forests and one species in the Cerrado (Savannah) of Brazil and Bolivia. They are trees or shrubs with simple leaves attached near the apex of the branches.[19] The names of the species, synonyms, geographical distribution and main morphological differences are described in Table 1.

In Brazil, *H. brasiliana* is popularly known as: "casca d'anta", "pau paratudo",[38] "durão", "pratudo", "para-tudo-vermelho", "laranjinha", "coronel", "lima d'anta", "limão-bravo", "limão-de-forquilha", "limeirinha"[19]; in Bolivia: "isonaranja", "catcha"; in Colombia: "paco"; no Ecuador: "cucharillo terug" and in Panama: "nusmas". Pio-Corrêa[38] refers the popular use of *H. brasiliana* barks to treat fever and Groppo and Pirani[19] to treat malaria, diarrhea, vomiting and liver diseases.

Hortia oreadica, known *as* "quina",[39] "quina-do-campo"[38] and "para-tudo"[19] is used in folk medicine as antipyretic[39] and substitute for quina.[38] Besides, Groppo and Pirani[19] described the use of bark as tonic and for stomach diseases.

Hortia excelsa Ducke is popularly known as "cachaceiro" and pau-marfim",[19,38] *Hortia longifolia* as "cachaceiro" and *Hortia superba* as "pau-amarelo".[19]

Phytochemical Studies of Hortia species

A total of 59 substances were identified from crude extracts obtained from bark, branches, leaves and roots by maceration in ethanol, hexane and dichloromethane and by extraction with Soxhlet in toluene or column chromatography using as chloroform and ethanol solventes (Table 2).[20,21,40-42] 29 substances, including alkaloids, coumarins and terpenoids, were identified in *H. longifolia* crude extracts obtained from bark, branches and leaves by maceration in benzene and ethanol, in hexane and methanol or by hydrodistillation (Table 2).[43-46]

In crude extracts of *H. oreadica* 36 substances were identified from subterranean stem, stems and leaves by maceration in dichloromethane, hexane and methanol. The alkaloids were found in all studied parts of the plant, limonoids and coumarins in stem and stem subterranean, dihydrocinnamic acid derivatives in subterranean stem and leaves (Table 2)[25,41,42,47,48] In the leaves essential oils were identified the amorphous -4,7 (11)-diene (29.27% in flowers, 20.26% in fruits, 27.66 a 37.89% in leaves) and bicyclogermacrene (23.28% in flowers, 20.64% in fruits, 14.71% to 31.37% in leaves) as major compounds.[27]

Severino *et al.*[42,49] analyzed crude extracts of *H. superba* obtained from stem bark and branches by maceration in dichloromethane, ethanol and methanol and identified 25 substances distributed among alkaloids, coumarins, limonoids, flavones and dihydrocinnamic acid derivatives. Phytochemical studies of *H. regia* carried out on crude extracts obtained from roots by percolation in heated methanol or in ethanol identified 9 substances (Table 2).

Biological activities of Hortia species

Studies have reported *in vitro* antimicrobial activity against *Mycobacterium tuberculosis* by rutaecarpine **(7)** (15.62 µg/ml), γ-fagarine **(2)** (31.25 µg/ml), bergapten (250 µg/ml) and dihydrocinnamic acid derivatives: 5,6-dimethoxy-2,2-dimethyl-2H-1-benzopyran-8-propanoic acid and 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid (62.50 µg/ml), all substances isolated from *Hortia* species.[49] Dictamnine (1) was active against *Lactobacillus casei* (0.1mg/ml).[48]

Severino *et al.*[49] identified antimicrobial activity of methanol fraction of *H. brasiliana* stems against *Mycobacterium kansasii* (250 µg/ml) and *Mycobacterium tuberculosis* (500 µg/ml). Studies with *H. oreadica* reported antimicrobial activity from subterranean stem hexane fraction against *Streptococcus salivarius* (0.2 mg/ml) and *Streptococcus sanguinis* (0,2mg/ml).[48] Fiuza *et al.*[26] verified antimicrobial activity from crude ethanol extract of *H. oreadica* leaves against *Staphylococcus epidermidis* (250 µg/ml), *Candida krusei* (31.25 µg/ml) and *Candida tropicalis* (15.62 µg/ml); hexane fraction of leaves against *Pseudomonas aeruginosa, Staphylococcus epidermidis* and *Salmonella* sp. (250 µg/ml). Severino *et al.*[49] described antimicrobial activity from dichloromethane and hexane fractions from *H. oreadica* leaves and subterranean stem, methanol fraction of the leaves, stem and subterranean stem against *M. kansasii* (250 µg/ml), *M. tuberculosis* (31.25 a 250 µg/ml) and antimicrobial activity of methanol fraction of *H. superba* against *M. tuberculosis* (250 µg/ml).

Table 1: Hortia Vand. Species.

Species *Hortia* Vand. (1788)	Botanical features	Occurrence
***Hortia brasiliana* Vand. (ex DC.) (1824)** Synonym: *Hortia arborea* Engl. (1874) *Hortia colombiana* Gleason (1933) *Hortia chocoensis Cuatr.* (1962) *Hortia badinii* M. A. Lisboa (1974)	Tree from 4 to 30 m high. Flowers with about 13 mm in diameter; leaves with prominent secondary and tertiary veins on both faces, diverging from the median rib at 60-69º; fruit globose to ovoid (4.5 a 5.5 +4.5 cm).	It grows in Atlantic rainforest and restingas on sandy soils near sea level; inland, inhabits the mesophilic and submontane forests. It can be found in southeastern and northeastern Brazil, distributed from the states of Pernambuco, Bahia to Rio de Janeiro and São Paulo at altitudes of 50 to 1120 m. In Colombia, Ecuador, Bolivia and Panama occurs in the Amazon rainforest, in the non-flooded forests and on the Andes slopes, in montane and submontane forests of sea level up to 1.800 m of altitude[19] (De Candolle, 1824; Groppo and Pirani, 2012).
***Hortia coccinea* Spruce (ex Engl.) (1874)**	Treelet or shrub from 1 to 2 m high. With tomentosa petals on the adaxial side.	Found in river banks periodically flooded, in enclaves of Amazonian savannah with sandy soils and in riverside vegetation, at altitudes 13 to 140 m. In Brazil, it occurs in the Rio Negro and its tributaries and in Venezuela, in the Cassiquiare and Orinoco river basins.[16]
***Hortia excelsa* Ducke (1922)**	Tree from 2 to 38 m high. Has smooth blade or slightly bullate; branched distal inflorescences 3 to 4 mm in diameter; petals tomentosa on the adaxial side, trichomes of 0.5 to 0.6 mm in length.	It occurs in non-flooded forests with clayey or sandy loam soils in Amapá and northern Pará, with a record in Amazonas, Brazil and another in Loreto, Peru.[17,19]
***Hortia longifolia* Spruce (ex Engl.) (1874)** Synonym: *Hortia megaphylla Taub.* (1892) *Hortia duckei Huber* (1909)	Tree from 4 to 25 m high. It presents an lamina oblong lanceolate to almost linear, length 8-9 times longer than wide, 40-84,6 cm long; non-obvious tertiary veins.	It was found in non-flooded forests and open vegetation on sandy soils. It occurs in the Brazilian Amazon, from the western part of Pará to the east of the state of Amazonas, Roraima and north of Mato Grosso.[16,19]
***Hortia neblinensis* Maguire and Boom (1989)**	Tree 25 m high. Leaves glabrous; chalice verrucous, anthers with teak.	Found in submontane forest at 1000 m altitude in Pico da Neblina, Amazonas, Brazil.[19]
***Hortia nudipetala* Groppo (2005)**	Treelet 2 to 3 m high. Petals glabrous on both sides.	Species found on periodically flooded river banks and along some streams in sandy soils; in vegetation of meadows of 13 to 140 m of altitude, in the state of Amazonas, Brazil, region of the upper Rio Negro, near São Gabriel da Cachoeira.[19]
***Hortia oreadica* (2005)**	Shrub 0.3 to 2 m high. Leaves (sub) sessile, petioles up to 4 mm in length; shrubs with branches that rise at ground level directly from the subterranean stem forming clumps.	Found frequently in "cerrados" and "campos sujos" from 700 to 1.300 m of altitude. Occasionally they inhabit "cerradão" areas or rupestrian fields at high altitudes. It occurs in Central Brazil, Goiás, Federal District, Mato Grosso, Mato Grosso do Sul, Rondônia, western Minas Gerais and Bolivia at 1.800 m, in the Andes.[37]
***Hortia regia* Sandwith (1931)**	Tree from 10 to 20 m high. Leaves puberulous in the basal portion of the central rib in the abaxial face; non-verrucous calyx, anthers with prolonged bifid teak in the lower portion.	Found in non-flooded forests and gallery forests, sometimes bordering swampy regions (sandy soil), from sea level up to 600 m altitude. It occurs in the Amazon rainforest of Guyana and Venezuela.[19,33]
***Hortia superba* Ducke (1935)**	Tree from 5 to 25 m high. Lamina bullate; branching distally of inflorescences with sows of 2 mm in diameter; villous petals on the adaxial side, trichomes 1 to 1.2 mm in length.	It occurs only in central Amazonia in igapós or forests not flooded with sandy soils to sandy of 13 to 140 m of altitude.[17,19]
***Hortia vandelliana* Groppo (2005)**	Tree or shrub from 2 to 20 m high. Flowers with about 8 mm in diameter; leaves with secondary and tertiary veins immersed in the mesophyll, non-prominent and most often not visible, diverging from the median vein at 35-53º; ellipsoidal fruits.	In Solimões river basin in the Amazon "caatinga" in sandy soil, non-flooded forests and Rio Negro river basin in clay soil. One record in Roraima and another in Venezuela. From sea level up to 600 m of altitude.[19,37]

In vitro cytotoxicity studies reported moderate activity of flavonoid 13 (R1, R2, R3, R4 = H) isolated from *H. oreadica* stems against breast adenocarcinoma (GI_{50}: 29.5 ± 3.5 μM), against non-small cell lung cancer (GI_{50}: 35.0 ± 1.0 μM) and against melanoma (GI_{50}: 32.5 ± 2.5 μM). The dihydrocinnamic acid derivative methyl 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoate showed antimalarial activity against *Plasmodium falciparum* (IC_{50}: 23.6 μM) and trypanocidal against *Tripanossoma brucei rhodesienses* (IC_{50}: 15.6 μM).[47] Dictamnine **(1)** (IC_{50}: 2.1 μM) and rutaecarpine **(7)** (IC_{50}: 2.0 μM) demonstrated activity against *Tripanossoma cruzi*.[50]

Table 2: Isolated substances from Hortia species.

H. brasiliana		
Part of the plant	**Substances**	**References**
Stem bark	Coumurrayin, dictamnine **(1)**, erythro-2-hydroxy-4-methoxy-3-(1,2,3-trihydroxy-3-methylbutyl)benzenepropanoic acid, γ-fagarine **(2)**, nor-γ-fagarine, N-methyl-flindersine **(6)**, hortiacine **(8)**, hortiamine **(9)**, 6-methoxyrhetsinine, rutaecarpine **(7)**, sitosterol, skimmianine **(3)**, stigmasterol.	[20,21,23,40-42]
Branch	Aloxantoxiletina, bergapten, γ-fagarine **(2)**, flindersine, N-methyl-flindersine **(6)**, hortiacine **(8)**, hortiolide, A, hortiolide B, methyl 3 -[2,5-dimethoxy-6',6'-dimethylpyrano(3',2':3,4)-phenyl-propionate, methyl 3-[2,4-dimethoxy-3-prenylphenyl]-propionate, methyl 3-[2,6-dimethoxy-6',6'-dimethylpyrano(2',3':3,4)-phenyl]-propionate, methyl 3-[2-methoxy-6',6'-dimethylpyrano(2',3':3,4) phenyl]-propionate, nerolidol **(15)**, 10,11-epoxynerolidol, n-methyl-4-methoxy-quinolin-2-one, rutaecarpine **(7)**, scoparon **(12)**, 5-methoxy-seselin **(11)**, skimmianine **(3)**, N-[2-(4-hydroxyphenyl)ethyl]-tigliamide, N-[2-(4-prenyloxyphenyl)ethyl]-tigliamide, 2,4-dimethoxyquinoline, 3-[2,5-dimethoxy-6',6'-dimethylpyrano(3',2':3,4)-phenyl]-propionic acid, 3-[2,6-dimethoxy-6',6'-dimethylpyrano(2',3': 3,4)phenyl]-propionic acid, 3-[2,6-dimethoxy-6',6'-dimethylpyrano(2',3': 3,4)phenyl]-l-propanol, 3-[2-methoxy-6',6'-dimethylpyrano (2',3':3,4)phenyl]-l-propanol, 5,6-dimethoxy-2,2-dimethyl-2H-1-benzopyran-8-propanoic acid, 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid, 5-methoxy-2,2-dimethyl-2h-1-benzopyran-8-propanoic acid.	[21,23,24,41,42]
Leaves	α-curcumene, trans-bergamotol, trans-α-bergamotene, β-bisabolene, caryophyllene oxide, dihydrolinalool, eicosane, guaiol, hortiacine (8), methyl 5,8-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoate, methyl 5-methoxy-2,2-dimethyl-2H-1-benzopyran-6-pronanoate, nonacosane, β-sesquiphellandrene, 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid, 5,8-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid.	[41,42,51]
Roots	Chalepin, clausindine, hortiline, hortinone, hortiolone, isoangenomalin, 3-(α,α-dimethylaliy)psoralen, xanthyletin, 3-(α,α-dimethylaliy)xanthyletin.	[22].
H. longifólia		
Part of the plant	Substances	References
Stem bark	N-[2-(4-prenyloxyphenyl)ethyl]tigliamide, Skimmianine **(3)**.	[44]
Branch	(E)-methyl-5'-hydroxy-O-prenyl cinnamate, coumurrayin, Dictamnine **(1)**, (E)-methyl-O-prenyl ferulate, hortiacine **(8)**, integrifoliodiol, limonin **(14)**, linarin, trans-nerolidol, N-[2-(4-prenyloxyphenyl)ethyl]tigliamide, 4-methoxy-1-methil-2-quinolone, 4-methoxy-2-quinolone, scoparon **(12)**, scopoletin, sitosterol, skimmianine **(3)**.	[43,45,46]
Leaves	caryophyllene epoxide, α-copaene, α-curcumene, β-elemene, humulene epoxide II, mustakone, γ-muurolene, β-santalene, spathulenol.	[46]
H. oreadica		
Part of the plant	Substances	Referência
Leaves	Dictamnine **(1)**, guianin **(13)**, rutaecarpine **(7)**, 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoate, methyl 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoate, 5,8-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid, E-3,4-dimetoxi-(3-hidroxi-4-carbomethoxyphenyl) cinnamic acid.	[25,42]
Stem	6-hydroxyhortiolide C, 9,11-dehydro-12α-hydroxyhortiolide A, 11β-hydroxyhortiolide C, 12β-hydroxyhortiolide E, bergapten, hortiolide D, hortiolide E, N-methyl-4-methoxy-quinolin-2-one.	[25,42]
Stem bark	Bergapten, braylin, dictamnine **(1)**, γ-fagarine **(2)**, guianin **(13)**, hortiacine **(8)**, hortiolide A, 9,11-dehydro-12α-acetoxyhortiolide A, 9α-hydroxyhortiolide A, hortiolide C, 6-hydroxyhortiolide C, 11α-acetoxy-15-deoxy-6-hydroxyhortiolide C, hortiolide D, hortiolide E, 12β-hydroxyhortiolide E, limonin **(14)**, methyl 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoate, methyl 5,8-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoate, methyl 5-methoxy-2,2-dimethyl-2H-1-benzopyran-6-pronanoate, n-methylatanine, psoralen, robustine **(4)**, rutaecarpine **(7)**, 7,8-dehydrorutaecarpine, scoparon **(12)**, 5-methoxy-seselin **(11)**, xanthotoxin, 1(S*)-acetoxy-7(R*)-hydroxy-7-deoxoinchangin, 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid, 5,8-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid, 5-methoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid.	[25,41,42,47]
H. regia		
Part of the plant	Substances	References
Roots	Chromene, guianin **(13)**, hortiamide, methyl(E,E)-10,l l-dihydroxy-3,7,1l-trimethyl-2,6-dodecadienoate, rutaecarpine **(7)**, scoparon **(12)**, skimmianine **(3)**, 5-methoxy-2,2-dimethyl-1-2H-benzopyran-6-propanoic acid, 5-methoxy-2,2-dimethyl-1-2H-benzopyran-6-propanoic acid methyl ester.	[59,86,96]
H. superba		
Part of the plant	Substances	References
Stem bark	Dictamnine (1), heraclenol isosakuranetin, prangol, rutaecarpine **(7)**, sitosterol, stigmasterol	[42]
Branch	Acacetin, edulitine, flindersine **(5)**, N-methyl-flindersine **(6)**, heraclenol, hortiacine **(8)**, hortiolide C, hortiolide D, integriquinolone isosakuranetin, neoponcirin, n-methyl-4-methoxy-quinolin-2-one, prangol, rutaecarpine **(7)**, scoparon **(12)**, seselin **(10)**, 5-methoxy-seselin **(11)**, 5,6-dimethoxy-2,2-dimethyl-2H-1-benzopyran-8-propanoic acid, 5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran-6-propanoic acid, 4-methoxy-N-methyl-2-quinolone, 4-methoxy-quinolin-2-one.	[42,49]

Antimetabolic activity studies of cinnamic acid derivative (E)-methyl-5'-hydroxy-O-prenyl cinnamate (IC_{50}: 3.86 µg/ml), of amides (E)-methyl-O-prenyl ferulate (IC_{50}: 8.14 µg/ml) and N-[2-(4-prenyloxyphenyl)ethyl] tigliamide (IC_{50}: 6.91 µg/ml) and the coumarin scopoletin (IC_{50}: 5.07 µg/ml) isolated from branches of *H. longifolia* showed significant pancreatic lipase inhibition. Scopoletin demonstrated strong inhibitory activity (IC_{50}: 0.89 µg/ml) over the α-glucosidase enzyme.[45]

In vivo toxicity assay in saline artemia with the hexane extract obtained from *H. longifolia* and with the isolated substance N-[2-(4-hydroxyphenyl)ethyl]-tigliamide, showed lethality 100% (250 µg/ml) for both.[44] The essential oil from *H. longifolia* leaves showed LC_{50} of 34.3 ± 1 µg/ml in 24 hrs and LC_{50} of (32.9 ± 1 µg/ml) in 48 hrs against third instar larvae of *Aedes aegypti*. The author attributed this activity to trans-nerolidol.[46]

Magalhães *et al.*[51] found anti-inflammatory activity of the hexane extract of *H. brasiliana* leaves with reduction of pleurisy in rats induced by carrageenan, total leukocyte inhibition (100 mg/kg, oral) and decrease in exudate volume (200 mg/kg, oral). They observed analgesic activity by the decrease of abdominal writhes caused by intraperitoneal injection of acetic acid in mice (100 mg/kg, oral).

Isolated substances - molecular structures and biological activities

Among the identified and/or isolated substances from *Hortia* species, the most frequent ones in the genus were evaluated by *in silico* prediction according to the " Lipinski's Rule of five" and selected for research on biological activities described in literature and presentation of molecular structure (Figure 1).

It was selected the alkaloids dictamnine (1), γ-fagarine (2), skimmianine (3), robustine (4), flindersine (5), N-methyl-flindersine (6), rutaecarpine (7), hortiamine (9) and hortiacine (8); the coumarins seselin (10), 5-methoxy-seselin (11) and scoparon (12) and the terpenes guianin (13), limonin (14) and nerolidol (15).

Dictamnine **(1)** was isolated from the bark of *H. brasiliana*, from branches of *H. longifolia*, from leaves and subterranean stem of *H. oreadica* and on the stem bark of *H. superba*[20,42,43,47,48] (Figure 1). It is a furanoquinolin initially identified in species of *Dictamnus* (Rutaceae), used in Chinese traditional medicine (*Dictamnus dasycarpus* Turczand, *Dictamnus angustifolius* G. Don ex Sweet) whose root barks are used for the treatment of rheumatism, bleeding, itching, jaundice, chronic hepatitis and skin diseases.[52,53]

For dictamnine **(1)** it was verified cytotoxic activities against lung lymphoma L1210 cell line,[54] T human cancer-cell-lines HeLa (IC_{50}, 65.0 µM) and HCT-116 (IC_{50}, 85.0 µM) (*in vitro*);[55] antifungal activity against *Cladosporiurn cucumerinum* (0.6 µg on TLC plate); antimicrobial activity against *Bacillus subtilis* (DSMZ 704) (MIC=17.7 µg/ml), *Pseudomonas agarici* (DSMZ 11810) (MIC=15.1 µg/ml).[56]

Dictamnine (1) is the biosynthetic precursor of γ-fagarine (2) (has an extra methoxy group at position 8) and skimmianine (3) (has two additional methoxyl groups at positions 7 and 8).[57] γ-fagarine (2) was isolated from stem bark and branches of *H. brasiliana* and from the subterranean stem of *H. oreadica*[20,23,24,42] and skimmianine (3) was isolated from the branches of *H. brasiliana*, from stem bark and branches of *H. longifolia* and from roots of *H. regia*[20,23,24,42-45,58,59] (Figure 1). The literature consulted mentions the antimicrobial activity of γ-fagarine (2) against *Staphylococcus aureus* meticiline-resistant (MRSA) and *Micrococcus luteus* (MIC = 500µg/ml).[57] Akhmedzhanova *et al.*[55] verified the cytotoxic activities of γ-fagarine (2) (IC_{50}, 34.9 µM) and of skimmianine (3) (IC_{50}, 11.55 µM) against human cancer-cell-lines HeLa. The authors correlate the increase in the anticancer activity of these alkaloids against HeLa cells with the increase in the number of methoxyl groups in the molecule.

Yang *et al.*[60] verified the inhibitory activity *in vitro* of skimmianine **(3)** (IC_{50}, 8,6 µM) over acetylcholinesterase and Yoon *et al.*[61] verified the inhibitory activity of skimmianine **(3)** (IC_{50}, 7.0 µM) over the nitric oxide production in lipopolysaccharide-stimulated BV-2 microglia cells. The authors estimate that these substances are potential drug candidates for the treatment of neurodegenerative diseases.[60-62]

Robustine **(4)** (8-Hydroxydictanmnine) was isolated from the subterranean stem of *H. oreadica* [42] (Figure 1). Chen *et al.*[63] observed the anti-inflammatory activity of robustine **(4)** ($IC_{50} \leq 18.19$ µM) by dose-dependent inhibition of superoxide anion generation ($O_2^{\bullet -}$) by activated human neutrophils in response to FMLP/CB (formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B). The superoxide anion ($O_2^{\bullet -}$) is the precursor of some cytotoxins involved in inflammatory responses such as reactive oxygen species (ROS), granular proteases and bioactive lipids. Drug suppression of exacerbated neutrophil activation has been proposed as a way to decrease the response in inflammatory diseases.

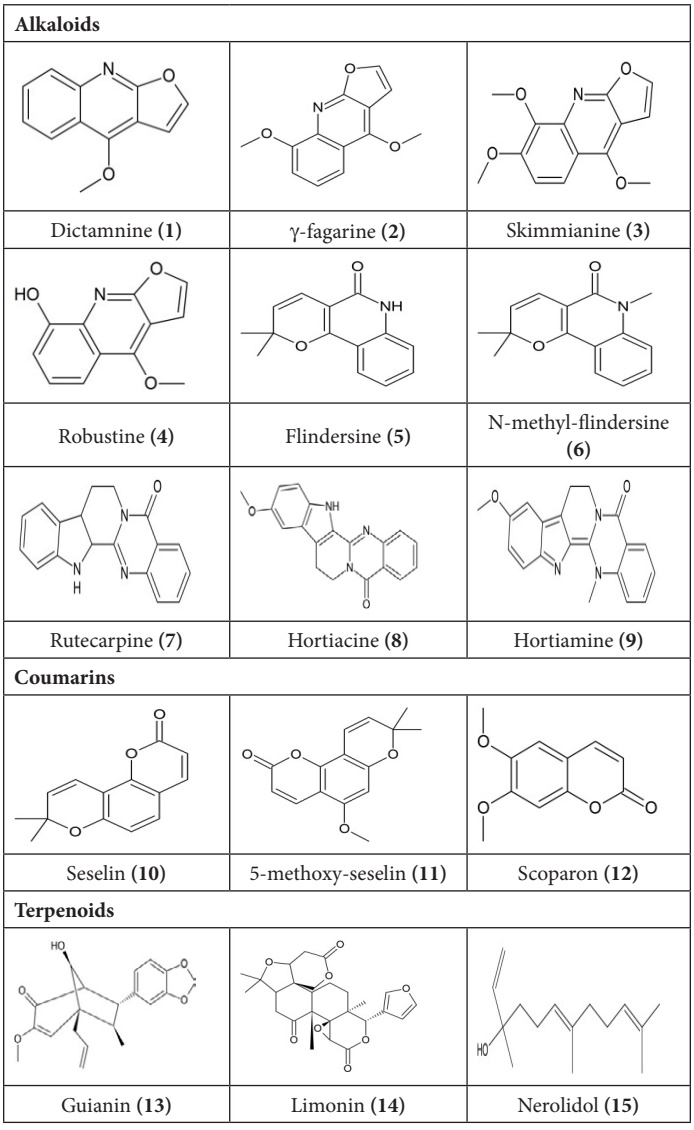

Figure 1: Molecular structures (1-15) of substances of greater occurrence in Hortia species.

Flindersine **(5)** was isolated from *H. brasiliana* and *H. superba* branches.[23,24,42] N-methyl-flindersine **(6)** was isolated from stem bark and branches of *H. brasiliana* and from branches of *H. superba*[23,42] (Figure 1). These two substances are quinolone alkaloids originally isolated from *Flindersia* (Rutaceae).[64-66] Duraipandiyan and Ignacimuthu[67] observed antimicrobial activity of flindersine **(5)** against *Bacillus subtilis* MTCC 441 (MIC=31.25µg/ml), *Enterococcus faecalis* ATCC 29212 (31.25µg/ml).

Varamini *et al.*[68] described the cytotoxic activity of flindersine **(5)** on human cancer cell-lines KG-1a (acute myelogenous leukemia) (IC_{50}, 44.6 ± 7.4 µM), RAJI (Burkitt's lymphoma) (IC_{50}, 14.9 ± 0.9 µM) and Jurkat (acute lymphoblastic leukemia) (IC_{50}, 20.9 ± 2.7 µM). Flindersine **(5)** showed a significantly greater effect (IC_{50}, 19.5 ± 3.2 µM) against HL-60/MX1, a multidrug resistant cell line, when compared to the etoposide control (IC_{50}, 61.5 ± 9.9µM) (p <0,05). Ahsan *et al.*[69] using as positive control vinblastine sulfate, identified the moderate action of 8-methoxy-N-methyl-flindersine (ED_{50} of 60.96 to 79.37 µM) on a six human cancer cell lines group from stomach cancer, SCL, SCL-6, SCL-3706, SCL-9, Kato-3 and NUGC-4.

Irudayaraj *et al.*[70] found in streptozotocin-induced diabetic rats that, in 28 days, the ethyl acetate fraction of *Toddalia asiatica* (L.) Lam. leaves (250 mg/kg) reduced blood glucose level (112.38 ± 0.74 mg/dl) in 60% in relation to diabetic controls (290.38 ± 1.89 mg/dl) similarly to the reference drug glibenclamide (101.38 ± 2.10 mg/dl) and suggested that this activity can be attributed to quinolones such as flindersine **(5)**.

Antonaccio[71] first described alkaloids in *Hortia* species (Rutaceae). Some complex quinazolinocarbolines occur in *Evodia* and *Hortia* species as rutaecarpine **(7)**, hortiamine **(9)** and hortiacine **(8)**.[72] Rutaecarpine **(7)**, initially identified in the fruits of *Evodia rutaecarpa* (Rutaceae)[73] was isolated from *H. brasiliana* and from *H. superba* stem bark and branches, from *H. oreadica* leaves and subterranean stem and from *H. regia* roots (Figure 1).[20,21,23,42,47,49,59] Xu *et al.*[74] reported the anti-atherosclerotic activity (EC50 = 0.27 µM) by a positive regulator effect of the ATP binding cassette transporter A1 (ABCA1). The vasodilator activity of rutaecarpine **(7)** EC50 (7.86 x 10^{-6} mol/L) was related by Chen *et al.*[75] to the stimulation of the endogenous release of peptides related to the calcitonin gene (CGRP). Rutaecarpine **(7)** showed trypanocidal activity against *Tripanossoma cruzi* (IC_{50}: 2.0 µM) in contrast to gentian violet (IC_{50}: 31µM).[50]

Hortiamine **(9)** was isolated from stem bark of *H. brasiliana*[20,21,23,42,43,76] and hortiacine **(8)** was isolated from the stem bark, leaves and branches of *H. brasiliana*, from branches of *H. longifolia* and *H. superba* and from subterranean stem of *H. oreadica* (Figure 1).[20,21,23,42,43,76] Baburin *et al.*[28] evaluated the proarrhythmic effect of hortiamine **(9)** in the I_{Kr} (IC_{50} = 144.8 ± 35.1 nM) block em cAVB (chronic atrioventricular block) of cardiomyocytes isolated from dogs and by the dose-dependent prolongation of APD (action potential duration) in hiPSC-CMs (human induced pluripotent stem cell-derived cardiomyocytes).

Coumarins are secondary metabolites from the phenolic compounds group. At pyranocoumarins the coumarin ring is condensed with pyran ring in position C7-C8.[77] Seselin **(10)** was isolated from branches of *H. superba* and 5-methoxy-seselin **(11)** was isolated from branches of *H. brasiliana* and *H. superba* and from subterranean stem of *H. oreadica*[42,49] (Figure 1). Abbaskhan *et al.*[78] demonstrated *in vitro* the spasmolytic activity of seselin **(10)** (EC_{50}, 0.04 ± 0.005 mg/ml) in segments of rabbit jejunum. The antifeedant activity was demonstrated by Mukandiwa *et al.*[79] in which seselin **(10)** inhibited feed intake in *Lucilia cuprina* fly larvae in the first (13.5 ± 0.5 mg) and in the second (22.4 ± 0.4 mg) instars in 1ppm minimum concentration, which resulted in significantly lower pupae mass. Larvicidal activity was observed by Mukandiwa *et al.*[80] in *Aedes aegypti* larvae exposed to dose-dependent seselin **(10)** ranging from LC_{50} in 24 hrs (13.90 ppm) and in 48 hrs (9.96 ppm). This activity is similar to that reported by Ghosh *et al.*[81] for other substances isolated from plants against *A. aegypti* (LC_{50} from 0.25 to 14.7 ppm).

Lin *et al.*[82] found a strong inhibitory activity (IC_{50}<10 µM) of 5-methoxy-seselin **(11)** (IC_{50}, 1.87 ± 0.12 µM) on phosphodiesterase-4 (PDE4) for the treatment of chronic obstructive pulmonary disease (COPD) using rolipram as a control (IC_{50} = 0.59 µM). The antimicrobial activity was evaluated by the disk diffusion method where the 5-methoxy-seselin **(11)** produced bacterial growth inhibition halos of about 11-16 mm on *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922) and *Proteus mirabilis*.[83]

Scoparon **(12)** was isolated from branches of *H. superba*, *H. brasiliana*, *H. longifolia*, from roots of *H. regia* and from subterranean stem of *H. oreadica*[42] (Figure 1). Atmaca *et al.*[84] evaluated the hepatoprotective effect of scoparon **(12)** (35mg kg/1, oral) by antioxidant action in promoting the increase of superoxide desmutase (SOD) and catalase (CAT) enzymes in hepatic injury induced by carbon tetrachloride (CCl4) in rats. In pretreated animals with scoparon **(12)** there was an increase in SOD activity (336 ± 32 U/mg of protein) and in CAT values in the liver (1.371 ± 63 UI), suggesting that the chemical structure of this coumarin plays important role in the prevention of oxidative stress. The strong antiulcerogenic activity of scoparon **(12)** (ED_{50}, 4.2 mg/kg) in HCl/ethanol induced gastritis in rats was observed by Choi *et al.*[85] compared to stillen® (eupatilin) (ED_{50}, 44.2 mg/kg) and selbex® (teprenone), (ED_{50}, 46.5 mg/kg).

The limonoid guianin **(13)** was isolated from the leaves and the subterranean stem of *H. oreadica* and from roots of *H. regia*[25,47,48,59,86] (Figure 1). The moderate antimicrobial activity of guianin **(13)** was evaluated against oral pathogens *Lactobacillus casei* (ATCC 11578), *Streptococcus mitis* (ATCC 49456), *Streptococcus sobrinus* (ATCC 33478) (MIC=0.3 mg/ml) and *Streptococcus mutans* (ATCC 25275) (MIC=0.4 mg/ml) compared to chlorhexidine (MIC=0.0001 mg/ml).[48]

Limonin **(14)** was isolated from *H. longifolia* branches and from *H. oreadica* subterranean stem[42,45] (Figure 1). Yoon *et al.*[87] observed the highest neuroprotective activity of limonin **(14)** (EC_{50}, 0.018 ± 0.001 µM and E_{max}, 75.9 ± 3.5% at 0.1 µM) by the MTT cytotoxicity assay in primary cultures of rat cortical cells when compared to the MK-801 positive control (EC_{50}, 0.480 ± 0.020µM and E_{max}, 83.8 ± 1.7% at 10.0 µM). Wansi *et al.*[88] demonstrated immunosuppressive activity of limonin **(14)** by inhibitory activity of oxidative burst of whole blood with dose-dependent suppressive effect on the phagocytic response upon activation with serum opsonized zymosan. Limonin **(14)** presented superior immunosuppressive activity (IC_{50}, 26.1 ± 1.1 μM) than the positive control ibuprofeno (IC_{50}, 54.3 ± 9.2 μM). Immunomodulatory agents represent special interest in the treatment of pathologies such as cancer, rheumatoid arthritis, systemic lupus erythematosus and organ transplantation.

Nerolidol **(15)** was isolated from *H. brasiliana* and *H. longifolia* branches[24,46] (Figure 1). Marques *et al.*[89] evaluated the anti-malarial activity (IC_{50}, 11.1 µg/ml) against *Plasmodium falciparum* W2 (resistant to chloroquine). Araújo *et al.*[90] observed, by the contact test, the repellent action of nerolidol **(15)** (0.7 µg/ml) against adult mites *Tetranychus urticae* Koch., which did not significantly differ from the positive control (eugenol) indicating potential for the development of a biopesticide for the integrated management of *T. urticae*.

This study analyzed the physicochemical properties related to the "Lipinski's Rule of Five" for the substances selected by molecular descriptors: number of hydrogen bonding acceptors, number of hydrogen bonding donors, molecular weight and Log P and it was observed that all are within the standards that the rule advocates (Table 3)

Table 3: Evaluation of the Lipinski five rule for the active compounds of *Hortia*.

NO	Description	Name	MWT	HBD	HBA	MLogP	Violations
(1)	CID 68085	Dictamnine	199.209	0	3	2.99	0
(2)	CID 107936	γ-Fagarine	229.235	0	4	3	0
(3)	CID 6760	Skimmianine	259.261	0	5	3.01	0
(4)	CID 164950	Robustine	215.208	1	4	2.7	0
(5)	CID 68230	Flindersine	227.263	1	2	3.12	0
(6)	CID 72819	N-methyl-flindersine	241.29	0	3	2.72	0
(7)	CID 65752	Rutecarpine	287.322	1	3	2.51	0
(8)	CID 378227	Hortiacine	317.348	1	4	3.27	0
(9)	-	Hortiamine	331.3678	0	5	3.58	0
(10)	CID 68229	Seselin	228.247	0	3	3.19	0
(11)	CID 290897	5-methoxy-seselin	258.273	0	4	2.99	0
(12)	CID 8417	Scoparon	206.197	0	4	1.81	0
(13)	CID 10893250	Guianin	342.391	1	4	2.14	0
(14)	CID 179651	Limonin	470.518	0	8	3.14	0
(15)	CID 5284507	Nerolidol	222.372	1	1	4.4	0

Legend: MTW- Molecular weight; HBD - number of hydrogen bond donors; HBA - number of hydrogen bonding acceptors.

The results showed that selected compounds meet Lipinski's assumptions and, possibly, will not have oral bioavailability problems becaude they present physicochemical properties necessary for good water solubility and intestinal permeability. The availability of drugs during clinical trials as well as the advantage of oral administration of drugs are important predictors in the development of new bioactive molecules.[91]

Molecular weights ranged from 199.209-470.518 g/mol, all below 500 g/mol, showing that they are small molecules. The passage of small and uncharged substances by the lipid bilayer is by osmosis or simple diffusion. In osmosis, the water moves freely through the membrane, always from the place of less concentration of solute to the one of greater concentration. The pressure at which water is forced through the membrane is known as osmotic pressure.[29]

The number of hydrogen bonding donors of all compounds was less than five and the number of hydrogen bond acceptors of all was less than 10. These parameters are important and are closely related to the partition coefficient. In general, the excessive number of donor hydrogen bonds impairs permeability through a lipid bilayer membrane due to its high solubility. The presence of many hydrogen bonding acceptors also prevents permeability by the lipid bilayer necessitating a balance between these two factors.[91,92]

The partition coefficient (log P) ranged from 1.81 to 4.4, with a higher frequency between 2 and 3, all below 5. Drugs with log P of 1 to 3 were considered as ideal. The compounds generally have good intestinal absorption, due to a good balance between solubility and permeability. Metabolism is also favored because of the low binding to metabolic enzymes. With log between 3 and 5 the compounds have good permeability, but the absorption is not significant due to the low solubility. The metabolism is more expressive in this range, due to the greater connection to the metabolic enzymes.[92]

For drug bioavailability during clinical trials it is important to evaluate whether there is dissolution, whether it does not ionize or remain neutral at different pHs, if there are no changes in hepatic metabolism, avoid active transport by bile, avoid renal excretion and avoid partition in unwanted tissues. In order to understand these biological processes and to obtain more efficient bioactive compounds, it is necessary to understand the physical and chemical properties of the molecules of interest.[29]

CONCLUSION

Several *Hortia* species have potential of therapeutic use and in the development of drugs to treat several diseases, such as microbial infections, cancer and degenerative disorders. Besides, the studied species showed to have a potential for the products development of interest in agriculture and public health in the control of pests, vectors and by the repellent and larvicidal actions. The identified compounds also present antioxidant activity that could may be of interest in the food and cosmetic industry. Therefore, phytochemical and biological studies with the wild species are necessary, seeking new potential genetic resources for application in different fields (medicine, agriculture and food science).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ATCC: American Type Culture Collection; **CAT:** Catalase; **EC_{50}:** Half maximal effective concentration; **ED_{50}:** Effective dose for 50% of the population; **GI_{50}:** Concentration for 50% of maximal inhibition of cell proliferation; **HBA:** Number of hydrogen bonding acceptors; **HBD:** Number of hydrogen bond donors; **IC_{50}:** Drug concentration causing 50% inhibition of the desired activity; **LC_{50}:** Median lethal concentration; **MIC:** Minimal inhibitory concentration; **MTCC:** Microbial type culture

collection; **MTW:** Molecular weight; **SOD:** Superoxide desmutase; **TLC:** Thin-layer chromatography.

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