New Caledonia: A 'Hot Spot' for Valuable Chemodiversity: Part 2: Basal Angiosperms and Eudicot Rosids

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Part 2: Basal Angiosperms and Eudicot Rosids

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The flora of New Caledonia encompasses more than 3000 plant species and almost 80% are endemic. New Caledonia is considered as a 'hot spot' for biodiversity. With the current global loss of biodiversity and the fact that several drugs and pesticides become obsolete, there is an urgent need to increase sampling and research on new natural products. In this context, we review the chemical knowledge available on New Caledonian native flora from economical perspectives. We expect that a better knowledge of the economic potential of plant chemistry will encourage the plantation of native plants for the development of a sustainable economy which will participate in the conservation of biodiversity. In the second part of this review, we focus on the results exposed in 60 scientific articles and describe the identification of 225 original compounds from basal angiosperms and eudicot rosids. We discuss the economic potential of plants and molecules from medicinal and industrial perspectives. This review also highlights several plants and groups, such as *Amborella* sp., Piperaceae, or Phyllanthaceae, that are unexplored in New Caledonia despite their high chemical interest. Those plants are considered to have priority in future chemical investigations.

Introduction. – The importance of biodiversity for the discovery of new natural products with economical value was recognized in 1990 during a meeting of the *International Society of Chemical Ecology*. In the Göteborg Resolution [1], natural product diversity was recognized as a 'treasury of immense value to human kind'. This resolution also pointed out the current alarming rate of species extinction that is rapidly depleting this treasury, with potentially disastrous consequences. This encouraged the research for valuable natural products for the valorization and protection of biodiversity [1]. From time immemorial, plants have provided a wide variety of foods, drugs, cosmetics, fibers, and building materials, and have been fundamental for the development of human societies [2]. More recently, studies of plant chemistry have led to the discovery of many bioactive products, such as for pharmacological, agronomical, or cosmetic applications. The discovery of aspirin from *Filipendula ulmaria* or of artemisinin from *Artemisia annua* are among the most popular examples that illustrate the importance of such research [3][4]. Despite the development of combinatorial chemistry and rational drug design, many authors argue that natural products are likely to continue to provide the best lead-molecules in the future [5][6]. In this context, species-rich areas, such as tropical and subtropical forests, are of particular interest.

New Caledonia, an archipelago located in the South-West Pacific, is considered as one of the 34 major 'hot spots' for marine and terrestrial biodiversity [7]. A review published in 2004 by *Laurent* and *Pietra* highlighted the pharmacological potential of the Neo-Caledonian marine organisms [8], but no review of terrestrial phytochemical investigations is available yet. Considering higher plants, it is evaluated that New Caledonia contains 3270 native species, of which 78% are endemic to this territory [9]. This botanical diversity also represents a huge reserve of original natural compounds and provides a real interest for green chemistry, pharmacology, cosmetics, and agronomy. The term 'hot spot' also points out that the biodiversity is highly threatened by human activities and therefore, this habitat must be protected [10]. For this purpose, the discovery of interesting chemicals from plants will encourage the reforestation and thus, the protection of biodiversity. Investigations of the New Caledonian chemodiversity already provided original compounds and/or interesting drugs. As an example, methoxyellipticine, an alkaloid found in a New Caledonian Apocynaceae, was used to develop a drug (*Celiptium*®) used to treat breast and liver cancers [11].

Despite phytochemical interest, plant chemistry remains largely unexplored in New Caledonia. During the second part of the 20th century, research mainly focused on

the discovery of original compounds (*e.g.*, [12–14]). Later, biological evaluations started to be systematically associated to phytochemical analysis (*e.g.*, [15–17]). This was the beginning of research for economical evaluation, in a purpose of biodiversity conservation. Following the review of isolated alkaloids from New Caledonian flora by *Sévenet* and *Pusset* [18], we present here a broader review of the phytochemistry of New Caledonian plants and discuss their economic potential. This review summarizes publications available on SciFinder from 1972, when the first formal phytochemical studies of endemic plants were published, up to early 2015.

The knowledge available in scientific literature about the chemistry of New Caledonian native plants is reported exhaustively. The data are organized by families of plants, according to the phylogeny proposed by the Angiosperm Phylogeny Group III (APG III; see *Fig. 1*) [19]. This allows a comprehensive chemotaxonomical organization of this review. Florical was used as taxonomical reference for the New Caledonian flora [9]. This review points out the economic interest of terrestrial biodiversity of New Caledonia and highlights new groups which have been poorly studied and may contain novel compounds. This compilation highlights that the original flora from New Caledonia also contains a wide range of original compounds. Originality of New Caledonian compounds was updated using the Dictionary of Natural Products [20]. We considered compounds as originals when encountered only in a restricted number of endemic species stemming from a unique genus.[1]) We also point out that a lot of work remains to be done for the development of economical applications based on this biodiversity. This review is divided into three parts. The first part covers the knowledge of the chemistry of New Caledonian conifers [21], whereas the two following parts focus on the metabolites isolated from angiosperms. The second part, which is presented here, compiles the results obtained by investigation of basal angiosperms, monocots, basal eudicots, and eudicot rosids.

In New Caledonia, angiosperms are particularly diverse since this group encompasses 3099 species, more than 90% of all vascular plants, and is characterized by its remarkable originality, showing 77.8% endemism [9]. More in detail, several groups which are abundantly represented in the tropics are totally absent in New Caledonia, such as Balsaminaceae and Begoniaceae, and other groups, such as Annonaceae, Asteraceae, or Bignoniaceae, are clearly under-represented [9]. In parallel, we can find several relictual taxa, *Amborella trichopoda* being the perfect example, and a high level of speciation in several gondwanian groups, such as Lauraceae (47 endemic species) or Cunoniaceae (90 endemic species, corresponding to 30% of the world diversity of this group) [9]. Myrtaceae and Rubiaceae are the most important families, encompassing 257 and 211 species, respectively. As will be shown, many of the published phytochemical studies on New Caledonian angiosperms led to the isolation of original natural compounds. Also, several of them were shown to be highly bioactive, showing high potential for pharmaceutical applications. On the contrary, other economic perspectives for New Caledonian plants, such as cosmetic or agronomic applications, are poorly documented. As summarized in *Fig. 1*, we can also notify that we did not find any publication related to endemic species from 60% of the angiosperm families.

Protoangiosperms, Monocots, and Basal Eudicots. – *Annonaceae.* This family is represented by twelve species (including eleven endemic species) that are divided into six genera. Annonaceae is a huge tropical botanical family that encompasses more than 2000 species including several comestible fruits (*e.g.*, *Annona squamosa* and *Annona muricata*) or plants used for perfumery (*e.g.*, *Cananga odorata* and *Mkilua fragrans*). Annonaceae are known to contain polyphenols (including unusual C-benzylflavonoids), terpenes, acetogenins, and alkaloids (mainly from the isoquinoline group) as shown in many publications dedicated to these plants (*e.g.*, [22] and [23]). They are also frequently described in folk medicines [24] and numerous species show strong bioactivities, such as insecticidal or antitumoral activities [25][26].

The chemistry of five species has been investigated in New Caledonia: *Xylopia pancheri*, *Xylopia vieillardii*, *Meiogyne tiebaghiensis* (syn.: *Desmos tiebaghiensis*), *Hubera nitidissima* (syn.: *Polyalthia nitidissima*), and *Goniothalamus dumontetii*. Thirteen isoquinoline alkaloids, including an unusual morphinanedienone (pallidine; shown in *Fig. 2*) were identified from *M. tiebaghiensis* [18]. *X. pancheri* and *H. nitidissima* contain a great variety of aporphine and isoquinoline alkaloids from benzylisoquinoline and protoberberine groups, including four lindoldhamine derivatives (namely *N*,*N*'-dimethyllindoldhamine*, isodaurisoline*, 7-*O*-methyllindoldhamine*, and 7′-*O*-methyllindoldhamine*) that are presented in *Fig. 2* [18][27][28]. Only few biological tests were associated to those studies despite that several classical drugs, such as morphine, possess an isoquinoline skeleton. Indeed, only *X. pancheri* demonstrated light peripherical vasodilatory activity [18].

H. nitidissima also contains several flavonoids, such as mangiferin (see *Fig. 3*) and quercetin derivatives. Leaves of this plant contain a high concentration of mangiferin and are considered as an important natural source for this natural colorant and powerful antioxidant [29]. *G. dumontetii* was also investigated for protein kinase inhibition activity (DYRK1A and CDK1/cyclin B) for anticancer perspectives or neurodegenerative treatment. It contains aristolactams (namely velutinam, aristolactams AII and AIIIa) and one lignan called (−)-medioresinol (see *Fig. 3*). Aristolactam AIIIa (see *Fig. 2*) is a strong inhibitor of DYRK1A and CDK1/cyclin B showing IC_{50} values of 0.08 and 0.2 μM on these enzymes [30][31]. Despite strong evidence for the possible economical potential

[1]) Original compounds are tagged by an asterisk in the text and figures.

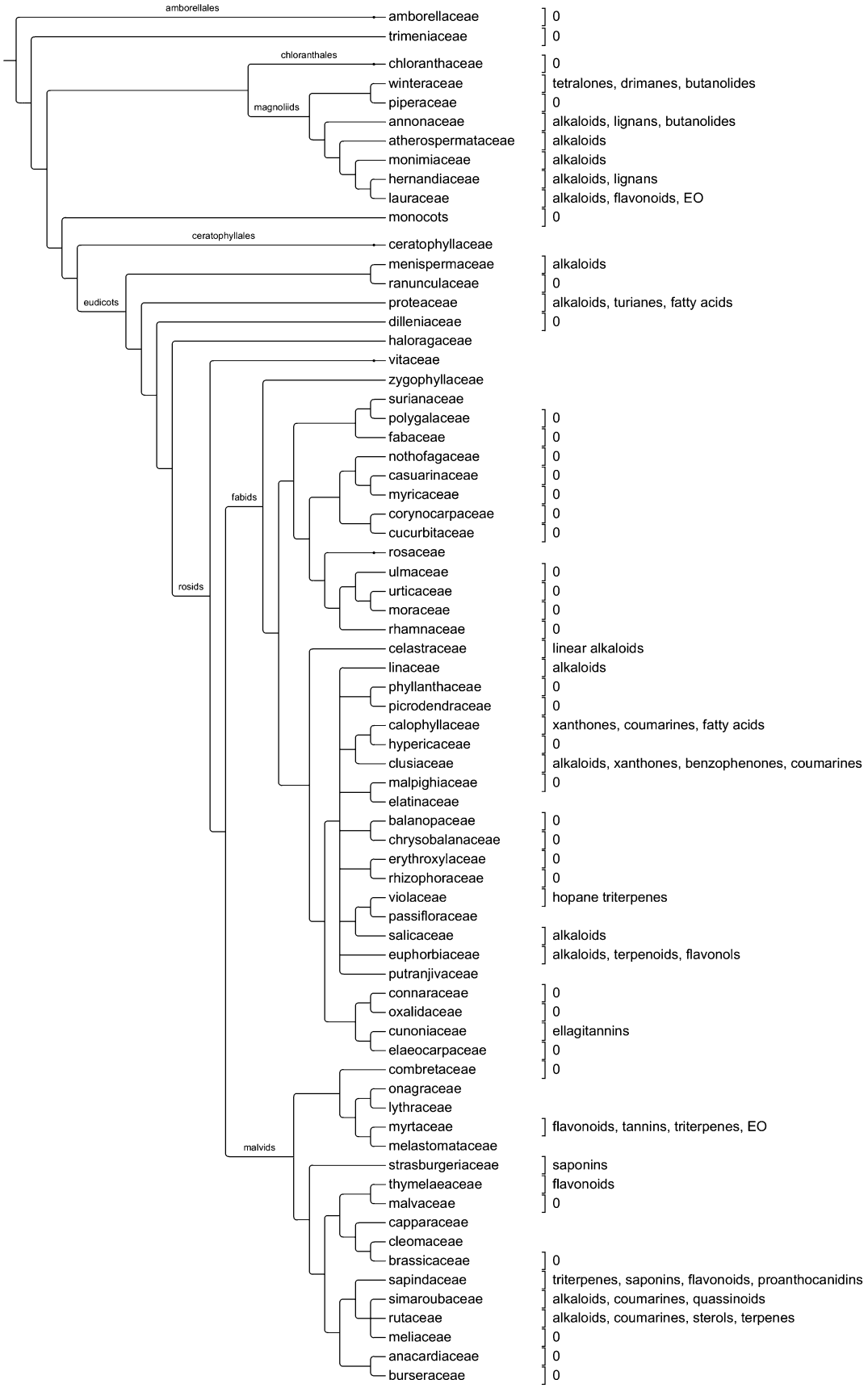


Fig. 1. *Phylogenetic tree of New Caledonian basal angiosperms and eudicot rosids realized with TreeGraph and data from APGIII* (see the *Supporting Information*[2]) for the entire phylogenetic tree of New Caledonian plant families). Chemical families encoutered in endemic species are mentioned on the right. EO, essential oil. 0 Corresponds to complete absence of chemical knowledge for any endemic species of a family (nothing is mentioned for families containing no endemic species).

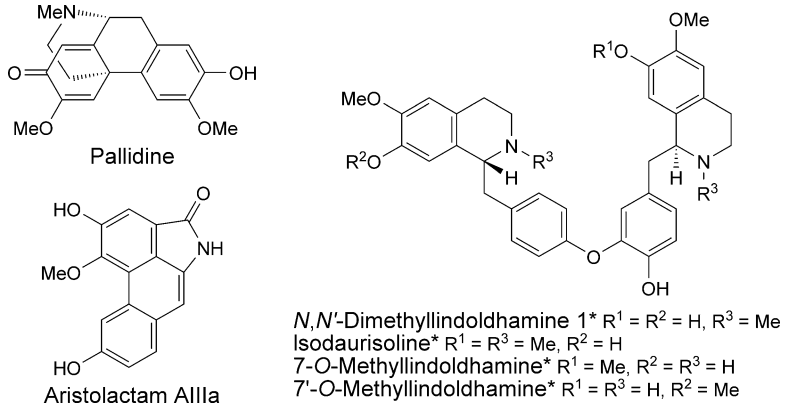


Fig. 2. *Structures of original and bioactive compounds isolated from Annonaceae*

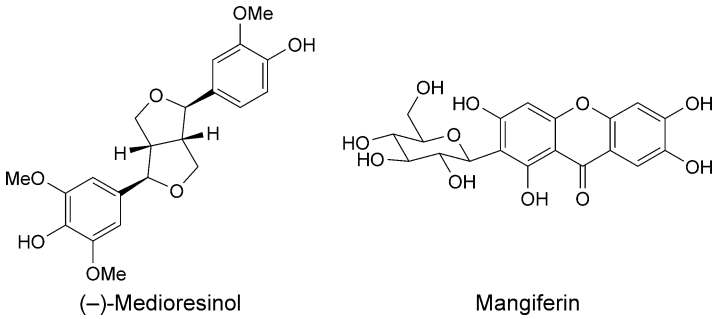


Fig. 3. *Remarkable polyphenols isolated from Annonaceae*

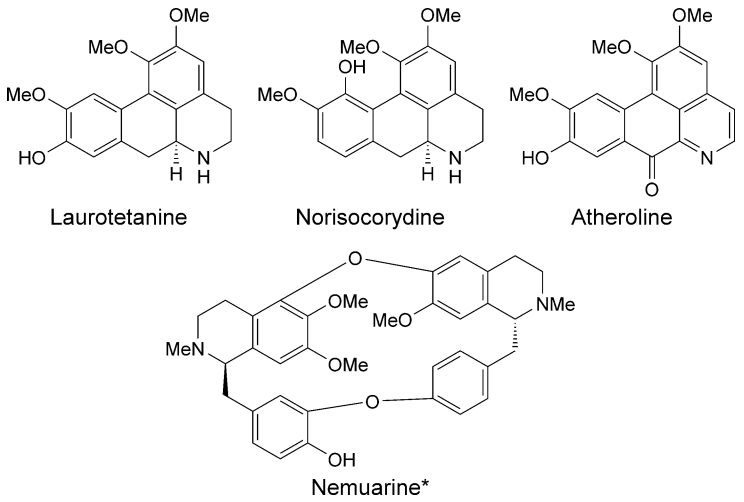


Fig. 4. *Examples of alkaloids isolated from Atherospermathaceae*

of this family, especially for drug discovery and cosmetics, the knowledge concerning the chemistry of New Caledonian Annonaceae is scarce and should be further studied.

Atherospermaceae. Nemuaron is a monospecific genus and *Nemuaron vieillardii* is the only member of the family Atherospermaceae in New Caledonia. This tree is found in humid forests of the main island. Elsewhere in the world, this family is known to produce phenolic compounds, such as chalcones or flavanones, and to biosynthesize alkaloids, mainly belonging to the isoquinoline group. Bisbenzylisoquinolines are even considered as chemical markers of this family [20]. Barks and leaves of *N. vieillardii* were investigated for their alkaloidal content. Consistent with the chemotaxonomic knowledge presented above, this study revealed the presence of numerous isoquinoline alkaloids, such as laurotetanine, norisocorydine, atheroline, and nemuarine*, an original bisbenzylisoquinoline [18]. The structures of these alkaloids are presented in *Fig. 4*. *N. vieillardii* also produces anise smelling aromatic com-

[2]) Supporting material is available upon request from the authors.

pounds. Thus, the plant is a potential source of essential oils and could be of interest for the perfume industry. However, according to our knowledge, no analysis of the essential oil content of this plant has been reported yet.

Hernandiaceae. This family is represented in New Caledonia by two genera and three species, including the endemic plant *Hernandia cordigera.* Species from this family, including *Gyrocarpus americanus* which is native to New Caledonia, are described to contain lignans and alkaloids [32][33]. *H. cordigera* also produces several characteristic lignans, such as 5′-methoxyyatein*, 5′-methoxypodorhizol, and cubebininolide, that are presented in *Fig. 5*, and aporphine alkaloids (*e.g.*, cassythicine, nandigerine, nantenine, hernagine, and ogiverine which are presented in *Fig. 6*) [18].

Hernandia nymphaeifolia (ex *Hernandia peltata*) also contains alkaloids including aporphine derivatives, together with furanoid lignans which showed potent antiplatelet aggregation activities and could potentially be used as natural anticoagulants in the future [34]. Further biological evaluation should be encouraged by the fact that aporphine alkaloids and lignans, such as the antiprotozoal agent lysicamine [35] or the anticancer agent aviculin [36], can be highly active natural compounds. Otherwise, the heart wood of *H. cordigera* has been exploited in the past for carpentry and is also traditionally used in New Caledonia for attracting and trapping chrysomelids (*Monolepta semi-violacea*), an important pest for crop fields [37]. A preliminary investigation of volatiles from this plant did not allow us to explain this biological activity.

Lauraceae. The family Lauraceae is represented in New Caledonia by six genera (including the endemic genus *Adenodaphne*) and 48 species, all being endemic except *Cassytha filiformis.* Lauraceae is an important tropical and subtropical family in terms of diversity, comprising 30 to 50 genera and *ca.* 2000 species, but also from an economical point of view, since it contains important species exploited for timber (*e.g.*, *Ocotea bullata*), food (*e.g.*, *Persea americana*), or fragrances (*e.g.*, *Aniba rosaeodora*). Phytochemicals in Lauraceae are diverse and include alkaloids (*e.g.*, benzylisoquinoline and aporphine derivatives), essential oils, polyphenols, and terpenoids [20][38].

New Caledonian Lauraceae were first investigated for their alkaloidal content (see original structures in *Fig. 7*). In 1985, *Tillequin*, *Koch et al.* described the presence of two new morphinane alkaloids with a saturated *C*-ring (oreobeiline* and 6-epioreobeiline*) together with known alkaloids (wilsonirine, thaliporphine, isoboldine, and pallidine) in *Beilschmiedia oreophila* [39]. Among the 19 endemic *Cryptocarya* species that are referenced in New Caledonia, five species were investigated for their chemical content.

Bioguided fractionation of a leaf extract of *Cryptocarya chartacea* led to the isolation of pinocembrin and six new mono- and dialkylated flavanones named chartaceones

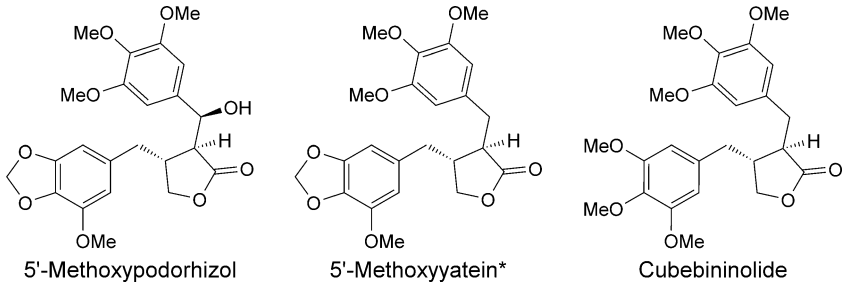


Fig. 5. *Lignans isolated from* H. cordigera

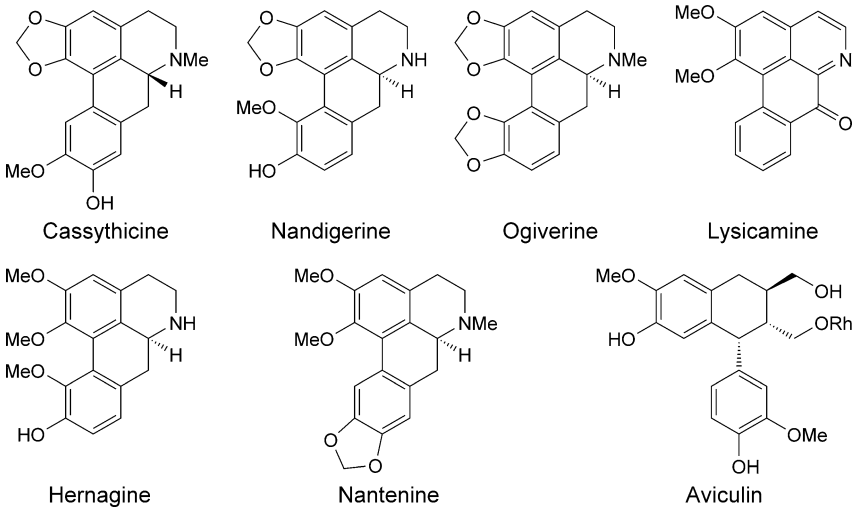


Fig. 6. *Examples of alkaloids isolated from Hernandiaceae*

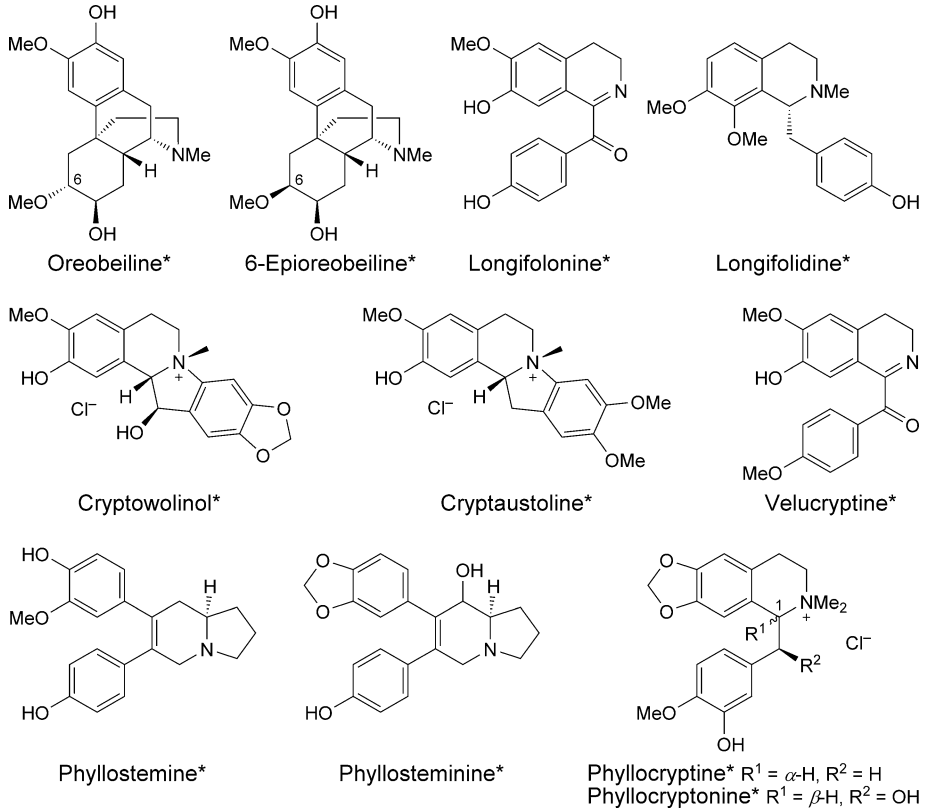


Fig. 7. *Original alkaloids isolated from Lauraceae*

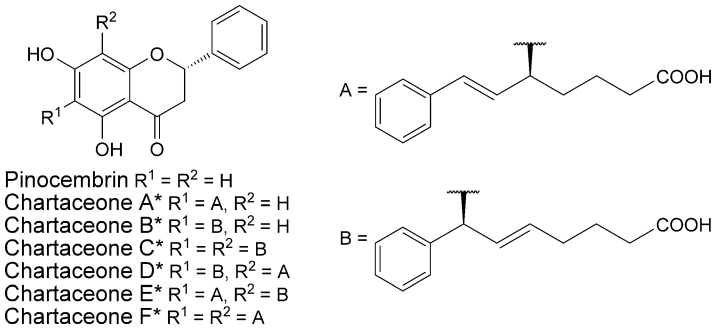


Fig. 8. *Original flavonoids isolated from* C. chartacea

A*–F* (see *Fig. 8*). Chartaceones C*–F* show strong inhibitory activities on the dengue virus RNA polymerase, with IC_{50} values ranging from 1.8 to 4.2 μM, and thus could lead to the discovery of a new antiviral drug [40].

Cryptocarya longifolia, *Cryptocarya odorata*, and *Cryptocarya oubatchensis* contain many isoquinoline alkaloids, such as antofine, laurotetanine, and laurolitsine, and original structures, such as longifolidine* and longifolonine* (see *Fig. 7*), which were isolated from *C. longifolia* [18]. Thus, *C. oubatchensis* contains two original *seco*-dibenzopyrrocoline alkaloids called cryptowolinol* and cryptaustoline* (see *Fig. 7*). *Cryptocarya phyllostemon* also was characterized by the presence of cryptowoline*, phyllostemine*, phyllosteminine*, phyllosterone, phyllocryptine*, and phyllocryptonine* (see *Fig. 7*) [18]. Velucryptine* (see *Fig. 7*) was isolated from *Cryptocarya velutinosa* [18]. The cytotoxic activities of some of these compounds were evaluated against KB cells and revealed a significant anticancer potential of antofine derivatives, which displayed IC_{50} values ranging from 1 to 6.3 nM [18][41]. Otherwise, essential oil obtained from the wood of *Cryptocarya odorata* was also studied and was characterized by the presence of uncommon α-pyrone derivatives, such as 6-heptyl-5,6-dihydro-2*H*-pyran-2-one [18].

Two of the 14 endemic *Litsea* species were also investigated. Aporphinoid alkaloids, tetrahydroisoquinoline, and an orphinane dienone alkaloid were isolated from the leaves of *Litsea lecardii.* Corydine, glaucine, and *N*-methylcoclaurine were isolated from the leaves of *Litsea triflora* and were later found in other plant families as well [18]. Other endemic Lauraceae have not been investigated yet. Moreover, an extended evaluation of bioactivities of

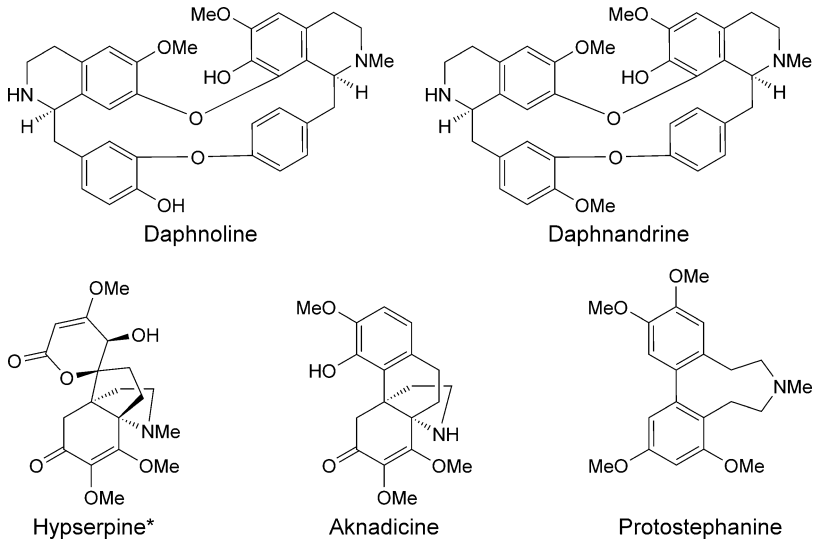


Fig. 9. *Typical alkaloids encountered in Menispermaceae*

these plants may lead to the discovery of new natural drugs in view of the alkaloidal content of these plants. Also, some species are highly aromatic and should be studied for cosmetic perspectives.

Menispermaceae. Menispermaceae are represented in New Caledonia by seven species (five endemic) and are divided into four genera. Among the endemic species, only *Pachygone loyaltiensis* (ex *Pachygone vieillardii*) has been investigated. This plant is described as purgative in Melanesian traditional pharmacopoeia. It is characterized by dimeric alkaloids, such as daphnoline and daphnandrine (see *Fig. 9*), together with other alkaloids that have not been identified yet [18]. Otherwise, an original alkaloid called hypserpine* (see *Fig. 9*) was isolated from the bark of *Hypserpa neocaledonica*. Finally, the chemistry of *Stephania japonica* has been investigated, mostly for alkaloids of different groups (*e.g.*, aknadicine and protostephanine which are shown in *Fig. 9*) and for several bioactivities, such as antimicrobial and multidrug resistance reversing activities [42].

Monimiaceae. This family is represented in New Caledonia by ten endemic species: *Kibaropsis caledonica*, the only member of this genus, and nine *Hedycarya* species. Other members of this family are known to contain essential oil and various original and/or bioactive chemicals, such as alkaloids and butanolides [43]. In New Caledonia, only *Hedycarya baudouinii* was investigated by phytochemists. It contains a wide range of alkaloids, including isoquinoline, pavine, and aporphine derivatives including the original compound hedycarine* which is shown in *Fig. 10* [18]. Other Monimiaceae should be investigated, at least for their alkaloidal content and to search for new bioactive compounds.

Monocots. Among all studies on monocots (more than 500 species and 48% endemism) we could not find any publication dealing with the chemistry of an endemic species from New Caledonia. Indeed, the chemistry of *Appendicula reflexa*, a native Orchidaceae, has been

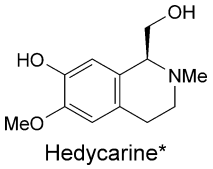


Fig. 10. *Original alkaloid isolated from* H. baudouini

investigated recently due to its anticancer potential [44]. A bioguided fractionation of this plant extract was performed to find new compounds with anticancer or antineurodegenerative potential. This study led to the isolation of six phenanthrene derivatives, including two novel derivatives, namely 2,3,5,6-tetramethoxyphenanthrene-1,7-diol and blestrin E (see *Fig. 11*). The most active compounds, 2,3,5,6-tetramethoxyphenanthrene-1,7-diol and 3,4,6-trimethoxyphenanthrene-2,7-diol (see *Fig. 11*), exhibited IC_{50} values of 0.07 and 0.2 μM on CDK1/cyclin B, respectively [44]. Orchidaceae comprises more than 200 species and half of them are endemic to New Caledonia. All of these plants are strictly protected and their chemical investigation should be associated with horticultural multiplication to be considered.

Proteaceae. Proteaceae is an important tropical and subtropical family. It contains *ca.* 2000 species that are mostly concentrated in the southern hemisphere. In New Caledonia, it is represented by 43 endemic species, classified into nine genera. Only few species have been investigated for their chemical content or economical potential. Eleven original tropane alkaloids were isolated from leaves of *Eucarpha strobilina* (ex *Knightia strobilina*): acetylknightinol*, strobiline*, dihydrostrobiline*, knightoline*, knightinol*, 3α-(cinnamoyloxy)tropan-6-ol*, 6β-(benzoyloxy)-3α-hydroxytropane (also found in *Erythroxylum* spp.), strobamine*, chalcostrobamine*, strobolamine*, knightalbinol*, and knightolamine* [13][45]. Two examples of these structures are given in *Fig. 12*.

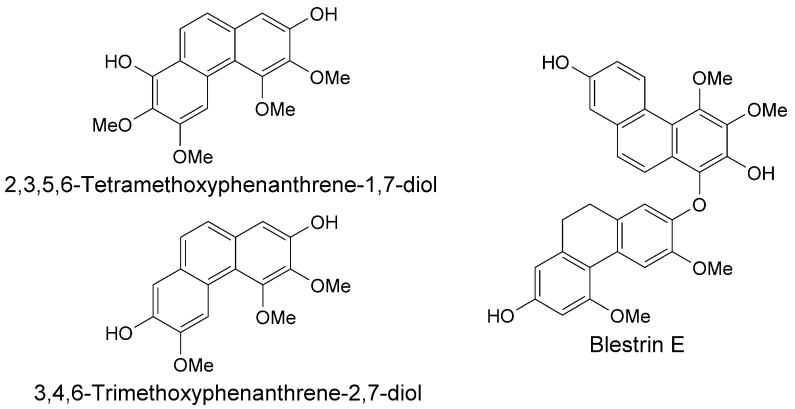


Fig. 11. *Original and bioactive phenanthrene derivatives encountered in a native Orchidaceae species*

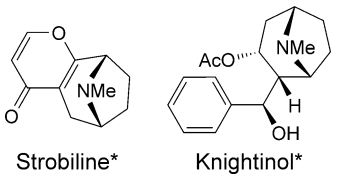


Fig. 12. *Typical original tropane alkaloids encountered in endemic Proteaceae*

Other related original tropane alkaloids were also isolated from leaves of *Eucarpha deplanchei* (ex *Knightia deplanchei*): 2-benzyltropane-3,6-diol*, *O*-acetyl-2-benzyltropanol*, 3-*O*-benzoyl-2-benzyltropanol*, 6-(benzoyloxy)-2-(hydroxybenzyl)tropan-3-ol*, and 6-(benzoyloxy)-3-(cinnamoyloxy)-2-(hydroxybenzyl)tropane* [18]. Original cyclophanes from the turriane group were isolated from *Kermadecia elliptica:* kermadecins A*–H* [46]. Kermadecins I* and J* and isokermadecins D* and F* were isolated from the bark of *Kermadecia rotundifolia* [47]. Kermadecins A* and B* (see *Fig. 13*) showed significant anticancer activities against L1210 and KB cells [46], while kermadecins D* and F* and isokermadecin D* (see *Fig. 13*) possess significant inhibitory effects on acetylcholinesterase [47].

Other members of this family, such as from the endemic genera *Beaupreopsis*, *Garnieria*, *Sleumerodendron*, and *Virotia*, are still untouched. Recently, fatty acids from seeds of *Grevillea exul* var. *rubiginosa* and *Alphitonia neocaledonica* (Rhamnaceae) have been investigated. They are characterized by a high percentage of unsaturated fatty acids and are even considered by the authors as a promising source of *ω*-5-monoenes that are uncommon in the plant kingdom [48]. As shown in this article, the investigation of the nutritive potential of seeds is also an original axis for the research of economical valorization of the New Caledonian flora. It could be extended to other families. Finally, *Grevillea* spp., *Beauprea* spp., *Virotia* spp., and *Stenocarpus milnei* are under investigation by Stratoz SAS and local research centers for their content of manganese binders with industrial application in catalysis for green chemistry. These investigations are closely associated with *revegetalization* programs of damaged sites after mining.

Winteraceae. Zygogynum is the only genus of this family that is present in New Caledonia. It comprises 31 endemic species. *Sévenet* and *Pusset* revealed the uncommon alkaloidal content of *Zygogynum pauciflorum* [18]. They isolated the original alkaloids called bubbialine* and

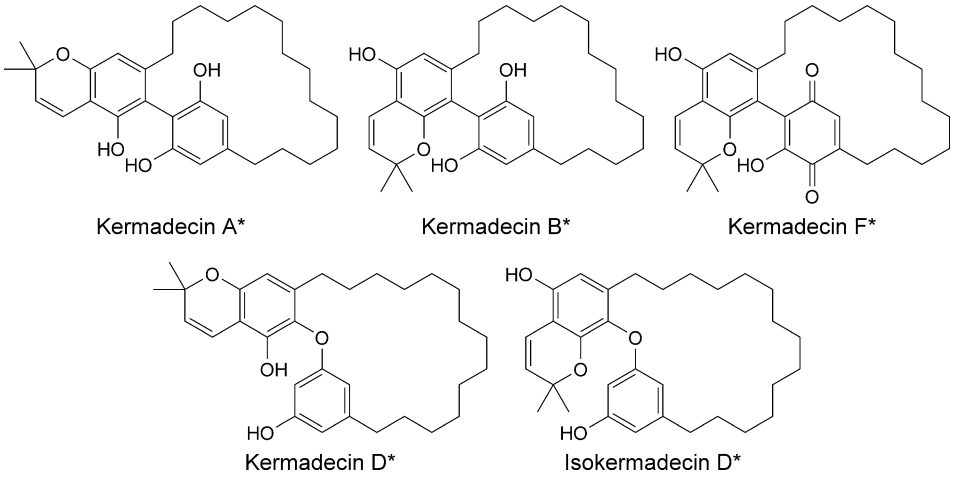


Fig. 13. *Examples of bioactive original cyclophanes isolated from* Kermadecia *spp.*

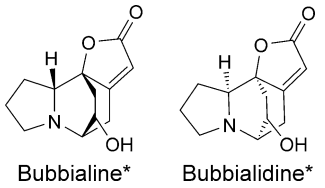


Fig. 14. *Original alkaloids isolated from Winteraceae*

bubbialidine* (see *Fig. 14*) which are structurally related to nor-securinine, a compound that was previously isolated from Euphorbiaceae.

Other phytochemical studies led to the isolation of four original and bioactive tetralones, namely zygolone A*, 4′-*O*-methylzygolone A*, 3′-deoxyzygolone A*, and isozygolone A* (see *Fig. 15*), from *Zygogynum stipitatum*, *Zygogynum pancheri*, *Zygogynum acsmithii*, and *Zygogynum baillonii* [49]. These compounds expressed potent binding activities on peroxisome proliferator-activated receptor-γ and thus could be potentially used for treatment of diabetes. Tetralones also showed cytotoxic activities against KB cancer cells with IC_{50} values ranging from 1.4 to 6.5 μM [49].

In a second study, *Allouche et al.* isolated three additional original butanolides, (3*S*,4*R*,5*S*)-3-[(7*Z*)-hexadec-7-en-1-yl]dihydro-4-hydroxy-5-methylfuran-2(3*H*)-one (**1**), methyl (2*S*,9*Z*)-2-[(1*R*)-1-hydroxy-2-oxopropyl]octadec-9-enoate (**2**), 3-[(7*Z*)-hexadec-7-en-1-yl]-4-hydroxy-5-methoxy-5-methylfuran-2(5*H*)-one (**3**), which are shown in *Fig. 16*, together with twelve drimane sesquiterpenes (six new structures including the two examples shown in *Fig. 17*) from *Z. pancheri* and *Z. acsmithii* [50]. Two original drimanes, namely isodrimanial* and 1β-{[(*E*)-4-methoxycinnamoyl]oxy}bemadienolide* (*Fig. 17*) were also isolated from the bark of *Z. baillonii* [51].

Drimanes endowed with a dialdehyde functionality, such as isodrimanial* that is shown in *Fig. 17*, showed potent cytotoxic activities against KB, HL60, and HCT116 cancer cells (IC_{50} values *ca.* 1 μM) [51].

Eudicot Rosids. *Fabiids. Calophyllaceae.* This family consists of four species in New Caledonia, half of them being endemic, and comprises two genera. Pantropical *Calophyllum inophyllum* (tamanou) has been widely studied, especially for the oil obtained from its seeds which proved to be vulnerary and cicatrizing. Calophyllolide, inophyllum, and other complex polyphenols are considered as responsible for such effects [52]. Moreover, inophyllums showed inhibition of HIV-1 reverse transcriptase *in cellulo*, with IC_{50} values ranging from 1.4 to 1.6 μM [53].

Otherwise, *Calophyllum caledonicum* contains characteristic calolongic acid and caledonic acid* together with twelve original xanthones, such as caledonixanthones A*–M* (see *Fig. 18*) [54–56]. The latter compounds displayed

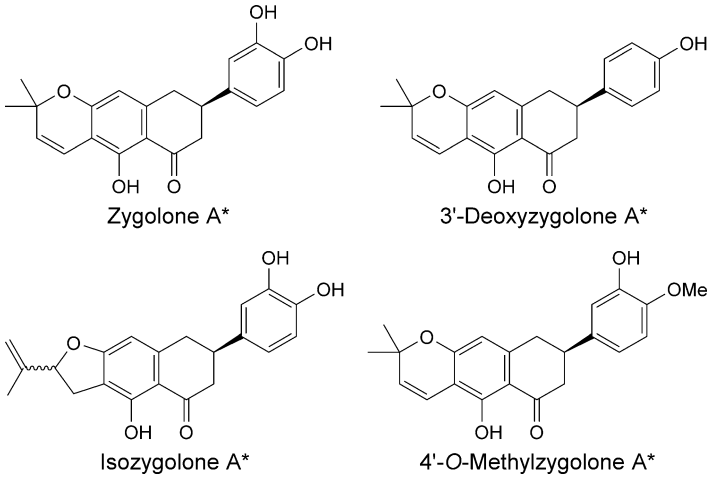


Fig. 15. *Original zygolone derivatives identified in Winteraceae*

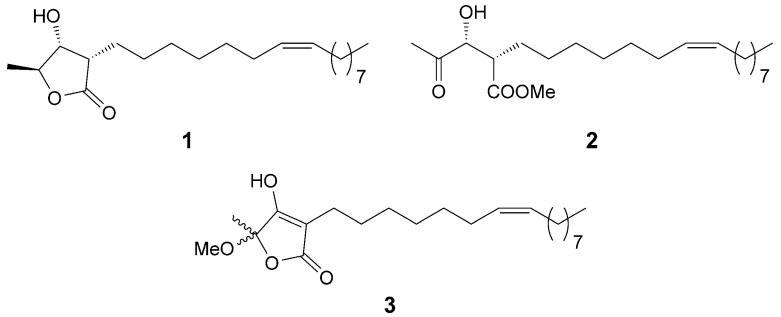


Fig. 16. *Original butanolide derivatives identified in Winteraceae*

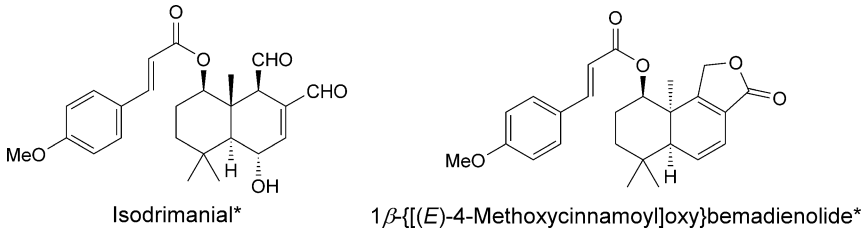


Fig. 17. *Original bioactive drimane sesquiterpenes isolated from Winteraceae*

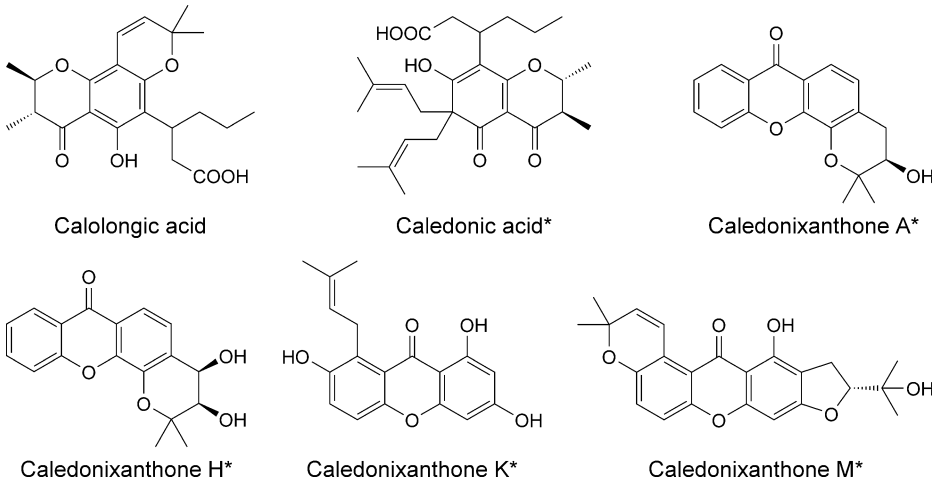


Fig. 18. *Examples of acids and original xanthones encountered in Calophyllaceae*

antifungal and antimalarial activities [56][57]. It could be also interesting to investigate the coumarin content of endemic Calophyllaceae, since they have been previously identified in this family and are frequently described to exhibit pharmacological and cosmetic potential [58][59].

Celastraceae. This family is represented by 24 species, including 21 endemics, and comprises seven genera (including three endemics). Despite the originality of New Caledonian Celastraceae, only two endemic species have been investigated for their alkaloidal content yet. *Peripterygia marginata* contains original cinnamoylspermidine derivatives (namely periphylline*, dihydroperiphylline*, isoperiphylline*, and neoperiphylline*) and *Dicarpellum pronyensis* contains α-aminoalcohols together with uncommon linear sympathomimetic alkaloids called dicarprines A*–C* [18]. Examples of these structures are presented in *Fig. 19*.

Also, *Celastrus paniculatus*, a traditional ayurvedic medicinal plant used because of its various neuroactive properties (*e.g.*, memory enhancing, analgesic, and sedative properties) has been studied, especially with regard to its oil content [60]. Most of the New Caledonian members of this family remain totally unexplored. In view of the results obtains previously, Celastraceae represent an attractive group for the discovery of new bioactive compounds.

Clusiaceae (ex Guttiferae). This family is represented in New Caledonia by 20 species and is divided into two genera (*Garcinia* and the endemic genus *Montrouziera*). Some Clusiaceae are majestic trees, such as *Montrouziera cauliflora*, and can be used for joinery work. From a chemical point of view, four of the 14 endemic *Garcinia* species were shown to contain xanthones that are related to various biological activities, such as antimalarial and antileishmanial activities [56][60–64]. Examples of original and bioactive xanthones are given in *Fig. 20*.

Five new depsidones (garcinisidones B*–F*) were isolated from *Garcinia neglecta* and *Garcinia puat* (var. *puat*). These compounds expressed antiviral activities against the *Epstein–Barr* virus and potential for cancer chemoprevention [61]. *Garcinia vieillardii* also contained numerous xanthones, such as pancixanthones A and B, isocudraniaxanthones A and B, original vieillardiixan-

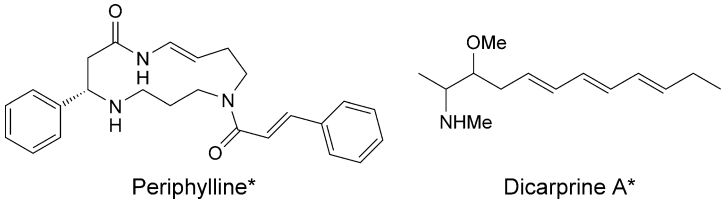


Fig. 19. *Original and unusual alkaloids encountered in Celastraceae*

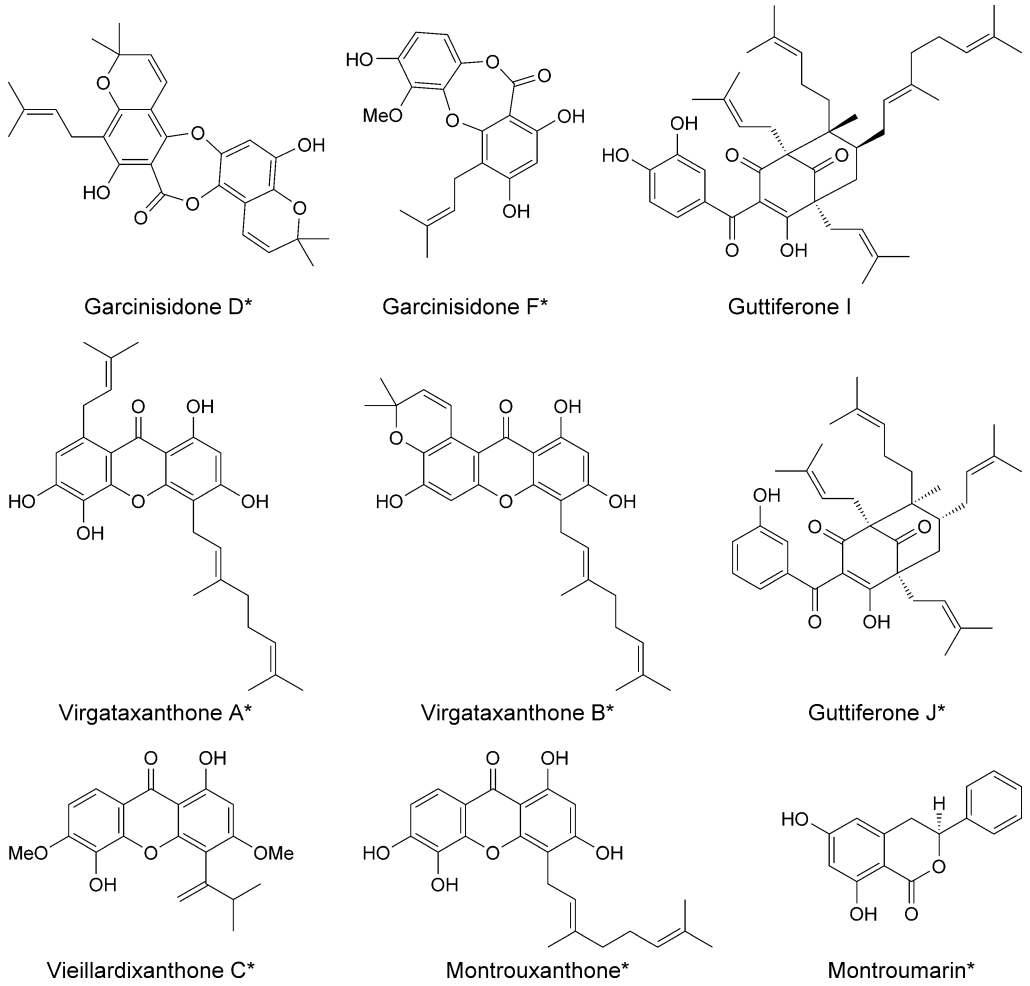


Fig. 20. *Examples of original xanthones isolated from* Garcinia *spp.*

thones A*–C* (see *Fig. 20*), and 5,6-di-*O*-methyl-2-deprenylrheediaxanthone*, together with two benzophenones, namely clusiachromene and 3-geranyl-2,4,6-trihydroxybenzophenone [57][62][63].

Garcinia virgata, which has been studied out of cosmetic interest, contains various xanthones, including the novel virgataxanthones A* and B* and the cytotoxic anti-KB guttiferones I and J* (see *Fig. 20*). It also produces original formylated tocotrienols* (see *Fig. 21*), together with *β*- and *δ*-tocotrienol, and benzophenones, such as cotoin [64][65]. Another study focused on tocotrienol derivatives from *Garcinia amplexicaulis* and confirmed the great interest in this genus from cosmetic perspectives due to antiangiogenic activity [66]. Finally, a new xanthone called montrouxanthone* and a dihydroisocoumarin, montroumarin* (see *Fig. 20*), along with the two known compounds 1,3,5-trihydroxy-4-(3,7-dimethylocta-2,6-dien-1-yl)-9*H*-xanthen-9-one and kaerophyllin, were isolated from *Montrouziera sphaeroidea* [67]. Other *Montrouziera* species have not been investigated yet.

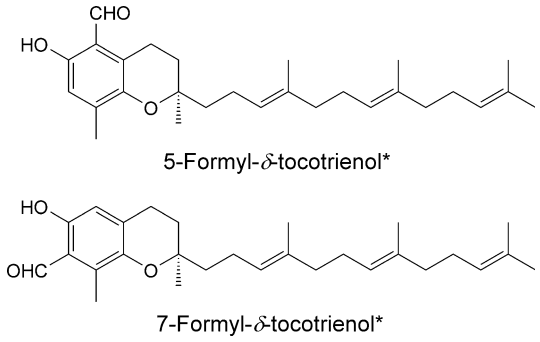


Fig. 21. *Original and bioactive tocotrienol derivatives isolated from Clusiaceae*

Cunoniaceae. Despite the wide diversity and originality of the Cunoniaceae in New Caledonia, only little is known about the chemistry of these plants. This family is represented by 90 species, all being endemic, and comprises four genera (including two endemic genera: *Codia* and *Pancheria*). *Fogliani* and co-workers studied various biological activities of 50 Cunoniaceae crude extracts, such as antimicrobial, anti-inflammatory, or antidiabetical activities, searching for inhibitors of xanthine oxidase and scavengers of superoxide anions. They demonstrated the presence of ellagitannins (ellagic acid 4-*O*-*β*-D-xylopyranoside, mallorepanin, and mallotinic acid along with corilagin, chebulagic acid, ellagic acid, and gallic acid) with anti-

microbial activity in *Cunonia macrophylla* [68–70]. Further investigations are necessary to find out whether the local unusual botanical diversity of this group (30% of Cunoniaceae species being endemic to New Caledonia) is related to an original chemical composition.

Euphorbiaceae. This family is highly represented in New Caledonia: 19 genera that consist of 72 species (58 endemics). Other Euphorbiaceae are also of high economic importance throughout the world. Indeed, their chemical investigation led to the discovery of many active compounds and several of them, such as prostratin and jatrophane, are now commercialized as drugs [71]. To assess their important pharmacological potential, we should mention that Euphorbiaceae species are often cited by traditional healers in New Caledonia as in other countries [24].

However, only few species were chemically investigated: the genus *Croton* is frequently described in the literature as a rich source of biologically active compounds, such as compounds showing antiulcer, antitumor, and cocarcinogenic activities. In New Caledonia, this genus is represented by two species, and one of them has been investigated. Several original diterpenes, including the new trachylobanes crotinsularin and crotinsulactone, and the new clerodane-type terpenoids furocrotinsulolides A and B, and a new phenolic disaccharide (3,4-dimethoxyphenyl rutinoside) were isolated from the non-endemic species *Croton insularis* [72]. The structures are shown in *Fig. 22*. Also, *Macaranga vedeliana* has been studied by ethnopharmacologists. This plant is used by traditional Kanak healers to relieve pain and cure tonsillitis. Chemical investigations of the leaves of *M. vedeliana* led to the discovery of macarangin, a geranyl-substituted flavonol, and vedelianine, a hexahydroxanthene derivative, that have been found later in other *Macaranga* spp. [73][74]. Other pantropical species have been studied, for example *Excoecaria agallocha*, which contains numerous original terpenoids, such as *seco*-labdane diterpenes of the excoecarin series and phorbol esters (*e.g.*, [75] and [76]). Otherwise, the bioguided fractionation of bark extracts from *Trigonostemon cherrieri* led to the isolation of antiviral O-bearing daphnane diterpenoid orthoesters with an uncommon chlorinated moiety: trigocherrins A*–F* and trigocherriolides A*–D* [77][78]. Examples of these compounds are presented in *Fig. 22*. These results confirm the interest in terpenoids from Euphorbiaceae, especially for the search of antiviral compounds [71]. Other species, such as *Homalanthus* spp., that are described in the traditional Kanak pharmacopoeia proved to be active in preliminary biological screening and should be subjected to further investigations.

Chemical investigations of Euphorbiaceae can also be oriented toward other goals. *Codiaeum peltatum* and *Fontainea pancheri* are known to be strongly refused by herbivorous animals. A chemical investigation of *F. pancheri* led to the identification of a new guanidine-type

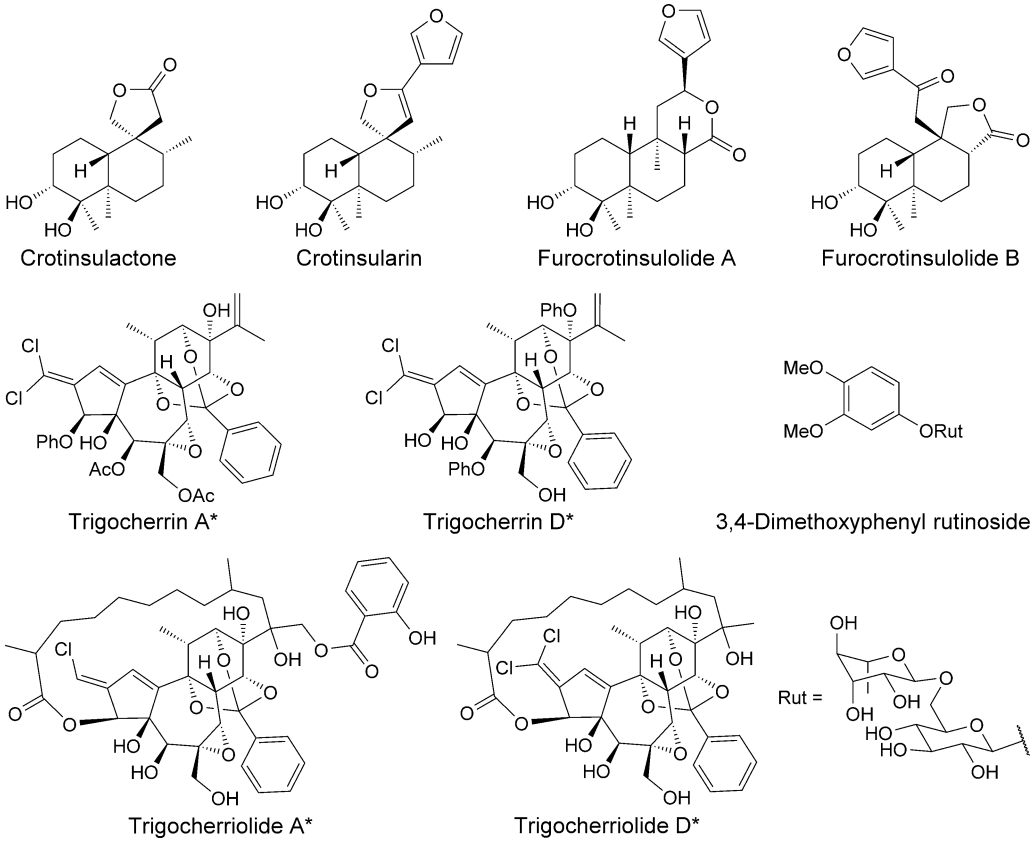
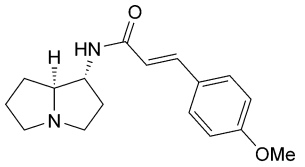


Fig. 22. *Examples of significant bioactive and original terpenoids encountered in Euphorbiaceae*

alkaloid: fontaineine [79]. This indication may lead to the discovery of other interesting toxic compounds in *C. peltatum*. The family Euphorbiaceae also contains aromatic plants which could be investigated for potential use in perfumery (*e.g.*, flowers of *Baloghia* spp.). *Cocconerion balansae*, famous in New Caledonia for its bloody sap, may contain flavonoids or coumarins but no scientific publication is available concerning this plant. We are convinced that this group should be further investigated due to cosmetic and pharmacological potential.

Linaceae. This family is represented in New Caledonia by six *Hugonia* species, all but one being endemic. Absouline*, an original alkaloid presented in *Fig. 23*, and four other pyrrolizidin alkaloids were isolated from *Hugonia oreogena* and *Hugonia penicillanthemum* [18]. Pyrrolizidin alkaloids might be synthetized by plants to protect themselves against herbivores and were frequently reported to be responsible for plant toxicity [80].

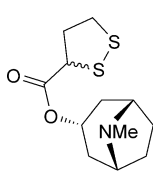


Absouline*

Fig. 23. *Original alkaloid found in* Hugonia *spp.*

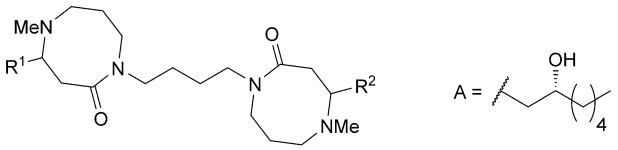
Rhizophoraceae. Rhizophoraceae is represented in New Caledonia by twelve species (five endemic) and is divided into four genera. These plants comprise the mangroves and thus, are restricted to an extreme environment. The particular edaphic conditions related to Rhizophoraceae could also affect their chemical composition. Among the five endemic species that are listed in New Caledonia, three of them belong to the genus *Crossostylis: Crossostylis biflora*, *Crossostylis multiflora*, and *Crossostylis sebertii*. Each of them contains alkaloids, such as hygrine and tropanol derivatives, including the uncommon disulfurated brugine (see *Fig. 24*), an alkaloid that has been found only in Rhizophoraceae [18]. To the best of our knowledge, no other species have been investigated regarding their chemical content.

Salicaceae (ex Flacourtiaceae). Salicaceae are represented in New Caledonia by 56 species, all but one being endemic, and are divided into four genera. *Homalium* encompasses 18 species and one of them, *Homalium guillainii* (ex *Homalium pronyense*), has been studied. Four alkaloids with a macrocyclic spermidine structure



Brugine

Fig. 24. *Original sulfurated tropane alkaloid found in Rhizophoraceae*



Homaline $R^1 = R^2 = \beta$-Ph
Hopromine* $R^1 = \beta$-Me$(CH_2)_4$, $R^2 = \alpha$-Me$(CH_2)_6$
Hopromalinol* $R^1 = \beta$-Ph, $R^2 = \beta$-A
Hoprominol* $R^1 = \beta$-Me$(CH_2)_4$, $R^2 = \beta$-A

Fig. 25. *Alkaloids isolated from Salicaceae*

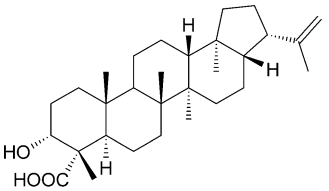
were isolated from the leaves of this plant (see structures in *Fig. 25*): homaline, hopromine*, hopromalinol*, and hoprominol* [18].

Other members of this family may contain original and/or bioactive compounds. We think that this group should receive more attention from phytochemists, especially the endemic *Lasiochlamys* genus that contains eleven species. *Casearia silvana*, *Lasiochlamys peltata*, and *Xylosma vincentii* were studied for their Ni content [81]; these species synthetize special binders of Ni, such as a citrate-complex form [82]. These organometallic complexes are of high interest since they are used to improve the yield and stereoselectivity of chemical synthesis [83].

Violaceae. This family is represented in New Caledonia by nine species, all being endemic, and is divided into two genera. Only one species was studied: *Hybanthus austrocaledonicus.* A new hopane-type triterpenoid, 3-epiwoodwardinic acid* (see *Fig. 26*) together with other previously isolated compounds, such as 24-methylidene cycloartenone, 24-methylidene cycloartenol, β-sitostanone, 21β-hydroxycaloncobalactone, and daucosterol, were isolated from the leaf extract of this plant [84].

Moreover, *H. austrocaledonicus* is known as hyper Ni-accumulating species and shown to contain several metabolites synthetized especially for heavy metal chelation [85].

Malvids. Meliaceae. This family is represented in New Caledonia by 13 species, including eight endemics, and is divided into four genera. Two *Dysoxylum* spp. have been studied and both contain bioactive terpenoids. *Dysoxylum macranthum* contains eleven original tirucallane-type triterpenes, dymacrins A*–K* (see examples in *Fig. 27*), together with two previously described tetracyclic triterpenes and two known pregnane steroids [86]. Dymacrins B*, C*, H*, and J* showed moderate cytotoxic activities against KB cells (IC_{50} values between 1 and 8.3 mg ml^{-1}). Five new apotirucallane derivatives, dysorones A*–E*,



3-Epiwoodwardinic acid*

Fig. 26. *Original hopane triterpene isolated from* H. austrocaledonicus

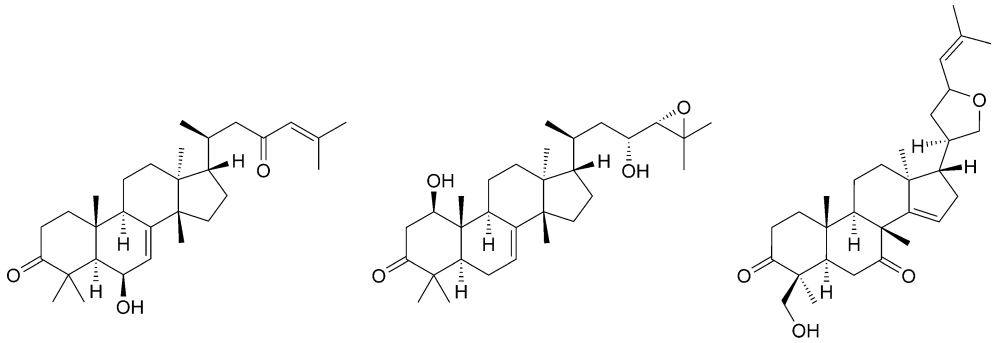


Fig. 27. *Examples of original bioactive triterpenes isolated from Meliaceae*

were isolated from the leaves of *Dysoxylum roseum* together with β-sitosterol. Dysorone E* (see *Fig. 27*), the major compound, exhibited anti KB activity (IC_{50} 3.5 μg ml^{-1}) [87]. Other *Dysoxylum* species may contain further original bioactive triterpenes.

Myrtaceae. This family is the most represented in New Caledonia. It contains 22 genera, including six endemics, and 257 species, only three being non-endemic: *Melaleuca quinquenervia*, *Sannantha virgata*, and *Syzygium malaccense*. Myrtaceae are often described in the literature for containing essential oils, terpenes, and flavonoids [88]. Despite the importance of this group, only a few species have been investigated yet. For example, we were unable to find any publication concerning the endemic *Syzygium* spp. although *Syzygium* is the third most important genus in New Caledonia (71 species).

Volatiles from several endemic species have been analyzed. Thus, the essential oils obtained from the leaves of all seven endemic *Melaleuca* species were analyzed. They were shown to contain high amounts of mono- and sesquiterpene hydrocarbons [89]. Essential oils from endemic species were significantly different from the one obtained from *M. quinquenervia* (niaouli) which is known to contain various sesquiterpene alcohols and to exhibit antimicrobial activity [90][91]. Essential oils obtained from three *Eugenia* species have also recently been analyzed for chemotaxonomical reasons [92]. Thus, *Eugenia gacognei*, *Eugenia horizontalis*, and *Eugenia noumeensis* were shown to contain acetophenone derivatives together with mono- and sesquiterpenes [92]. Finally, leaf essential oil from *Arillastrum gummiferum*, the only member of the endemic genus *Arillastrum*, has been investigated: it contains limonene (80%), other monoterpenes, such as α- and β-pinene, and caryophyllene was the major sesquiterpene [93]. We should notice that this tree is characteristic for some of the biotopes we can observe on serpentine soils, forming 'monospecific forests' in some cases. It has been extensively exploited in the past for carpentry, seeing its population highly reduced, and is now threatened by mining activities (see *www.oeil.nc*). This tree should be integrated into reforestation plans and a better knowledge of its chemistry could give supplementary reasons for that.

The chemistry of three *Tristaniopsis* species (*Tristaniopsis callobuxus*, *Tristaniopsis yateensis*, and *Tristaniopsis glauca*) is also described in the literature. They contain ellagic acid and another original tannin called 3,4,5-trimethoxyphenyl (6-*O*-galloyl)-β-D-glucopyranoside [94]. These plants demonstrated *in vitro* antiplasmodial activities. Ellagic acid and glycoside A3A were identified as antimalarial active compounds (IC_{50} 0.5 and 3.2 μM, resp.) and exhibited very low cytotoxic activities on human skin fibroblast cells and HepG2 [94][95]. Recently, bioguided fractionation of leaf extract from *Carpolepis laurifolia* for antiviral activity against DENV has led to the isolation of betulinic acid and five apigenin derivatives, including an unusual *C*-methylapigenin [96].

Other species may contain valuable chemicals, such as polyphenols with antioxidant or dying properties. Also, fruit chemistry seems to be interesting in this family since several species (*e.g.*, from *Eugenia* and *Syzygium* genera) produce aromatic and tasty fruits.

Rutaceae. This family is represented in New Caledonia by 86 species, including 77 endemics, and is divided into 22 genera. Rutaceae is widely known for its alkaloid-containing genera. More than 60 alkaloids were isolated from *Boronella*, *Melicope*, *Sarcomelicope*, *Myrtopsis*, *Geijera*, *Comptonella*, *Dutaillyea*, *Zanthoxylum*, or *Flindersia* species [18][97]. Some of these compounds, such as acronycine derivatives, showed potent antitumor activities. Some examples representing the diversity of the original structures found in New Caledonian species are presented in *Fig. 28*.

Alkaloids from Rutaceae are furoquinoline, acronydine, acronycine, acridone, or indole derivatives and therefore should be associated with many bioactivities. However, only few biological evaluations of these plants have been published. Otherwise, coumarins were isolated from several New Caledonian species: ramosin, myrsellin*, and myrsellinol* (see *Fig. 29*) were isolated from leaves of *Myrtopsis sellingii* and *Myrtopsis corymbosa* [18][98]. Other previously described coumarins are also represented in *Myrtopsis* spp., such as bergapten, phellopterin, seselin, and osthol, this class of compounds is showing cosmetic potential, such as for sun-protection [99]. These plants also contain unusual alkaloids such as myrtopsine and 8-

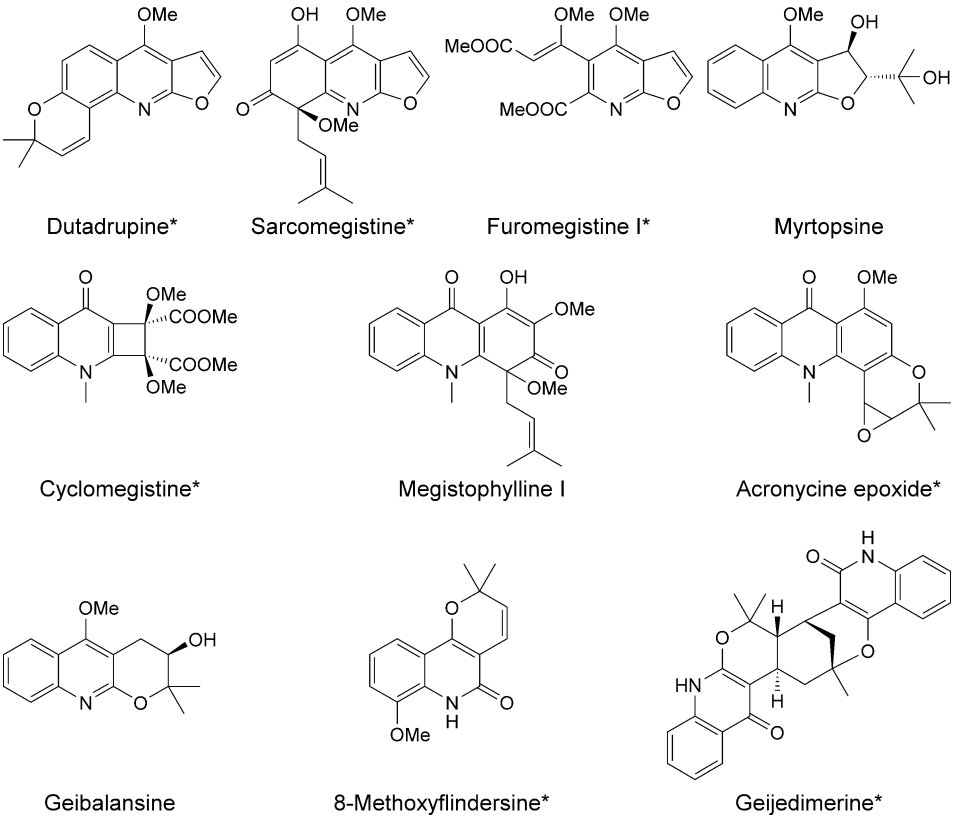


Fig. 28. *Examples for significative diversity of original alkaloids isolated from Rutaceae*

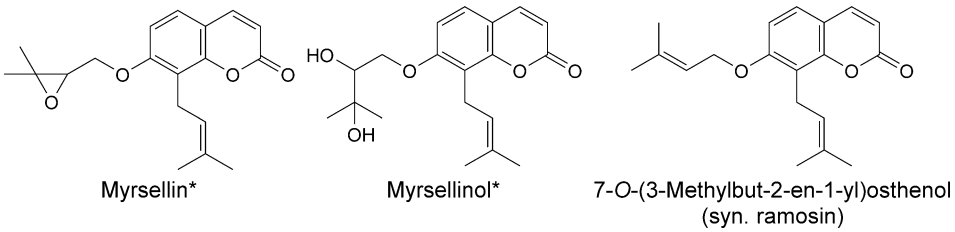


Fig. 29. *Original and unusual coumarins encountered in Rutaceae*

methoxyflindersine* (see *Fig. 28*), triterpenes, and sterols (lupeol and sitosterol) [18].

Despite the fact that Rutaceae express a high economical potential, these plants remain widely unexplored. Also, no investigation of the volatiles from any endemic species has been done yet, despite the fact that oil bodies beneath their leaves are characteristic for Rutaceae. Moreover, endemic Rutaceae are mostly represented on serpentine soils and should be further investigated to find new economic justifications for their integration into revegetalization programs after mining prospection and exploitation.

Sapindaceae. This family is represented in New Caledonia by 71 species, including 65 endemics, and is divided into 14 genera. Triterpenoid saponins and acylated prosapogenins were isolated from stem bark of *Harpullia austrocaledonica* [17][100]. Four original acylated farnesyl diglycosides called crenulatosides A*–D* (see one example in *Fig. 30*) were isolated from leaves of *Guioa crenulata* [101].

Otherwise, linear triterpenes called cupaniopsins A*–E* were isolated from barks of *Cupaniopsis azantha*, *Cupaniopsis phalacrocarpa*, and *Cupaniopsis trigonocarpa* and were evaluated for their activities against peroxisome proliferator-activated receptor-γ (PPAR-γ) [102]. The most potent compound, cupaniopsin A* (K_i 15 nM), is presented in *Fig. 30*. As *Guioa gracilis* extracts are used in cosmetics and pharmaceutical preparations for treatment of skin aging [103], *Guioa crenulata* and *Guioa villosa* were subjected to bioguided fractionation for tyrosinase inhibitory activity. This study led to the isolation of seven farnesyl diglycosides called crenulatosides A*–G* (see two examples in *Fig. 30*), flavonoids, one trimeric proanthocyanidin, two triterpenes, and a cerebroside called soyacerebroside I (see *Fig. 30*) which appeared to be a potent tyrosinase inhibitor [104].

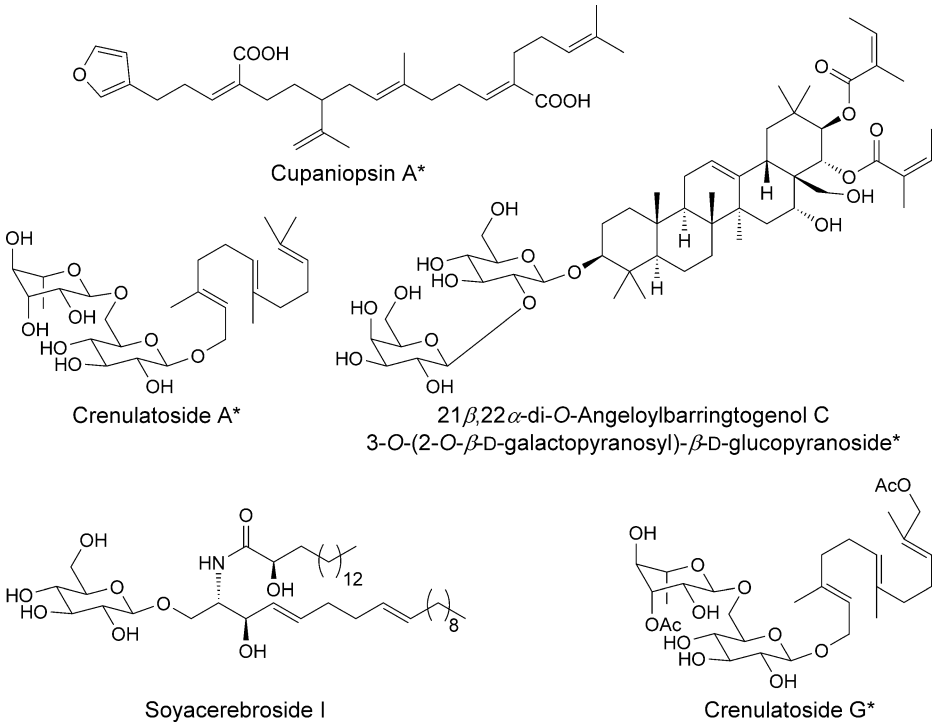


Fig. 30. *Examples of original and bioactive sesquiterpene and triterpene derivatives isolated from Sapindaceae*

Simaroubaceae. Simaroubaceae are represented in New Caledonia by eleven endemic *Soulamea* species. According to the literature available on this family [105][106], the investigation of endemic *Soulamea* species led to the isolation of numerous quassinoids: picrasin B and 6-hydroxypicrasin B* from *Soulamea pancheri* [107], isobrucein A* and soulameolide (also found in *Quassia indica*) and antileukemic soularubinone* from *Soulamea tomentosa* [108 – 110], soulameanone*, 1,12-diacetylsoulameanone, and Δ^2-picrasin B* from *Soulamea muelleri* [111]. Finally, the study on *Soulamea fraxinifolia* led to the isolation of a coumarin (scopolerol), two alkaloids (1-(2-hydroxyethyl)-β-carboline*, and pavettine*), and quassinoids (including Δ^2-picrasin B* and isobrucein A*) [112]. Original compounds isolated from this family are presented in *Fig. 31.*

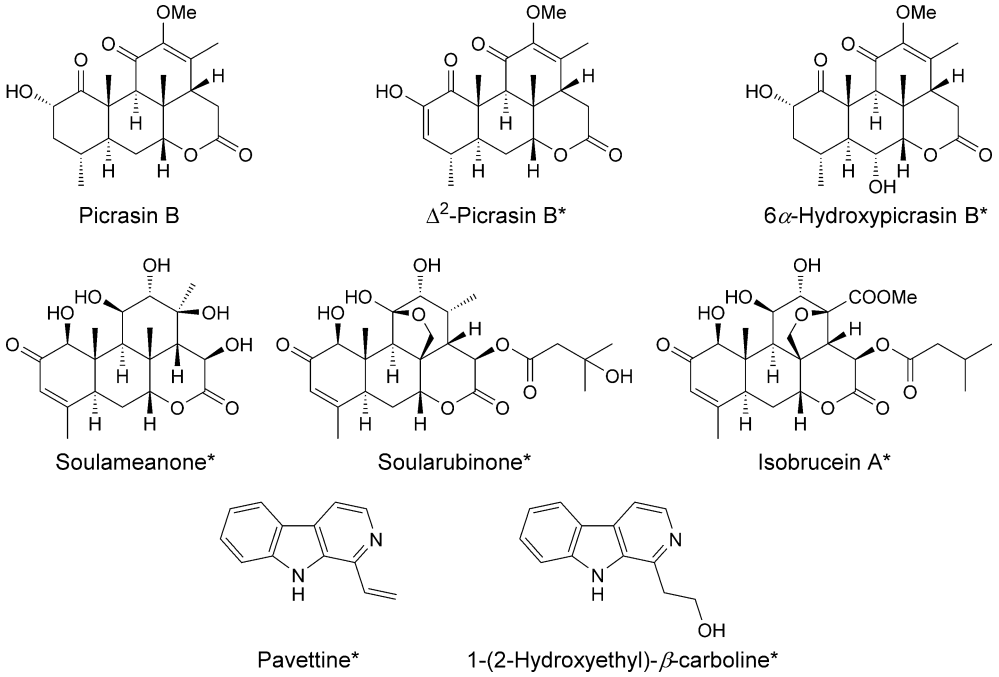
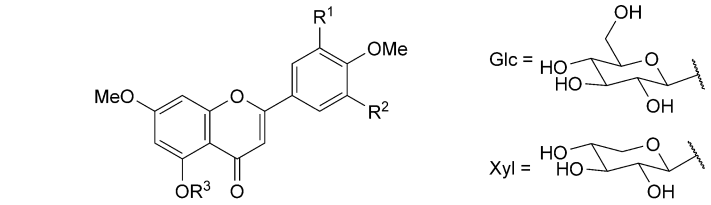


Fig. 31. *Original compounds isolated from Simaroubaceae*



Lethedocin* R^1 = MeO, R^2 = OH, R^3 = H
Lethedoside A* R^1 = H, R^2 = MeO, R^3 = Glc
Lethedoside B* R^1 = R^2 = MeO, R^3 = Glc
Lethedoside C* R^1 = MeO, R^2 = OH, R^3 = Glc
Lethedioside A* R^1 = H, R^2 = MeO, R^3 = Xyl-(1→6)-Glc–
Lethedioside B* R^1 = R^2 = MeO, R^3 = Xyl-(1→6)-Glc–

Fig. 32. *Original flavone derivatives isolated from* L. salicifolia

Strasburgeriaceae. This family is only represented by the endemic species *Strasburgeria robusta*. Three known saponins were isolated from the stem bark of this plant: 1-*O*-(24-hydroxytormentoyl) glucopyranoside and nigaichigosides F1 and F2 [113]. No biological test was associated with this study, but related saponins previously showed pharmacological activities and more generally, saponins are associated with various traditional and industrial applications, such as for fish poisoning and production of steroid hormones for the pharmaceutical industry [114]. Also, an improved knowledge of the chemistry of *S. robusta* could allow a better understanding of its isolated and ancestral position in the phylogenic tree (see *Fig. 1*).

Thymelaeaceae. This family is represented in New Caledonia by 19 species, all but one being endemic. New Caledonian Thymelaeaceae are divided into four genera, including the two endemic *Deltaria* and *Solmsia*. Only one endemic species was studied in New Caledonia: *Lethedon salicifolia* (ex *Lethedon tannensis*).

Investigation of a leaf extract from this plant led to isolation of several 5-hydroxy-7-methoxyflavones and glycoside derivatives, including original lethedosides A*–C*, lethediosides A* and B*, and lethedocin* (see structures in *Fig. 32*). These flavones showed cytotoxic activities against human nasopharynx carcinoma KB cells [115][116]. This family remains vastly unexplored, especially regarding the endemic genera *Deltaria* and *Solmsia* that are dedicated to serpentine soil and thus are especially threatened by mining activities and degradations.

Conclusions. – As shown in several recent review articles, natural products offer new perspectives for industrial innovations, such as for pharmaceutical or cosmetic applications. This renew of interest in natural compounds is both related to ecological preoccupations and to the great extent of tools available for phytochemical studies [117]. As an example, coupling possibilities offered by new chromatographic instruments, such as 2D-LC associated with HR-MS or NMR with high throughput screenings and modern informatics software, allowed the beginning of efficient complex mixture studies (metabolomics, synergies, *etc.*). We hope that this new economic interest in natural compounds will encourage the protection of particular original biotopes called 'hot spots' and of the New Caledonian flora.

This review compiles published data concerning the chemistry of New Caledonian basal angiosperms (14 families, 176 species including 160 endemics), monocots (29 families, 572 species including 276 endemics), and eudicot rosids (56 families, 1287 species including 1093 endemics). We focused on endemic species and present an update of original compounds that can be considered as specific to New Caledonian flora. We also highlighted economic perspectives for these natural compounds and endemic plants. Thus, this review compiles data provided by 60 articles dealing specifically with chemical investigations of endemic basal angiosperms and eudicot rosids and includes more than 60 previous articles also dedicated to these plants cited in a previous review by *Sévenet* and *Pusset*.

According to the bibliography we summarized here, we identified 225 original compounds that are specific to New Caledonian endemic species. Until now, phytochemical research mainly focused on alkaloids and terpenoids, leading to the discovery of 83 and 47 original structures, respectively[3]). This is clearly linked to the research of bioactive compounds for pharmaceutical applications. This review highlighted the economic potential of several plants, such as from Annonaceae, Clusiaceae, and Rutaceae families. In most cases, a lot of work remains to be done before industrial application. However, for some plants that contain heavy metal binders, the chemical synthesis of these compounds is studied, and they should be soon exploited for industrial utilization. This project is closely associated with revegetalization of serpentine soils and is a perfect example of the economic potential of the New Caledonian plant diversity. It illustrates the necessity to protect the New Caledonian flora and to pursue its chemical investigation.

Several families that proved to contain interesting and/or original compounds are still largely unexplored, for example Euphorbiaceae, Myrtaceae, and Celastraceae. Many groups have remained completely untouched despite the fact that several of them seem to be particularly attractive for phytochemical investigations. Though *A. trichopoda* is considered as the most basal flowering plant

[3]) Compounds are considered as originals when encountered only in a restricted number of endemic species stemming from a unique genus.

in the world, no chemical investigation of this plant has been performed yet. However, such an investigation could lead to interesting results for chemotaxonomy and plant evolution. Also, none of the endemic monocots has been investigated yet. Finally, Chloranthaceae (three endemic species), Piperaceae (15 species including eight endemics), Elaeocarpaceae (47 species including 44 endemics), Picrodendraceae (18 species including 17 endemics), and Phyllanthaceae (120 species including 113 endemics) which have not been investigated either, are, according to our opinion, prime targets for the search of original and bioactive compounds.

The authors are thankful to all researchers working for increasing the knowledge of New Caledonian plants and promoting their protection, to those we had the chance to work with and to the others that have inspired us. We express our special thanks to botanists and ecologists *T. Jaffré*, *J. Munzinger*, *P. Birnbaum*, *V. Hequet*, *T. Ibanez*, and *L. Barrabé* who helped us during this work. We are also grateful to *A. Fourney* and the reviewers who accepted to read and comment this manuscript.

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