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Connaraceae: An updated overview of research and the pharmacological potential of 36 species

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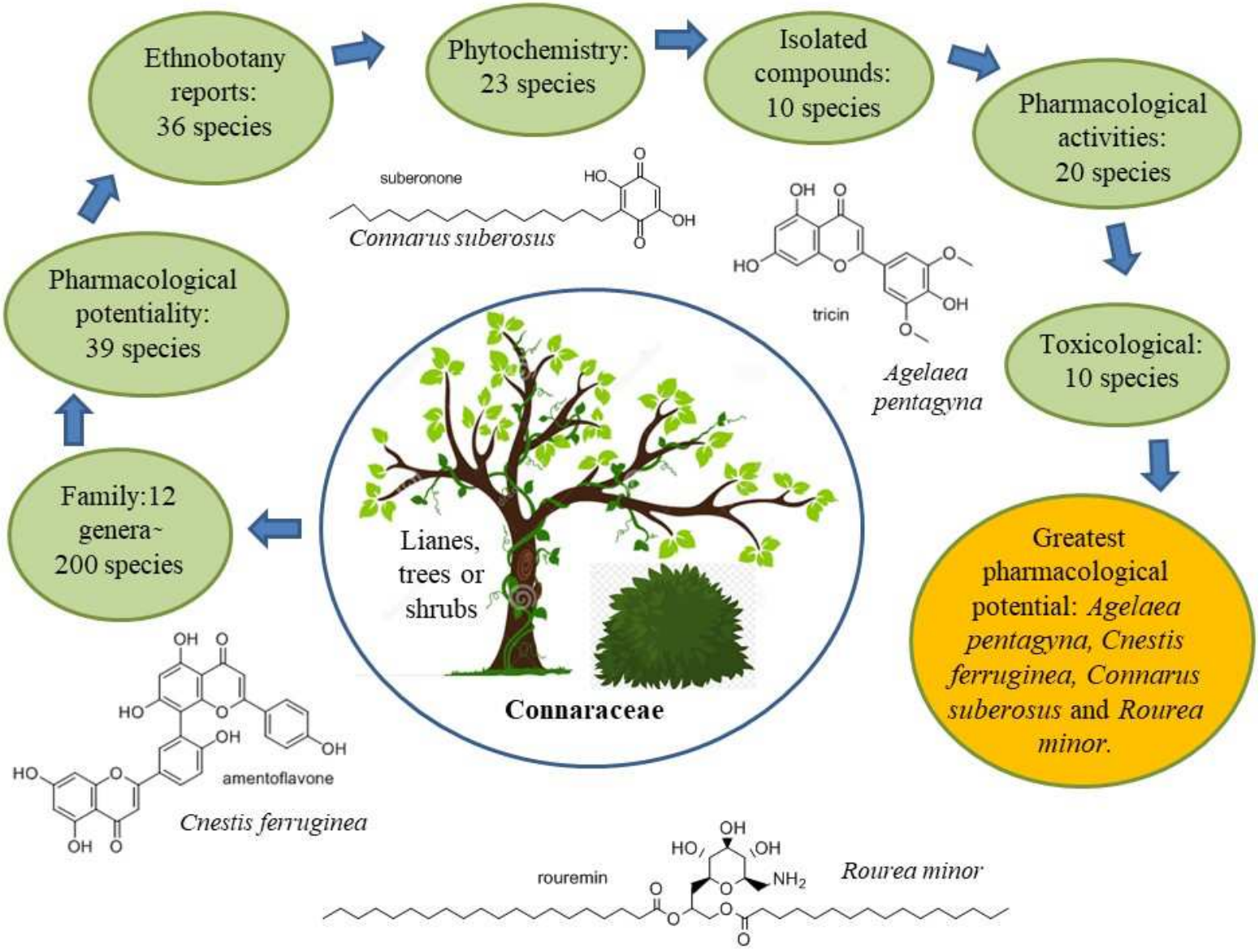
Ethnobotany reports: 36 species
Phytochemistry: 23 species
Isolated compounds: 10 species
Pharmacological activities: 20 species
Toxicological: 10 species
Greatest pharmacological potential: Agelaea pentagyna, Cnestis ferruginea, Connarus suberosus and Rourea minor.
Pharmacological potentiality: 39 species
Family:12 genera~ 200 species
Lianes, trees or shrubs
Connaraceae
suberonone
Connarus suberosus
tricin
Agelaea pentagyna
amentoflavone
Cnestis ferruginea
rouremin
Rourea minor

Connaraceae: An updated overview of research and the pharmacological potential of 36 species.

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Abstract

Ethnopharmacological relevance: An interdisciplinary scientific investigation of biologically active agents is fundamental to search for natural substances with therapeutic action. This review collected the most relevant information about traditional knowledge related to the use of plants of the Connaraceae family. This work is the first to compile all the published ethnobotanical, chemical, pharmacological, and toxicological information about this important plant family.

Aim of the study: Our objective was to provide the scientific community with an up-to-date overview of the pharmacological potential of Connaraceae plants.

Material and methods: This review searched NCBI Pubmed Central, Google Scholar, Scientific Electronic Library Online (SciELO), ScienceDirect, SciFinder, and Scopus databases to review the research on ethnobotanical, chemical, pharmacognostical, pharmacological, and toxicological studies with Connaraceaes. Books that address the theme were also included.

Discussion and conclusion: The literature review indicated that 36 species of Connaraceaes have pharmacological potentiality. Ethnobotany reports listed 32 of the 36 species discussed. Pharmacognostical studies have been conducted with 24 species and isolates, and chemical compounds have been identified for only 16 species. At least one study has been published about the pharmacological activities for 22 of the 36 species analyzed. For *Agelaea pentagyna, Cnetis ferruginea, Connars suberous* and *Rourea minor*, pharmacological activity experiments were performed using isolated compounds, which are those with the highest current pharmacological potential. Studies employing a toxicological approach cover only 10 of the 36 Connaraceaes species. Thus, the scientific community needs to conduct much more research for a broader understanding of this plant family.

Key-words: Ethnobotanical, Traditional knowledge, Medicinal Plants, Chemical composition, Pharmacology, Toxicology

1. Introduction

Rainforests contain a vast reservoir of plants with associated pharmacological potential and could provide chemical compounds for the development of new drugs (Ishola et al., 2012a). In this context, the Connaraceae family of plants stands out because it includes many species with high medicinal potential (A. Akindele and Adeyemi, 2007; Amos et al., 2002; I.O. Ishola et al., 2013; Kuwabara et al., 2003; Laikowski et al., 2017). Connaraceae species grow in the tropics, mostly in South and Central America, Africa, and Asia; the neotropical region are the heart of the family, containing over half of the total number of taxa (Breteler, 1989; Lemmens et al., 2004). In the New World, family species occur mainly in the Amazon Rainforest and Atlantic Rainforest (Forero, 2002, 1983; Groppo et al., 2010; Toledo and Souza, 2019).

Different studies about Connaraceae using the ethnobotanical approach have encouraged investigation of folk medicine to contribute and facilitate discoveries of bioactive molecules by the scientific community (A. Longanga Otshudi et al., 2000; Soejarto et al., 2012). Numerous plants in the family are used as a source of traditional medicines in different parts of the world (Ajibesin et al., 2008; Chifundera, 2001; Choudhury et al., 2015; de Moura et al., 2015; Ghorbani et al., 2011; Holaly et al., 2015; Lee et al., 2019; Samuel et al., 2010; Soelberg et al., 2015; Tchicaillat-Landou et al., 2018; Yetein et al., 2013). However, all of these works focus on only one or a few species, and information about this plant family has never been compiled. Based on the literature, the scientific community lacks up-to-date work on the research landscape and pharmacological potential of the family, with only one review focused on a single species (Ha, 2017). Moreover, the study of pharmacological activities with Connaraceae may help to protect biomes (Charneau et al., 2015) because it reinforces the chemical potential of this family and contributes to the development of new drugs.

The pharmacological potential of many species of Connaraceae have been reported in the literature (Ishola et al., 2012c; Kulkarni et al., 2014; Laikowski et al., 2017; Yakubu and Atoyebi, 2018). Some studies have demonstrated relevant pharmacological activities by isolating and characterizing major chemical compounds (da Costa et al., 2014; Ishola et al., 2012c; Kuwabara et al., 2003; Laikowski et al., 2017). Some of these species are candidates to provide hypoglycemic medications (Adisa et al., 2010; Dada et al., 2013; Kulkarni et al., 2014; Laikowski et al., 2017), other medications act on the central nervous system (CNS) (Aruoma et al., 2003; Ishola et al., 2012c; Ismail O. Ishola et al., 2013; Ishola et al., 2016) or

antimicrobial agents (Ahmadu et al., 2006; Bero et al., 2009; Farias et al., 2013; Mesia et al., 2008), and others have different pharmacological effects (Akindele and Adeyemi, 2006; Chung et al., 2009; Reanmongkol et al., 2000). Some authors have described species of Connaraceaes as toxic (Garon et al., 2007; Vickery and Vickery, 1974). *Rourea coccinea* (Schumach. & Thonn.) and *Cnestis ferruginea* Vahl ex DC have pharmacological and toxicological activity reports. However, chemical molecules responsible for each biological action have not been identified, and the safe and toxic dosages need to be established.

The aim of this work is to provide an updated and expanded overview of the ethnobotany use, pharmacological potential, chemical composition, and toxicological profile of Connaraceae species, to facilitate the understanding of scientific development in this subject. Such information, combined with a discussion about the distribution and number of species in the family, may be used to support future research of drug development from Connaraceae species. Thus, the data presented here may assist in conducting work to scientifically confirm ethnobotanical uses not yet studied.

2. Materials and methods

This review includes published scientific papers containing botanical, ethnobotanical, pharmacognostical, chemical, pharmacological, and toxicological information about Connaraceae species with associated pharmacological potential. This potential is characterized by the description of a particular species in at least one scientific study with ethnobotany approach or report in at least one study about pharmacological activity with application to human health.

NCBI PubMed Central, Google Scholar, Scientific Electronic Library Online (SciELO), ScienceDirect, SciFinder, and Scopus databases were searched for relevant studies. The following descriptors were used: Connaraceae, ethnobotanical, botanical characteristics, chemical composition, pharmacology, and toxicology. The inclusion criteria of articles and books followed the methodology described by (Medeiros et al., 2013) with some modifications. All studies, from anywhere in the world, published up to September 2019 that clearly met the following criteria were included: (1) presents relevant botanical characteristics for species with ethnobotanical or pharmacological potential or describes the geographic location of the species; (2) addresses at least one species of Connaraceae in an study employing ethnobotanical research; (3) describes the qualitative or quantitative profile of secondary metabolites of one

or more species in the family; (4) identifies and/or isolates secondary metabolite(s); and (5) includes at least one in vivo or in vitro experiment focusing on the pharmacological and/or toxicological activities of at least one extract obtained from Connaraceae species. Finally, all selected scientific publications were reviewed for acceptability of scientific species names, according to the Tropicos (http://www.tropicos.org/) and The Plant List (http://www.theplantlist.org/) with all publications grouped under the currently accepted scientific name.

3. Botanical features

The Connaraceae family can be morphologically recognized by its alternate leaves, composed and without stipules, stamens alternating in size, gynoecium with one or five free carpels and fruits usually in follicles (Forero, 1983; Lemmens et al., 2004). Due to the characteristics of the leaves and fruits, the family was once included within the order Sapindales (Candolle, 1825; Jussieu, 1789), but recent phylogenetic studies have proven that Connaraceae belongs to Oxalidales and is a sister group of the family Oxalidaceae (APG IV, 2016). Of this, Connaraceae differs mainly in their carpels, which are completely free, and the follicular fruits.

There is no consensus about the number of genera and species recognized in the family. Some authors state that 16 genera and 300–350 species occur (Forero, 1983; Schellenberg, 1938), while others indicated 12 genera and about 200 species (Breteler, 1989; Lemmens et al., 2004). In this review, we chose to recognize the more restricted taxa presented in these last two papers, emphasizing that a more comprehensive study about Connaraceae is still needed to identify the correct number of species. Moreover, new species of the family have been described in recent years (Morales, 2007; Toledo and Souza, 2019, 2018) reinforcing the need for a taxonomic update.

4. Traditional uses

This review found that 32 of the 36 Connaraceae species with associated pharmacological potential have traditional medicinal use around the world (Table 1). The traditional uses reported in the different ethnobotanical studies include a wide range of therapeutic functions, which can guide research for actions that have not been confirmed yet by the scientific community. Additionally, the popular names can assist researchers in obtaining samples at the locations where each species can be found. In addition, we indicate

which part of the plant is traditionally used to ensure that future research can properly select the plant organ to study.

Table 1

Description of Connaraceaes species with reports of ethnobotanical use and/or pharmacological study description with emphasis on human health**.**

Species	Habit	Continent	Vernacular names	Plant part	Traditional uses	References
Agelaea borneensis (Hook.f.) Merr.	Liane	Asia	Akar rusa-rusa	Bark	Inflammatory conditions	(Chung et al., 2009)
Agelaea macrophylla (Zoll.) Leenh.	Liane	Asia	Akar pinang kutai	Leaves	Acne	(Samuel et al., 2010)
Agelaea pentagyna (Lam.) Baill	Liane or shrub	Africa	Ahanhlazu, acroe, Vahimainty, Kanhandi, Vahimenty Rangahtsara, oboki	Bark and leaves	Aphrodisiac, urine retention, diarrhea, general fatigue, stomachache, human salmonellosis, malaria, scabies, and gonorrhea	(Beaujard, 1988; Sima Obiang et al., 2015; Soelberg et al., 2015; Vickery and Vickery, 1974)
Cnestis corniculata Lam.	Liane or shrub	Africa	Kizikizamba, Nyamawa	Roots	Allergic shock, pain, and hemorrhoids	(Kanteh and Norman, 2015; Lautenschläger et al., 2018; Vickery and Vickery, 1974)
Cnestis ferruginea Vahl ex DC	Liane or shrub	Africa	Fura amarya; Oen-tolôe, treventi-ito (ba), naporó, nerego, nológo (bj), udju-di-onça, utin ewa, utin ebua, n'konkone, Oko-Aja' or 'Gboyín-Gboyín'	Branches, fruits, leaves, and roots	Diabetes, inflammatory conditions, periodontitis, headache, bronchitis, eye troubles, dysmenorrhoea, pains, sinusites, tootach, conjunctiviris, ear pus, diarrhea, snakebites, and scabies	(Ajibesin et al., 2008; L. Catarino et al., 2016; Luís Catarino et al., 2016; Diehl et al., 2004; Frazão-Moreira, 2016; Holaly et al., 2015; Houghton

						and Osibogun, 1993; Ishola et al., 2011; Lautenschläger et al., 2018; Soelberg et al., 2015)
Cnestis palala (Lour.) Merr	Liane or shrub	Asia	Terkilir, Binsangut, Maa tai mi-phaak-laak, Belimbing Utan, Kan Yam Dia, Ngonkai; Akar sembelit	Leaves, steam and roots	Fever stomachache, malaria, urinary trouble, anemia in postpartum, bruises, constipation, and snakebites	(Mahyar et al., 1991; Nordin and Zakaria, 2016; Ong and Nordiana, 1999; Panyaphu et al., 2011; Samuel et al., 2010)
Cnestis polyphylla Lam.	Liane or shrub	Africa	Sefana, Sefa, Sodifafana	Leaves and steam	Diarrhea, fever, malaria, fatigue, and skin injuries	(Aruoma et al., 2003; Beaujard, 1988; Rakotoarivelo et al., 2015; Rasoanaivo et al., 1992; Riondato et al., 2019)
Connarus africanus Lam.	Liane	Africa	Ganganlisé	Leaves	Haemorrhage	(Allabi et al., 2011)
Connarus cochinchinensis Pierre	Not described	Asia	Sembilat	Leaves	Tuberculosis	(Zarr, 2010)
Connarus detersus Planch.	Tree	América	Cabelo de Negro	***	***	(Farias et al., 2013)
Connarus elsae Forero	Tree or shrub	América	***	***	***	(Forero, 1981; Graham et al., 2003)

Connarus favosus Planch.	Bush or liane	América	Veronica	Bark	Snakebites	(de Moura et al., 2015; Silva et al., 2016)
Connarus lambertii (DC.) Britton	Bush or liane	America	Tuktuk	Bark and leaves	Diarrhea and as an astringent	(Coe et al., 2010; Jiménez et al., 2001)
Connarus monocarpus L.	Tree	Asia	Agil	Roots	Snakebites	(Aiyar et al., 1964; Dharmadasa et al., 2016)
Connarus paniculatus Roxb.	Tree	Asia	Uroshichak	Leaves	Stomach and diarrhea	(Choudhury et al., 2015; Henkin et al., 2017; Le et al., 2005; Roy Choudhury et al., 2015)
Connarus perrottetii (DC.) Planch.	Tree	America	Barbatimão do pará, marassacaca, muraçacaca, pajurana, pajujurana, raparigeira	Bark	**W**ashing postpartum, genitourinary infections, uterus problems, ovarian cysts, vaginal discharge, stomachache, and headache	(Coelho-Ferreira, 2009; Paracampo, 2011; Pastore et al., 2017; Pires et al., 2017; Suffredini et al., 2007; Yazbek et al., 2016)
Connarus planchonianus Schellenb.	Liane	Asia	Sembelit angin	Stems and roots	Flatulence	(Ong and Nordiana, 1999)

Connarus ruber (Poepp) Planch.	Bush or tree	America	Pitso tapa	Fruit and leaves	Diabetes	(Castilho et al., 2014; Paniagua Zambrana et al., 2017; Pastore et al., 2017)
Connarus semidecandrus Jack	Liane	Asia	Đho Rđo, Bob Jei Pei	Leaves, steam and roots	Diarrhea and fever	(Lee et al., 2019; Reanmongkol et al., 2003; Srithi et al., 2009)
Connarus suberosus Planch.	Bush or tree	America	Tropeiro ou bico de papagaio, galinha-choca	Bark	Diarrhea and heart problems	(Charneau et al., 2015; da Costa et al., 2014; Taveira et al., 1988)
Manotes expansa Sol. Ex Planch	Liane	Africa	Menga-menga, M'memenga	Leaves	Hypertension, hemorrhoids, bleeding, stomach pains, scoliosis, dysenteria, and ophthalmic problems	(Lautenschläger et al., 2018; Makambila-Koubemba et al., 2011; Malan et al., 2015; Mesia et al., 2008; Tchicaillat-Landou et al., 2018)

Pseudoconnarus macrophyllus (Poepp.) Radlk.	Liane	America	***	***	***	(Suffredini et al., 2007)
Rhynchosioides (Standl.) Prance	Liane	America	Saracura	Bark	Exhaustion, sexual stimulant, and malaria	(Pedrollo et al., 2016)
Rourea coccinea (Schumach. & Thonn.)	Liane	Africa	Ploem-tjo, sjo-tami (for the fruit); Tsaamiyar-kasa; Oke abolo; Orikoteni; Amuje; Ganganlissè;Vikplomba	Whole plant	Jaundice, veneral diseases, as a sedative, diarrhea, inflammation, urogenital diseases, urinary problems, tumours, earache, muscular, human salmonellosis, malaria rheumatic pains, breast milk enhancement, anti-cancer activity, and high blood pressure	(Ahmadu et al., 2007; Akindele et al., 2014; A. J. Akindele and Adeyemi, 2007; Bero et al., 2009; Chhabra et al., 1993; Dougnon et al., 2017; Kankara et al., 2015; Soelberg et al., 2015; Soladoye et al., 2010; Yetein et al., 2013)
Rourea commutate Planch.	Liane or shrub	Asia	Anone-lou-chari, hrung-mung	Leaves	Skin inflammation, menstrual bleeding, and wounds	(Alam, 1992)
Rourea cuspidata Benth ex. Baker	Liane	America	Cipo miraruina	Bark	Diabetes	(Laikowski et al., 2017)
Rourea doniana Baker	Liane	America	***	***	***	(Oliveira et al., 2012, 2010)
Rourea humilis Blume	Not described	Asia	Akar Kayu Mengecut; Akar sekecut	Roots	Uterine contraction stimulant	(Jamal et al., 2011; Nordin and Zakaria, 2016)

Rourea induta Planch	Shrub	America	Hohocré, chapeudinha, pau-de-porco or campeira	Leaves and roots	Rheumatisms, Chagas diseases, and as abortive	(Kalegari et al., 2011; M. Kalegari et al., 2014; Rodrigues, 2007; Yazbek et al., 2016)
Rourea microphylla (Hook. & Arn.) Planch	Liane or shrub	Asia	Beririt	Leaves	Kidney stone, diruretic, desintery, and bile diaseases	(Ghorbani et al., 2011; Kong et al., 2008; Kulkarni et al., 2014; Mahyar et al., 1991; NguyêñXuãn Duñg and kDôTâtLi, 1991)
*Rourea mimosoides** (Vahl.) Planch.	Liane	Asia	Sembelit merah darah	Roots	Cough with blood, bloody diarrhoea, and diuretic	(Grosvenor et al., 1995; Sabran et al., 2016)
Rourea minor (Gaertn.) Alston	Liane	Africa	Ha ji me wo	Leaves and roots	Abrasions, diabetes, lesions, dengue, kidney stones, polio, and fever	(Ghorbani et al., 2011; Gyllenhaal et al., 2012; Henkin et al., 2017; Mahyar et al., 1991; Soejarto et al., 2012; Soro et al., 2012)

Rourea obliquifoliolata Gilg	Liane or shrub	Africa	Lungagula	Root bark	Diarrhea, dysentery, toothache, and elenphantiasis	(A. Longanga Otshudi et al., 2000; A Longanga Otshudi et al., 2000; Longanga Otshudi et al., 2001)
Rourea orientalis Baill.	Shrub or small tree	Africa	Kazingini, munhadozwarozwa, sambaucaranga, muziriri	Stems, bark, leaves and roots	Diarrhea, antiemetic, menstrual troubles, and skin injuries	(Bruschi et al., 2011; Chhabra et al., 1993; Chinsembu, 2016; Jeannoda et al., 1985)
Rourea puberula Baker	Shrub or small tree	America	Murku waska	Stems	Health tonict, broken bones, leishmanisis, rheumatism, and vaginal pains	(Sanz-Biset and Cañigueral, 2011)
Rourea thomsonii (Baker) Jongkind	Liane or shrub	Africa	Lwamba	Bark	laxative and constipation	(Chifundera, 2001)

Of the approximately 200 recognized Connaraceae species (Lemmens et al., 2004), 36 or about 18% are known to have potential pharmacological activities. This relatively low percentage of species studied suggests that the huge pharmacological potential for Connaraceae has only been superficially explored by the scientific community and more research should be conducted.

Moreover, this review verified that among the 12 recognized genera of Connaraceae, only six (*Agelaea, Cnestis, Connarus, Manotes, Pseudoconnarus,* and *Rourea*) have reported ethnobotany use or were the focus of pharmacological investigation. Consequently, half of the genera do not have phytochemical and or pharmacological studies. From the total species studied for each of these genera, we observed that Agelea, *Cnestis, Connarus, Manotes, Pseudoconnarus,* and *Rourea* present three, four, thirteen, one, two, and thirteen species, respectively.

Exploration of the geographical distribution of the genera found that the African continent is home to the genera *Agelaea* (Novy, 1997; Schellenberg, 1938), *Cnetis* (Garon et al., 2007; Jeannoda et al., 1984; Schellenberg, 1938) *Connarus* (Schellenberg, 1938), *Manotes* (Mesia et al., 2008; Schellenberg, 1938), and *Rourea* (Bero et al., 2009; He et al., 2006; Schellenberg, 1938). In the Americas, *Connarus* (de Moura et al., 2015; Jiménez et al., 2001; Pires et al., 2017; Taveira et al., 1988), *Pseudoconnarus* (Suffredini et al., 2007) and *Rourea* (Forero, 2007; Groppo et al., 2010; Kalegari et al., 2011; Laikowski et al., 2017; Oliveira et al., 2012; Pastore et al., 2017) have been studied, while on the Asian continent reports emphasis *Agelaea* (Samuel et al., 2010), *Cnetis* (Samuel et al., 2010), *Connarus* (Chung et al., 2009; Le et al., 2005; Srithi et al., 2009), and *Rourea* (Sabran et al., 2016). Considering the total distribution of taxa with pharmacological potential, among the 36 species analyzed in this review, 13 are from the Americas, while Africa and Asia each have 11 and 12 species, respectively. The genera *Pseudoconnarus* and *Manotes* have the most

restricted distribution and thus require special attention to manage their populations ensuring the sustainable use of ecosystems that contain them, to preserve the species, and to conduct studies employing the pharmacological approach about these species.

5. Phytochemistry

The distribution of secondary metabolites for the Connaraceae family is as varied as the phytochemistry classification of the already identified secondary metabolites (table 2).

Table 2

Secondary metabolite classes reported for Connaraceae.

Species	Active components	Refs
A. borneensis	Volatile oils	(Sardans et al., 2015)
A. macrophylla	NS	
A. pentagyna	Alkaloids, coumarins, flavonoids, and phenols, saponins	(Kuwabara et al., 2003; Sima Obiang et al., 2015; Vickery and Vickery, 1980)
C. corniculate	Coumarins	(Vickery and Vickery, 1980)
C. ferrugínea	Alkaloids, anthraquinones, coumarins, flavonoids, glycosides cardiotonics, phenols, reducing sugars, saponins, sterols, tannins, and volatile oils	(Ishola et al., 2011; Ogunwande et al., 2013; Olugbade et al., 1982; Vickery and Vickery, 1980)
C. palala	Coumarins, glycosidic, volatile oils	(Dej-adisai et al., 2015)
C. polyphylla	Flavonoids, protoanthocyandins, saponins, and tannins	(Aruoma et al., 2003)
C. africanus	NS	

C. cochinchinensis	Saponins	(Zarr, 2010)
C. *detersus*	Alkaloids, flavonoids, phenols, saponins, and tannins	(Farias et al., 2013)
C. elsae	NS	
C. favosus	Coumarins, flavonoids, leucoanthocyandins, phenols, and tannins	(Silva et al., 2016)
C. lambertii	Alkaloids, flavonoids, and volatile oils	(Coe et al., 2010; Jiménez et al., 2001)
C. monocarpus	Anthocyandins, coumarins and phenols	(Aiyar et al., 1964)
C. paniculatus	Alkaloids	
C. perrottetii	Coumarins, flavonoids, glycosides cardiotonics, phenols, saponins, and tannins	(Pires et al., 2016, 2017)
C. planchonianus	NS	
C. ruber	Flavonoids and tannins	(Nakamura et al., 2011)
C. semidecandrus	Coumarins	(Reanmongkol et al., 2003)
C. suberosus	Saponins and tannins	(Worthley and Schott, 1969)
M. expansa	Anthraquinones, coumarins, flavonoids, saponins, tannins, and volatile oils	(Makambila-Koubemba et al., 2011)
P. macrophyllus	NS	
P. rhynchosioides	NS	
R. coccinea	Alkaloids, anthraquinones, coumarins, flavonoids, glycosidic, phenols, saponins, sterols, tannins, and volatile oils	(Akindele et al., 2014; Vickery and Vickery, 1980; Yakubu and Atoyebi, 2018)
R. commutata	NS	
R. cuspidata	Anthocyandins, flavonoids, and phenols	(Laikowski et al., 2017)
R. doniana	Coumarins, flavonoids, and volatile oils	(Pires et al., 2017)
R. humilis	NS	

R. induta	Flavonoids, phenols, and protoanthocyandins	(M. Kalegari et al., 2014)
R. microphylla	Volatile oils	(Huo et al., 2011)
R. mimosoides	NS	
R. minor	Alkaloids, anthraquinones, coumarins, flavonoids, and tannins	(Jiang Jian-qin, 1990; Kulkarni et al., 2014; Mali and Borges, 2003)
R. obliquifoliolata	Flavonoids, saponins, reducing sugars, tannins, and volatile oils	(A Longanga Otshudi et al., 2000)
R. orientalis	NS	
R. puberula	NS	
R. thomsonii	NS	

NS = Not studied

For 24 of the 36 species listed in this review, at least one group of constituents has been identified; therefore, for the other 12 species, of phytoconstituents are not yet known. This reinforces the need for qualitative and quantitative studies that profile compounds to broaden knowledge about these phytoconstituents and confirm or reject the pharmacological activities described by popular use. Additionally, new studies employing analytical devices and metabolomics tools may help to answer any questions about the taxonomy, facilitating the grouping of species and elucidating more accurate number of taxa in this plant family.

Agelaea

For the genus *Agelaea* two of the three species with associated pharmacological potential have identified chemical compounds (Fig. 1). Essential oils, coumarins, and just one flavonoid has been were isolated and characterized in *Agelaea*. For *Agelaea borneensis*, the study conducted by (Sardans et al., 2015) identified monoterpenes (limonene and α-pinene) and sesquiterpenes (β-caryophyllene and D-germacrene). For *Agelaea pentagyna,* the presence of coumarin compounds (o-coumaric acid, 4-hydroxycoumarin, and dicoumarol)

was reported (Vickery and Vickery, 1980), in addition, the flavonoid tricin was isolated from methanolic extract of *A. pentagyna* leaves (Kuwabara et al., 2003).

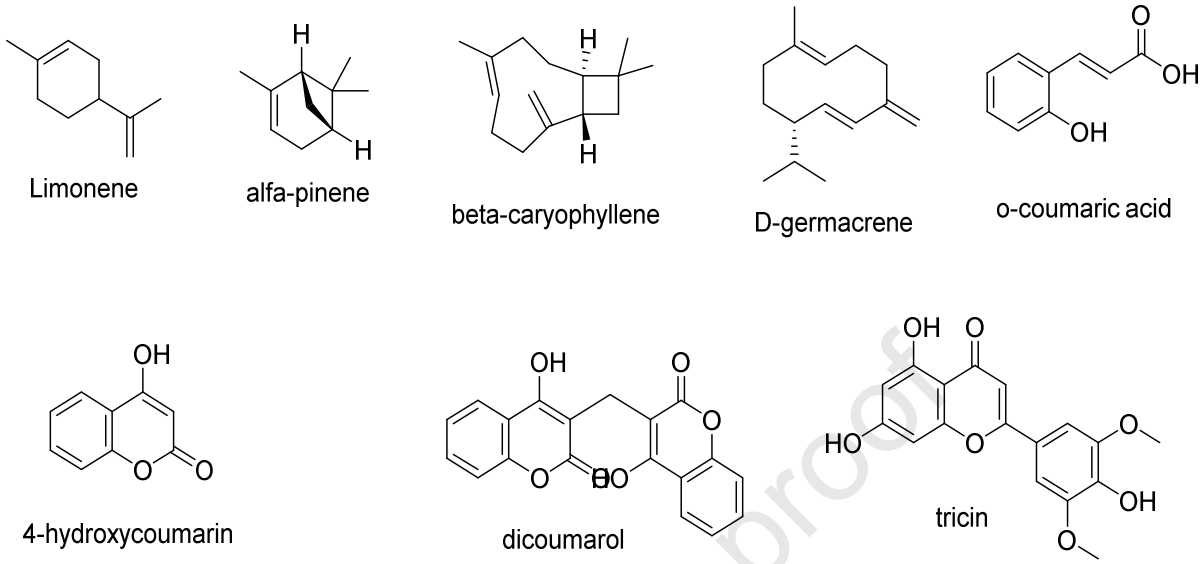

Figure 1: Structures of chemical constituents identified in the genus *Agelaea*.

Although the literature reports the chemical compounds belonging to the alkaloids, phenols and saponins classes in the species *A. pentagyna* (Sima Obiang et al., 2015), they have not been qualitatively described yet.

Cnestis

For the genus *Cnestis*, three species with at least one isolated and identified chemical compound are *Cnestis ferruginea*, *Cnestis palala*, and *Cnestis polyphylla*. Different classes of compounds are present in this plant genus (Fig. 2).

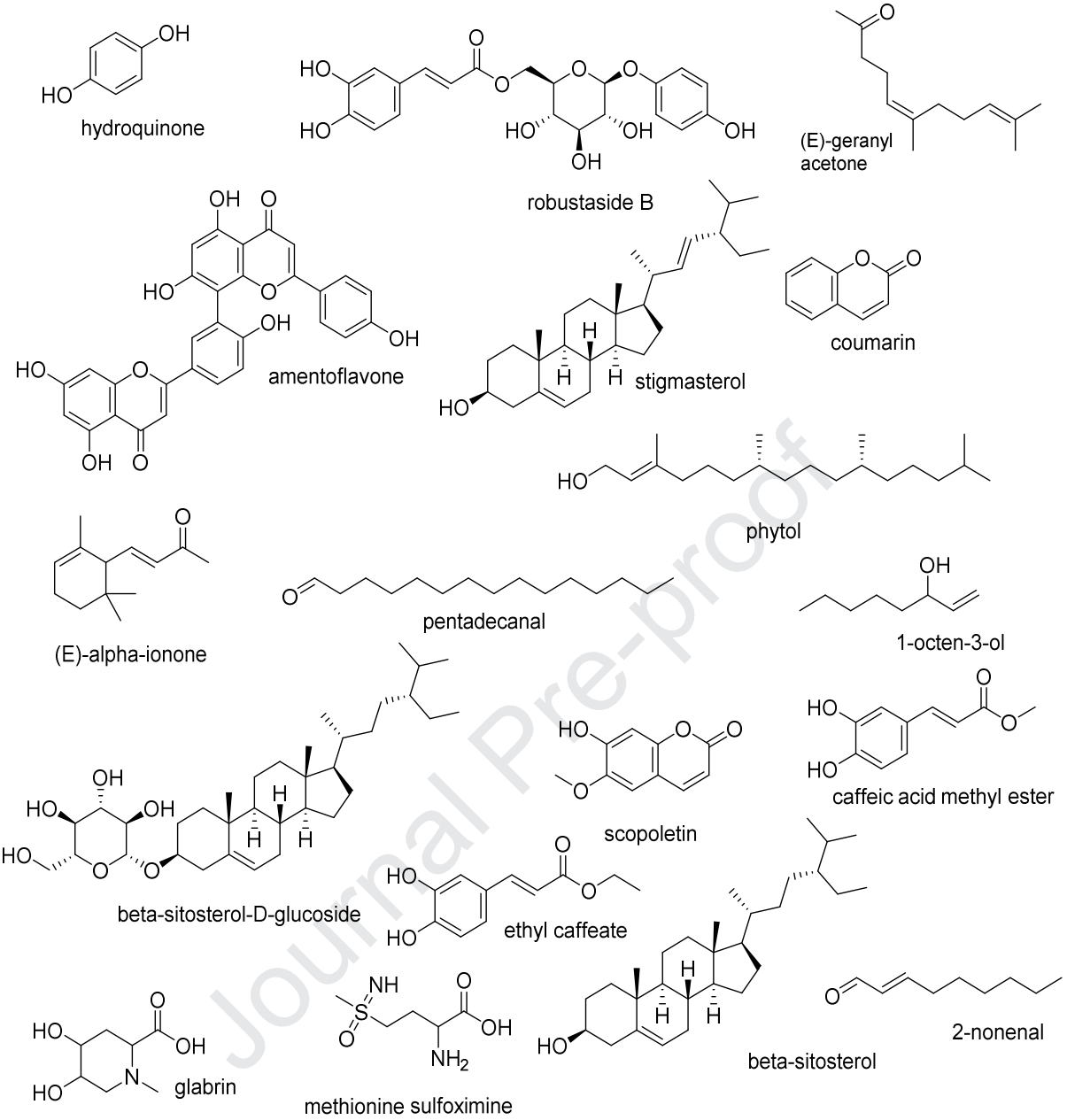

Figure 2: Structures of chemical constituents identified in the genus *Cnestis*.

Biflavonoid amentoflavone, an apigenin dimmer, has been reported for methanolic extract of *C. ferruginea* roots (Ishola et al., 2012c). Parahydroxyphenol (hydroquinone) and robustaside B (6·-O-Caffeoylarbutin) were isolated in the leaves of this species (Adisa et al., 2011; Adisa and Olorunsogo, 2013). The compounds β-sitosterol and stigmasterol were identified in the ethanolic extract of the roots (Ojo et al., 2019), and β-sitosterol in the leaves of this species (Olugbade et al., 1982). Caffeic acid methyl ester and hydroquinone were

isolated from *C. ferruginea* leaves (Kouakou et al., 2019). An evaluation of the phytochemistry composition found in different parts of *C. palala* isolated hydroquinone, β-sitosterol, β-sitosterol-glucoside (daucosterin), ethyl caffeate, scopoletin, and 2 nonenal compounds (Dej-adisai et al., 2015). In another study with *C. palala*, the presence of the compound L-methionine sulfoximine (MSX) was reported from the ethanolic extract of seeds, pods, petioles, roots and stems, but was not found in the leaves of this plant (Murakoshi et al., 1993). The unusual amino acid MSX is classified as very toxic (Murakoshi et al., 1993). Thus, the lack of this metabolite in plant leaves is in line with the traditional use of this part of the plant, reported in the ethnobotanical studies, which describe using the leaf of *C. palala* (Mahyar et al., 1991; Nordin and Zakaria, 2016; Samuel et al., 2010). From the roots of *C. polyphylla,* (Jeannoda et al., 1984) isolated glabrin, which is related to the neurotoxic effect of this plant.

Connarus

The five species of the genus *Connarus* that contain compounds which have been isolated and identified (Fig. 3) by the scientific community include *C. monocarpus*, *C. paniculatus*, *C. perrottetii*, *C. semidecandrus,* and *C. suberosus.*

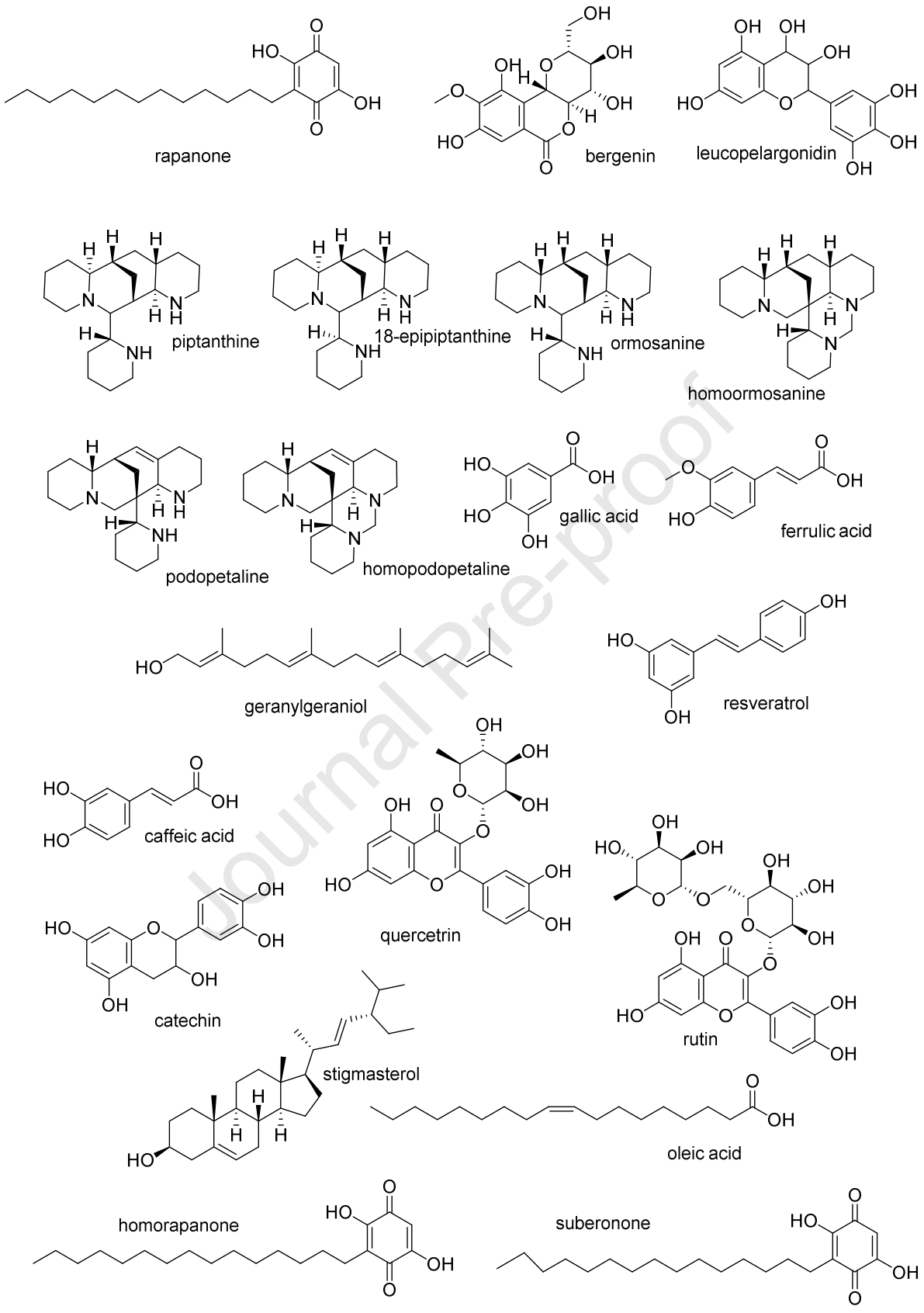

Figure 3: Structures of chemical constituents identified in the genus *Connarus*.

Rapanone, bergenin, and (-)-leucopelargonidin compounds were isolated from *Connarus monocarpus* roots (Aiyar et al., 1964). Six alkaloids with quinolizidine nucleus, piptanthine, 18-epipiptanthine, ormosanine, homoormosanine, podopetaline, and homopodopetaline were isolated from the fruits and leaves of *C. paniculatus* (Le et al., 2005) From the barks of *C. perrottetii*, (Pires et al., 2017) isolated three phenols (gallic, ferulic, and caffeic acid), three flavonoids (o-heterosidic catechin, rutin, and quercitrin) and one phytoalexin (resveratrol). The presence of suberone, rapanone, β-sitosterol, oleic acid, and geranylgeraniol compounds was reported for extracts from *C. suberosus* barks (da Costa et al., 2014). Different authors have reported the presence of alkaloids in Connaraceaes (A. J. Akindele and Adeyemi, 2007; Farias et al., 2013; Ishola et al., 2011); however, (Le et al., 2005) have been the only researchers to successfully isolate and identify such compounds from any of these species.

Manotes and Pseudoconarus

No studies have been published employing a qualitative and/or quantitative approach to elucidate the chemical compounds in the genera *Manotes* and *Pseudoconannrus*.

Rourea

The genus Rourea contains six plant species (*R. coccinea, R. doniana, R. cuspidata, R. induta, R. microphylla,* and *R. minor*) with isolated and identified chemical compounds (Fig. 4a and 4b)

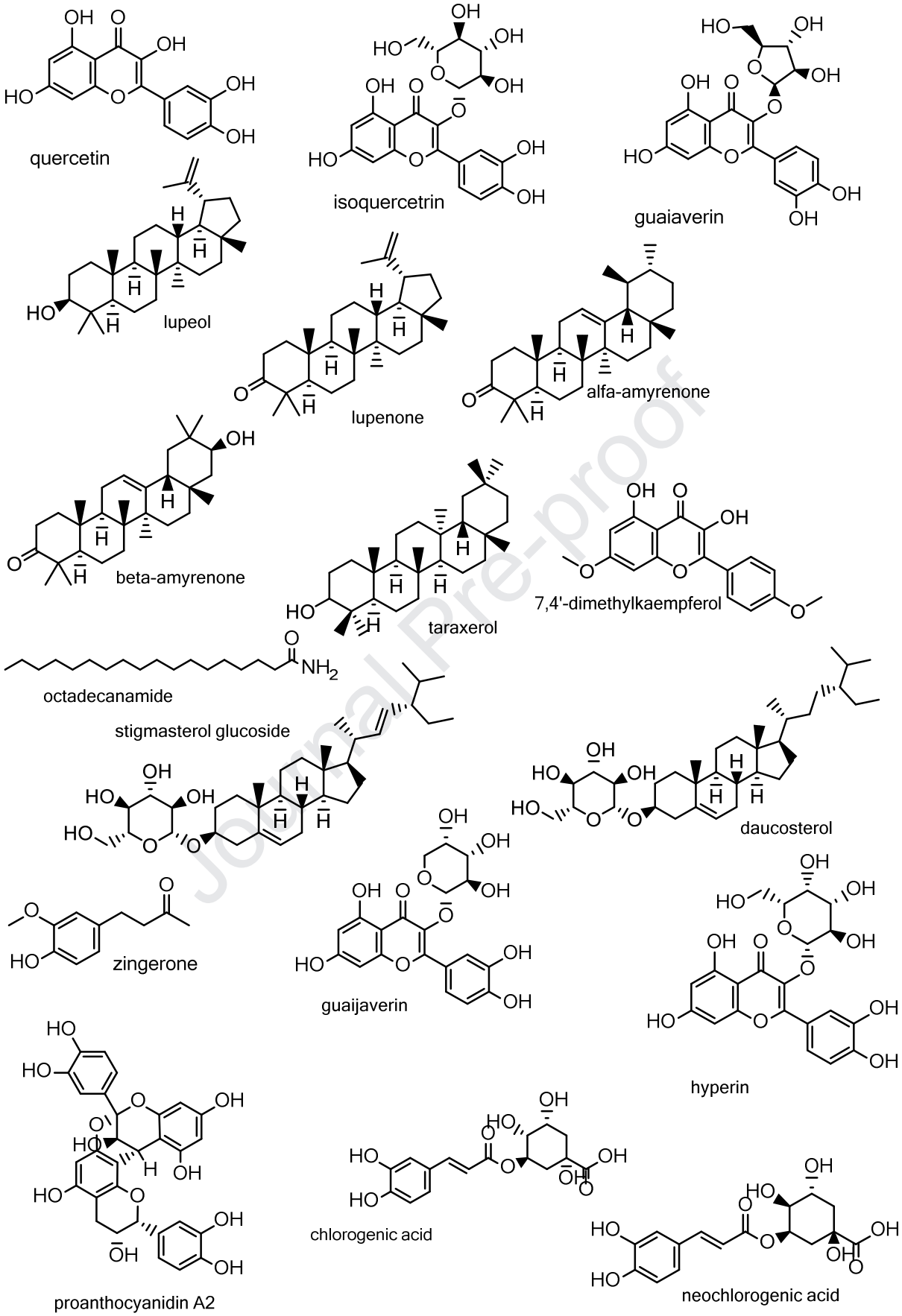

Figure 4a: Structures of chemical constituents identified in the genus Rourea.

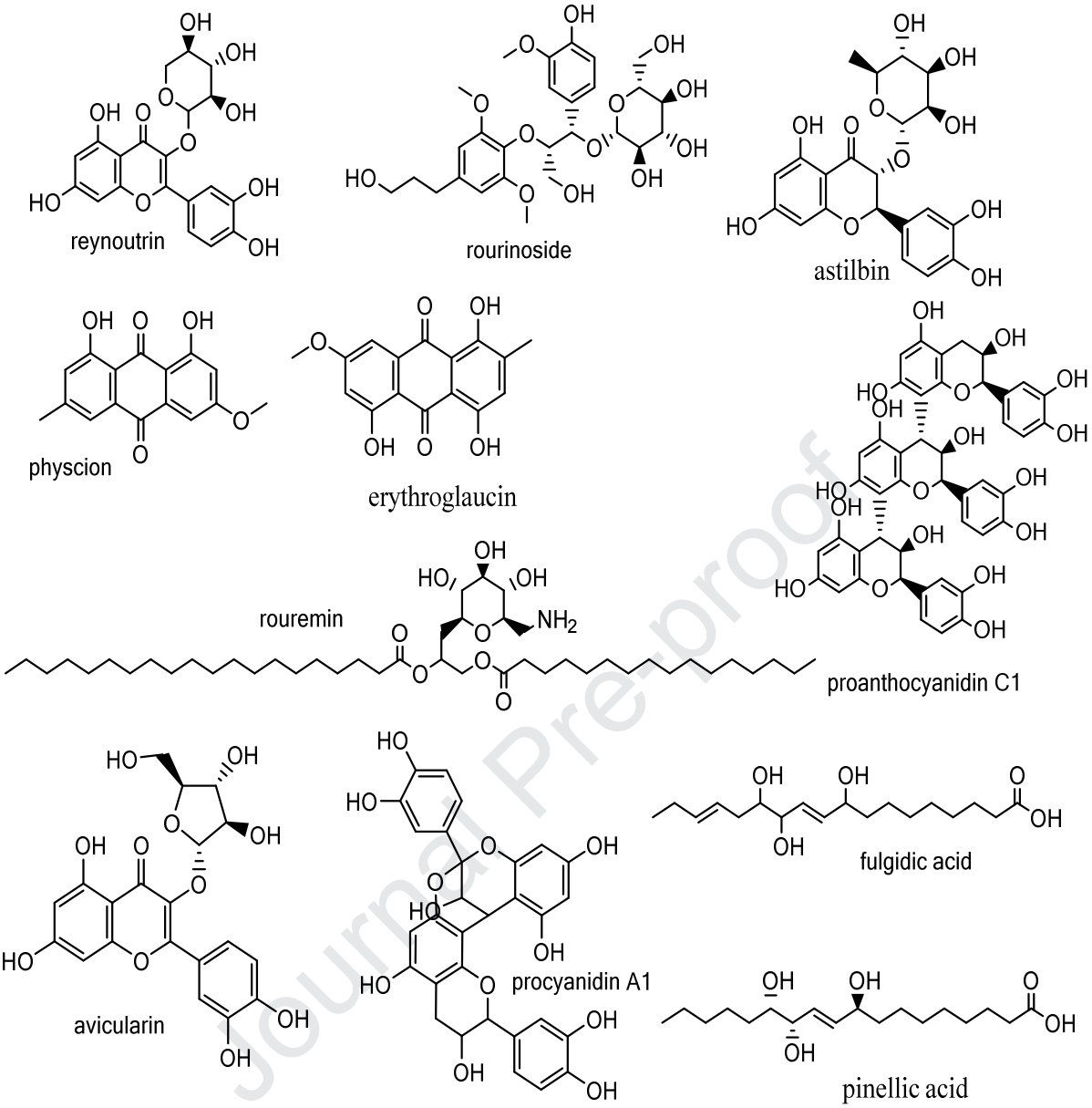

Figure 4b (continued): Structures of chemical constituents identified in the genus *Rourea*.

From leaves of *R. coccinea*, (Ahmadu et al., 2007) isolated an aglycone flavonoid called quercetin and two O-glycoside-type heterosides identified as quercetin 3-O-β-D-glucoside (isoquercetin) and quercetin 3-O-α-arabinoside (guaiaverin). Another study on the same species reported the presence of chlorogenic acid, rutin, and quercetin for the extract obtained also from the leaves (Akindele et al., 2014). From the leaves and branches of *R. doniana*, (Oliveira et al., 2012) isolated five triterpenes (lupeol, lupenone, α-amyrenone, β-amyrenone, and taraxerol), one flavonol (7,4·-dimethylkaempferol), one coumarin

(scopoletin), and four phytosteroids (β-sitosterol, stigmasterol, β-sitosteryl-3-O-β-D-glucopyranoside [daucosterol]) and stigmasteryl-3-O-β-D-glucopyranoside [stigmasterol glucoside]). In *R. cuspidata* six chemical compounds have been identified (Laikowski et al., 2017): a ketone called zingerone, a stearic acid-derived amide known as octadecanamide; an aglycone epicatechin flavonoid or its catechin isomer; two O-glycoside flavonoids called guaijaverin (quercetin 3-O-alpha-L-arabinoside) and hyperin (Quercetin-3-O-galactoside); and an anthocyanidin called proanthocyanidin A2. A study identified in the leaves of *R. induta* phenols (chlorogenic and neochlorogenic acid), flavonoids: hyperin, quercetin-3-O-β-xyloside (reynoutrin), quercetin-3-O-α-arabinofuranoside (avicularin) and quercetin; as well as anthocyanidin proanthocyanidin C1 (M. Kalegari et al., 2014). The leaves and branches of *R. microphylla* contain the flavonoids: quercetin-3-O-α-L-rhamnopyranoside (quercetrin), hyperin, quercetin, astilbin; glycosydes: β-sitosterol, β-sitosteryl-β-D-glucopyranoside; and the anthraquinone compounds: physcion and erythroglaucin (Jiang Jian-qin, 1990). The stems of *R. minor* species contain: bergenin, (+)-catechin-3-*O*-*β*-D-xylopyranoside, 11-*O*-syringylbergenin, (+)-catechin-3-*O*-α-L-rhamnopyranoside, 11-*O*-(4-*O*-methylgalloyl) bergenin, (−)-epicatechin, (+)-catechin, 11-*O*-(3,4-dimethylgalloyl) bergenin, 11-*O*-vanilloylbergenin, procyanidin A1, 2*α*,3*α*-epoxy-5,7,3′,4′-tetrahydroxyflavan-(4*β* → 8)-epicatechin, dehydrodicatechin A, (2*α*,3*β*)-7-*O*-methylcedrusin, (−)-syringaresinol, scopoletin, fulgidic acid, pinellic acid, *α*-dimorphecolic acid, 13-oxo-9*E*,11*E*-octadecadienoic acid, 9-oxo-10*E*,12*Z*-octadecadienoic acid, and 9-oxo-10*E*,12*E*-octadecadienoic acid (Ngoc et al., 2019). In another study, (He et al., 2006) isolated two components identified as rourinoside and rouremin, which were obtained from the stem bark of this plant. The rapanone and leucopelargonidin compounds were isolated from *R. minor* roots (Ramiah et al., 1976).

6. Pharmacological activities

The main pharmacological activities reported in studies containing extracts and/or isolated substances conducted in vivo and in vitro with Connaraceaes are presented in this section.

Antipyretic activity

Antipyretic activity has been reported for methanolic extract obtained from *C. semidecandrus* roots; when administered to mice at different dosages between 100 and 400 mg/kg, the extract reduced yeast-induced fever (Reanmongkol et al., 2000). A similar effect was observed for *R. coccinea* when the aqueous extract of leaves produced an antipyretic effect in rats at doses of 100, 200, and 400 mg/kg. Those authors verify the antipyretic effect through yeast and amphetamine induced hyperemia models and attributed the effect to a possible inhibition of prostaglandin production promoted by the extract (A. Akindele and Adeyemi, 2007).

Anti-inflammatory activity

Methanolic extract obtained from *A. borneensis* bark showed anti-inflammatory activity in vitro through lipoxygenase inhibition mechanism, IC_{50}% 1.6 μg/mL. The authors attribute the anti-inflammatory activity of this plant to the presence of flavonoids and terpenoids (Chung et al., 2009). For the genus Cnestis, methanolic extracts obtained from *C. ferruginea* roots demonstrated an anti-inflammatory effect on xylene-induced and formaldehyde assays in rats at doses starting at 200 mg/kg (Ishola et al., 2011). Another bioguided study with *C. ferruginea* associated the anti-inflammatory effect with biflavonoid amentoflavone isolated from this species (Ishola et al., 2012a). In that study, the richest fraction of biflavonoid had the highest anti-inflammatory effect of those tested, indicating that such effect can be associated with this compound (Ishola et al., 2012a). Another study demonstrated the ability of methanolic extract to decrease nitrite release, mitigate free radical generation, and reduce

malondialdehyde formation in Rat C6 glioma cell line treated with lypopolysaccharide (LPS) (I.O. Ishola et al., 2013). The authors observed increased glutathione level (GSH) and reduced expression of tumor necrosis factor-α (TNF-α), attributing this effect to the presence of the amentoflavone compound in the fraction of the studied extract (I.O. Ishola et al., 2013). Ethanolic extract from *C. ferruginea* roots reduced cyclooxygenase-2 (COX-2) expression following exposure of mice to kainic acid; the extract administered at 400 mg/kg was able to reduce enzyme expression in the hippocampus reducing neuroinflammation in these animals (Ojo et al., 2019).

In *R. coccinea* species the aqueous extract obtained from the leaves when administered to rats at doses of 100, 200, and 400 mg/kg demonstrated anti-inflammatory effect through inhibition of phospholipase A2 or inhibition of cyclooxygenases. Those authors indicate the need to isolate and identify the chemical compounds responsible for the anti-inflammatory effect (A. J. Akindele and Adeyemi, 2007).

Analgesic activity

Methanolic extracts obtained from *C. ferruginea* roots demonstrated analgesic effect in rats, possibly mediated through peripheral and central mechanisms by inhibiting release of histamine, serotonin, and prostaglandins (Ishola et al., 2011). The bark extract of *C. suberosus* exhibited an analgesic effect in mice at the dose of 100 mg/kg in test on the reaction time to thermal stimulus (Taveira et al., 1988). The aqueous extract of *M. expansa* leaves presented a significant analgesic effect to different pain models in mice treated with 250 mg/kg of aqueous extract (Makambila-Koubemba et al., 2011). The aqueous extract of *R. induta* leaves administered at doses of 30 to 300 mg/kg in mice had an analgesic effect, which was verified by different pain measurement experiments, and appear to involve inhibiting the release of inflammatory cytokines, mediated by quercetin-derived flavonoids including the hyperin compound (M. Kalegari et al., 2014)

Antihistamine activity

In vitro tests using rat basophilic leukemia cells (RBL-2H3) indicated that flavonoid tricin isolated from *A. pentagyna* leaves had antihistamine activity, in which degranulation inhibition assay presented IC_{50}% 4.83 μm against β-hexosaminidase. According to those authors, flavonoid produced a potent antihistamine release (Kuwabara et al., 2003)

Anticholinesterase activity

Studies with methanolic extract of *C. ferruginea* roots demonstrated anticholinesterase activity in scopolamine-treated mice, in which the acetylcholinesterase enzyme activity reduced with the plant extract tested at doses of 100 and 200 mg/kg and for the amentoflavone sub-fraction at doses of 12.5 and 25 mg/kg, suggesting that compound is responsible for the observed effect (Ismail O. Ishola et al., 2013). At a concentration of 5 mg/mL an ethanolic extract of from *C. detersus* seeds promoted a 91.9% inhibition of acetylcholinesterase enzyme activity; however, the researchers did not isolate and identify the compounds responsible for this action (Farias et al., 2013).

Anticonvulsant activity

In vivo studies from ethanolic extract of *C. ferruginea* roots demonstrated an antiepileptic effect in mice with kainic acid-induced epilepsy. The authors demonstrated that the anticonvulsant effect of the extract administered orally at a dose of 400 mg/kg was related to the reducing activity of neuroinflammation and oxidative stress in the hippocampus of these animals (Ojo et al., 2019).

Neuroprotective activity

In vivo studies about methanolic extract of *C. ferruginea* roots evidenced memory protective activity in mice, which had improved locomotion patterns and neuroprotective effect (Ismail O. Ishola et al., 2013). The observed effects produced by the extract and the isolated compound indicate that both may be candidates for neuroprotective medications. The

aqueous extract of *C. ferruginea* fruits showed GABAergic activity in rats with ketamine-induced psychosis; when administered for seven days at a dose of 2 g/kg, the extract increased the gamma aminobutyric acid (GABA) levels in the nervous system of these animals (Ebuehi and Aleshinloye, 2010).

Antidepressant and anxiolytic activity

An in vivo study about methanolic extract of *C. ferruginea* roots evidenced an anxiolytic and antidepressant effect in mice treated with cyproheptadine a 5HT2 receptor antagonist using doses ranging from 25 to 200 mg/kg (Ishola et al., 2012c). That study also demonstrated anxiolytic and antidepressant effect for an amentoflavone compound isolated from this plant extract administered at doses of 6.25 to 50 mg/kg. According to the study, which used different agonist and antagonist substances from different receptors, these effects are apparently mediated through the involvement of GABAergic, noradrenergic, and serotonergic systems and present a favorable safety profile for the development of human medications (Ishola et al., 2012c).

Antioxidant activity

The ethanolic extract of *A. pentagyna* leaves exhibited antioxidant activity in an 2,2-diphenyl-1-picrilhydraz (DPPH) assay, with an IC_{50} of 177.02 µg/mL. The authors stated that this potential antioxidant effect is related to the presence of saponins, flavonoids, and phenols present in secondary metabolites of this plant (Sima Obiang et al., 2015).

The antioxidant potential *C. ferruginea* has been demonstrated in several studies (Adisa et al., 2011; Adisa and Olorunsogo, 2013; Ojo et al., 2019). Fractionated extracts of *C. ferruginea* demonstrated antioxidant action by various extracts and sub-fractions in different vitro assays, including superoxide anion scanning, DPPH, inhibition of xanthine oxidase activity, and inhibition of Fe2 +/ascorbate (Adisa et al., 2011). Another study of the same plant species indicated potent antioxidant action for the robustaside B and para-

hydroxyphenol isolated substances obtained from the leaves (Adisa and Olorunsogo, 2013). The compounds were incubated at different concentrations (0.05–1 mM) with mitochondria obtained from rat-liver tissue, and a significant reduction of thiobarbituric acid reactive substances (TBARS) was observed in a concentration-dependent manner (Adisa and Olorunsogo, 2013). In another approach, ethanolic extract of *C. ferruginea* attenuated oxidative stress induced by kainic acid. In this study, the 400 mg/kg extract promoted increased glutathione (GSH), reduced nitrite and MDA production, and attenuate TNF-α mediated signaling (Ojo et al., 2019). In addition, methanolic extract of *C. ferruginea* roots tested at 100 and 200 mg/kg, as well as the sub-fraction rich in amentoflavone administered at 12.5 and 25 mg/kg reduced the production of malondialdehyde and increased GSH levels in mice (Ismail O. Ishola et al., 2013).

The aqueous extract of *C. favosus* bark at a concentration of 5 mg/mL exhibited antioxidant activity in the DPPH and Fe^{3+}/Phenanthroline in vitro screening assays with 4.0 ± 0.3 and 1.7 ± 0.3 equivalents of ascorbic acid [AAeq]. The extracts with AAeq value between 1.0 and 2.0 exhibited a high antioxidant potential, which was demonstrated by the DPPH assay. This result is associated with the presence of phenolic compounds present in the metabolites of this plant (Silva et al., 2016). An evaluation of the methanolic extract of *C. paniculatus* branches about the inhibitory activity of glycation end product formation demonstrated that this species could inhibit formation of these products, with an IC_{50} of 2.75 ± 0.31μg/mL (Tran, 2015). The aqueous extract of *C. perrottetii* bark (10% w/v) and the ethanolic, butanolic, and ethy acetate fractions (5% w/v) eliminated the DPPH radical above 70%. This antioxidant action is credited to the presence of flavonoids catechin and rutin isolated from the extracts of this plant, which is widely used in traditional Brazilian medicine (Müller et al., 2016). The extract obtained from *C. ruber* barks at a concentration of 200 ppm inhibited 80% of the DDPH radical (Nakamura et al., 2011).

The hydroethanolic extract of *R. coccinea* leaves presented favorable antioxidant profile in rats treated with the extract at doses of 100, 200, and 400 mg/kg (Akindele et al., 2014). These researchers observed increased catalase (CAT), superoxide dismutase (SOD), GSH, and glutathione peroxidase (GPX) activity, as well as a reduced malondialdehyde levels, measured in the cardiac tissues of these animals attributed to to the flavonoids and other chemical constituents in the extract of this plant (Akindele et al., 2014). Another study of the same species demonstrated in vivo antioxidant effect for an aqueous extract of leaves on isoniazid-induced oxidative stress in rats (Andrew et al., 2017). In this study, there was a quantitative reduction in serum catalase enzyme units at a dose of 200 mg/kg. In carbon tetrachloride (CCl4) induced oxidative stress, the aqueous extract of the leaves was equally promising. Administered for seven days concomitantly with CCl4, the extract at doses of 200, 400 and 1,000 mg/kg quantitatively increased the CAT, SOD, and hepatic peroxidase enzymes, reduced glutathione, as well as being able to decrease malondialdehyde (Akindele et al., 2010).

The ethanolic extract of *R. induta* leaves administered to rats at dose 500 mg/kg had an antioxidant effect after induction of oxidative stress by carbon tetrachloride. This study also demonstrated that the extract could restore the CAT, GPx, SOD, and GSH antioxidant defenses as well as reduce TBARS levels, which were attributed to the presence of hyperin , quercetin-3-O-α-arabinofuranoside and quercetin-3-O-β xyloside (Kalegari et al., 2014). The essential oils obtained from the leaves of *R. microphylla* eliminated the DPPH and 2,2·-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) $ABTS^{\cdot+}$ radicals due to the presence of oxygenated compounds among the secondary metabolites isolated in this plant (Huo et al., 2011).

The aqueous extract of *C. favosus* barks showed protective activity against mercury poisoning in the in vivo model with zebrafish (*Danio rerio*). This study demonstrated the

activity of the 5% extract added to their food, which was administered to animals at a dose of 250 mg/kg over a period of 60 days (Gombeau et al., 2019). The observed effects include reduced lipid peroxidation among animals exposed to mercury and supplemented by the extract compared to animals only exposed to the metal (Gombeau et al., 2019). According to the authors, the observed effect is derived from the reduction of mercury-induced lipid peroxidation at the brain and liver levels by this plant in the face of exposure to heavy metals, which is mediated by antioxidant mechanisms.

Hypoglycemic activity

Methanolic and ethyl acetate extracts obtained from *C. ferruginea* leaves exhibited a hypoglycemic effect at the dose of 250 mg/kg in rats with diabetes induced by streptozotocin (STZ) (Adisa et al., 2010). In addition to the hypoglycemic effect, they reduced lipid peroxidation and improved liver and renal function. The extract obtained from the leaves and branches of *C. lambertti* inhibited the microsomal glucose-6-phosphatase enzyme in an in vitro assay, indicating that this plant could be used as an adjuvant to control hyperglycemia in diabetic patients (Jiménez et al., 2001)

A hydroethanolic extract of *R. coccinea* leaves showed hypoglycemic effect on alloxan-induced diabetic rats at different dosages, which could be related to the presence of saponins in the extract (Dada et al., 2013). In addition to the reduction in glycemia, the oxidative stress markers improved for the 800 mg/kg dose, which indicates the great potential of this plant for future clinical applications in diabetes control. The hydroethanolic fraction of *R. cuspidata* extract demonstrated hypoglycemic activity at a dose of 200 mg/kg in rats with STZ-induced diabetes in a 28-day study (Laikowski et al., 2017). For the *R. minor* species, the ethanolic and aqueous extracts obtained from the roots promoted blood glucose reduction in rats with STZ-induced diabetes for both the 200 and 400 mg/kg dose in a 15-day exposure (Kulkarni et

al., 2014). Those authors attribute the hypoglycemic effect to the synergistic effect of the chemical compounds present in this plant extract.

Triglyceride and/or cholesterol reducing activity

Hydroethanolic extract of *R. coccinea* leaves exhibited cholesterol and triglyceride-lowering activity in rats after administration of 100, 200, and 400 mg/kg dosages for 56 weeks (Akindele et al., 2014). The authors attributed these effects to the presence of flavonoids and other phytoconstituents in the extract of this plant but did not chemically identifying them (Akindele et al., 2014). In another study with the same species, the hydroethanolic extract of the leaves lowered total cholesterol and increased HDL fraction in diabetic rats (Dada et al., 2013).

For the *R. minor* species, the ethanolic and aqueous extracts obtained from the barks reduced the total cholesterol and triglycerides, and increased the serum HDL cholesterol level in diabetic rats at a dose of 400 mg in a 15-day exposure (Kulkarni et al., 2014).

Antibacterial activity

Methanolic extract obtained from *A. bornensis* bark and leaves was active in the disc diffusion assay against gram-positive bacteria *Staphylococcus aureus* (Chung et al., 2004). This study was conducted only from dry crude extract, and no studies have elucidated which compounds are responsible for this antibacterial action.

A study to evaluate the antimicrobial activity of *C. ferruginea* fruits demonstrated activity against different bacterial strains, in which the aqueous extract of fruits presented MICs of 5 to 10 mg/mL against 11 different clinical isolates including *S. aureus, Streptococcus mutans, Escherichia coli, Citrobacter freundii,* and others (Ndukwe et al., 2005). In another work, different solvents were used to extract secondary metabolites which were submitted to antimicrobial evaluation (Kouakou et al., 2019). Those authors demonstrated that aqueous extract had the best antimicrobial profile and was active against

10 of the 11 strains tested, including both gram-negative and positive bacteria, and this effect was attributed to the presence of hydroquine and caffeic acid methyl ester among the secondary metabolites identified in this plant (Kouakou et al., 2019). The antimicrobial effect of *C. ferruginea* methanolic extract was proven against multidrug resistant (MDR) bacterial strains, by employing the disk diffusion method against different MDR strains of *S. aureus*, *Escherichia coli*, and *Salmonella* spp. impregnated with 7.5 mg/mL of the ethanolic extract of the stems, with similar inhibition to the erythromycin antibiotic (EC et al., 2015). For *C. palala* species, antibacterial activity was found in the ethanolic and crude extract fraction against gram-positive bacteria *S. aureus* and *Staphylococcus epidermidis,* in different parts of the plant. The authors isolated the hydroquinone compound and related it to the antimicrobial effect of this plant species (Dej-adisai et al., 2015). *Connarus elsae* dichloromethane extract had promising inhibitory activity against *Mycobacterium tuberculosis* inhibiting more than 50% of this bacterium tested using the Bactec 460® detector (Graham et al., 2003). Despite the promising result against tuberculosis-causing bacteria, no further studies have been conducted to clarify the chemical constitution and safety of using this plant.

The antimicrobial effect of aqueous extract of *C. favosus* bark revealed activity against *Morganella morganii* and *Serratia marcescens* inhibited at 250 μg/mL; *Yersinia enterocolitica* 125.0 μg/mL; and *Pseudomonas fluorescens* 15.6 μg/mL (Silva et al., 2016). Apparently, this effect is related to phenols and tannins present in the extract at high concentrations. *C. ruber* shoot extract was active against *Enterococcus faecalis* in the disk diffusion assay (Castilho et al., 2014). In addition to the antimicrobial effect, crude extract, n-butanolic, and aqueous fractions were significantly active against *E. faecalis* biofilm formation, and *C. ruber* could be use in dentistry against formation of biofilm associated with virulence of this microorganism (Castilho et al., 2013). For *R. coccinea,* antimicrobial activity was demonstrated for the n-butanolic and ethyl acetate fractions against *E. coli, S.*

aureus, and *Salmonella typhi* bacteria; this activity is related to the presence of flavonoids and tannins, which were found in both fractions of the plant extract (Ahmadu et al., 2006). Different extracts obtained from the root bark of *R. obliquifoliolata* showed activity against strains of the genus *Vibrio, Shigella* and *Campylobacter* at MICs 31.25; 62.5, and 125 µg/mL, respectively, which was attributed to the presence of tannins and other secondary metabolites in this plant (A. Longanga Otshudi et al., 2000); however, so far the chemical compounds responsible for this activity have not been identified. The extract obtained from *R. coccinea* leaves exhibited antibacterial activity against *S. aureus, E. coli,* and *S. typhi* species with MICs of 1.75, 0.44, and 1.75 mg/mL, respectively (Ahmadu et al., 2006).

Antifungal activity

The ethanolic extract of *C. palala* seeds showed similar activity to the ketoconazole pattern in disc diffusion assays against dermatophytes *Trichophyton mentagrophytes*, *Trichophyton rubrum,* and *Microsporum gyseum* (Dej-adisai et al., 2015). Additionally, those authors were able to demonstrate activity against *Candida albicans* yeast fungus for ethanolic extracts of seeds, bark, and roots, and these effects were compared to the amphotericin B pattern (DEJ-ADISAI et al., 2015). Antifungal activity was also demonstrated for n-butanolic extract obtained from *R. coccinea* leaves against *C. albicans* isolates with MIC of 0.88 mg/mL (Ahmadu et al., 2006).

Antiprotozoal activity

Different fractions of ethyl acetate extract obtained from *C. suberosus* barks exhibited activity against *Leishmania (Leishmania) amazonensis* with IC_{50} 27.57 to 94.00 µg/mL (da Costa et al., 2014). Although the authors identified different chemical compounds in this plant extract, the chemical identity of the compounds responsible for the action against *L. amazonensis* could not established. For *C. suberosus*, the hexane extract of root bark and wood demonstrated activity against *Trypanosma falciparum* and *Trypanosma brucei*

gambiense, causative agents of malaria (Charneau et al., 2015). In that work, the extract was active against the free and intracellular forms of the *T. falciparum* protozoan. The erythrocyte forms had a the IC_{50} of 1.2 ± 0.5 μg/mL for the root wood extract and 1.2 ± 0.3 μg/mL for the root bark extract (Charneau et al., 2015). In the evaluation against the bloodstream forms of *T. brucei gambiense*, the IC_{50} was 1.7 ± 0.1 μg/mL for wood extract and 1.8 ± 0.0 μg/mL for the bark (Charneau et al., 2015). Methanolic extract from *M. expansa* barks exhibited actitation against *Trypanosma brucei brucei* at IC_{50} 37.0 ± 3.1 μg/mL; however, the authors did not continue research with this plant because the species *T. falciparum* had an IC_{50}% higher than 64 μg/mL (Mesia et al., 2008). The dichloromethane fraction extracted from aerial parts of *R. coccinea* showed activity against T. *brucei brucei* IC_{50}% 14.7 ± 1.2 μg/mL; therefore, the potential of the species as an antiprotozoal agent indicates the need for isolation and identification of the substances responsible for the biological effect against the causative agent of African trypanosomiasis (Bero et al., 2009). The dichloromethane extract obtained from the aerial parts of *R. coccinea* had an IC_{50}% of 41.6 ± 22.1 μg/mL against *P. falciparum* (3D7) (Bero et al., 2009).

Antiviral activity

The species *C. cochinchinensis* showed antiviral activity involving the measles virus (Zarr, 2010). The methanolic extract of leaves administered concomitantly with the virus was able to decrease viral infection of Vero cells and was highly active against this pathogen. Those authors indicated that saponins, which are present among the secondary metabolites of this plant, may exert an antiviral effect.

Restoration of sexual function, fertility, and activity in gonads

In *C. ferruginea* species, the aqueous extract of the roots administered to rats at a dose of 52 mg/kg stimulated sexual activity by increasing testosterone levels in these animals (Toyin and Olaide, 2012). The aqueous extract from *R. coccinea* roots administered to rats

with paroxetine-induced sexual dysfunction improved sexual performance and reestablished testicular function at a dose of 150 mg/kg, which may be related to increased testosterone and nitric oxide synthesis; however, the authors did not isolate and characterize the active principles responsible for the observed effects (Yakubu and Atoyebi, 2018).

The aqueous extract of *C. ferruginea* leaves administered to female rats at a concentration of 50 and 100 mg/kg was able to promote hormonal changes responsible for increased fertility in these animals (Zougrou et al., 2016) In the 30-day study both doses were able to increase serum levels of the hormones FSH, LH, estradiol, progesterone, and prolactin. Evidence suggests that the presence of estrogenic compounds in the extract may be responsible for the effect observed in these animals (Zougrou et al., 2016).

Hydroethanolic extract of R. coccinea leaves administered at doses of 25 and 50 mg/kg to rats exhibited uterotonic effect (Amos et al., 2002). According to the authors, the effect of the extract may be antagonized by administration of the β-receptor agonist salbutamol, indicating that the uterotonic effect is mediated via the adrenergic pathway.

Antidiarrheal activity

For *R. coccinea* the aqueous extract obtained from the leaves had an antidiarrheal effect in mice treated with 400 mg/kg, which may be related to inhibition of α-adrenergic receptors that control intestinal propulsion and intestinal fluid secretion (Akindele and Adeyemi, 2006). In this study, different classes of chemical compounds were identified in the plant extract; however, the authors did not conduct experiments to elucidate which compounds are responsible for the effect. A methanolic extract of *R. obliquifoliolata* demonstrated antidiarrheal activity at the dose of 750 mg/kg in rats measured by decreasing the frequency of defecation and water loss through the stool (Longanga Otshudi et al., 2001).

Snakebites

Aqueous extract from *C. favosus* roots proved to be effective in completely blocking lyophilized Bothrops jararaca venom-induced hemorrhage in mice (Silva et al., 2016). In this experiment, the antihemorrhagic effect was observed for the diluted venom extract at a concentration of 12/1 p/p, and according to the authors, the antiophidic effect is probably associated with the blockage of venom metalloproteinases by the phenolic compounds contained in the plant extract (Silva et al., 2016).

Genotoxicity suppression

The extract obtained from *C. ruber* bark added to water from mice exposed to cigarette smoke at a dose of 758 ppm was able to reduce the appearance of micronucleated reticulocytes and erythrocytes in these animals (Nakamura et al., 2011).

Antiproliferative activity

The aqueous extract of *C. perrottetti* leaves was moderately active against human colon carcinoma cells (KM-12), with a lethality of 15% for the tested extract at a concentration of 100 μg/mL (Suffredini et al., 2007). This study reflects the need for fractionation of the extract to identify more active fractions as well as to isolate and identify which compounds are responsible for the antiproliferative effect demonstrated in the in vitro study. Methanolic extract from *M. expansa* bark demonstrated cytotoxic activity against the human lung fibroblast strain (MRC-5) IC_{50}% 27.0 ± 2.2 μg/mL (Mesia et al., 2008). The organic extract (dichloromethane/methanol 1/1) from *P. macrophyllus* aerial parts was moderately active against human colon carcinoma cells (KM-12) with a lethality of 15% for the tested extract at 100 μg/ml (Suffredini et al., 2007). Different fractions of the ethanolic/ethanolic extract (1:1) of *R. coccinea* leaves showed antiproliferative activity for HT29 cells at concentrations of 100 μg/mL (Akindele et al., 2016, 2011). However, no experiments were conducted to elucidate the chemical constituents responsible for the effect, and but the authors state that

the antiproliferative effect of this plant is due to the synergistic effect of different constituents present in the extract (Akindele et al., 2011). Another study about the same plant species identified an antiproliferative effect of methanolic extract at a concentration of 200 μg/mL against human cells derived from breast (BT-549, BT-20) and prostate (PC-3) adenocarcinomas (Fadeyi et al., 2013). According to the authors extracts of this plant can be considered very active as some cell lines inhibited ≥ 50% in cells treated with the extract at a concentration of 20 μg/mL. Those authors emphasis the need for bioguided studies to elucidate which chemical compounds are responsible for the antiproliferative action of plant extracts.

7. Toxicological

Studies using a toxicological approach on the Connaraceae family still include few species, and the safety profile for most of those reported in ethnobotanical and/or pharmacological studies is still totally unknown. However, the presence of potentially toxic substances has been reported for some species of the Connaraceae family (Garon et al., 2007; Jeannoda et al., 1985; Vickery and Vickery, 1974).

The presence of certain coumarin-derived compounds may be related to anticoagulant effects that produced rabbit death (Vickery and Vickery, 1980). A study on the toxicity to rabbits of the leaves of different Connaraceae species demonstrated different symptoms in vivo and postmortem evaluation of the animals. With exposure to *A. pentagyna*, the LD_{50} of the leaves was established at a dose between 20 and 50 g/kg, and the main effects observed were the onset of convulsions, hyperhidrosis, conjunctivitis, liver alterations, and tracheal edema, with death occurring between 2 to 5 days after rabbits were exposed to the plant (Vickery and Vickery, 1974). For the species *C. corniculata, C. ferruginea,* and *R. coccinea*,

the LD_{50}s were 10, 25, and 50 g/kg, respectively, and the toxic effects observed in rabbits were similar to those found for *A. pentagyna* (Vickery and Vickery, 1974).

The compound L-methionine sulfoximine (MSX) has neurotoxic action and was found in the extract obtained from *C. ferruginea* leaves (Garon et al., 2007) and in different parts of *C. palala* (Murakoshi et al., 1993). For *C. ferruginea*, the presence of MSX was demonstrated for the aqueous extract of the plant in a study that measured cell viability (Chinese Hamster Ovary (CHOK1) cells) by (2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)- 5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide) (XTT) and found viability reduced as the extract concentration increased (Garon et al., 2007). Considering the toxic effects of MSX, the decrease in viability could be related to the presence of that compound. In *C. palala*, the toxicological effect of ground seeds was evaluated at a dose of 347 mg/kg in dogs, and the observed effects included the onset of vomiting in the first hours after exposure, locomotor and respiratory disorders, salivation, and seizures ultimately leading to death 24 hours after exposure (Murakoshi et al., 1993). The toxic effects observed in these two species are directly related to the MSX compound. A study with the fraction of alkaloids obtained from *C. ferruginea* roots observed enzymatic and histological changes (Atere and Ajao, 2009). In that study, the administration of alkaloids rich extract at doses of 3, 6, and 9 mg/kg increased the serum concentration of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and promoted changes in liver tissue histology in the largest doses tested (Atere and Ajao, 2009). However, the popular uses of this plant do not use the enriched fractions of the extract, but the preparation of decocts and macerates, and thus the findings of that study cannot be extrapolated to the hepatotoxicity forms of the traditional preparation. Moreover, recent studies with *C. ferruginea* have indicated a toxicological profile favorable to future pharmacological applications of this plant (Hong and Lyu, 2011; Ishola et al., 2011). The acute toxicity of methanolic extract obtained from *C. ferruginea* roots was assessed by

oral administration to rats at doses of 1, 2, 4, 8, and 10 g/kg (Ishola et al., 2011). At doses of 1 and 2 g/kg no deaths occurred; however, at the dose of 10 g/kg, 100% of the experimental animals died within 24 hours of administration (Ishola et al., 2011). The authors were able to establish that the LD_{50} of the oral dry methanolic extract for this plant is 5.22 g/kg and that oral administration of this plant can be considered safe as $LD_{50} \geq 5.00$ g/kg. Another study on sub-chronic toxicity of methanolic extract from *C. ferruginea* roots demonstrated relative safety of this plant which can also induce antioxidant enzymes in rats (Ishola et al., 2012b). In this evaluation, the authors elucidated the effect of the extract at different dosages against biochemical, histological, and hematological parameters, and the main effects were related to the absence of sperm production at a concentration of 1,000 mg/kg and reduced body weight with some tested dosages, although most of the deleterious effects were in much higher dosages than those used by traditional medicine. The genotoxicity of *C. ferruginea* was ruled out for whole plant methanolic extract in a mutagenicity assay with *Salmonella typhimurium* and *E. coli* WPuvr (Hong and Lyu, 2011)

In the genus *Connarus*, the evaluation of *C. cochinchinensis* in the toxicological assay of methanolic extract of leaves at concentrations of 10 to 1,000 ppm against *A. salina* had an LD_{50} of over 1,000 mg/L, demonstrating a favorable safety profile of this species (Zarr, 2010). In the cytotoxicity assay with Vero Cells, the extract of this plant presented toxicity with cellular cytotoxicity value (CTC_{50}) at 104.5 mg/L (Zarr, 2010). Preliminary toxicity evaluation of the ethanolic extract of *C. lambertii* leaves and twigs in an assay with *A. salina* revealed that this species has microcrustacean toxicity, and the LD_{50} of the extract for these animals was established at 0.15 mg/mL (Jiménez et al., 2001). In another study about the same species, the aqueous extract of the leaves presented an LD_{50} of 16.52 mg/mL against *A. salina* (Coe et al., 2010). The difference in the solvents used may be the reason for the discrepancies of the values found in these two studies. Administered orally to mice at doses

between 500 and 2,000 mg/kg, the aqueous extract of *C. ruber* barks did not cause mortality (Nakamura et al., 2011). The toxicological activity of the water-soluble extract and the ethanolic fraction of *C. suberosus* barks was evaluated after the mice were exposured to different doses of intraperitoneally administered extracts , and the water soluble fraction presented a LD_{50} of 310 ± 52 mg/kg while the ethanolic fraction was 210 ± 22 mg/kg (Taveira et al., 1988). According to those authors, *C. suberosus* has toxicological potential as the LD_{50} of the extracts are less than 500 mg/kg. As this species is used for traditional medicinal purposes (da Costa et al., 2014; Taveira et al., 1988), other experiments should be conducted to confirm the safety of using this plant.

The acute toxicity of hydroethanolic extract obtained from *R. coccinea* leaves was assessed by oral and intraperitoneal routes in rats (Akindele et al., 2014). Orally administered at a dose of 10 g/kg for 14 days, the extract did not kill the animals; However, intraperitoneal administration had a 100% mortality rate at 800 mg/kg, and the LD_{50} for this extract was set at 288.40 mg/kg (Akindele et al., 2014) The toxicological potential is similar to that found for *C. suberosus* and demands additional studies to evaluate its toxicity. An evaluation of the acute toxicological potential of ethanolic extract of *R. coccinea* barks indicated a favorable safety profile for the use of this plant (Kossivi et al., 2015). In this study administered orally at the dose of 5,000 mg/kg to rats no behavioral changes and mortality were observed. At sub-chronic exposure to the same extract for 28 days, no enzymatic, hematologic, and vital organ changes were observed in the animals (Kossivi et al., 2015).

The acute toxicity of aqueous extract of *R. coccinea* leaves was evaluated by oral and intraperitoneal routes in mice (Akindele and Adeyemi, 2006). When orally administered at a dose of 10 g/kg, the extract did not produce mortality, whereas for intraperitoneal administration, the LD_{50} was set at 141.3 mg/kg. In another acute exposure study of the same species in rats, intraperitoneally administered hydroethanolic leaf extract had an LD_{50} of

547.7 mg/kg (Amos et al., 2002). The differences found between these studies for the LD_{50} may be related to the different extract types and breeds of rats used in the experiments. Studies on the ethanolic extract of *R. induta* leaves against the *Artemia salina* assay and in tube plaque hemolysis tests at concentrations of 1,000 to 10 µg/mL presented a favorable safety profile for the use of this plant (Kalegari et al., 2011). That study demonstrated that even at the highest dose tested, the extract did not cause mortality of *A. salina* or promote hemolysis in either assay. A study evaluating acute oral toxicity of aqueous and ethanolic extracts of *R. minor* roots in rats at different doses between 10 and 3,000 mg/kg demonstrated a safety profile favorable to the medicinal use of this species, since no mortality was observed at the doses tested (Kulkarni et al., 2014).

8. Conclusions and future perspectives

This review discussed 165 publications on Connaraceae, including 159 articles and 6 books. Analysis of the number of papers found by this study in five-year intervals (Fig. 5) verifies that 100 out of the 165 publications were done in the last decade, representing approximately 2/3 of the total research conducted with this family. The growing interest of the scientific community in this plant family can be gauged by this increase in publications in the last ten years.

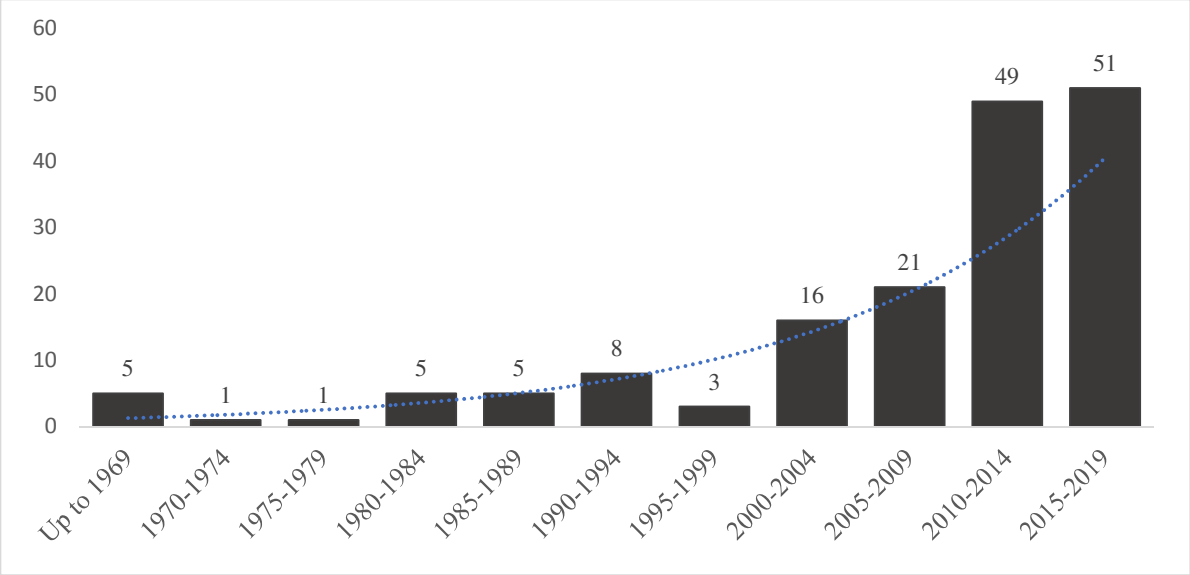

Figure 5: Histogram of number of publications over time of Connaraceaes selected by the study. Range 230 years, increment: (5 years), adjusted estimate of classes (11).

This pioneering review compiled and analyzed data to establish a general overview of research about Connaraceaes along with the pharmacological potential for each plant species (Fig. 6).

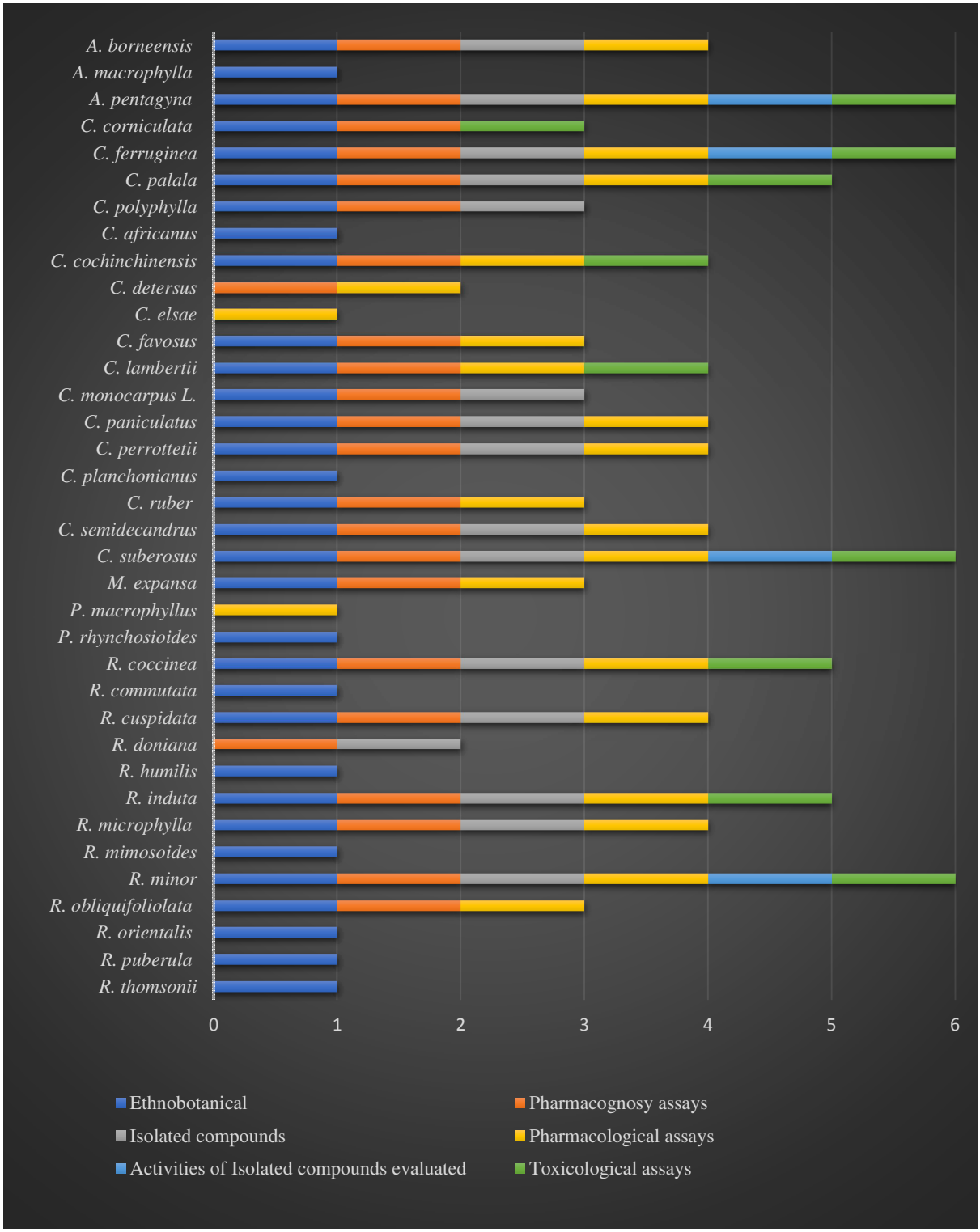

Figure 6: Overview of research with different Connaraceaes species

Reports of ethnobotany use include 32 of the 36 species described here with associated pharmacological potentiality. Pharmacognostical studies were conducted with 24 of these

species, and chemical compounds were isolated and identified from only 16 of the 36 species reported here.

At least one published study of pharmacological activities was observed for 22 of the 36 species, but for four, *A. pentagyna, C. ferruginea, C. suberous,* and *R. minor*, experiments of pharmacological activity were performed using isolated compounds. Finally, studies with a toxicological approach cover only 10 of the 36 Connaraceaes species studied here.

The overview of Connaraceaes research establish that *A. pentagyna, C. ferruginea, C. suberosus,* and *R. minor* have the greatest pharmacological potential; moreover, reports including ethnobotany, pharmacognostical analysis, isolation of compounds, pharmacological assays, pharmacological activities of isolated compounds, and preliminary toxicological tests. Hence, it is possible to infer that *C. ferruginea* and *R. coccinea* present the largest number of studies with pharmacological and toxicological approach and, therefore, the greatest pharmacological potential for this family of plants.

In this review, 36 species of the Connaraceae family were found with associated pharmacological potential. This implies that these plants are widely used as a source of traditional medicines around the world, and they have a high diversity of identified secondary chemical metabolites. The systematized data demonstrate that the Connaraceae family has good potential to contribute to the discovery of new therapeutic options, especially the species A. *pentagyna, C. ferruginea, C. suberosus,* and *R. minor*. Considering that the distribution of these species is concentrated in the tropical areas of the planet, which suffer from anthropic pressures due to from environmental impacts, deforestation, burning, urbanization, and expansion of agricultural frontiers, the scientific community needs to urgently assist with new studies that support policies for the preservation and sustainable use of these pharmacological resources before they are completely destroyed.

This review found that a large number of species have been studied to confirm the biological activities and some of these activities have been scientifically proven. However, comparing the activities reported by traditional use with the pharmacological activities described in this review found that many remedies have not been studied by the scientific community. Studies that sought to identify biological activities for chemical compounds isolated from Connaraceae species are still rare. It is urgent that further research with these species be conducted to scientifically confirm the pharmacological activities reported by popular use, which contribute to the discovery of new therapeutic alternatives, as well as to stimulate protection measures of the biomes in which these plants are found.

Authors' contributions

Luis Fernando N. A. Paim collected the information and wrote the manuscript; Cássio A. P. Toledo, Joicelene R. L. da Paz, Aline Picolotto, and Guilhereme Ballardin assisted in the modification and adaptation of the text. Sidnei Moura and Mirian Salvador made the final revision of the manuscript. All authors approved the final submitted version of the manuscript.

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