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Chemistry and Biological Activity of Condamineeae Tribe: A Chemotaxonomic Contribution of Rubiaceae Family

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Abstract

This study is a review of the Condamineeae tribe, through the acquisition of data from phytochemical studies and evaluation of genera activities that constitute the tribe, in order to contribute to chemotaxonomic classification of this tribe in the Rubiaceae family. This review also states the scarcity of phytochemical investigations of several genera and consequently a lot of species of family.

Keywords

Biological Activity, Condamineeae, Chemotaxomy, Phytochemistry, Rubiaceae

1. Introduction

The Rubiaceae family has approximately 660 genus and around 11,150 species [1]. Based on molecular phylogenetic studies [2] [3] this family is partitioned in three subfamilies: Cinchonoideae, Ixoroideae and Rubioideae.

It is widely distributed, mainly on tropical and subtropical regions but also on cold and temperate regions in Europe and north of Canada [4]. In America this family is represented by approximately 229 genus and 5200 species [5]. Nowadays it has around 118 genus and 1347 species in Brazil, corresponding to one of the main families of Brazilian flora [6].

This vast family is composed by classes of secondary metabolites with highly significant pharmacological potential. Into these classes the iridoids, anthraquinones, triterpenes and indole alkaloids, which are considered chemotaxonomic markers of the family [7], are highlighted. Many of chemical constituents as flavonoids, other

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phenolic derivates and terpenoids (diterpens) are also found on this family.

In Ixoroideae subfamily the iridoids are presented as chemotaxonomic markers, while in Cinchonoideae there is a predominance of indolic alkaloids. In Rubioideae, the antraquinoms are the main class of secondary metabolites found [8]. Although the chemotaxonomic markers of Ixoroidae, it is also observed the occurrence of iridoids in the remaining subfamilies.

2. Methods

The data survey was done through academic researches and database sites and portals: www.ibict.br, www.scielo.org, www.sciencedirect.com, https://scifinder.cas.org, and www.periodicos.capes.gov.br. The terms used on the search strategy of scientific publications were restricted to species, genera, subfamilies, families and tribes. Aiming to provide greater scope to the bibliographic survey there were also selected some specific terms related to phytochemical and biological activities.

The academic investigations and scientific publications obtained for each genus are classified and presented in this study into four items: phytochemical studies, biological activities, ethno pharmacological activities and other studies, according to the available information.

3. The Genera of Condamineeae Tribe—Ixoroideae Subfamily

The Ixoroideae subfamily is represented by trees or scrubs and is characterized by levogyrous or valvular aestivation in most tribes. It presents pantropical e pan subtropical distribution and is composed by 15 tribes, including the Condamineeae, tribe that *Simira genus* belongs [9].

Phylogenetic molecular investigations revealed several relations on Rubiaceae systematic [10]. In a study conducted by [2] an initially divergent clade of the Ixoroideae subfamily was composed by genus previously classified into several distinct tribes, including *Calycophylleae*, *Cinchoneae*, *Condamineeae*, *Hippotideae*, and *Rondeletieae*. This clade was considered asan unique tribe and referred as Condamineeae, composed by the genus *Alseis*, *Calycophyllum*, *Capirona*, *Chimarrhis*, *Condaminea*, *Emmenopterys*, *Pentagonia*, *Pinckneya*, *Pogonopus*, *Rustia*, *Simira* and *Warszewiczia* [11].

Phylogenetic molecular studies associates several other genus to Condamineeae, such as *Bathysa*, *Bothriospora*, *Dioicodendron*, *Dolichodelphys*, *Ferdinandusa*, *Hippotis*, *Macbrideina*, *Macrocnemum*, *Mastixiodendron*, *Parachimarrhis*, *Picardaea*, *Sommera* and *Wittmackanthus* [3], and *Mussaendopsis* [12]. The *Dialypetalanthus* genus seemed to belong to Ixoroideae subfamily [13] and later classified as part of Condamineeae tribe [9].

The Condamineeae tribe is constituted by species very different morphologically wherein rare morphological characteristics of Rubiaceae are found into the tribe. The genus that compose the tribe are presented on **Table 1** [11].

The result of bibliographic survey showed that only genres *Alseis*, *Bathysa*, *Calycophyllum*, *Chimarrhis*, *Condaminea*, *Elaeagia*, *Emmenopterys*, *Pentagonia*, *Pogonopus*, *Rustia*, *Simira*, *Sommera* and *Warszewiczia* had some type of phytochemical study. Presented studies evaluating biological activity, genres *Alseis*, *Bathysa*, *Calycophyllum*, *Capirona*, *Chimarrhis*, *Elaeagia*, *Emmenopterys*, *Macrocnemum*, *Pentagonia*, *Pogonopus*, *Simira*, *Sommera* and *Warszewiczia*. E ethnopharmacological activity reports to the generos A *lseis*, *Bathysa*, *Bothriospora*, *Calycophyllum*, *Capirona*, *Condaminea*, *Hippotis*, *Macrocnemum*, *Pentagonia*, *Pogonopus*, *Rustia*, *Simira*, *Sommera* and *Warszewiczia*.

The results of the literature survey data related to the genres of Condamineeae tribe is presented below, with the exception of *Simira* genre, which has already been presented in our previous research [14].

3.1. Alseis

3.1.1. Phytochemical Studies

It was found only one screening with 299 samples representing 133 species from 48 genera of plants of Panama Rubiaceae family. Samples of each extract were diluted in ammonia and chloroform for acid-base extraction to produce the alkaloids extracts. The extractions were applied on filter paper to comparison effects with emetine, with Dragendorff reagents. The samples were also chromatographed in silica gel plates for TLC with standards and pulverized with Dragendorff and $FeCl_3/HClO_4$ reagents to detect the presence of alkaloids. The *A. blackiana* species presented positive results for alkaloids on these chromatographic tests [15].

Table 1. Genera that constitutes the Condamineeae tribe.

Condamineeae		
Alseis	*Bathysa*	*Bothriospora*
Calycophyllum	*Capirona*	*Chimarrhis*
Condaminea	*Dialypetalanthus*	*Dioicodendron*
Dolichodelphys	*Dolicholobium*	*Elaeagia*
Emmenopterys	*Ferdinandusa*	*Hippotis*
Holtonia	*Macbrideina*	*Macrocnemum*
Mastixiodendron	*Mussaendopsis*	*Parachimarrhis*
Pentagonia	*Picardaea*	*Pinckneya*
Pogonopus	*Rustia*	*Schizocalyx*
Semaphyllanthe	*Simira*	*Sommera*
Tammsia	*Warszewiczia*	*Wittmackanthus.*

3.1.2. Biological Activity

A. yucatanensis extracts were tested to it effect upon the induced contraction by norepinephrine (NE) 0.3 μM or 55 ml KCl in cropped aorta of free endothelial rings. The extract of *A. yucatanensis* shell presented vasoactive activity (relaxed vase) being capable of relax induced contractions by NE and KCL with effective dose for 50% (ED50) of 0.12 and 1.73 mg/mL; respectively [16] [17].

3.1.3. Ethnopharmacological Activity

It was found only one ethnopharmacological investigation citing *A. floribunda* in a survey of plants named "bitter plants" used as substitutes of *Chinchona* spp. on Brazilian traditional medicine [18].

3.2. Bathysa

3.2.1. Phytochemical Study

It is noteworthy the phytochemical study that isolated the paeonol phenolic compound **(1)** of *B. meridionalis* roots (**Figure 1**) [19].

Positive results are found for indolic alkaloids and flavonoids on chromatographic tests with *B. australis* extracts analyzed by HPLC [20]. For *B. cuspidata* the presence of alkaloids was evaluated by thin layer chromatography [21] and phytochemical analyzes were done through chromatographic reagent tests to the presence of flavonoids, phenolic compounds, alkaloids, tannins, cumarins and triterpenes [22].

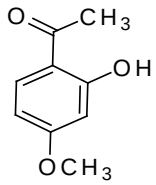
Studies with stem extracts of *B. veraguensis* species, as well as to *B. panamensis* [15], also presented positive results on TLC chromatographic tests (with Dragendorff reagents) to alkaloids [23].

3.2.2. Biological Activity

Special emphasis is given to studies evaluating the antifungal activity of secretory proteins of *B. nicholsonii* against *Fusarium oxysporum*, *Colletotrichum musae* e *Colletotrichum lindemuthianum*. The inhibition of fungal growth was tested with conidia (20,000 cells/mL in 1mL of saline solution) incubated under 28˚C in microplates of 200 μL, followed by addition of the exudates (secretory proteins) to a final concentration of 100 μg/mL, revealing an inhibitory effect on the growth around 15%, 20% and 64%, respectively, after 48 h [24].

Inhibitory activity evaluation of *B. australis* against *Mycobacterium fortuitum* and *M. malmoense* using the resazurin as a viable cell indicator, the crops were placed on microplates in contact with the extracts to be evaluated, in raw and partition forms. It was incubated under 37˚C and after 48 hours, for *M. malmoense*, and four days, for *M. fortuitum*, it was added the resazurin. Firstly it was done the susceptibility screening to determine the activity of extracts and partitions of vegetable extracts in fixed concentrations (100 μg/mL). The *B. australis* extracts did not inhibited the growth of the microorganisms involved [25].

The ethanolic extract of *B. australis* was evaluated on the activity of the protein Pdr5p ATPase of plasmatic



(1)

Figure 1. Chemical Structure of paeonol.

membranes of yeasts, on concentration ranges of 0 to 400 μg/mLwith IC_{50} of 35.3 μg/mL. Based on this result the ethanolic extract was fractionated by liquid-liquid partition resulting in hexane, dichloromethane, ethyl acetate and butanol fractions. After the solubilization in 20% of dimethylsulfoxid, the fractions were tested in Pdr5p ATPase on fixed concentration of 200 μg/mL and it was observed that the ethyl acetate, dichloromethane and hexane fractions presented and inhibition on the Pdr5p ATPase activity very similar (around 80%) compared with the ethanolic raw extract, while the butanol fraction produced a very small inhibition (around 20%) [20].

The antifungal evaluation of *B. meridionalis*, against *Alternaria anternata*, that causes diseases on tangerines. The methanolic extracts of leaves, bark, flowers and stems were dissolved in 500 μL of 1% (v/v) of Tween 80 and mixed with 100 μL of suspended conidae of *A. anternata* in 2.6 - 3.0 × 10^5 conidae/ml and the conidae suspension resultant was poured in pits (Pfizer, 0.55 mg/ml de PDA). After three days at 25˚C and a 12 hours photoperiod, the extracts that hindered the fungal growth were considered active. The *B. meridionalis* extracts did not presented any significant result [26].

On a study of the effect of the bark extract of *B. cuspidata* in pulmonary injuries induced by paraquat (PQ) herbicide in rats, briefly, PQ was dissolved in 0.5 mL of NaCl saline solution at 0.9% (10 mg/mL) and injected intraperitonially in a unique dose of 30 mg/kg of corporal weight. The ethanolic extract of *B. cuspidata* bark of the stem was resuspended in 700 μL of DMSO vehicle and administrated for animals through wash. In the investigation the intoxicated rats' treatments, with 200 and 400 mg/kg of ethanolic extract, reduced the animal mortality to 30% and 20% respectively [27].

The hepatoprotective effect of the *B. cuspidata* bark extract on hepatic injury is induced by carbon tetrachloride. The hepatic injury was induced by intraperitoneal injection with administration of CCl_4 (60% v/v, 1ml/kg) at each 48h during 12 days, the administration of the extract in 200 mg/kg and 400 mg/kg was started six days before the first application of CCl_4 and progressed to be administrated to animals during the 12 days. A significant reduction on serum aspartate transaminase, alanine and gamma-glutamyl transferase and a significant increase on the activity of the antioxidant enzyme superoxide dismutase, low proportions of cellular necrosis and lipid droplets were observed, results that confirm the hepatoprotective activity pronounced of the bark extract of *B. cuspidata* and suggests this effect can be associated with the inhibition of oxidative damages [28].

Antioxidant effect of *B. cuspidata* extract on hepatic damage and glucose kinetic on rats' blood exposed to paraquat. On rats treated with *B. cuspidata* (400 mg/kg), the bark extract was capable of inhibit large glucose variations on blood and reduce the hepatic damage [22].

Yet for *B. cuspidata* studies are found evaluating the mutagenic potential of leaves and stems extracts tested by Ames test on TA98 and TA100 lines of *Salmonella typhimurium* on absence and presence of metabolic activation, revealing that the leaves ethanolic extract did not exert effect on plasmid DNA while the stem extract revealed mutagenic activity of metabolic activation on *S. typhimurium*. The extract effects directly on DNA were assessed by plasmodial cleavage, indicating the absence the genotoxic activity for both stem and leave extracts [21].

And finally, a study investigating the applicability potential of ethanolic extracts ointment from *B. cuspidata's* peel, for wounds treatment in Rats. The circular wounds of 12 mm diameter were done by surgical incision on the back of animals, which were divided in four groups, according to the received application. One group received a 0.9% saline solution, the second group received lanolin, and a third group received 2.5% of the lanolin emulsified extract. After 21 treatment days, the groups with the extract had given better results according to the skin regeneration and wound healing. This study suggests that the healing effects observed in ointment with the *B. cuspidata*'s extract are related to polyphenols compounds, including flavonoids, found in these extracts and which had their presence identified by phytochemical tests [29].

To the *B. veraguensis* stem extracts were prepared and tested for inhibitory activity of acetylcholinesterase. A

concentration of 100 μg was applied on plates of TLC and eluted with a mix of $CHCl_3$-MeOH-H_2O (65:35:5) to polar extracts and AcOEt-n-hexane (1:1) to non-polar, respectively. The extracts revealed moderate inhibitory activity to acetylcholinesterase when compared to the HBr galatamine inhibitor tested at 0.01 μg on TLC. On this same study the extracts of *B. veraguensis* were tested for inhibition activity to DPPH free moiety. The extracts revealed moderate activity of inhibiting the DPPH free moiety compared to quercetine, tested as reference compound (0.1 μg) [23].

3.2.3. Ethnopharmacological Activity

For *B. australis* and *B. cuspidata* it was found an ethnophamacological study with a data survey of plants named "bitter plants" used as substitutes of *Chinchona* spp. on Brazilian traditional medicine [18].

3.3. Bothriospora

Ethnopharmacological Activity

It is noteworthy the ethnopharmacological study in biodynamic plants employed by the indians of amazonic region with medicines, poisons and narcotics. To *B. corymbosa* it is stated the use of fruits against intestine parasites [30].

3.4. Calycophyllum

3.4.1. Phytochemical Study

In a plant screening in Costa Rica the presence of alkaloids is found on leaves and stems of *C. candidissimum* through the chromatographic tests [31].

The phytochemical investigation of *C. spruceanum* presented the isolation of seco-iridoids 7-methoxydiderroside **(2)**, 6'-O-acetyldiderroside **(3)** and 8-O-tigloyldiderroside **(4)**, kingside **(5)**, diderroside **(6)** and loganetin **(7)** (**Figure 2**), isolated from the wood bark along with the iridoids loganin **(8)** and secoxyloganin **(9)** (**Figure 2**) [32].

3.4.2. Biological Activity

To the species *C. multiflorum*, it was found an investigation of the antifungal activity evaluation of dichloromethane extracts, methanol and aqueous of the bark against *Cryptococcus neoformans*, *Microsporum gypseum* and *Trichophyton mentagrophytes*. The extracts were evaluated through the disc method—agar diffusion. The dichloromethane extract presented a pronounced activity, with 5 mg per disc, diameters to the inhibition zone with

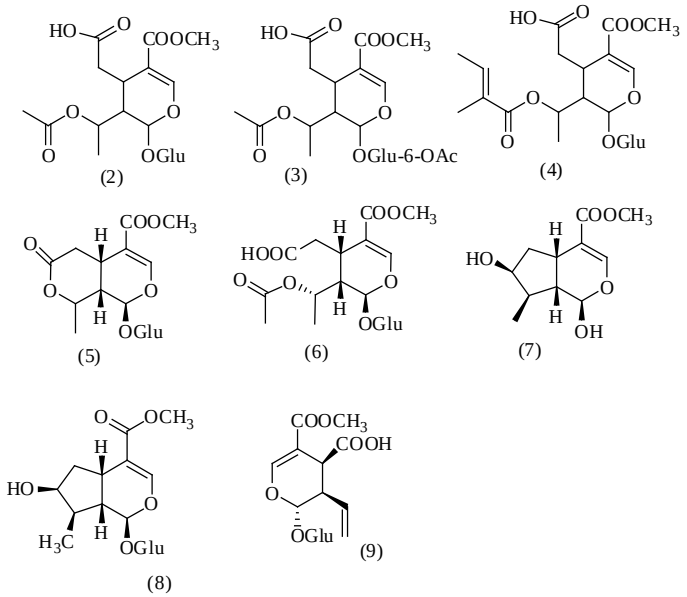


Figure 2. Seco-iridoids and iridoids of *C. spruceanum*.

the values: 21 mm, 18 mm and 18 mm, and to the dichloromethane extract with 10 mg per disc, diameters to the inhibition zone with the values: 24 mm, 20 mm and 20 mm for *C. neoformans*, *M. gypseum* and *T. mentagrophytes* respectively. Besides, the aqueous extracts containing 5 mg and 10 mg per disc present inhibition diameters with the values 23 and 25 respectively to *T. mentagrophytes* [33].

Special emphasis is given to studies evaluating the activities of *C. spruceanum* against leishmania with MTT (3-(4,5-dimethiliazol-2ul)-2,5-difenil bromide of tetrazoline) presenting absence of activity [34].

The antimalarial evaluation of the bark of *C. spruceanum in vivo* determined by the suppression test of four days, and *in vitro*, the infected erythrocytes with malaria were sown on well of microtiter plates, exposed to different concentrations in both tests [35].

Yet, to *C. spruceanum*, the antibacterial evaluation against *Mycobacterium tuberculosis* the radiometric *in vitro* trials using semiautomatic detector for growth monitoring was applied. The raw extracts of dichloromethane of vegetal material were dissolved to the concentration of 1 mg/ml of 100% dimethilsulfoxid (DMSO) and injected on bottles to obtain a final concentration of 50 μg of plant extract per ml of broth culture. The extracts presented less than 50% of inhibition, results considered non-significant [36].

The evaluation of antifungal activity against *Candida albicans* ATCC 90028, *Sporothrix schenckii* IHEM 15,503 and *Trichophyton mantagrophytes* IHEM 0584, *in vitro*, compared with amphotericin B. did not presented significant results [37].

The evaluation of the compounds 7-metoxididerrosideo, 6'-O-acethyldiderrosideo, secoxyloganin **(9)** and diderrode **(6)** exhibited poor activity *in vitro* against *Trypanosoma cruzi* with values of IC_{50} equal to 59, 0, 90, 2, 74, 2 and 84.9 mg/ml, respectively [32].

3.4.3. Ethnopharmacological Activity

The species *C. acreanumi*, *C. obovatum* and *C. spruceanum* are cited on an ethnobotanical investigation as employed by indians of the Amazon region. The shells of *C. acreanum* are scraped and placed in warm water about fungal infections. These shells are employed in infusions to combat intestine parasites. And for *C. spruceanum* a shell decoction is used as black scab (caused by arachnids) and the dry shell can be pulverized and applied on fungal infections [30].

To *C. spruceanum* species, it was found an ethnobotanical and ethnopharmacological investigation of plants used by indians of Peruvian Amazonia against skin infections on shell, fruits and leaves decoction forms [38] [39].

3.5. Capirona

3.5.1 Biological Activity

It is noteworthy an investigation of the antileishmania activity to *C. decorticans*. The leishmanicide activity *in vitro* of ethanolic extracts was evaluated for amastigote and promatigotes cultures by the MTT method, obtaining $IC_{50} > 100$ μg/mL for both forms, no significant results [40].

3.5.2. Ethnopharmacological Activity

The *C. decorticans* species is also used on formulation of medicines against leishmania by the traditional medicine of ethnic groups on Peruvian Amazonia [34]. It is also used for warts, infected wounds, fungal infections and scabies treatments. The shell is scraped and applied as a cataplasm on the affected area, and the broth of the shell is also used on wounds [40].

3.6. *Chimarrhis*

3.6.1. Phytochemical Study

To *C. turbunata* were stated phytochemical investigations where were isolated and indentified the indolic alkaloid monoterpenic glycosylated strictosidine **(10)**, the derived corinanteans 5-α-carboxystrictosidine **(11)**, isovallesiachotamine **(12)**, vallesiachotamine **(13)**, turbinatine **(14)**, 3,4-dehydro-strictosidine **(15)**, 3,4-dehydrostrictosidine acid **(16)**, strictosidine acid **(17)**, and the alkaloids *β*-carbolinic: cordifoline **(18)**, desoxycordifoline **(19)**, and harman-3-carboxylic acid **(20)** [7] [41] [42] (**Figure 3**).

Yet for C. turbinata in phytochemical investigations found the flavonoids chimarrhoside **(21)** quercetin-3-*O*-rutinoside **(22)**, kaempferol-3-*O*-rutinoside **(23)**, kaempferol-3-*O*-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-ga-

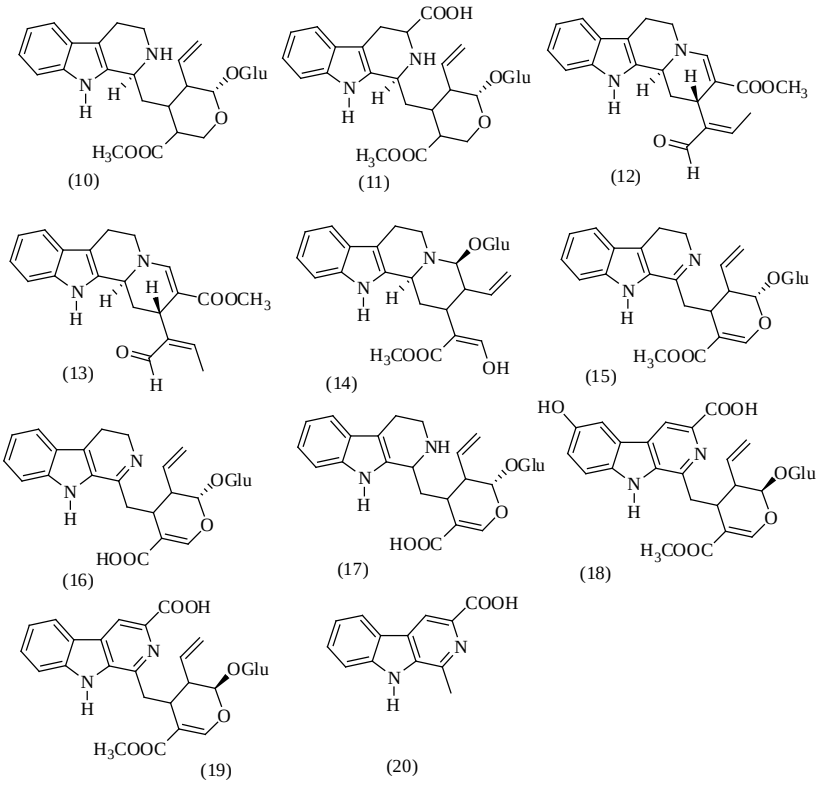


Figure 3. Alkaloids isolated of *C. turbinata*.

lactopyranoside **(24)**, quercetin-3-*O*-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-galactopyranoside **(25)**, 6-hydro-xy-rutin **(26)**, kaempferol-3-*O*-D-galactopyranoside **(27)**, kaempferol-3-*O*-D-glucopyranoside **(28)**, kaempferol-3-*O*-*α*-L-rhamnopyranosyl-(1→6)-*α*-L-rhamnopyranosyl-(1→4)-*β*-D-glucopyranoside **(29)**, catechin **(30)** and catechin-(4*α*→8)-catechin-procyanidin B-3 **(31)** [43] (**Figure 4**).

Also the *C. turbinata* leaves were stated on phytochemical investigations that isolated and identified the derived chlorogenic acid 1-(3',4'-dihydroxycinnamoyl) cyclopentane-2,3-diol **(32)**, *trans*-chlorogenic acid methyl ester **(33)** and *cis*-chlorogenic acid methyl ester **(34)** and the chimarrhinin **(35)** [44] [45] (**Figure 5**).

The *C. parviflora* species also presented positive results for alkaloids on TLC tests with chromatographic reagents [15].

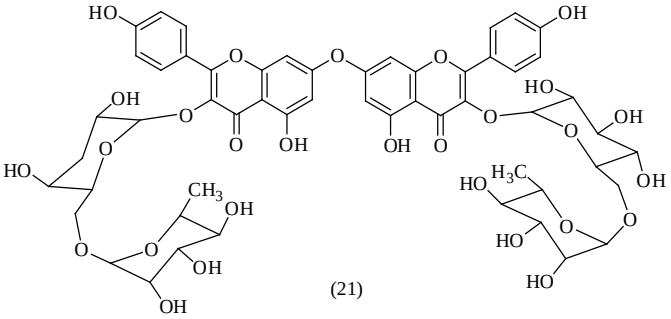
3.6.2. Biological Activity

Special emphasis is given to an investigation of *in vitro* evaluation of medicines based on *C. turbinata* by traditional medicine of French Guiana against *Plasmodium falciparum*, but did not presented significant results, with IC_{50} upper than 11 μg/mL being considered inactive, and for the test *in vivo* (suppressive test in four days) the medicines based on *C. turbinata* did not presented any activity [46].

The isolated compounds **(10)** to **(14)** exhibited poor, but selective, activity with values around IC_{12} > 250 and 100 μg/mL or more, on mutant yeast strains RS 188N (RAD+) and RS 322YK (rad 52Y), respectively [41] [47].

The compounds **(10)**, **(11)** and from **(14)** to **(20)** were tested for the moiety 1,1-difenil-2-picrilhidrazil (DPPH). The alkaloid **(18)** presented high scavenging activity to the DPPH radical (IC_{50} 18.3 μg/mL), using the antioxidant rutine pattern (IC_{50} 12.3 μg/mL) as reference, while all other alkaloids isolated revealed poor activity (IC > 40 μM). Besides, these alkaloids were submitted to TLC screening for acehylcolinesterase inhibitors. The compounds **(14)** and **(19)** revealed moderated inhibition to a concentration of 0.1 and 1.0 μM, respectively. A trial *in vitro* with rats' brains **(14)** presented moderated activity (IC_{50} 1.86 μM) compared to the standard compound, galantamine (IC_{50} 0.92 μM) [42].

The isolated *C. turbinata* flavonoids were submitted to an antioxidant activity evaluation on DPPH test, using rutine as standard (IC_{50} 21.34 μg/mL) and BHT (IC_{50} 62.50 μg/mL). The compounds **(22)** with IC_{50} 21.3 μg/mL,



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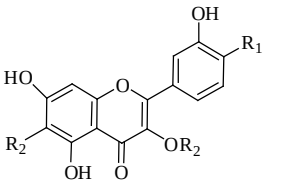
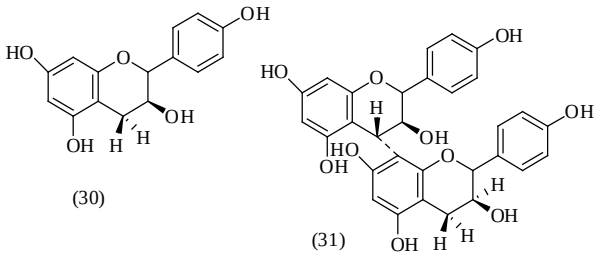
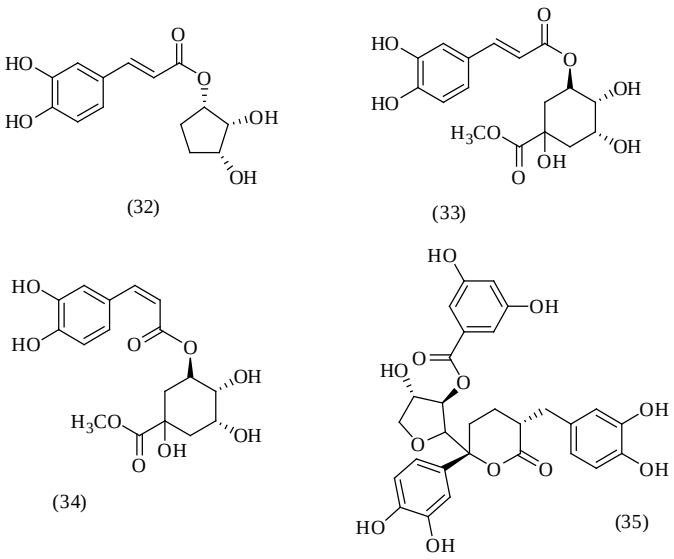


	R_1	R_2	R_3
(22)	OH	Glu-Rha	H
(23)	H	Gal-Rha	H
(24)	H	Glu-Rha	H
(25)	OH	Gal-Rha	H
(26)	H	Glu-Rha	OH
(27)	H	Gal	H
(28)	H	Glu	H
(29)	H	Glu-Rha-Rhu	H



(30) (31)

Figure 4. Flavonoid of *C. turbinata*.



(32) (33) (34) (35)

Figure 5. Other compounds of *C. turbinata*.

(25) with IC_{50} 30.1 μg/mL, **(26)** with IC_{50} 25.4 μg/mL, **(30)** with IC_{50} 33.4 μg/mL, and **(31)** with IC_{50} 11.5 μg/mL presented higher activities [43].

The oxidant activity with DPPH of the compounds **(33)** to **(35)** were evaluated using as standard the antioxi-

dant reference BHT (IC_{50} 62.50 (0.6 μmol·L^{-1}) and chlorogenic acid (IC_{50} 20.0 (0.2 μmol·L^{-1}). The compound **(34)** revealed the best results with IC_{50} value (7.50 ± 0.5 μmol·L^{-1}) below the BHT standard. The compounds **(33)** and **(34)** revealed IC_{50} 18.60 ± 0.4 μmol·L^{-1} and IC_{50} 18.50 ± 0.6 μmol·L^{-1}, respectively. The results indicate the free moiety scavenging activity of these molecules [45].

3.7. Condaminea

3.7.1. Phytochemical Study

Positive result to *Condaminea corymbosa* alkaloids on TLC tests with chromatographic reagents with Rubiaceae species at Panama [15].

3.7.2. Ethnopharmacological Activity

The ethnopharmacological investigation where is cited the use of *C. corymbosa* stem as tonic on Peruvian Amazonia traditional medicine is highlighted [48].

3.8. *Dialypetalanthus*

A taxonomical study of *D. fuscescens* species analyzed the composition of polysaccharides on the cell walls of *D. fuscescens* leaves and compared with *Bathysa meridionalis*. The analyses demonstrated both species have very similar chemical composition of the cell wall corroborating as additional evidence of their taxonomic proximity as is actually accepted [49]. In addition to studies that classify the genus on Ixoroideae subfamily and Condamineeae tribe through molecular phylogenetical investigations [3] [5] [11].

3.9. Elaeagia

3.9.1. Phytochemical Study

The *E. nitidiflora* species presented positive results for alkaloids on tests with chromatographic reagents and on this same investigation the *E. auriculata* species presented negative results [15].

The study in subfraction of ethanol extract obtained from the leaves of *E. utilis*, analyzed by CG/MS. Terpenes, sesquiterpenlactones and simple phenolic compounds were identified in it for comparison with mass and retention time values from literature (**Table 2**) [50].

3.9.2. Biological Activity

The *E. auriculata* species activity was also evaluated for against *Aphis gossypii* and *A. craccivora* (aphids). The trial was realized on microplates covered by parafilm containing leaves extract (60 μg/ml) and proteins of leaves extract (33.3 μg/mL). The aphids fed up of these extracts on holes in the parafilm. The mortality rate was verified at each 24, 72 and 120 hours and the results were expressed in percentage. The leaves extract of *E. auriculata* presented 29.5% of mortality rate while the proteins presented 3.7%, no significant results [51].

E. utilis species' antimicrobial activity was evaluated against the bacteria that cause dental caries: *Streptococcus mutans*, *S. sobrinus* e *Lactobacillus acidophilus*. Two extracts, one from light petroleum and an ethanolic one, were obtained from the leaves of *E. utilis*. Both were fractionated and sub-fractionated, according to the presented activities in the evaluation, done by diffusion method in a concentration of 10 mg/well. In each well, 50 μl of extract were placed, fraction or sub-fraction, dissolved in DMSO. As a positive control, 50 μl of Vancomycin were used with 150 μg/ml concentration and 50 μl of DMSO as negative control. After 24 h of incubation, the inhibition zones were measured and, the minimum inhibitory concentration, calculated (MIC; at least 6

Table 2. Compounds identified by GC-MS in *E. utilis*.

Compounds in *E. utilis*	
Benzyl alcohol	3-methoxy-4-hydroxybenzaldehyde
Benzoic acid	4-vinylphenol
Benzoic acid, 2-hydroxy-, phenyl methyl ester	2,5-dimethyl-(3-methoxymethyl)-p-benzoquinone
2,3-dihydrobenzofuran	1,Z-5,E-7-dodecatrien
4-((1e)-3-hydroxy-1-propenyl)-2-methoxyphenol2	2,6-dimethoxy-4-(2-propenyl) phenol
-methoxy-4-vinylphenol	Loliolide

mm). Between the ethanolic extract fractions, the fraction of dichloromethane presented the greatest level of activity, being sub-fractionated in three fractions, of which the MeOH: H_2O fraction presented MIC = 0.1 µg/well with three tested bacteria. In this fraction, the presence of terpenes, sesquiterpenlactones and phenolic compounds, was confirmed through phytochemical tests, suggesting the relation between these compounds and the presented activity [50].

3.10. Emmenopterys

3.10.1. Phytochemical Study

Special emphasis is given to the phytochemical investigations for *E. henryi* reporting the isolation and investigation of cumarins: scopoletin **(36)**, umbelliferone **(37)** and umbelliferone-7-*β*-D-glucoside **(38)**; the steroids: *β*-sitosterol **(39)** and 3-O-*β*-D-glucopyranosylsitosterol **(40)**; the ursane triterpenes: taraxerol **(41)**, taraxerone **(42)**, ursolic acid acetate **(43)**, 3*β*, 19*α*, 23-trihydroxyurs-12-en-24-al-28-oic acid **(44)**, 3*β*, 19*α*, 24-trihydroxy-23-norurs-12-en-28-oic acid **(45)**, 12*β*-hydroxy-5*α*-pregnane-14.16-dien-3.20-dione **(46)**, pomolic acid **(47)**, 3*β*, 6*β*, 19*α*, 23-tetrahydroxyurs-12-en-28-oic acid **(48)**, 3*β*, 6*β*, 23-trihydroxyolean-12-en-28-oic acid **(49)**, 3*β*, 6*β*, 19*α*, 23-tetrahydroxyolean-12-en-28-oic acid **(50)** and 3*β*, 23.24-trihydroxyolean-12-en-28-oic acid **(51)**; and the pregnanes derivatives: 3*β*, 12*β*-dihydroxy-5*α*-pregnane-14.16-dien-20-one **(52)**, 12*β*-hydroxy-5*α*-pregnane-14, 16-dien-3.20-dione **(53)**, 3*β*, 12*β*-dihydroxy-5*α*-pregnane-16-en-20-one **(54)** and 12*β*-dihydroxy-5*α*-pregnane-16-en-3.20-dione **(55)** [52] [53] (**Figure 6**).

3.10.2 Biological Activity

The petroleum ether extract of the *E. henryi* stem presented antifeedant activity against *Plutella xylostella* on larvae trial treatment. The extract presented 80.09% of mortality rate against *Plutella xylostella* and 62.80% against *Spodoptera litura*, indicating high activity compared to industrially marketed standards on China and suggests further investigations for the use of this species as an insecticide [54].

3.11. Hippotis

In addition to studies which classify the genus on Ixoroideae subfamily and Condamineeae tribe through molecular phylogenetic investigations [3] [11], it was found only one ethnopharmacological study suggesting the *H. tubiflora* stem is used as tonic on Peruvian Amazonia traditional medicine [48].

3.12. Macrocnemum

3.12.1. Biological Activity

Evaluation of *M. roseum* leaves and bracts ethanolic extracts against leishmania using MTT method to determine the extract activities. For bioassays the extracts were dissolved on DMSO (final concentration 1%) at 10 mg/mL concentration, presenting moderate activity with IC_{50} 37 g/mL to bracts extract and IC_{50} 22 g/mL to leaves extract [34].

3.12.2. Ethnopharmacological Activity

An investigation of *M. roseum* states the use of leaves to treat wounds on traditional medicine of Peru. The leaves are boiled on water and the wounds washed the same water, but cold [34] [55].

3.13. Pentagonia

3.13.1. Phytochemical Study

It is noteworthy a phytochemical investigation with *P. gigantifolia* root ethanolic extracts where were isolated the compounds: 6-octadecynoic acid **(56)** and 6-nonadecynoic acid **(57)** [56] (**Figure 7**).

3.13.2. Biological Activity

The investigation with *P. gigantifolia* root ethanolic extract presented antifungal activity against *Candida albicans*, with $IC_{50} < 20$ µg/mL. Susceptibility tests to antifungal agents were realized using a modified version of NCCLS methods. After being chromatographed one of the fractions was tested and presented the highest activity with $IC_{50} < 2$ µg/mL [56].

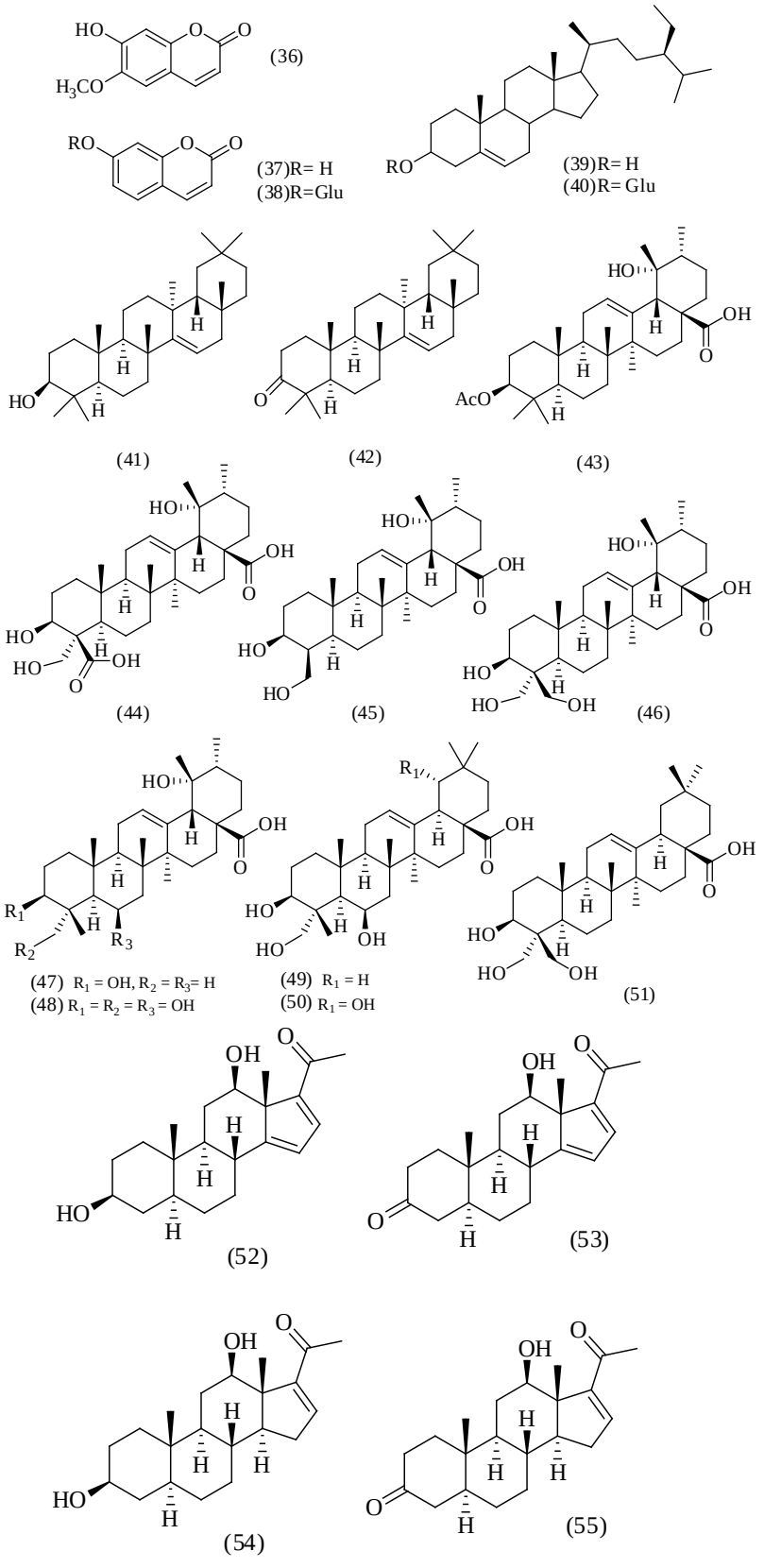


Figure 6. Compounds isolated from *E. henryi*.

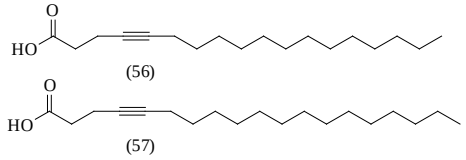


Figure 7. Fatty acids of *Pentagonia gigantifolia*.

The evaluation of compounds **(56)** with IC_{50} range of 0.45 to 0.65 µg/mL and **(57)** with IC_{50} range of 0.25 to 0.45 µg/mL presented activity with many *C. albicans* strains [56].

3.13.3. Ethnopharmacological Activity

It was found a study that states the use of *P. pubens* shell boiled on water to combat malaria and also it use as ornamental plant [57].

3.14. *Pogonopus*

3.14.1. Phytochemical Study

Phytochemical study of *P. specious* branches extracts led to the isolation of the alkaloids 1', 2', 3', 4'-tetradehydrotubulosine **(58)**, tubulosine **(59)** and psychotrine **(60)** [58]. The phytochemical investigation of *P. tubulosus* branches extracts, besides the compounds **(59)** and **(60)**, the alkaloid cephaeline **(61)** was also isolated [59] (**Figure 8**).

3.14.2. Biological Activity

On cytotoxicity trial the *P. tubulosus* extract obtained by acid-base extraction revealed IC_{50} = 0.015 µg/mL against epidermoid carcinoma KB cells in culture. The **(58)** and **(59)** alkaloids were evaluated against several human tumor cell lines presenting poor cytotoxicity with ED_{50} = 2.2 to 9.0 µg/mL for **(58)** and ED_{50} = 2.3 to 13.3 µg/mL for **(60)**, activity considered poor compared to the most potent activity observed for tubulosine (59), with ED_{50} < 0.001 to 0.22 µg/mL [58].

The raw ethanolic extract and a *P. tubulosus* extract obtained by acid-base extraction were also evaluated for antiproliferative activity against several lines of human neoplastic cells: ATCC-CCL-23, laryngeal carcinoma, ATCC-HTB-22, breast carcinoma, ATCC-CRL-1932, liver carcinoma, ATCC-HTB-38, colon carcinoma, and murine cancer: ATCC-CRL-6322, murine melanoma. The raw extract presented IC_{100} range of 2.2 to 6.9 µg/mL and the extract of acid-base extraction with IC_{100} range of 0.24 to 2.2 µg/mL presented high antiproliferative activity against all neoplastic cells lines [60].

The alkaloids **(59)**, **(60)** and **(61)** were also tested against sensible strains and resistant to *Plasmodium falsiparumin vitro* and against *P. berghei* and *P. vinckei petteri* (*in vivo*). Tubulosine **(59)** presented *in vitro* IC_{50} = 0.006 µg/mL against sensible *P. falciparum* and IC_{50} = 0.011 µg/mL against resistant *P. falciparum*. And *in vivo* presented antimalarial activity with ED_{50} = 0.05 mg/Kg/day for *P. vinckei petteri* and ED_{50} = 0.45 mg/Kg/day for *P. berghei* against *Plasmodium falciparum in vitro* tests. The *in vivo* tests were done through the classic suppression method during four days [59] [61].

The psychotrine alkaloid **(60)** presented *in vitro* IC_{50} = 0.14 µg/mL against sensible *P. falciparum* and IC_{50} = 0.39 µg/mL against resistant *P. falciparum*. And *in vivo* presented antimalarial activity with ED_{50} > 2 mg/Kg/day for *P. berghei*. The cefaeline alkaloid **(61)** presented *in vitro* IC_{50} = 0.027 µg/mL against sensible *P. falciparum* and IC_{50} = 0.011 µg/mL against resistant *P. falciparum*. And *in vivo* presented antimalarical activity with ED_{50} = 6 mg/Kg/day for *P. berghei* [59].

3.14.3. Ethnopharmacological Activity

Studies of the use of *P. tubulosus* on traditional medicine of Bolivia against malaria in the stem bark decoction form [62].

3.15. *Rustia*

3.15.1. Phytochhemical Study

The study of essential oil extracted from *Rustia formosa* secretory cavities, analyzed by CG/MS, presented a

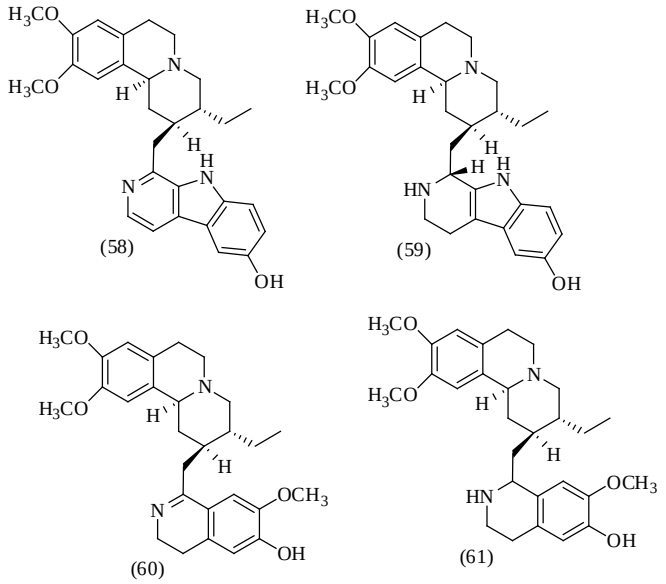


Figure 8. Alkaloids Isolated of *Pogonopus* genus.

complex mix of 75 terpenic components, formed mainly by sesquiterpens, substances solely identified for comparison with mass and retention time values from literature (**Table 3**) [63].

3.15.2. Ethnopharmacological Activity

An investigation states the use of *R. formosa* species on Brazilian traditional medicine as substitute of *Chinchona* spp., based on pharmacological studies [18].

3.16. *Sommera*

3.16.1. Phytochemical Study

The phytochemical investigation of *S. sabiceoides* roots ethanolic extracts presented five fatty acids: 6-hexadecynoic acid **(62)**, 6-heptadecynoic acid **(63)** and 6-icosynoic acid **(64)** (**Figure 9**) and 6-octadecynoic acid **(56)** and 6-nonadecynoic acid **(57)** [63] (**Figure 7**).

3.16.2 Biological Activity

The *S. sabiceoides* dichloromethane extract presented 96% of inhibition against *Mycobacterium tuberculosis*, in 50 μg/mL and presented MIC < 6.25 μg/mL, considered excellent results. The *in vitro* experiments (trials) were done using a radiometric detector semiautomized to monitor the *Mycobacterium tuberculosis* growth [36].

The methanolic extract tested against *Candida albicans* presented 50% inhibition with IC_{50} < 20 μg/mL. The *in vitro* cytotoxocity was determined by the neutral red method. On the *in vivo* cytotoxicity experiment the compounds were dissolved on peanut oil until the desired concentration. Six rat groups received 100 μL intraperitoneal injections, providing compound doses of 3, 4, 17 or 34 μmol/kg of body weight.

The *S. sabiceoides* compounds **(56)** and **(57)** presented positive results against *Trichophyton mentagrophytes* ATCC MYA-4439, *T. mentagrophytes* ATCC 9533, *T. rubrum* ATCC 10218, and *T. rubrum* ATCC MYA-4438 presenting MFC range from 0.7 to 11.1 μM. The *S. sabiceoides* compounds **(62)** and **(64)** along with **(56)** and **(57)** were also active against *Candida krusei* ATCC 6258 with MIC range from 4.4 to 10.6 Mm [64].

The compound **(57)** also presented activity against *C. albicans* (MIC range from 1.3 to 8.0 μM) against *Aspergillus fumigatus* (MIC range from 2.7 to 6.6 μM), against *T. mentagrophytes* e *T. rubrum* strains (MIC range from 0.7 to 3.3 μM) and against fluconazol-resistant *C. albicans* (MIC range from 1.3 to 8.0 μM).

The compounds **(62)** and **(64)** did not presented *in vitro* toxicity to concentrations until 32 μM on cytotoxicity test with SK-MEL cells (melanoma), KB (epidermic carcinoma, oral), BT-549 (ductal carcinoma, breast), SK-OV-3 (ovary carcinoma), and LLCPK-1 (pork kidney epithelial). And on cytotoxicity test **(56)** and **(57)** did not presented toxic effects on doses less than 34 μmol/Kg/day [64].

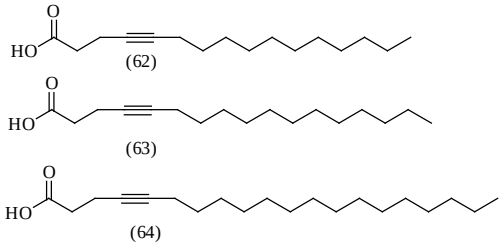


Figure 9. Fatty acids of *Sommera sabiceoides*.

Table 3. Compounds identified in *R. formosa* essential oil.

Compounds in *R. formosa* essential oil					
β-elemene	germacrene D	*α*-humulene	*α*-muurolene	curzerenone	germacrene B
γ-muurolene	*γ*-elemene	*cis*-*β*-guaiene	caryophylleneoxide	*α*-cadinene	*epi*-*α*-muurolol
β-caryophyllene	*β*-selinene	*α*-cadinol	*δ*-cadinene	*epi*-α-cadinol	germacrone

3.17. *Warszewiczia*

3.17.1. Phytochemical Study

The *W. coccinea* shell was tested on a histochemical study for alkaloid presence, presenting negative result [65], however presented positive results on another investigation regarding chromatographic techniques [15].

Still, *W. coccinea* investigations stated the presence of the triterpens 3*β*, 6*β*, 19*α*-trihydroxy-urs-12-en-28-oic acid **(65)** and 3*β*, 6*β*-dihydroxy-olean-12-en-28-oic acid **(66)** [23] and the tiramine methabolites **(67)** and cyanidin 3-glicoside **(68)** [66] (**Figure 10**).

3.17.2. Biological Activities

Evaluation of *W. cordata* antileishmania activity. The experiments were conducted on promastigotes and axenic amastigotes of *Leishmania amazonensis* and the extract activity was determined through MTT method. The *W. cordata* branches ethanolic extract presented IC_{50} = 60.6 μg/ml for the amastigote form, moderated activity, presented no result for promastigote form [67].

An investigation of the *W. coccinea* ethanolic extract activity against leishmania (*Leishmania amazonensis*) revealed poor activity determined through MTT method, presenting IC_{50} > 100 μg/mL to shell extract and IC_{50} = 54.3 μg/mL to branches extract. To the antimalaric (*Plasmodium falciparum* FCR3 *in vitro*) there was no activity [68].

The *W. coccinea* stem extract strongly inhibited acetylcholinesterase in 100 μg on TLC, and inhibited poorly free DPPH moieties on antioxidant test. On the same investigation the compounds **(65)** and **(66)** were active on the inhibition acetylcholinesterase test with 1 μg at each TLC plate [23].

3.17.3. Ethnopharmacological Activity

An ethnobotanic investigation stated the use of *W. coccinea* grated shell in cold water intake for convulsion and epilepsy treatment on Peruvian traditional medicine [68].

There were also found ethnobotanic investigations wherein the *W. coccinea* roots are dried and the powder is applied with oil to fungal skin disorders or the root is boiled and applied as decoction to pain relief [30].

W. coccinea shells are also used as haemostatic by Colombian indians, to nosebleed treatment at Peru and fever at Porto Rico [23].

The *Dioicodendron*, *Dolichodelphys*, *Dolicholobium*, *Ferdinandusa*, *Holtonia*, *Macbrideina*, *Mastixiodendron*, *Mussaendopsis*, *Parachimarrhis*, *Picardaea*, *Pinckneya*, *Schizocalyx*, *Semaphyllanthe*, *Tammsia* e *Wittmackanthus* genus presented absence or irrelevant investigations to this review.

4. Results and Discussion

In relation to the phytochemical studies, from the 33 genus in the Condamineeae Tribe, approximately 13 presented at least one studied species, containing isolated or identified secondary metabolites. In a total of 110

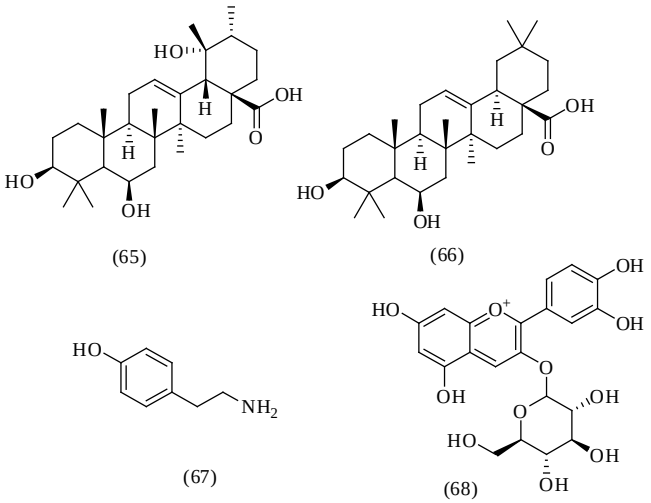


Figure 10. Compounds isolated of *W. coccinea*.

isolated and identified substances in these species, including the results of the review for the genus *Simira* [14], approximately 24.54% were from the alkaloid's class, and from these substances, approximately 81.18% are indole alkaloids, which are considered as chemotaxonomic markers from family [7]. The class of terpenoids metabolites, including diterpens, triterpens, and steroids, presents a bigger percentage, approximately 27.27% of the substances found in this tribe until this moment (**Graphic 1** and **Graphic 2**)

According to the biological activity, from the 33 genus in the tribe, 13 presented some evaluation of biological activity, and 14 presented reports of ethnopharmacological application, but not necessarily showed biological activity.

From the 13 genus which presented biological activity, 9 genus, including the genus *Simira*, presented studies reporting the presence of alkaloid or a positive result when tested for alkaloids. And from these 9 genus, 7 also presented ethnopharmacological reports (**Graphic 3** and **Graphic 4**).

5. Conclusions

It was observed the species that belongs to the genera of Condamineeae tribe presented a considered number of metabolites in similar biosynthetic origin and a lot of them presenting some kind of biological activity.

The alkaloids found for *Simira* genus are indolic [14] as the alkaloids presented for *Chimarrhis* and *Pogonopus* genus, considered as taxonomic markers of the family, belongs to the most investigated secondary metabolic groups aiming to prove the phyologenetic correlation between Ruibiaceae chemistry and taxonomy. Evidences based on indolic alkaloids skeletons, used for chemical and morphological evolutionary comparisons between Rubiaceae, Apocynaceae and Loganiaceae [8].

The presence of iridoids and it derivatives secoirioids of *Calycophyllum* genus also demonstrates the connection between the genus presenting monoterpenes indolic alkaloids, as *Chimarrhis* and *Pogonopus*, since the secoiridoids are involved on the construction of the basic skeleton of indolic alkaloids [69]. This proximity relationship can extend to the genus that presented positive results for alkaloids on chromatographic tests as *Alseis*, *Bathysa*, *Condaminea*, *Elaeagia*, *Macrocnemum*, *Pentagonia*, *Rustia*, *Sommera*, *Warszewiczia* e também o gênero *Simira*. The *Calycophyllum* genus presented positive results for alkaloids.

For *Chimarrhis* genus it was found the harman-3-carboxilic acid **(20)** (**Figure 3**), structure that could derive from harmana alkaloid, considered as a taxonomic tracer in *Simira* genus [14] corroborating the proximity between the *Simira* and *Chimarrhis* genus.

This review also states the scarcity of phytochemical investigations of several genera and consequently a lot of species of Rubiaceae family. It could contribute more significantly to this family taxonomy.

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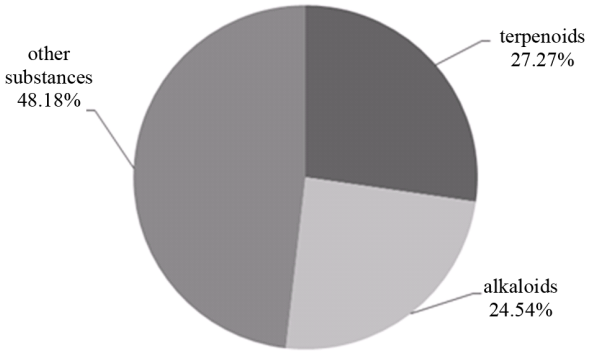
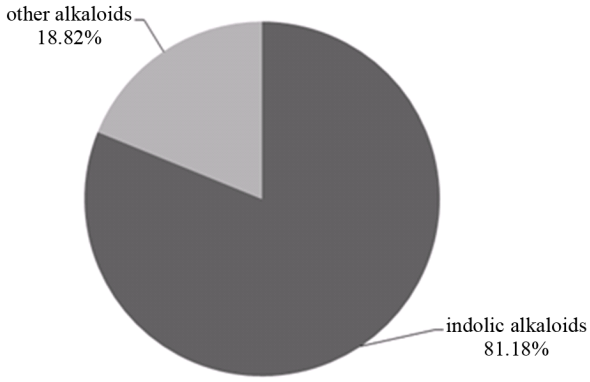
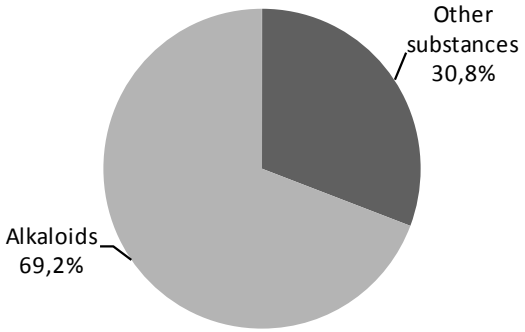


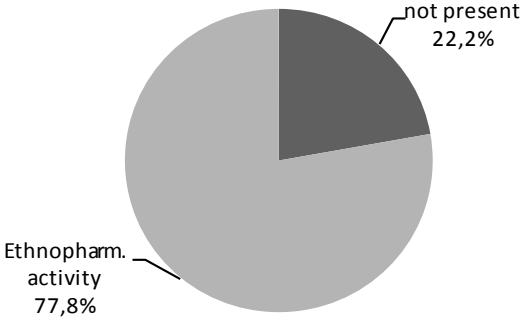
Graphic 1. Percentage of the compounds isolated in Condamineeae tribe.



Graphic 2. Percentage of alkaloids isolated in Condamineeae tribe.



Graphic 3. Alkaloids percentage in genus with biological activity.



Graphic 4. Ethnopharmacological activity percentage in genus with alkaloids.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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