



Pharmacognosy

A chemophenetic study of the genus *Maytenus s.l.* (Celastraceae): contribution to the rational search of its bioactive metabolites

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Abstract

Maytenus s.l. is a genus of the Celastraceae family and many of its species are used in traditional medicine. Most of the substances responsible for the biological activities of plants come from their secondary metabolism, such as terpenoids and flavonoids, which have multiple functions in the plant and can occur in a similar way in plant groups. Chemophenetics analyzes the occurrence of these substances in a taxon and can infer evolutionary trends and contribute to the rational search for new drugs. Chemosystematic parameters were used to analyze the data obtained through a bibliographic survey. The species of *Maytenus s.l.* were separated into three groups: species with accepted names, synonymous species with the genus *Monteverdia* and synonymous species with the genus *Gymnosporia*. Due to their great occurrence and structural variety in *Maytenus s.l.*, triterpenes were chosen as chemosystematic markers, with friedelanes and quinone methide triterpenes being the most expressive types. Studies have already demonstrated the analgesic potential of quinone methides and the antitumor potential of phenolic triterpenes and dimers of these units. Together, the three classes assist in the circumscription of *Maytenus s.s.* and *Monteverdia*, while lupanes can be used in the separation of these genera. Oleanans are representative of *Gymnosporia*.

Key words: chemosystematics, chemotaxonomy, phytochemistry, plant chemophenetics, quinone-methides, triterpenes.

Resumo

Maytenus s.l. é um gênero da família Celastraceae e muitas de suas espécies são utilizadas na medicina tradicional. Grande parte das substâncias responsáveis pelas atividades biológicas das plantas provém do seu metabolismo secundário, como terpenoides e flavonoides, que desempenham múltiplas funções na planta e podem ocorrer de forma semelhante em grupos vegetais. A quimiofenética analisa a ocorrência dessas substâncias em um táxon e pode inferir sobre tendências evolutivas e contribuir na busca racional por novos fármacos. Foram utilizados parâmetros quimiosistemáticos para análise dos dados encontrados através de levantamento bibliográfico. As espécies de *Maytenus s.l.* foram separadas em três grupos: espécies com nomes aceitos, espécies sinonimizadas com o gênero *Monteverdia* e espécies sinonimizadas com o gênero *Gymnosporia*. Devido à sua grande ocorrência e variedade estrutural nas espécies de *Maytenus s.l.*, os triterpenos foram escolhidos como marcadores quimiosistemáticos, sendo os triterpenos friedelanos e quinonametídeos os mais expressivos. Estudos já demonstraram o potencial analgésico de quinonametídeos e o potencial antitumoral de triterpenos fenólicos e dímeros dessas unidades. Juntas, as três classes auxiliam na circunscrição de *Maytenus s.s.* e *Monteverdia*, enquanto os lupanos podem ser utilizados na separação destes gêneros. Os oleananos são representativos em *Gymnosporia*.

Palavras-chave: quimiosistemática, quimiotaxonomia, fitoquímica, quimiofenética, quinonametídeos, triterpenos.

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Introduction

One of the oldest forms of treatment and prevention of diseases is the use of medicinal plants. Even today, this practice is very widespread, especially in places where access to medicine is more difficult. In developed countries, the search for a healthier life based on nature has increased the consumption and use of plants as a therapeutic alternative (Petrovska 2012; Palhares *et al.* 2015). In Brazil, the government encourages this use through the National Policy of Medicinal Plants and Herbal Medicines (“Política e Programa Nacional de Plantas Medicinais e Fitoterápicos”) approved by the Decree no 5.813, of 22 June 2006, which contributes to the development of methodologies and technologies for research and consequent increase in scientific knowledge on medicinal plants pharmacological properties (Brasil 2006).

Most of the bioactive substances in plants are derived from special (or secondary) metabolism. Genetic and environmental components influence the quantity and the quality of these metabolites, which act in the defense of the plant, in the attraction of pollinators and seed dispersers, as agents in plant-plant competition and in plant-microorganism symbioses (Andrade & Casali 1999). These multiple functions, typical of the special metabolites, are justified from the evolutionary point of view because when a characteristic can have multifunctionality, it is possible that it is maintained by natural selection (Wink 2003).

Plant systematics was initially based on morphological characters, with other parameters added over the years. Since special metabolites normally occur similarly in members of the same clade, their occurrence or absence may be indicative of the common origin, and hence of parentage (Wink 2003). Chemosystematics shows that chemistry and botany can be used in a complementary way in the study of plants. It is based on the existence of chemical gradients of affinity between plant groups and can be of great importance for the direction of phytochemical studies (Conde *et al.* 2010). In this field of science, plant chemophenetics recently arose as a new term to describe chemosystematic studies focused on exploiting the array of special metabolites in a given clade, contributing to the characterization of taxa, endorsement of established phylogenetic systems and the rational search for bioactive natural products (Zidorn 2019).

The genus *Maytenus s.l.* (including *Gymnosporia*) occurs in a wide variety of locations and many of its species are traditionally used for multiple medicinal purposes. In Brazil, the native species *Monteverdia ilicifolia* (Martius ex Reissek) Biral (accepted name of *Maytenus ilicifolia* Mart. ex Reiss.) (Biral *et al.* 2017) is popularly known as “espinheira-santa”, and extensively used in the treatment of several diseases, especially gastritis and dyspepsia (Santos-Oliveira *et al.* 2009).

The genus *Maytenus* belongs to the family Celastraceae and was first described by Feuillee (1725), however, the first valid description for the genus was only published by Molina in 1782. Although providing a detailed description, the author attributed characteristics that do not correspond to the genus. The errors were recognized by Molina, in 1810, when the author updated the circumscription of *Maytenus* (Carvalho-Okano 1992). Due to this failure, the genus was recognized by other authors and mistakenly new names were attributed to this taxon, such as *Haenkea* by Ruiz and Pavon (1784), *Celastrus* by Willdenow (1798), *Senecia* by Lamarck (1817), *Boaria* by De Candolle (1844) and *Tricerma*, by Liebmann (1853). *Maytenus s.l.* includes about 150 species (McKenna *et al.* 2011). In Brazil there are 49 species and their center of diversity is the Atlantic Forest (Lombardi *et al.* 2015).

Regarded as a polyphyletic genus in the broadest sense, *Maytenus* was composed by three independent lineages, from Africa, Austral-Pacific and New World (Simmons *et al.* 2008). The first one was transferred to *Gymnosporia*, the second to *Denhamia* and the third incorporated *Moya* and *Tricerma* to redefine a new circumscription of the genus comprehending only species from the New World (McKenna *et al.* 2011). The paraphyly of the New World *Maytenus* was then determined by the position of a clade composed by *Fraunhoferia* and *Plenckia* nested within it (Grosso *et al.* 2014). Recently, a new phylogenetic analysis conducted by Biral *et al.* (2017), based on molecular characters and fruit morphology using a large sampling of taxa, proposed the maintenance of *Fraunhoferia* and *Plenckia*, the reestablishment of *Tricerma* and the segregation of the other two lineages into two genera: *Maytenus*, containing the type of the genus name, and *Monteverdia*.

In this scenario that includes several circumscriptions changes and considering that the morphological characteristics usually present a constant pattern within the genus,

the chemophenetic study may be useful in the delimitation of the genus *Maytenus s.l.*. Also, in a group of species with diverse descriptions of medicinal use, the recognition of the distribution of its main chemical constituents can help to direct phytochemical research that leads to the isolation of its active constituents.

The objective of this study was to carry out a chemophenetic study of the genus *Maytenus* aiming to identify evolutionary trends and contribute to the rational search of their bioactive metabolites.

Material and Methods

Bibliographic survey

Using the keyword “*Maytenus*” in the online database “Science Direct”, articles were collected from 1965 to 2016. Articles that did not address the isolation, identification or characterization of substances were excluded from the bibliographic survey.

Election of chemical markers of the genus *Maytenus s.l.*

The data obtained from the bibliographic research were typed in the Microsoft Excel program, composing an organized database on the occurrence of chemical substances in *Maytenus s.l.* species. The chemosystematic markers were selected based on the occurrence and variety of chemical structures in the species studied (Santos *et al.* 2010).

Chemosystematic parameters

After obtaining data on the metabolic production of the genus *Maytenus s.l.*, different chemical parameters were calculated, such as the number of occurrences (NO), the number of types (NT), the diversity index (DI) and the oxidation index (OI) (Santos *et al.* 2010).

Results and Discussion

Using the Science Direct database, 117 articles were found containing information about *Maytenus* species, regarding isolation or identification of chemical metabolites. The data were tabulated considering works published between 1965 and 2016. According to this database, only 43 species of *Maytenus* were investigated chemically until 2016.

A total of 307 substances were found during the bibliographic survey, which were chemically classified, and the number of occurrences (NO) of

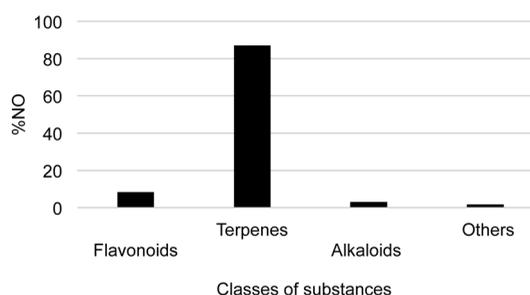


Figure 1 – Percentage of the number of occurrences (% NO) for the classes of substances described in literature for *Maytenus* species.

each group of substances was calculated showing a greater relevance for the occurrence of terpenes (NO = 417) within the genus *Maytenus* (Fig. 1).

The NO is a chemical parameter that indicates the degree of relevance of a particular class of substances to a taxon under study. The trend of production of a substance is observed by counting the number of times it is found in different species of the same taxon. The NO can also be expressed as a percentage (%NO).

After analysis 268 terpenes were identified, which were initially classified by the number of carbon atoms. The triterpenes showed the highest number of occurrences (NO = 322), followed by the agarofuran sesquiterpenes (NO = 89), characteristic of the Celastraceae family, and for which there are studies showing great biological potential with promising results in assays involving the evaluation of antitumor (Núñez *et al.* 2016), insecticide (González *et al.* 1993) and leishmanicidal activities (Delgado-Méndez *et al.* 2008). Figure 2 shows the distribution of terpenes in *Maytenus* based on the percentage of the number of occurrences.

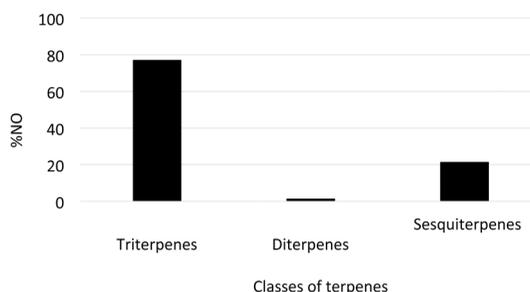


Figure 2 – Percentage of the number of occurrences (% NO) for groups of terpenes produced by species of *Maytenus* according to literature data.

In addition to their vast occurrence, the triterpenes identified in *Maytenus* also showed a great structural variety and were chosen as chemosystematic markers of the genus. The amount of different structural types of a given chemical class for a particular taxon can be expressed as the number of types (NT). According to their structural features, 11 types of triterpenes (NT = 11) were found in *Maytenus*, the most expressive being friedelanes (NO = 79) and quinone methides derivatives (NO = 69) (Fig. 3).

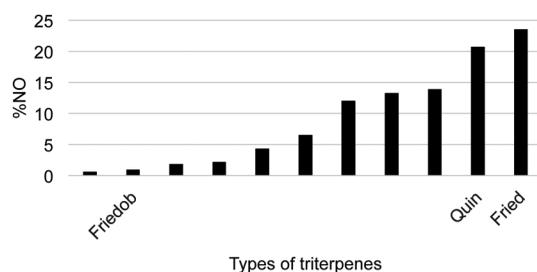


Figure 3 – Percentage of the number of occurrences (% NO) for types of triterpenes found in species of *Maytenus* in literature. Hop = hopanes; Friedob = D:B friedobaccharanes; Sec = secofriedelanes; Urs = ursanes; Dam = dammaranes; Ole = oleananes; Phe = phenolics; Lup = lupanes; Dim = dimers; Quin = quinone methides; Fri = friedelanes.

The diversity index (DI) for the triterpenes identified in *Maytenus* was 85, a value considered high (Santos *et al.* 2010). It represents another way to express the distribution frequency of a given chemical class and is calculated based on the NO and the NT. From the evolutionary point of view, according to Borin & Gottlieb (1993), the higher this index, the greater the probability of the taxon in question being a progenitor for other taxa, since it presents a great variety of structural types.

The compounds with the highest number of occurrences among the triterpenes were the quinone methides derivatives tingenone (NO = 17) and pristimerin (NO = 12) (Fig. 4a-b). These substances have attracted much attention due to their potential as anticancer agents, as well as other quinone methides from Celastraceae species (Gomes *et al.* 2011; Rodrigues *et al.* 2019). Tingenone also demonstrated antimicrobial (Mena-Rejón *et al.* 2007) and peripheral antinociceptive effect (Velo *et al.* 2017).

Friedelin was the friedelane triterpene with greater occurrence (NO = 11) (Fig. 4c). Studies demonstrated that this substance has several biological activities, such as antiulcerogenic (Mossi *et al.* 2004), antimicrobial (Kuethe *et al.* 2007), anti-inflammatory, analgesic and antipyretic (Antonisamy *et al.* 2011), hypolipidemic (Duraipandiyam *et al.* 2016) and cytotoxic potential (Subash-Babu *et al.* 2017). Besides its own biological properties, friedelin acts as a precursor of quinone methide triterpenes in Celastraceae. Corsino *et al.* (2000) demonstrated that friedelin is synthesized in the leaves of *Monteverdia aquifolia* (Mart.) Biral (Biral *et al.* 2017) and is transported to the roots where it is converted by oxidoreductases to tingenone and pristimerin (Souza-Moreira *et al.* 2016).

Phenolic triterpenes (NO = 39) are also characteristic of the genus *Maytenus* and are formed from the reduction of quinone methides derivatives (Rodríguez *et al.* 2005). 6-oxo-tingenol (NO = 4) (Fig. 4d) is a representative of these substances and had demonstrated potential cytotoxicity against tumor cells (Shirota *et al.* 1994).

The species of *Maytenus* used for the chemophenetic study were divided into three groups, according to the classification of the Tropicos database (Tropicos.org 2019): species with accepted names, species that are synonymous of others of the *Monteverdia* genus proposed by Biral *et al.* (2017) and species synonymous of the genus *Gymnosporia*. The distribution of triterpene types was analyzed in these three groups, considering the number of occurrences (Fig. 5).

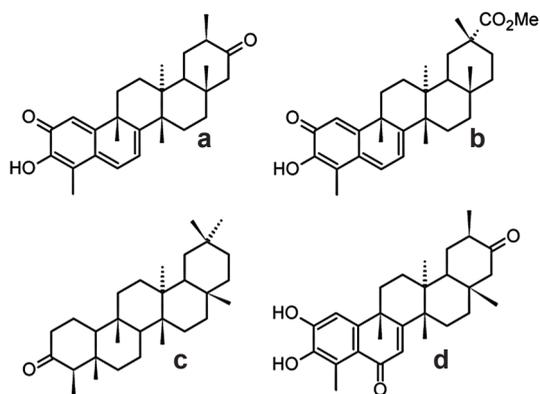


Figure 4 – a-d. Examples of triterpenes found in *Maytenus* species – a. tingenone; b. pristimerin; c. friedelin; d. 6-oxo-tingenol.

Interpreting Figure 5 it is possible to observe that, in relation to the types of triterpenes, there is a greater similarity between the group of species with accepted names and those whose names were synonymized with *Monteverdia*. This is more evident if we consider phenolic triterpenes, dimers and quinone methides, which are restricted to these two groups. It is noteworthy that 85% of the dimers found are formed by units of quinone methide triterpenes bound to phenolic triterpenes, and the others by two units of phenolic triterpenes, which corroborates the importance of these skeletons in the circumscription of *Maytenus* and *Monteverdia*. The species synonymized with *Gymnosporia* are characterized by a greater occurrence of oleananes and friedelane triterpenes. The lupane triterpenes, on the other hand, may be useful in the separation between *Maytenus* and *Monteverdia*, since their occurrence is much more expressive in the second group.

The oxidation index (OI) shows the level of oxidation of a substance. It was calculated for all triterpenes identified in this study and the

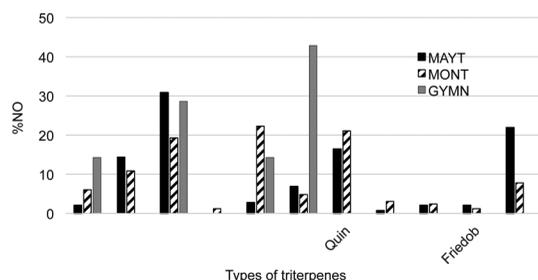


Figure 5 – Percentage of the number of occurrences of different types of triterpenes in three groups of *Maytenus*. MAYT = species with accepted names; MONT = *Monteverdia* synonyms; GYMN = *Gymnosporia* synonyms; Dam = dammaranes; Phe = phenolics; Fri = friedelanes; Hop = hopanes; Lup = lupanes; Ole = oleananes; Quin = quinone methides; Sec = secofriedelanes; Urs = ursanes; Friedob = D:B friedobaccharanes; Dim = dimers.

evolutionary index based on oxidation (EAo) was calculated for each group of triterpenes, showing that the triterpenes which represent a more derived characteristic in *Maytenus* are the quinone methides.

Oxidation reactions are evolutionarily important since the reactions that lead to most primary metabolites are mainly based on condensation and reduction and the pathways leading to the secondary metabolites, from these precursors, require oxidative steps. For this reason, most derived species are expected to produce substances with higher oxidation indexes than the basal ones (Gottlieb 1990).

By analyzing the evolutionary index concerning the oxidation in the three groups of plants, we find close values of EAo. However, when comparing the diversity indexes of triterpenes found in these groups, it is observed that the group of species with accepted names and the group of synonyms of the *Monteverdia* genus have a great diversity of triterpene structural types when compared to the group of species synonymized with *Gymnosporia*, characterizing a more derived character for this last group of species (Tab. 1).

Conclusions

The chemophenetic study of the genus *Maytenus s.l.* highlighted the occurrence of triterpenes, particularly triterpenes more oxidized such as the quinone methides, which drags much interest in terms of pharmacological potential. Due to its popular use in the treatment of gastric ulcers, the chemical studies in Brazil tend to focus on *Monteverdia ilicifolia*, but the chemophenetic analysis suggests the pharmacological potential of the genus as a whole and provides subsidies for new research with other species, reducing the overhead production in a single species.

The three groups of *Maytenus s.l.* presented different triterpene composition profiles. The

Table 1 - Diversity index (DI) and evolutionary index based on oxidation (EAo) for triterpenes from the three groups of *Maytenus*.

Chemosystematic parameters	Accepted names for <i>Maytenus</i>	<i>Monteverdia</i> synonyms	<i>Gymnosporia</i> synonyms
DI	89	83	38,5
EAo	-1,17	-1,24	-1,03

occurrence of quinone methides, phenolic derivatives and dimers of these triterpene units can assist in the circumscription of *Maytenus s.s.* and *Monteverdia*, while lupanes may be used in the separation of these groups, since its occurrence is more representative in *Monteverdia*. The oleananes are more representative in *Gymnosporia*. A difference was also observed regarding the diversity index of triterpenes, which was much lower in *Gymnosporia* than in the other two groups.

Acknowledgements

The authors are grateful to FAPERJ for fellowships (process numbers E-26/201,159/2016 and E-26/200,232/2017).

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Area Editor: Dr. Leopoldo Baratto

Received in June 30, 2019. Accepted in September 30, 2019.

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