UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS

Hypericeae e Vismieae: desvendando aspectos químicos e etnobotânicos de taxons de Hypericaceae

KRIPTSAN ABDON POLETTO DIEL

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Dissertação apresentada por **Kriptsan Abdon Poletto Diel** para obtenção do GRAU DE MESTRE em Ciências Farmacêuticas

Orientador(a): Profa. Dra. Gilsane Lino von Poser

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RESUMO

As espécies de Hypericaceae são distribuídas em três tribos bem sustentadas, que são Hypericeae, Cratoxyleae e Vismieae. No Brasil, esta família é representada por dois gêneros: *Hypericum* L. (tribo Hypericeae), com 24 espécies, a maioria distribuída no sul do país, e *Vismia* Vand. (tribo Vismieae), com 30 espécies de árvores ou arbustos que ocorrem principalmente na região amazônica. Neste trabalho foram desenvolvidos estudos com espécies das tribos Hypericeae, constituída apenas pelo gênero *Hypericum*, e Vismieae, que inclui os gêneros *Vismia*, *Psorospermum* e *Harungana*. No primeiro capítulo da presente dissertação relata-se o isolamento de derivados de floroglucinol e a análise qualitativa e quantitativa de flavonoides presentes em extratos obtidos de diferentes espécies do gênero, nativas do Brasil. O isolamento foi realizado a partir do extrato hexano das partes aéreas de *Hypericum pedersenii,* através de técnicas cromatográficas e, como eluente, solventes em polaridade crescente. As frações obtidas foram reunidas por semelhança utilizando a cromatografia de camada delgada. Os compostos foram submetidos a análises espectroscópicas e espectrométricas para identificação. Para a análise de flavonoides, as partes aéreas de diferentes espécies de *Hypericum* foram submetidas à maceração estática com hexano seguida de diclorometano, para remoção da fração lipofílica, seguida de acetato de etila, e metanol, por períodos de 24 horas até o esgotamento do material vegetal. Os extratos acetato de etila e metanol foram analisados por cromatografia líquida de alta eficiência, com duas fases móveis e gradiente de eluição. Ao comparar os tempos de retenção de picos padrão com aqueles de amostra, a identidade de pico de flavonoides foi atribuída. Como resultados, foi possível realizar o isolamento de um acilfloroglucinol dimérico, identificado através de técnicas de RMN, como hiperbrasilol B, presente em outras espécies do gênero. Este foi o primeiro relato da identificação para *H. pedersenii*, sendo uma nova fonte de obtenção deste composto. Em relação aos flavonoides, grande parte das espécies analisadas apresentaram hiperosídeo como o componente majoritário, o que já se observou também em diversas espécies de *Hypericum.* Importante salientar a ausência deste flavonoide em *H. teretiusculum.* O segundo capítulo apresenta uma revisão da literatura sobre espécies da tribo Vismieae. Essa tribo é um grupo bem estabelecido, mas suas relações internas não, ou seja, a delimitação taxonômica dos gêneros permanece confusa e não resolvida. Segundo alguns autores, a tribo seria

constituida pelas especies de *Vismia* (americanas e africanas) e as espécies de *Psorospermum* deveriam ser incluidas no gênero *Harungana*. Outros reforçam a permanência do gênero *Psorospermum*, que deveria ainda incluir as espécies de *Vismia* africanas (*Afrovismia*). Analisando a tribo Vismieae do ponto de vista químico, os derivados antracênicos e as xantonas são as classes de compostos que estão presentes de forma mais expressiva, ocorrendo em todos os táxons, sendo observada uma certa uniformidade nos três gêneros de Vismieae (*Harungana*, *Psorospermum* e *Vismia*). Porém, diferenças também podem ser observadas. É possível supor que seria adequado preservar os três gêneros e manter *Afrovismia* como um gênero separado, ao invés de unir este grupo de plantas. Ainda é prematuro propor alguma mudança, já que um número realtivamente pequeno de espécies foi estudado quimicamente. Porém, no futuro, com mais informações disponíveis, seria útil incluir os dados químicos nas revisões taxonômicas deste grupo de plantas. Os resultados obtidos nesse estudo demonstram que a família Hypericaceae é uma rica fonte de compostos biologicamente ativos e merece estudos mais aprofundados.

Palavras-chave: Hypericaceae; *Hypericum;* derivados de floroglucinol; flavonoides; Vismieae; taxonomia.

ABSTRACT

Hypericaceae species are distributed in three well-supported tribes, which are Hypericeae, Cratoxyleae and Vismieae. In Brazil, this family is represented by two genera: *Hypericum* L. (Hypericeae tribe), with 24 species, most of them distributed in the south of the country, and *Vismia* Vand. (Vismieae tribe), with 30 species of trees or shrubs that occur mainly in the Amazon region. In this work, studies were developed with species from the Hypericeae tribes, constituted only by the *Hypericum* genus, and Vismieae, which includes the genera *Vismia, Psorospermum* and *Harungana*. In the first chapter of this dissertation, we report the isolation of floroglucinol derivatives and the qualitative and quantitative analysis of flavonoids present in extracts obtained from different species of the genus, native to Brazil. The isolation was carried out from the hexane extract of the aerial parts of *Hypericum pedersenii*, using chromatographic techniques and, as an eluent, solvents in increasing polarity. The fractions obtained were pooled according to similarity, determined by thin layer chromatography. The compounds were subjected to spectroscopic and spectrometric analysis for identification. For the analysis of flavonoids, the aerial parts of different *Hypericum* species were subjected to static maceration with hexane followed by dichloromethane, to remove the lipophilic fraction, followed by ethyl acetate, and methanol, for periods of 24 hours until exhaustion of the plant material. The ethyl acetate and methanol extracts were analyzed by high performance liquid chromatography, with two mobile phases and elution gradient. When comparing the retention times of standard peaks with sample peaks, the peak identity of flavonoids was assigned. As a result, it was possible to isolate a dimeric acylfloroglucinol, identified through NMR techniques, as hyperbrasilol B, present in other species of the genus. This was the first identification report for *H. pedersenii*, being a new source for obtaining this compound. Regarding flavonoids, most of the analyzed species present hyperoside as the major component, which has also been observed in several species of *Hypericum*. It is important to note the absence of this flavonoid in *H. teretiusculum*. The second chapter presents a review of the literature on species from the Vismieae tribe. This tribe is a well-established group, but their internal relations are not, that is, the taxonomic delimitation of the genera remains confused and unresolved. According to some authors, the tribe would be constituted by the species of *Vismia* (American and African) and the species of *Psorospermum* should

be included in the genus *Harungana.* Others reinforce the permanence of the genus *Psorospermum*, which should also include the African *Vismia* species (*Afrovismia*). Analyzing the Vismieae tribe from a chemical point of view, anthracenic derivatives and xanthones are the classes of compounds that are most significantly present, occurring in all taxa, with a certain uniformity being observed in the three genera of Vismieae (*Harungana*, *Psorospermum* and *Vismia*). However, differences can also be observed. It is possible to suppose that it would be appropriate to preserve the three genera and to maintain *Afrovismia* as a separate genus, instead of uniting this group of plants. It is still too early to propose any changes, since a small number of species have been studied chemically. However, in the future, with more information available, it would be useful to include chemical data in the taxonomic reviews of this group of plants. The results obtained in this study demonstrate that the Hypericaceae family is a rich source of biologically active compounds and deserves further studies.

Keywords: Hypericaceae; *Hypericum*; floroglucinol derivatives; flavonoids; Vismieae; taxonomy.

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1. INTRODUÇÃO GERAL

Clusiaceae Lind. (Guttiferae Juss.) inicialmente incluía mais de 1.500 espécies, a maioria delas pertencendo aos gêneros *Hypericum*, *Calophyllum*, *Garcinia* e *Clusia*. Esta família foi dividida em seis subfamílias, Kielmeyeroideae, Calophytiloideae, Clusioideae, Moronoboideae, Lorostemonoideae e Hypericoideae (Engler, 1893). No entanto, análises filogenéticas moleculares mostraram que esta família, amplamente circunscrita, é parafilética (Gustafsson *et al*., 2002). Portanto, foi dividida em novas famílias, uma das quais, Hypericaceae, um táxon distinto de outros membros de Clusiaceae, inclui o grupo de plantas anteriormente classificadas como subfamília Hypericoideae (Stevens, 2007).

Segundo a classificação de Crockett & Robson (2011), a família Hypericaceae, de origem tropical, compreendia nove gêneros: *Cratoxylum* Blume, *Eliea* Cambess., *Harungana* Lamarck, *Hypericum* L., *Lianthus* N.Robson, *Santomasia* N.Robson, *Thornea* Breedlove & McClintock, *Triadenum* Rafinesque e *Vismia* Vand. No entanto, após posteriores estudos filogenéticos, os gêneros *Lianthus*, *Santomasia*, *Thornea* e *Triadenum* foram transferidos para o gênero *Hypericum* (Robson, 2016). Nesta circunscrição, o gênero *Psorospermum* não é reconhecido e todas as suas espécies incluídas no gênero *Harungana*. Porém, como será visto na sequência, essa é uma questão bastante polêmica.

As espécies de Hypericaceae são distribuídas em três tribos bem sustentadas, que são Hypericeae, Cratoxyleae e Vismieae (Ruhfel *et al*., 2011, 2013; Robson, 2012). No Brasil, esta família é representada por dois gêneros: *Hypericum* L. (tribo Hypericeae), com 24 espécies, a maioria distribuída no sul do país (Vogel Ely *et al*., 2020a,b), e *Vismia* Vand. (tribo Vismieae), com 30 espécies de árvores ou arbustos que ocorrem principalmente na região amazônica (Martins *et al*., 2018; Vogel Ely *et al*., 2020b).

Neste trabalho foram desenvolvidos estudos com espécies das tribos Hypericeae, constituída apenas pelo gênero *Hypericum*, e Vismieae, que inclui os gêneros *Vismia*, *Psorospermum* e *Harungana*. Os dados obtidos estão organizados em dois capítulos.

O primeiro capítulo da dissertação apresenta resultados obtidos experimentalmente com diferentes espécies de *Hypericum*, nativas do Brasil (*H.*

caprifoliatum Cham. & Schltdl., *H. carinatum* Griseb., *H. cavernicola* L.B. Sm., *H. gentianoides* (L.) Britton, Sterns & Poggenb., *H. mutilum* L., *H. pedersenii* N.Robson, *H. polyanthemum* Klotzsch ex Reichardt, *H. rigium* A. St.-Hil. e *H. teretiusculum* A. St.-Hil.). Nesse capítulo relata-se o isolamento de derivados de floroglucinol de *Hypericum pedersenii* e a análise qualitativa e quantitativa de flavonoides presentes em extratos obtidos das espécies acima citadas.

O segundo capítulo apresenta uma revisão da literatura sobre espécies da tribo Vismieae. Os dados estão relatados em um artigo publicado *online* no periódico *Phytochemistry Reviews* (10.1007/s11101-021-09740-w).

2. CAPÍTULO I

Tribo Hypericeae - gênero *Hypericum*

2.1 Introdução

Estudos científicos envolvendo produtos naturais vêm sendo realizados há muito tempo, porém esta área permanece com seu potencial parcialmente explorado. Em relação à constituição química, uma pequena parcela das espécies vegetais conhecidas, foi investigada (Hamburguer & Hostettmann, 1991; Verpoorte, 1998; Balunas & Kinghorn, 2005; Jone *et al*., 2006).

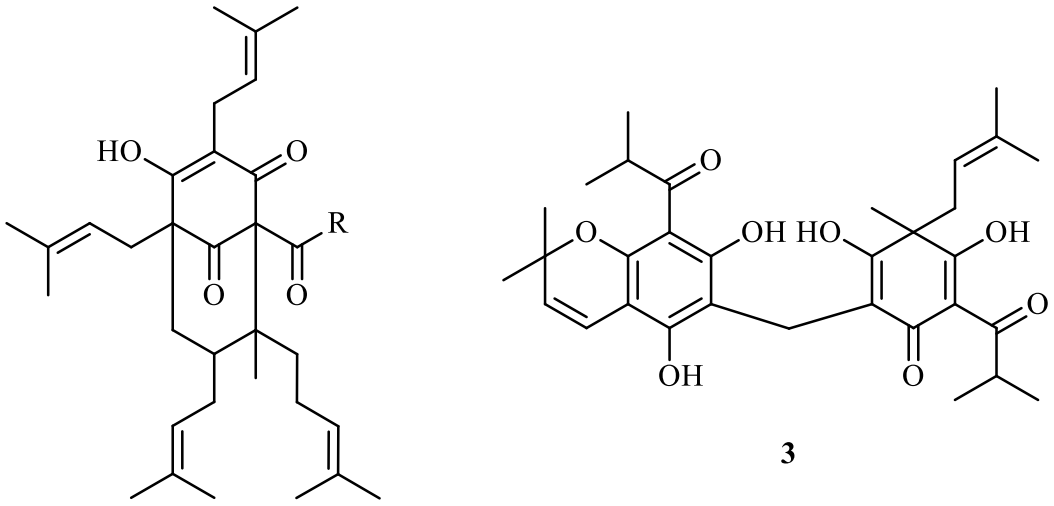
O gênero *Hypericum* L. (Hypericaceae) possui cerca de 500 espécies, sendo elas pequenas árvores, arbustos e subarbustos, distribuídas em 36 seções taxonômicas. Sua distribuição se dá por todos os continentes, com exceção da Antártica (Crockett & Robson, 2011; Robson, 2012).

No Brasil ocorrem 24 espécies espécies nativas de *Hypericum*, a maioria distribuída no sul do país (Vogel Ely *et al*., 2020a,b), sendo elas divididas nas seções *Brathys* e *Trigynobrathys*, as duas maiores seções do gênero (ROBSON, 2012). Estudos voltados à prospecção química envolvendo estas espécies, relatam a identificação de compostos como benzopiranos, benzofenonas, floroglucinóis diméricos, xantonas e flavonoides (Meirelles *et al.*, 2019).

As espécies de *Hypericum* caracterizam-se pela presença de diferentes tipos de estruturas especializadas no acúmulo de metabólitos. Glândulas translúcidas são comuns a todas as espécies, enquanto glândulas escuras ocorrem em cerca de 2/3 delas (Crockett & Robson, 2011). O que delimita esses dois tipos de glândulas é a presença de floroglucinóis ou naftodiantronas, que são biossintetizados em células secretoras das glândulas translúcidas e escuras, respectivamente (Zobayed *et al*., 2006; Soelberg *et al.*, 2007; Crockett & Robson, 2011).

Em relação aos derivados de floroglucinóis encontrados no gênero *Hypericum*, cinco grupos principais os diferenciam: floroglucinóis monoméricos, diméricos, poliprenilados, benzofenonas e floroglucinóis com adutos de terpeno (Bridi *et al*., 2018).

Das espécies de *Hypericum*, muitos derivados de floroglucinol prenilados vêm sendo isolados, podendo ser divididos em dois grupos principais, os floroglucinóis poliprenilados semelhantes à hiperforina (**1**) e a *ad*-hiperforina (**2**) (**Figura 1**) presentes em *H. perforatum* (Jürgenliemk & Nahrstedt, 2002; Crockett *et al*., 2005). O segundo grupo inclui os floroglucinóis diméricos, constituídos por uma unidade de floroglucinol ligada através de uma ponte metilênica a uma unidade de ácido filicínico como, por exemplo, hiperbrasilol B (**3**) (**Figura 1**), encontrados em espécies nativas do Brasil (Rocha *et al*., 1995, 1996; Ferraz *et al*., 2002; Dall'Agnol *et al*., 2005; Bridi *et al*., 2016).



3

1: R= CH_3
2: R= CH_2CH_3

Figura 1. Hiperforina (1), *ad*-hiperforina (2) e hiperbrasilol B (3).

Os derivados de floroglucinol podem ser considerados bons marcadores químicos para o gênero *Hypericum*. As seções *Brathys* e *Trigynobrathys*, as quais englobam as espécies nativas do Brasil, demonstram especialização na biossíntese de derivados diméricos, que são de ocorrência restrita a essas duas seções, podendo ser, portanto, considerados marcadores taxonômicos destes táxons (Nör, 2006; Bridi *et al*., 2018).

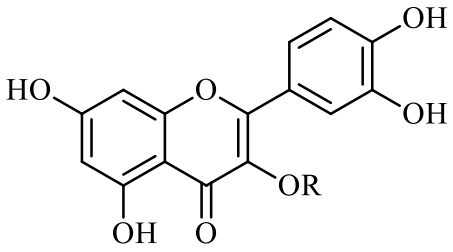
Além dos compostos anteriormente citados, muitos estudos são conduzidos com objetivo de isolar e identificar flavonoides presentes nessas plantas, muitas vezes em quantidades elevadas (von Eggelkraut-Gottanka *et al*., 2002; Su *et al*., 2008; Huang &

Liaw, 2017). Os principais compostos identificados nessas espécies, incluindo as brasileiras, são diversos glicosídeos da quercetina (Nör *et al*., 2008; Hass, 2010; Barros, *et al*., 2013)

Os flavonoides são qualitativa e quantitativamente um dos maiores grupos de produtos naturais conhecidos e estão presentes em quase todos os vegetais superiores. São abundantes nas espécies de *Hypericum* e, em *H. perforatum*, representam o total de 7% nas folhas e 11% nas flores (Kartnig *et al*., 1989; Havsteen, 2002).

A biossíntese dos flavonoides ocorre por meio de uma combinação das vias do ácido chiquímico e do acilpolimalonato e são compostos com a estrutura básica de dois anéis fenil e um anel heterocíclico. Esses compostos existem amplamente nas plantas e desempenham papéis importantes na floração, crescimento e autoproteção (Di Carlo *et al.*, 1999).

Os flavonoides de maior frequência encontrados no gênero *Hypericum* são as agliconas: luteolina, canferol e quercetina e os glicosídeos derivados da quercetina (**4**): quercitrina (**5**), isoquercitrina (**6**), hiperosídeo (**7**) e rutina (**8**) (**Figura 2**). Diversas espécies também apresentam biflavonoides (Kartnig *et al*., 1996; Dias *et al*., 1998; Bilia *et al*., 2002; Jürgenliemk & Nahrstedt, 2002).



4: R= H
5: R= ramnose
6: R= glicose
7: R= galactose
8: R= rutinose

Figura 2. Quercetina (4), quercitrina (5), isoquercitrina (6), hiperosídeo (7) e rutina (8).

Um estudo qualitativo para glicosídeos flavônicos foi realizado com algumas espécies de *Hypericum* do sul do Brasil, demonstrando a presença de compostos comumente relatados, como: hiperosídeo, quercitrina, isoquercitrina e traços de rutina, sendo sempre o hiperosídeo com os maiores teores encontrados (Dall'Agnol *et al*., 2003).

As espécies sul-brasileiras de *Hypericum* vêm sendo estudadas há mais de 20 anos, mostrando ser promissoras fontes de compostos biologicamente ativos. Sendo assim, é relevante analisar espécies que ainda não foram trabalhadas, identificando seus perfis químicos, visando caracterizar novos derivados de floroglucinol, e outros componentes presentes nas plantas.

2.2 Objetivos

Este capítulo está dividido em duas partes. Na primeira são apresentados os processos de isolamento e identificação de floroglucinóis de *Hypericum perdesenii*.

Na segunda parte apresenta-se uma análise qualitativa e quantitativa de flavonoides presentes nas partes aéreas de diversas espécies do gênero.

2.3 Material e métodos

2.3.1 Coleta de material vegetal

As partes aéreas floridas de *H. caprifoliatum, H. carinatum, H. cavernicola, H. gentianoides, H. mutilum, H. pedersenii, H. polyanthemum, H. rigium* e *H. teretiusculum* foram coletadas em diferentes localidades no estado do Rio Grande do Sul. As mesmas foram devidamente identificadas pelo botânico Prof. Dr. Sergio Augusto de Loreto Bordignon (Unilasalle). Estes vegetais foram submetidos à secagem em temperatura ambiente, moídos e armazenados no laboratório de Farmacognosia, protegidos da luz direta e umidade.

2.3.2 Extração de floroglucinois

As partes aéres de *H. pedersenii* foram submetidas à maceração estática com hexano, por períodos de 24 horas até o esgotamento do material vegetal, ou seja, até não haver alteração na massa de extrato (relação droga vegetal/solvente: 1/3).

A eliminação do solvente foi realizada com o auxílio do evaporador rotatório, sob pressão reduzida e temperatura inferior a 45 ºC. O extrato seco foi retomado em acetona para remover substâncias insolúveis, indesejaveis, como ceras epicuticulares e certos triterpenos. A fração solúvel foi filtrada e levada a secura em evaporador rotatório.

2.3.3 Isolamento de floroglucinóis

O extrato hexânico de *H. pedersenii* foi submetido à cromatografia em coluna utilizando sílica gel 60 e cromatografia circular centrífuga com o equipamento Chromatotron®, e como eluentes misturas de hexano e diclorometano, hexano e acetato de etila, em polaridade crescente.

As frações obtidas foram reunidas por semelhança utilizando a cromatografia de camada delgada (CCD) empregando como fase móvel, hexano e acetato de etila (95:5 v/v), com posterior revelação com anisaldeído sulfúrico.

Os compostos foram submetidos a análises espectroscópicas (RMN ^{1}H e ^{13}C, 400 e 100 MHz, respctivamente), empregando acetona deuterada ($(CD_3)_2CO$) como solvente.

2.3.4 Extração de flavonoides

As partes aéreas de cada espécie de *Hypericum* foram submetidas à maceração estática com hexano seguida de diclorometano, para remoção da fração lipofílica, seguida de acetato de etila, e metanol, por períodos de 24 horas até o esgotamento do material vegetal (relação droga vegetal/solvente: 1/3). A eliminação do solvente foi realizada com o auxílio do evaporador rotatório, sob pressão reduzida e temperatura inferior a 45 ºC.

2.3.5 Preparação das amostras para análise cromatográfica de flavonoides

2.3.5.1 Cromatografia líquida de alta eficiência (CLAE)

Extratos acetato de etila e metanol foram submetidos à analise. As amostras foram diluídas em metanol de modo a obter concentração final de 1 mg/mL e posteriormente filtradas (0,22 μm de tamanho de poro). Os padrões de flavonoides utilizados para a quantificação foram quercetina e seus derivados glicosilados: quercitrina, isoquercitrina, guajaverina, hiperosídeo e rutina. A curva padrão foi realizada utilizando como padrão o flavonoide hiperosídeo (R^2 = 0,9984), nas concentrações de 1, 5, 25, 50, 125 e 250 μg/mL.

As análises de CLAE/HPLC foram realizadas seguindo um método descrito por Tatsis *et al.* (2007) com algumas modificações (Ccana-Ccapatinta *et al.*, 2014). Separações foram realizadas em uma coluna Waters Nova-Pack C18 (4 mm, 3,9 mm x 150 mm) adaptada a uma pré-coluna Waters Nova-Pack C18 60 A˚ (Waters, Milford, MA, EUA) usando um sistema Shimadzu HPLC (Shimadzu Corporation, Kyoto, Japão).

As fases móveis consistiram de uma mistura de água (A) e uma mistura de acetonitrila e metanol (8:2) (B), ambas acidificadas com ácido fórmico 0,1%. A eluição

de gradiente foi realizada da seguinte forma: gradiente linear de 10% B a 100% B ao longo de 30 min, mantido em 100% B por 20 min, seguido de reequilíbrio por 20 min. Todas as separações foram realizadas a 25 ºC e vazão de 1,0 mL/min, com detecção realizada a 220 e 350 nm, em triplicata. Uma alíquota de 10 μL de extrato por amostra foi injetada. Ao comparar os tempos de retenção (t_R) de picos padrão com picos de amostra, a identidade de pico de flavonoides foi atribuída.

2.4 Resultados e discussão

2.4.1 Derivados de floroglucinol

Nos primeiros estudos que envolveram o isolamento de derivados de floroglucinol das espécies de *Hypericum*, três compostos foram isolados: uliginosina A e uliginosina B de *H. thesiifolium* (sin. *H. uliginosum*) (Parker & Johnson, 1968; Taylor & Brooker, 1969) e hiperforina de *H. perforatum* (Gurevich *et al*., 1971; Bystrov *et al*., 1975). O número de derivados de floroglucinol identificados ao longo do tempo foi crescendo, conforme todo o gênero foi sendo melhor estudado quimicamente.

Das partes aéreas de *H. pedersenii* foi possível o isolamento de hiperbrasilol B (**9**) (**Figura 3**), identificado através de técnicas de RMN (^{1}H e ^{13}C) e comparando os espectros com dados já relatados na literatura (Dados presentes em anexo).

O hiperbrasilol B é um acilfloroglucinol dimérico, constituído por uma unidade de floroglucinol ligada através de uma ponte metilênica a uma unidade de ácido filicínico, e foi isolado pela primeira vez de *H. brasiliense* (Rocha *et al*., 1996).

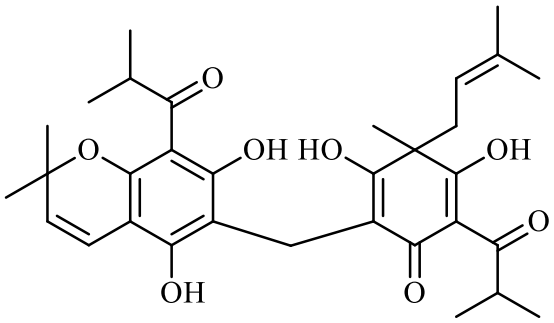


Figura 3. Hiperbrasilol B.

Os espectros de RMN de ^{1}H de acilfloroglucinóis diméricos são altamente informativos, com características que revelam detalhes em relação à estrutura. Os sinais que sugerem dois hidrogênios presentes na ponte metilênica e/ou hidrogênios da hidroxila são indicativos desse tipo de composto. A presença de sinais de hidrogênios metilênicos (δ 3,46-3,60) na ligação entre o ácido filicínico e a porção floroglucinol é típica de quase todos os acilfloroglucinóis diméricos, representando a ponte metilênica.

Além disso, sinais na posição em torno de δ 18,00 ppm são característicos do sistema enolizável β-tricetona, comprovando a porção do ácido acilfinicílico.

O isolamento de hiperbrasilol B já ocorreu em espécies como *H. laricifolium*, espécie andina, e *H. brasiliense*, *H. caprifoliatum* e *H. connatum*, sendo estas espécies sul-brasileiras (Rocha *et al*., 1996; Ferraz *et al*., 2002; Nör *et al*., 2004; Ccana-Ccapatinta & von Poser, 2015).

Este é o primeiro relato do isolamento deste composto de *H. pedersenii*, sendo uma nova fonte de obtenção deste derivado de floroglucinol. Outro composto, também um acilfloroglucinol dimérico, de provável estrutura inédita também foi isolado, mas ainda está em vias de elucidação.

Das 36 seções taxonômicas nas quais espécies de *Hypericum* estão alocadas, aquelas que apresentam derivados de floroglucinol são *Adenosepalum, Androsaemum, Ascyreia, Brathys, Campylosporus, Coridium, Crossophyllium, Drosocarpium, Hirtella, Hypericum, Humifusoideum, Myriandra, Oligostema, Olympia, Roscyna, Sampsonia, Takasagoya, Thasia* e *Trigynobrathys* (Bridi *et al*., 2018). Mas em relação aos acilfloroglucinois diméricos, as seções *Brathys* e *Trigynobrathys* incluem todas as espécies das quais estes compostos foram isolados até o momento. De fato, todos os 36 derivados de floroglucinol conhecidos, com uma estrutura dimérica, são oriundos de espécies dessas seções. E é devido a esses dados que estes compostos podem ser considerados marcadores quimiotaxonômicos, tendo em vista que as espécies sul-brasileiras são exclusivas dessas duas seções (Meirelles *et al*., 2019).

Infelizmente, segundo Bridi *et al*. (2018), apenas 6% das espécies da seção *Brathys* e 12% das espécies da seção *Trigynobrathys* foram exploradas, havendo muitos dados químicos a ser descobertos e documentados.

2.4.2 Flavonoides

As espécies nativas de *Hypericum*, como já relatado, possuem os metabólitos fenólicos típicos: ácido clorogênico, hiperosídeo, quercitrina, isoquercitrina, guaijaverina (Bernardi *et al*., 2007; Nunes *et al*., 2010). Porém, uma característica das espécies sul-brasileiras de *Hypericum* é a completa ausência ou apenas a presença de

traços do flavonoide rutina, que é abundante em outras espécies do gênero (Meirelles *et al*., 2019).

Nas tabelas a seguir estão presentes os resultados da quantificação dos flavonoides quercetina, quercitrina, isoquercitrina, guajaverina, hiperosídeo e rutina nos extratos acetato de etila (**Tabela 1**) e metanol (**Tabela 2**) das espécies *H. caprifoliatum, H. carinatum, H. cavernicola, H. gentianoides, H. mutilum, H. pedersenii, H. polyanthemum, H. rigium* e *H. teretiusculum*. Os resultados estão expressos em porcentagem em relação à massa de extrato.

Na extração com acetato de etila, a maior concentração de hiperosídeo foi encontrada na espécie *H. carinatum*, com valores de 19,15 ± 0,25%, seguido de *H. gentianoides*, com 9,01 ± 0,11%. A espécie *H. cavernicola* apresentou em seu extrato 18,51 ± 0,16% de guajaverina, já *H. rigidum* apresentou este composto na concentração de 7,95 ± 0,05%. Quercitrina esteve presente em 14,48 ± 0,04% do extrato de *H. mutilum*. *Hypericum pedersenii* apresentou 7,47 ± 1,06% de quercetina, seguido de *H. polyanthemum*, com 5,50 ± 0,08%. O extrato com a maior quantidade de flavonoides analisados foi o proveniente de *H. carinatum* (28,15 ± 0,38%).

O extrato metanol possibilitou a extração de quercitrina de *H. mutilum* com 11,19 ± 0,16%. Hiperosídeo representou 9,66 ± 0,36 e 7,58 ± 0,06% do extrato de *H. pedersenii* e *H. carinatum*, respectivamente. De *H. cavernicola*, a guajaverina foi identificada sendo 7,38 ± 0,02% do extrato. O total de flavonoides extraídos de *H. mutilum* foi de 17,38 ± 0,24%, a maior porcentagem dentre os extratos com metanol. Os demais resultados obtidos foram menores do que os apresentados.

O extrato metanol extraiu menores quantidades de flavonoides, tendo em vista que o material vegetal já havia passado pela extração anterior com acetato de etila.

Tabela 1. Compostos analisados do extrato acetato de etila das partes aéreas de espécies de *Hypericum* (% do extrato).

Acetato de etila	Hiperosídeo	Isoquercitrina	Guajaverina	Quercitrina	Quercetina	Rutina	**Total**
H. caprifoliatum	2,45 ± 0,06	1,19 ± 0,03	0,73 ± 0,01	2,28 ± 0,03	3,10 ± 0,05	-	9,74 ± 0,18
H. carinatum	19,15 ± 0,25	1,55 ± 0,10	4,95 ± 0,01	-	2,49 ± 0,03	-	28,15 ± 0,38
H. cavernicola	2,62 ± 0,02	1,39 ± 0,02	18,51 ± 0,16	-	-	-	22,52 ± 0,19
H. gentianoides	9,01 ± 0,11	3,03 ± 0,07	0,79 ± 0,00	-	5,03 ± 0,07	-	17,86 ± 0,26
H. mutilum	3,15 ± 0,02	1,31 ± 0,01	0,91 ± 0,02	14,48 ± 0,04	0,79 ± 0,01	-	20,64 ± 0,09
H. pedersenii	3,37 ± 0,11	3,18 ± 0,17	0,93 ± 0,03	0,46 ± 0,00	7,47 ± 1,06	-	15,41 ± 1,38
H. polyanthemum	4,91 ± 0,11	1,66 ± 0,06	1,17 ± 0,08	1,75 ± 0,02	5,50 ± 0,08	-	15,00 ± 0,35
H. rigium	1,39 ± 0,02	2,33 ± 0,04	7,95 ± 0,05	7,43 ± 0,15	1,63 ± 0,03	0,76 ± 0,01	21,48 ± 0,29
H. teretiusculum	-	1,99 ± 0,01	1,51 ± 0,01	1,77 ± 0,01	0,72 ± 0,01	0,68 ± 0,00	6,67 ± 0,04

Tabela 2. Compostos analisados do extrato metanol das partes aéreas de espécies de *Hypericum* (% do extrato).

Metanol	Hiperosídeo	Isoquercitrina	Guajaverina	Quercitrina	Quercetina	Rutina	**Total**
H. caprifoliatum	4,79 ± 0,03	2,31 ± 0,12	0,93 ± 0,00	2,33 ± 0,01	1,46 ± 0,01	-	11,82 ± 0,17
H. carinatum	7,58 ± 0,06	1,18 ± 0,05	2,23 ± 0,02	-	1,11 ± 0,01	-	12,10 ± 0,14
H. cavernicola	2,32 ± 0,01	1,16 ± 0,01	7,38 ± 0,02	-	-	-	10,86 ± 0,05
H. gentianoides	4,34 ± 0,06	1,49 ± 0,05	0,49 ± 0,00	-	0,61 ± 0,01	-	6,93 ± 0,12
H. mutilum	3,44 ± 0,03	1,40 ±0,02	0,58 ± 0,01	11,19 ± 0,16	0,77 ± 0,02	-	17,38 ± 0,24
H. pedersenii	9,66 ± 0,36	2,65 ± 0,01	0,83 ± 0,01	0,48 ± 0,00	0,68 ± 0,01	-	14,31 ± 0,39
H. polyanthemum	4,79 ± 0,07	1,75 ± 0,08	0,95 ± 0,04	1,29 ± 0,01	1,61 ± 0,02	-	10,39 ± 0,22
H. rigium	1,04 ± 0,02	1,84 ± 0,02	3,67 ± 0,01	1,18 ± 0,01	0,58 ± 0,01	0,69 ± 0,00	8,99 ± 0,08
H. teretiusculum	-	1,83 ± 0,02	0,96 ± 0,01	0,72 ± 0,01	0,43 ± 0,00	-	3,94 ± 0,05

Em todas as espécies foi possível a identificação de picos com os tempos de retenção de isoquercitrina e guajaverina. Quercetina não esteve presente apenas em *H. cavernicola*, mas foi identificada em todas as demais. Quercitrina esteve ausente em três espécies: *H. carinatum, H. cavernicola* e *H. gentianoides. Hypericum teretiusculum* foi a única espécie a não apresentar hiperosídeo, um metabólito frequentemente relatado para o gênero *Hypericum,* e também se destacou pelo baixo teor de flavonoides, em realação as demais. A presença de traços de composto com o perfil cromatográfico de rutina foi detectada em *H. rigidum* e *H. teretiusculum* (< 1,00%).

Hiperosídeo foi o metabólito mais presente em grande parte das espécies, com destaque para a maior concentração em *H. carinatum. Hypericum cavernicola* apresentou a maior concentração de guajaverina e *H. mutilum*, a maior em quercitrina. Essas espécies demonstraram ser ótimas fontes de obtenção destas substâncias. Em relação à quantidade total de flavonoides, *H. carinatum* e *H. mutilum* aparecem como as principais em porcentagem de extrato.

Alguns estudos já identificaram flavonoides em representantes do gênero *Hypericum* nativos do sul do Brasil, e o presente trabalho foi realizado de forma a incluir novas espécies, realizando a extração de forma fracionada, para obtenção de novos dados.

Nunes *et al.* (2010) investigaram a presença de compostos fenólicos nas partes aéreas em floração de espécies sul-brasileiras de *Hypericum* da seção *Trigynobrathys*, algumas das quais também foram analisadas no presente trabalho. Ácido clorogênico, hiperosídeo, isoquercitrina, guajaverina e quercitrina foram os metabólitos detectados no extrato metanólico do material vegetal.

Entre as espécies analisadas por Nunes *et al.* (2010) que também foram analisadas neste estudo estão *H. caprifoliatum, H. carinatum, H. polyanthemum* e *H. rigidum.* A concentração (% do extrato) de hiperosídeo, isoquercitrina, guajaverina e quercitrina estão localizados na **Tabela 3**. A rutina não foi detectada em nenhuma das espécies.

Tabela 3. Compostos analisados do extrato metanol das partes aéreas de espécies de *Hypericum* (% do extrato) (Nunes *et al*., 2010).

	Hiperosídeo	Isoquercitrina	Guajaverina	Quercitrina
H. caprifoliatum	4,69 ± 0,67	0,91 ± 0,04	0,20 ± 0,05	0,76 ± 0,15
H. carinatum	5,10 ± 0,002	1,02 ± 0,17	1,12 ± 0,13	0,71 ± 0,10
H. polyanthemum	6,01 ± 0,08	1,91 ± 0,002	0,76 ± 0,015	0,77 ± 0,07
H. rigidum	1,81 ± 0,16	0,47 ± 0,02	0,47 ± 0,03	0,04 ± 0,002

Hiperosídeo foi o flavonoide encontrado em maior quantidade em cada uma das espécies. O padrão da ordem de concentração dos compostos identificados foi similar aos encontrados neste trabalho, com exceção da quercitrina em *H. carinatum*, que não foi identificada no presente estudo. Já o perfil de concentração dos metabólitos de *H. rigidum* foi completamente diferente.

Os compostos fenólicos de flores de *Hypericum* foram analisadas por Barros *et al*. (2013). Os metabólitos foram os mesmos detectados por Nunes *et al*. (2010). *Hypericum caprifoliatum, H. carinatum* e *H. polyanthemum* foram as espécies analisadas em comum. *Hypericum caprifoliatum* e *H. polyanthemum* apresentaram a maior concentração (%/material vegetal seco) de hiperosídeo com, respectivamente, 1,553 e 1,063%. Já em *H. carinatum*, representou 0,758%.

Os compostos relatados nestes estudos, derivados glicosilados da quercetina, são comuns em muitas espécies deste gênero, dando ênfase principalmente ao hiperosídeo (Su *et al*., 2008). Este flavonoide foi o majoritário detectado em diversas espécies de *Hypericum.*

Condições ambientais como, por exemplo, a localização, estações do ano, temperatura, umidade, intensidade de luz, abastecimento de água, minerais e CO_2 influenciam o crescimento das plantas e são fatores muito comuns que podem causar variação no perfil químico dos vegetais (Ramakrishna & Ravishankar, 2011).

Makarova *et al.* (2021), em um estudo analisando polifenóis totais e flavonoides de *H. perforatum,* concluíram que diferentes datas de coleta afetaram o teor total destes compostos. Essa variação também pode ser devido à temperatura e estresse hídrico.

Ainda citando *H. perforatum*, experimentos demonstraram que a alta temperatura (35 ºC) prejudica a floração, enquanto o teor de hipericina das flores variou

de 0,6 para 1,2 mg/g de peso fresco na faixa de temperatura de 20 a 30 ºC. Além disso, grandes mudanças bioquímicas e fisiológicas ocorreram sob estresse hídrico como, por exemplo, um aumento na concentração de hiperforina e uma diminuição no conteúdo de hipericina (Zobayed *et al.*, 2005, 2007).

Como é sabido que a produção de metabólitos pode ser afetada pela luz, que é um fator físico, já foi relatada uma correlação entre o aumento da intensidade da luz e aumento dos níveis de compostos fenólicos (Chalker-Scott & Fuchigami, 1989).

Falando de flavonoides, a biossíntese desse metabólito é principalmente regulada positivamente como consequência do alto índice de raios UV-B e/ou radiação solar total (Ballaré, 2003). Já a biossíntese de outros compostos fenólicos, tanto derivados do ácido hidroxicinâmico quanto taninos hidrolisáveis, que estão em concentrações constitutivamente maiores do que os flavonoides, em condições de pouca luz, é muito pouco afetada por um aumento na radiação ultravioleta (Di Ferdinando *et al*., 2012).

Em um estudo com *H. brasiliense*, foram investigados os efeitos do estresse hídrico e da temperatura sobre o conteúdo de ácido betulínico e compostos fenólicos (quercetina, rutina, 1,5-di-hidroxixantona, isouliginosina B). Em relação à temperatura, o teor de 1,5-di-hidroxixantona aumentou em plantas mantidas a 30 °C durante a noite. Em contraste, a concentração de rutina e a quercetina diminuíram com este tratamento. Plantas que foram mantidas em câmaras de crescimento a 17 °C e 36 °C apresentaram aumento nos níveis dos compostos analisados, exceto para quercetina a 17 °C. A quantidade de rutina aumentou em resposta à seca e ao estresse por hipóxia, mas a quercetina aumentou apenas sob um déficit hídrico (Abreu & Mazzafera, 2005).

Assim sendo, esses estudos corroboram os dados obtidos na presente dissertação. Mesmo tratando-se da mesma espécie as plantas estão sujeitas a alteração de seus metabólitos, que pode ocorrer inclusive em compostos da mesma classe, sendo relacionada a vários fatores.

2.5 Perspectivas

Definir a estrutura do composto isolado de *H. pedersenii* e, confirmada a proposta, realizar uma futura investigação envolvendo experimentos biológicos.

Realizar estudos biológicos com as frações de flavonoides, visando a inibição da enzima ecto-5'-nucleotidase/CD73. Esse estudo está atualmente em andamento.

3. CAPÍTULO II

Tribo Vismieae: gêneros *Harungana*, *Psorospermum* e *Vismia*

3.1 Introdução

A tribo Vismieae compreende os gêneros *Harungana*, *Psorospermum* e *Vismia*, e todos possuem representantes amplamente utilizados na medicina tradicional principalmente para o tratamento de doenças de pele, além de serem considerados agentes antiprotozoários, febrífugos e purgativos (Hussain *et al*., 2012; Epifano *et al*., 2013; Happi *et al*., 2020).

Vismieae é um grupo bem estabelecido, mas suas relações internas não, ou seja, a delimitação taxonômica dos gêneros permanece confusa e não resolvida (Ruhfel *et al*., 2011, 2013). Portanto, ainda é necessário acumular mais evidências (moleculares, micro e macromorfológicas, químicas, entre outras) para circunscrever esses gêneros para que passem a refletir as relações evolutivas dessas plantas. Algumas revisões foram publicadas sobre os gêneros *Vismia* (Hussain *et al*., 2012; Vizcaya *et al*., 2012), *Psorospermum* (Epifano *et al*., 2013) e *Harungana* (Happi *et al*., 2020), destacando seus usos tradicionais, botânica, fitoquímica e propriedades farmacológicas. Entretanto, nenhuma comparação entre os gêneros estava disponível na literatura.

No gênero *Vismia* ocorrem, como os principais matabólitos, antraquinonas e outros derivados antracênicos, xantonas e benzofenonas, além de terpenoides e flavonoides (Hussain *et al*., 2012; Vizcaya *et al*., 2012). Os compostos isolados de *Psorospermum* compreendem antraquinonas simples e preniladas, antranoides, flavonoides e xantonas simples e preniladas (Epifano *et al*., 2013). Dentre os principais componentes químicos de *Harungana* estão incluídos antranoides, antraquinonas, xantonas e triterpenoides (Happi *et al*., 2020).

O objetivo do presente estudo é atualizar essas revisões e comparar os dados químicos para determinar se eles têm potencial para auxiliar na taxonomia dos gêneros dentro de Vismieae. Assim, neste trabalho, os gêneros são tratados como tradicionalmente circunscritos. Posteriormente, de posse dos dados publicados, verificou-se se a distribuição dos metabólitos secundários reforça alguma das diferentes proposições taxonômicas. Além disso, o estudo traça um paralelo entre as aplicações etnobotânicas dessas plantas, bem como os dados farmacológicos disponíveis na

literatura para espécies pertencentes aos três gêneros intimamente relacionados que compõem a tribo.

Os dados obtidos estão apresentados no artigo *Drawing a parallel between phytochemistry and other features of Vismieae species*, publicado *online* na revista *Phytochemistry Reviews*.

3.2 Artigo

Drawing a parallel between phytochemistry and other features of Vismieae species

Drawing a parallel between phytochemistry and other features of Vismieae species

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Abstract

The present study provides an overview, focusing on the botanical aspects, phytochemistry, ethnopharmacology and biological activities reported for species from the tribe Vismieae (Hypericaceae). These species, traditionally distributed in three genera (*Vismia*, *Psorospermum* and *Harungana*), occur predominantly in tropical areas of South America, mainland Africa and Madagascar, where several of them are used in the traditional medicine mainly as febrifugal, antimalarial and for treating wounds of diverse origin. The phytochemical investigations indicated that the plants produce anthraquinones, anthrones**,** xanthones, benzophenones, flavonoids and some terpenoids. A number of 221 different compounds were obtained from 32 species of the tribe. Several compounds were investigated for the pharmacological activities, being cytotoxic and antimicrobial the most cited. Nevertheless, a number of pharmacological researches were carried out with extracts and some finding experimentally evidenced the ethnopharmacological usefulness of several species. The distribution of the anthracenic derivatives, xanthones and benzophenone precursors is not uniform in the genera. Thus, the substitution pattern of these compounds was analyzed and the systematic relationship among the taxa is discussed in the light of these features. Of note, more species need chemical investigation in order to make a judgment about the taxonomic significance of the compounds, but it seems that, although the tribe has a certain homogeneity, each genus has particularities. Considering this statement, it is possible to say that in the chemical point of view, *Psorospermum* is diferent from *Harungana* and both are diferent from *Vismia*, which is clearly separate into two distinct groups, the African and the American species.

Keywords

Vismieae; *Vismia*; *Psorospermum*; *Harungana*; xanthones; anthracenes.

Abbreviations

ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AchE	Acetylcholinesterase
BchE	Butyrylcholinesterase
CC_{50}	Concentration causing 50% reduction of cell viability (CC = cytotoxic concentration)
CCl_4	Carbon tetrachloride
CUPRAC	Cupric reducing antioxidant capacity
DPPH	2,2-diphenyl-1-picrylhydrazyl
ED_{50}/ EC_{50}	Median effective dose for 50% of the group
Fe (II)	Iron in its +2 oxidation state
FRAP	Ferric reducing antioxidant power
GC-MS	Gas Chromatography – Mass Spectrometry
GI_{50}	Concentration causing 50% cell growth inhibition
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
$H_2O_2^-$	Hydrogen peroxide radical
HSV-1	Herpes simplex virus type 1
IC_{50}	Half maximal inhibitory concentration to inhibit 50%
KB	Keratin-forming tumor
LC_{50}	Concentration causing 50% cell death (LC = lethal concentration)
MDA	Malondialdehyde
MIC	Minimum inhibitory concentration
NO^-	Nitric oxide
O_2^-	Superoxide radical
OH^-	Hydroxyl radical
$ONOO^-$	Peroxynitrite
ORAC	Oxygen radical absorbance capacity
TBARS	Thiobarbituric acid reactive substances
TNF-α	Tumour necrosis factor alpha
WHO	World health organization

Introduction

Hypericaceae has long been a subfamily of Clusiaceae (Cronquist 1981). However, after phylogenetic studies, the taxon is now recognized as an independent family that has a cosmopolitan distribution (Ruhfel et al. 2011; APG IV 2016). The species are distributed in the tribes Vismieae, Cratoxyleae and Hypericeae.

This family is represented by two genera in Brazil: *Hypericum* L. (tribe Hypericeae), with 24 species and greater diversity in the south of the country (Vogel Ely et al. 2020a, b), and *Vismia* Vand. (tribe Vismieae), with 30 species of trees or shrubs that occur mainly in the Amazon region (Martins et al. 2018a; Vogel Ely et al. 2020b).

In addition to *Vismia*, the tribe Vismieae comprises the genera *Psorospermum* and *Harungana*. All the genera have representatives that are widely used in the traditional medicine mainly for treating skin diseases, as well as antiprotozoal, febrifugal and purgative agents (Hussain et al. 2012; Epifano et al. 2013; Happi et al. 2020).

Vismieae is a well-established group, but its internal relationships are not, that is, the taxonomic delimitation of the genera remains confused and unresolved (Ruhfel et al. 2011, 2013). Therefore, it will be necessary to accumulate more evidence (molecular, micro and macromorphological, chemical, among others) to re-circumscribe these genera so that they start to reflect the evolutionary relationships of these plants.

Some reviews have been published on genera *Vismia* (Hussain et al. 2012; Vizcaya et al. 2012), *Psorospermum* (Epifano et al. 2013) and *Harungana (Happi et al. 2020)*, highlighting their traditional uses, botany, phytochemistry and pharmacological properties. The purpose of the current article is to update these reviews and to compare the chemical data to determine if they have potential to assist in the taxonomy of the genera within Vismieae. Thus, in this review, genera are treated as traditionally circumscribed. Subsequently, in possession of the published data, it will be verified whether the distribution of secondary metabolites reinforces any of the different taxonomic propositions. In addition, the study draws a parallel between the ethnobotanical applications of these plants, as well as the pharmacological data available in the literature for species **belonging** to the three **closely related genera** that compose the tribe.

Botanical aspects

Clusiaceae

Clusiaceae Lind. (Guttiferae Juss.) formerly included more than 1500 species, most of them belonging to the genera *Hypericum*, *Calophyllum*, *Garcinia* and *Clusia*. This family had been divided into six subfamilies, Kielmeyeroideae, Calophytiloideae, Clusioideae, Moronoboideae, Lorostemonoideae and Hypericoideae (Engler 1893). However, molecular phylogenetic analyses have shown that this broadly circumscribed family is paraphyletic (Gustafsson et al. 2002). Therefore, it was splitted into new families, one of which, Hypericaceae, a distinct taxon apart from other members of Clusiaceae, corresponds to the former subfamily Hypericoideae (Stevens 2007).

Hypericaceae

According to Crockett and Robson (2011), the family, which has a tropical origin, encompasses nine genera: *Cratoxylum* Blume, *Eliea* Cambess., *Harungana* Lamarck, *Hypericum* L., *Lianthus* N.Robson, *Santomasia* N.Robson, *Thornea* Breedlove & McClintock, *Triadenum* Rafinesque, and *Vismia* Vand. However, after analyzing the results of further phylogenetic studies, the genera *Lianthus*, *Santomasia*, *Thornea* and *Triadenum* were transferred to the genus *Hypericum* (Robson 2016). In this circumscription, the species of *Psorospermum* were included in the genus *Harungana*. Nevertheless, other authors consider the group as an independent genus.

The species of Hypericaceae are divided into three well-supported tribes, namely Hypericeae, Cratoxyleae and Vismieae (Ruhfel et al. 2011, 2013; Robson 2012).

Tribe Vismieae

The tribe Vismieae, with almost 120 species, traditionally includes three genera, *Vismia*, *Psorospermum* and *Harungana*, predominantly distributed in tropical regions.

There are many controversies from the taxonomic point of view, but they are at the generic level. The tribe is a phylogenetically well-supported group but the genera traditionally recognized do not reflect evolutionary relationships within the tribe - that is, relationships and boundaries are still not very well defined.

The tribe Vismieae, as formerly defined by Bamps (1966), encompasses the genera *Vismia*, *Psorospermum* and *Harungana*. The genera *Psorospermum* and *Harungana* include species occurring in mainland Africa and Madagascar. *Vismia*, on the other hand, is separated into the subgenera *Vismia*, which contains the American species, and *Afrovismia*, that includes those found in Africa. Afterward, a study by Stevens (2007) suggested that the tribe should include only the genera *Harungana* and *Vismia*, the former containing the species distributed in the Old World (Africa and Madagascar) and the latter, those found in New World (Central and South America).

More recently, other studies demonstrated that none of the above proposals reveal phylogenetic relationships (Ruhfel et al. 2011, 2013). *Harungana* sensu Stevens (Old World Vismieae) is not a monophyletic group, including some American Vismieae. *Vismia* subgenus *Afrovismia* (sensu Bamps) is paraphyletic as well. Moreover, *Vismia guineensis* (L.) Choisy is best allocated in *Psorospermum*, and *Vismia rubescens* Oliv. is closely related to *Harungana madagascariensis* Lam. ex Poir. According to Ruhfel et al. (2011), limiting *Harungana* to *H. madagascariensis* and *Vismia rubescens*, and transferring all other species from Africa and Madagascar to a larger *Psorospermum* genus would be an alternative. These relationships need to be supported by further information. However, some generic recircumscriptions are already cited by Christenhusz et al. (2018).

Genus *Vismia*

The genus *Vismia*, as traditionally circumscribed, encompasses about 60 species distributed mainly in tropical regions of Central, South America and some areas of Africa (Stevens 2007;

Martínez y Pérez and Castillo-Campos 2008). *Vismia* species have been accommodated in two subgenera: *Vismia* subg. *Vismia*, comprising the American species, and *Vismia* subg. *Afrovismia*, which includes the African species (Marinho et al. 2016).

Among the species of *Vismia* recognized in Brazil, at least ten are endemic and 22 occur in the phytogeographic regions of the Amazon domain (Vogel Ely et al. 2020b)**.** Several of them are known by the popular names of "lacre" and "pau-de-lacre" (literally "seal" or "sealing wax" and "sealing stick"). These vernacular names refer to their characteristic exudates, usually yellowish, orange or red-orange (Martins et al. 2018a, b).

Species such as *Vismia cauliflora* A.C.Sm. occur only in Brazil, in the state of Amazonas (Vogel Ely et al. 2020b). Others, like *Vismia cayennensis* (Jacq.) Pers., *Vismia guianensis* (Aubl.) Choisy, *Vismia japurensis* Reichardt and *Vismia sandwithii* Ewan are also distributed in other countries of the Amazon region. Some species are found on the edge of secondary vegetation and degraded areas in sandy to clayey soil (Martins et al. 2018a). Several species such as *Vismia laurentii* De Wild. and *Vismia guineensis* are native to tropical Africa (Tamokou et al. 2009, 2013; Hussain et al. 2012). Others, as *Vismia camparaguey* Sprague & L. Riley and *Vismia baccifera* (L.) Planch & Triana occur in Mexico and in some countries of Central America. The latter also grows in the Amazon River Basin countries (Martínez y Pérez and Castillo-Campos 2008).

Genus *Psorospermum*

Species of the genus *Psorospermum* Baker are widely used in the traditional medicine in African countries, as well as in Madagascar. The most known species is *Psorospermum febrifugum* Spach. (Epifano et al. 2013). The genus encompasses species of shrubs or small trees that produce a yellowish exudate and generally grow in the tropical regions of Africa, and Madagascar (Epifano et al. 2013). The total number of species is uncertain (Ranarivelo 2017), but numbers around 55 species have been cited (Epifano et al. 2013). A recent molecular phylogenetic study supports the inclusion of the African *Vismia* and the African and Malagasy *Psorospermum* into a single genus *Psorospermum* (Ranarivelo 2017). This find is in accordance with the previous study by Ruhfel et al. (2011), cited above.

Genus *Harungana*

According to some authors, the genus is monotypic, having just the species *Harungana madagascariensis (Happi et al. 2020).* Nevertheless, according to the database "The Plant List" (http://www.theplantlist.org/), in addition to *Harungana madagascariensis*, *Harungana lebruniana* Spirlet, *Harungana montana* Spirlet and *Harungana robynsii* Spirlet are accepted species.

Harungana madagascariensis is widely distributed in Africa, where it has been used in the traditional medicine for treating several diseases (Schultz et al. 2020). This plant, likewise the species of *Vismia* and *Psorospermum*, produces exudates. When fragments of the trunk bark are removed, the presence of an intense orange exudate is verified, which helps in the identification of the plant *(Happi et al. 2020).*

Some molecular studies indicated that besides Harungana madagascariensis, the genus should encompasses the species Vismia rubescens (Ruhfel et al. 2011; Christenhusz et al. 2018).

Traditional uses

Regarding the ethnopharmacological usefulness of the plants belonging to Vismieae tribe, the wide use of species from the three genera in the treatment of several types of skin diseases is remarkable. The detailed information is presented in the Tables 1, 2 and 3.

The Table 1 describes the medicinal uses of American and African *Vismia* species. Some American species of *Vismia*, known as "lacre" or "pau-de-lacre", have been used in traditional medicine by Indigenous communities in regions of the Amazon rainforest to treat wounds, ulcers, herpes and as antifungal. The leaves are used medicinally by local communities in Amazon as purgatives, and their barks are considered to have benefits as a tonic and febrifugal (Nagem and de Oliveira 1997; Hussain et al. 2012). In other countries, mainly in Africa, some species are traditionally used to treat malaria and skin illness, such as herpes, dermatitis, leprosy, syphilis, scabies and eczemas (Kerharo and Adam 1974; Bilia et al. 2000).

In the Amazonian forest region, these plants are used to treat wounds due to cutaneous leishmaniasis, which are known as "ferida-brava" (literally "severe wound"). In spite of only one ethnobotanical study cite this use (Viza Junior et al. 2019), the exudate from *Vismia* sp. is popularly known as useful for treating leishmaniasis wounds (Fundação Rede Amazônica 2012).

Several species of the genus *Psorospermum* have long been used in the ethnomedical traditions of the African population, as it can be seen in Table 2. The main uses are as febrifuge, laxative and in the treatment of skin diseases including leprosy, dermatitis, eczema, subcutaneous and cancerous wounds (Epifano et al. 2013). Probably, as it was verified for the species of *Vismia*, the species of *Psorospermum* are used in folk medicine to treat wounds caused by cutaneous leishmaniasis, although reports on this use have not been found.

Harungana madagascariensis is cited in ethnopharmacological studies which report its use in African folk medicine for treating of a wide range of diseases (Table 3). Some authors also mention its usefulness in the European herbal medicine (Happi et al. 2020). The plant, known as Dragon's blood, haronga, orange-blood and orange-milk, in addition to its medicinal importance, is a source of firewood and is used in the production of charcoal.

Table 1. The medicinal uses of different American and African *Vismia* species.

American species	Country regions	Plant part used	Preparation	Documented medicinal uses	References
Vismia baccifera (L.) Planch. & Triana	Amazonian region	NI	NI	Purgative, treatment of disorders of the urinary tract, protecting against snake bites, skin diseases, antirheumatic and antipyretic	Trepiana et al. 2018
	Peru	Cortex	NI	Treatment of infected wounds	Hernández-Pasteur et al. 2019
	Mexico	Cortex of the trunk	Infusion	Mouth-wash and women's douche	Reyes-Chilpa et al. 2014*
Vismia cauliflora A.C. Sm.	Brazil	NI	NI	Treatment of dermatosis and inflammatory processes in the skin	Ribeiro et al. 2015b
Vismia guianensis (Aubl.) Pers.	Brazil	Leaves	NI	Treatment of problems related to the spine, kidneys and pain in general	de Albuquerque et al. 2007
	Brazil	Latex, leaves	Infusion of the leaves	Treatment of dermatomycoses and purging	Oliveira et al. 2017
	Brazil	Leaves, husks	Decoction, infusion	Tonic febrifuge and treatment of rheumatism	Oliveira et al. 2017
	French Guiana	Latex	NI	Treatment of oral fungal infections	Oliveira et al. 2017
	Brazil	Leaves	Leaves boiled with water and applied to the wound	Treatment of cutaneous leishmaniasis***	Viza Junior et al. 2019
Vismia japurensis Rchb.f.	Brazil	Latex	Fresh	General infection and wound healing	Ribeiro et al. 2017
Vismia latifolia (Aubl.) Choisy	Brazil	NI	NI	Tonic and febrifugal agent	dos Santos et al. 2000b
Vismia macrophylla Kunth	Peru	Stem barks, leaves, resin, seeds	Applying the resin or the powdered drug externally	Treatment of fungal infections	Roumy et al. 2020
	Colombia	Leaves	Lightly roasted leaves	Dressing on snakebites and placed on top of the wounds	Lopez et al. 2001
	Colombia	Barks	NI	Treatment of cutaneous infections	Lopez et al. 2001
	Colombia	Resin	NI	Treatment of a condition known as	Lopez et al. 2001

				"carate"****	
	Colombia	Sap	NI	Treatment of problems related with vision	Lopez et al. 2001
	Nicaragua	Leaves	Dried leaves	Treatment of skin infections	Mbwambo et al. 2004
Vismia tomentosa Ruiz & Pav.	Peru	Any part of the plant	NI	Treatment of dermatosis	Estevez et al. 2007

African species	**Country regions**	**Plant part used**	**Method of preparation**	**Documented medicinal uses**	**References**
Vismia guineensis (L.) Choisy	Guinea	Leaves, stem bark	Decoction	Treatment of malaria	Traore et al. 2013
	Ivory Coast	NI	NI	Treatment of malaria or fever	Ménan et al. 2006
	West Africa	Barks, roots	NI	Treatment of skin diseases, such as dermatitis, leprosy, syphilis, herpes, scabies and eczemas	Bilia et al. 2000; Politi et al. 2004
	Mali	Leaves, roots	Topical application (ointment)	Treatment of mycosis	Ahua et al. 2007**
	Tanzania	NI	NI	Treatment of syphilis	Ahua et al. 2007**
	NI	NI	NI	Febrifuge, purgative, treatment of leprosy	Nguyen et al. 2009**
	NI	Barks, roots, branches with leaves	Decoction	Treatment of skin conditions such as eczema, psoriasis, scabies, cold sores, and leprosy	Willcox et al. 2012**
	Mali	Roots	Ointment, made with 1% ether extract of root powder	Treatment of eczema	Willcox et al. 2012**
	NI	NI	NI	Treatment of skin diseases (eczema, psoriasis, scabies, cold sores, and leprosy), syphilis, and neuralgia	Epifano et al. 2013**
Vismia laurentii De Wild.	NI	NI	NI	Treatment of different affections including microbial infections.	Kemegne et al. 2017
	NI	Roots, twigs, leaves	NI	Treatment of fever, dermatitis, leprosy, scabies, eczemas and infected wounds	Kuete et al. 2007

	Cameroon	Barks, roots	NI	Tonic and febrifugal	Nguemeving et al. 2006; Tala et al. 2007; Wabo et al. 2007; Tamokou et al. 2013
	Cameroon	NI	NI	Treatment of skin diseases (such as dermatitis, leprosy, scabies, eczemas) and wounds	Nguemeving et al. 2006; Tala et al. 2007; Wabo et al. 2007; Tamokou et al. 2013
Vismia orientalis Engl.	Tanzania	Stem barks, latex	Fine powder from dried stem bark. Latex from a fresh slash of the stem bark is mixed with water and smeared on the affected part of the skin	Treatment of skin rashes and wounds	Mbwambo et al. 2004
Vismia rubescens Oliv.	Gabon	Yellowish red gum exuded from the stems	NI	Wound-dressing	Tamokou et al. 2009
	Cameroon	Barks, roots	Decoction	Febrifugal and in the treatment of various microbial infections (skin diseases, diarrhea and venereal diseases)	Tamokou et al. 2009

NI = Not informed; *Published as *Vismia mexicana* Schltdl.; **Published as *Psorospermum guineense* (L.) Hochr.; ***Known in Brazil as "ferida brava" (severe wound), is caused by parasites of the genus *Leishmania.;* ****Also known as pinta, azul, empeines, lota, mal del pinto and tina, is a rare infectious tropical disease that affects the skin and is caused by the bacterium *Treponema carateum*.

Table 2. The medicinal uses of *Psorospermum* species.

Species	Country regions	Plant part used	Preparation	Documented medicinal uses	References
Psorospermum androsaemifolium Baker	Madagascar	NI	NI	Remedy for spiders or scorpions bite and also healing stomach disease	Poumale et al. 2008; Epifano et al. 2013
Psorospermum aurantiacum Engl.	Cameroon	Leaves, barks	Decoction taken orally	Pimples	Manjia et al. 2019
	Cameroon	Leaves	Decoction	Treatment of gastrointestinal and urinary tract infections	Tchakam et al. 2012
	Cameroon	Stem barks	Combined with other plant extracts*	Treatment of epilepsy	Tchakam et al. 2012
	NI	NI	NI	Febrifuge, purgative, and to cure skin diseases	Epifano et al. 2013
Psorospermum corymbiferum Hochr.	NI	Roots, barks	NI	Treatment of dermal infections such as leprosy, scabies, eczema and herpes	Zubair et al. 2011; Epifano et al. 2013
	NI	Leaves	NI	Diuretic, strong febrifuge, antiseptic, antimicrobial and pro-wound healing properties	Zubair et al. 2011; Epifano et al. 2013
	NI	NI	NI	Treatment of snakebites	Molander et al. 2014
	Democratic Republic of the Congo	Leaves	Infusion with *Artemisia annua* leaves, taken orally	Treatment of malaria	Manya et al. 2020
Psorospermum febrifugum Spach	NI	NI	NI	Febrifuge, treatment of leprosy, poison antidote, purgative	Kupchan et al. 1980; Epifano et al. 2013
	Angola	NI	NI	Febrifuge, treatment of skin ulcerations and leprosy	Amonkar et al. 1981
	NI	Roots	NI	Treatment of wounds	Marston et al. 1986
	NI	Leaves, barks	NI	Treatment of skin diseases	Marston et al. 1986
	Uganda	Barks	Dried barks pounded fresh with honey, taken orally	Treatment of fever, stomach ache, cough	Hamill et al. 2003

	Uganda	Barks	Dried barks pounded fresh with vaseline, plant part is crushed and packed into the surface of the skin	Treatment of rash, ringworm	Hamill et al. 2003
	NI	NI	NI	Treatment of malaria, leprosy, wounds, skin diseases and fever	Queiroz et al. 2005
	Tanzania	Roots	The roots are powdered and applied on the wound	Treatment of cancerous wounds	Moshi et al. 2006
	Tanzania	Barks	Decoction taken orally, bathed with decoction	Skin infections (body sores, skin rushes, herpes zoster)	Kisangau et al. 2007
	NI	NI	NI	Febrifuge, purgative, treatment of leprosy	Nguyen et al. 2009
	Uganda	Stem barks, root barks, whole roots	NI	Skin sores in people living with HIV/AIDS	Lamorde et al. 2010
	NI	NI	NI	Treatment of malaria, epilepsy, diarrhea, febrifugal, antidote against poison and purgative, leprosy, skin diseases (such as dermatitis, scabies and eczemas) and subcutaneous wounds	Tamokou et al. 2013
	Guinea	Leaves, stem barks	Decoction	Treatment of malaria	Traore et al. 2013
	Uganda	Stem barks, leaves, root barks, entire roots	Decoction	Treatment of HIV /AIDS, aimed at lowering viral loads	Nyamukuru et al. 2017
	Uganda	NI	NI	Treatment of herpes zoster in people living with HIV/AIDS	Anywar et al. 2020
Psorospermum glaberrimum Hochr.	NI	Leaves, barks	Decoction	Treatment of epilepsy, respiratory affections, skin diseases and leprosy	Lenta et al. 2008
	NI	Root barks	Root barks extract	Treatment of severe cases of malaria	Lenta et al. 2008
	NI	Roots, barks, resin,	Pulped roots, barks	Treatment of skin diseases and leprosy	Lenta et al. 2008

		leaves	extracts, bark red resin powdered with dried leaves, used externally		
	NI	Leaves, barks	Leaves and barks extracts	Treatment of epilepsy, respiratory affections, skin diseases, leprosy, and malaria	Epifano et al. 2013
Psorospermum senegalense Spach	Mali	NI	NI	Treatment of epilepsy and convulsions	Pedersen et al. 2009
	Burkina Faso	Leaves	Decoction, sometimes in combination*	Treatment of malaria	Jansen et al. 2010
	NI	NI	NI	Treatment of malaria, skin disorders, epilepsy	Jansen et al. 2010
	NI	NI	NI	Treatment of skin diseases, analgesic, diuretic, stomachic	Epifano et al. 2013
Psorospermum tenuifolium Hook.f.	NI	NI	NI	Treatment of all skin ailments	Epifano et al. 2013

NI = Not informed. *Plant combinations were not cited

Table 3. The medicinal uses of *Harungana madagascariensis* Lam. ex Poir.

Country regions	Plant part used	Preparation	Documented medicinal uses	References
Cameroon	Barks, stems	Burnt, ash is applied topically	Treatment of skin irritation	Manjia et al. 2019
Cameroon	Barks	Decoction	Treatment of typhoid fever	Roger et al. 2015
Cameroon	Leaves	Decoction, taken orally	Management of colic	Noumi and Yomi 2001
Cameroon	Leaves	Recipe includes seven other plants, blended, bruised and macerated	Treatment of epilepsy	Noumi and Fozi 2003
Cameroon	Leaves	NI	Treatment of malaria	Agbor et al. 2007; Oboh et al. 2010
Cameroon	Leaves	NI	Treatment of typhoid fever	Kengni et al. 2013, 2016
Cameroon	Leaves	Decoction	Treatment of dysentery, diarrhea, anemia, typhoid and some heart ailments such as tachycardia	Happi et al. 2020
Cameroon	NI	NI	Treatment of anemia	Biapa et al. 2007
Cameroon	NI	NI	Treatment of anemia, jaundice, bleeding, gonorrhea, malaria, asthma, liver diseases, diabetes, pancreatic and biliary problems	Etame et al. 2017
Cameroon	Seeds	Seeds oil	Treatment of fever and parasitic diseases	Lenta et al. 2007b
Cameroon	Stem barks	Decoction, macerate	Treatment of jaundice	Betti and Lejoly 2009
Cameroon	Stem barks	Aqueous extract	Used as laxative	Tih et al. 2006
Democratic Republic of Congo	Stem barks	Decoction	Treatment of diabetes, amoebiasis, diarrhoea, cough	Mpiana et al. 2008
Democratic Republic of Congo	Stem barks	Decoction	Treatment of diarrhoea	Tona et al. 2000
Democratic Republic of Congo	Stem barks	Decoction	Management of sickle cell disease	Mpiana et al. 2010
Democratic Republic of	Stem barks	Decoction	Treatment of anemia, venereal diseases, nephrosis, gastro-intestinal disorders and fever	Muganza et al. 2012

Congo			including malaria	
East Africa	NI	Extract from the plant	Used to interrupt menstruation and induce breast enlargement	Madubunyi et al. 1995
European herbal medicine	NI	NI	Treatment of indigestion and poor pancreatic function	Kouam et al. 2005
European herbal medicine	Leaves, stem barks	Juice of the leaves and stem bark	Treatment of indigestion and poor pancreatic function	Happi et al. 2020
Ghana	Latex	NI	Treatment of skin diseases and as a dressing material for wounds	Happi et al. 2020
Ghana	Leaves	NI	Treatment of chest problems, dysentery	Madubunyi et al. 1995; Happi et al. 2020
Guinea	Leaves, stem barks	Decoction, maceration, infusion	Treatment of malaria	Traore et al. 2013
Ghana	Sap	Sap washed out of the bark, drunk	Treatment of "crawcraw"*, dressing for wounds	Olagunju et al. 2004; Adeneye et al. 2008b
Ghana	Stem barks	NI	Treatment of skin diseases and dressing material for wounds	Adeneye et al. 2008a; Johnson et al. 2016
Ivory Coast	Barks	Decoction drunk, taken as enema and for bathing, body smeared with mashed bark	Treatment of malaria	Malan et al. 2015
Ivory Coast	Barks	Kneading, purge	Treatment of malaria	Koffi et al. 2015
Kenya	Root bark, stem barks	Decoction	Treatment of malaria	Muthaura et al. 2007; Nguta et al. 2011
Ivory Coast	Stem barks	Decoction, taken orally	Treatment of anemia, abdominal pain, gastric ulcer	Koné et al. 2012
Kenya	Stem barks	Decoction	Management of malaria	Mukungu et al. 2016
Kenya	Stem barks, roots	Decoction taken orally	Treatment of colorectal, skin and breast cancer	Ochwang'i et al. 2014
Liberia	Buds	Eat the unopened buds beaten up with palm-oil	Treatment of puerperal infection	Olagunju et al. 2004; Adeneye et al. 2008a, b; Johnson et al. 2016
Nigeria	Leaves	NI	Remedy for hemorrhages, diarrhoea, gonorrhoea, sore throats, headaches and fevers	Adelodun et al. 2013
Nigeria	NI	NI	Used by traditional birth attendants to achieve	Akah 1994

			relatively painless delivery, hasten fetal delivery and evacuate retained placenta	
Nigeria	NI	Cold and hot infusions	Treatment of gastrointestinal disorders including diarrhoea, dysentery and typhoid fever.	Okoli et al. 2002
Nigeria	NI	Exudate	Treatment of acute enteritis, scabies, and jaundice	Adeneye et al. 2008b
Nigeria	NI	Alcohol extracts	Treatment of jaundice, stomach problems, skin diseases and leprosy	Madubunyi et al. 1995
Nigeria	Roots	Decoction	Treatment of drug-related liver and kidney poisonings	Adeneye et al. 2008a, b
Nigeria	Roots	Water extract	Used as an abortifacent and oxytocic	Madubunyi et al. 1995
Nigeria	Sap	NI	Treatment of scabies and as an anthelmintic (tapeworms)	Adelodun et al. 2013
Rwanda	Fresh roots	Peeled and ground	Treatment of gonorrhoea	Ramathal and Ngassapa 2001
Rwanda	Leaves	Decoction	Treatment of malaria	Muthaura et al. 2007
Sierra Leone	Leaves, stem barks	Red juice obtained from the leaves and stem bark	Arresting post-partum or post-abortal bleeding	Olagunju et al. 2004; Adeneye et al. 2008a, b; Johnson et al. 2016; Happi et al. 2020
Tanzania	Leaves	Decoction taken orally	Treatment of chronic diarrhea, malaria, jaundice	Kisangau et al. 2007
Tanzania	Roots, stem barks	NI	Treatment of malaria	Gessler et al. 1995
Uganda	NI	NI	Treatment of blood cancer/leukemia, cervical, intestinal, liver and skin cancer	Schultz et al. 2020
Uganda	Roots, barks	Decoction, taken orally	Treatment of dysentery, stop menstruation	Hamill et al. 2003
Uganda	Stem barks, leaves, fruits	Stem bark boiled, herbal bath, boiled in petroleum jelly or powdered and mixed in petroleum jelly, leaves and fruits powdered and mixed in petroleum jelly, then smeared on skin	Treatment of skin and soft-tissue infections	Schultz et al. 2020
Uganda	Stem barks, leaves,	Stem bark boiled taken orally,	Treatment of inflammatory disorders, such as	Schultz et al. 2020

	root barks	powdered in petroleum jelly then smeared or pressed against wound/swollen body part, leaves and root bark boiled, taken orally	pain, redness, heat, swelling and wounds	
Uganda	Stem barks, leaves, roots, whole plant	Aqueous decoction of stem bark and leaves, powdered into tea, aqueous decoction of roots and whole plant, taken orally	Treatment of symptoms of general infection	Schultz et al. 2020
Uganda	Stem barks, leaves, seeds, whole plant	Stem bark and leaves boiled, powdered into tea or water, seeds and whole plant boiled, taken orally	Treatment of malaria	Schultz et al. 2020
Uganda	Stem barks, leaves, stems	Decoction	Treatment of HIV /AIDS, aimed at lowering viral loads	Nyamukuru et al. 2017
Uganda	Stem barks, leaves, whole plant	Leaves boiled, powdered into tea, stem bark and whole plant boiled, taken orally	Treatment of tuberculosis	Schultz et al. 2020
Zimbabwe	NI	NI	Treatment of malaria	Nku-Ekpang Okot-Asi et al. 2018
NI	Barks	Decoction of the bark, taken orally	Remedy for malaria, the leaves are used as a fever remedy	Ochwang'i et al. 2014
NI	Barks	NI	Treatment of malaria, river blindness, ulcer, asthma, hepatitis, dysmenorrhea, and toothache	Antia et al. 2015
NI	Barks	Pounded bark along with *Pentaclethra macrophylla* Benth. (Fabaceae)	Treatment of leprosy	Olagunju et al. 2004; Adeneye et al. 2008b
NI	Barks, roots	NI	Treatment of gonorrhea, leprosy, hemorrhoids and to facilitate childbirth	Happi et al. 2020
NI	Fruits	NI	Abortive	Antia et al. 2015
NI	Gummy sap	NI	Used as enema to treat enteritis leprosy, ring worm, and treatment of skin diseases	Antia et al. 2015
NI	Leaves	Juice of the leaves, taken orally	Remedy for malaria and fever	Ochwang'i et al. 2014
NI	Leaves	Pound leaf paste	Treatment of diarrhoea, sore throat and venereal diseases	Ochwang'i et al. 2014

NI	Leaves	NI	Treatment of anemia	Schultz et al. 2020
NI	Leaves	NI	Treatment of haemorrhages, diarrhoea, gonorhoea, sore throat, fevers and worm infestations	Ramathal and Ngassapa 2001
NI	Leaves	Leaf juice	Treatment of amenorrhoea	Ramathal and Ngassapa 2001
NI	Leaves	NI	Treatment of chest pains and urogenital infections	Antia et al. 2015
NI	Leaves	Decoction	Treatment of leprosy and cutaneous mycoses	Moulari et al. 2006
NI	Leaves	Decoction	Treatment of leprosy and cutaneous mycosis and ovulation troubles	Moulari et al. 2005, 2007
NI	Leaves, roots	NI	Treatment of anemia, nephrosis, malaria, gastro-intestinal disorders and fever	Nku-Ekpang Okot-Asi et al. 2018
NI	Leaves, stem barks	NI	Treatment of anemia	Iwalewa et al. 2009c
NI	Leaves, stem barks	NI	Treatment of anemia, nephrosis, malaria and fever, as well as in the treatment of gastrointestinal disorders	Iwalewa et al. 2008a, b
NI	Leaves, stem barks	NI	Used against microbial diseases	Moulari et al. 2005
NI	Leaves, stem barks	NI	Treatment of anemia	Gbolade et al. 2009
NI	Leaves, stem barks, roots	NI	Treatment of jaundice, diarrhoea, typhoid fever and laxative	Moulari et al. 2005, 2007
NI	Root, barks	Infusion	Interrupt menses	Ochwang'i et al. 2014
NI	Root, barks	Mixture of the root and bark	Remedy for dysentery, bleeding and piles	Oboh et al. 2010
NI	Root, stem barks	Decoction	Remedy for dysentery, bleeding piles, trypanosomosis, fever, cold and cough	Adeneye et al. 2008b
NI	Sap	Sap washed out of the bark, drunk	Remedy for tapeworm infection	Olagunju et al. 2004; Adeneye et al. 2008b
NI	Sap	NI	Treatment of skin diseases, leprosy spots and wounds	Iwalewa et al. 2008a
NI	Sap	Sap from the bark	Wound healing properties	Gbolade et al. 2009
NI	Seeds	NI	Treatment of typhoid fever	Schultz et al. 2020

NI	Stem barks	NI	Treatment of diarrhea, hernia and worms	Schultz et al. 2020
NI	Stem barks	NI	Treatment of malaria	Antia et al. 2015
NI	Stem barks	NI	Treatment of nephrosis, malaria, gastro-intestinal disorders and fever	Iwalewa et al. 2008b, 2009c
NI	Stem barks	NI	Treatment of malaria	Gbolade et al. 2009
NI	Stem barks, leaves	NI	Treatment of syphilis, ulcers	Schultz et al. 2020
NI	NI	NI	Management of menstruation disorders, dysentery, female infertility, hernia, postpartum, malaria, fever, nervous depression, kidney e liver diseases	Roger et al. 2015
NI	NI	NI	Treatment of fever, diarrhoea and parasitic diseases	Lenta et al. 2007b
NI	NI	NI	Treatment of jaundice, diarrhoea, typhoid fever, constipation and as a laxative and abortifacient	Okoli et al. 2002
NI	NI	NI	Treatment of microbial infections and various symptoms related to bacterial, fungal and viral infections, antiseptic, and to treat wounds infections, angina, diarrhea, dysentery, syphilis, gonorrhea, asthma, tuberculosis, malaria, viral and parasitic skin diseases	Tankeo et al. 2016
NI	NI	NI	Used as abortifacient and antiseptic, in the treatment of anemia, asthma, tuberculosis, fever, angina, diarrhea, dysentery, syphilis, gonorrhea, malaria, parasitic skin diseases, and wounds	Iwalewa et al. 2009a
NI	NI	NI	Used as antiparasitic (antitrypanosomal and antiplas modial), anti-anaemic, spasmolytic and antibacterial in skin diseases and wounds	Iwalewa et al. 2009c
NI	NI	NI	Treatment of wounds, toothaches, painful menstruation and inflammations	Nwodo 1989; Madubunyi et al. 1995
NI	NI	NI	Treatment of leprosy, diarrhoea, dysentery and many skin diseases	Nwodo 1989
NI	NI	NI	Used against intestinal or dyspeptic diseases	Baldi et al. 1992

*NI = Not informed. *Pruritic papular skin eruption, which may lead to ulceration, in some cases caused by *Onchocerca*.

Phytochemistry

The genera *Vismia*, *Psorospermum* and *Harungana* have been submitted to several phytochemical studies aiming to isolate their specialized metabolites. Until now, these efforts resulted in the identification of 221 compounds of different classes: quinones, including anthraquinones (**1** – **22**), anthrones (**23** – **79**) and dimeric anthranoids (**80** – **90**), benzophenones (**91** – **103**), xanthones (**104** – **162**), sesquiterpenes (**163** – **179**), triterpenes (**180** – **196**), flavonoids (**197** – **210**) and miscellaneous compounds (**211** – **221**).

Quinones

Quinones are a wide group of organic compounds, considered as pigments, that can be found in different natural sources (Thomson 1991). These compounds present a varied chemical complexity, ranging from simple benzoquinone derivatives, through naphthoquinones and anthraquinones, to polycyclic molecules such as hypericin. A series of quinones derivatives have been isolated from species of Hypericaceae, especially from Vismieae (Figs. 1, 2 and 3). Probably these compounds are present in exudates, usually colored from yellow to red, as well as and in the glands commonly found in the plants of this tribe.

Anthraquinones

The first anthraquinone isolated from species of the genus *Vismia* was reported in the study by Gonçalves and Mors (1981). The dried leaves of *Vismia reichardtiana* (Kuntze) Ewan were extracted with petrol, and the compound vismiaquinone (**1**) was obtained as red needles (the same compound was also named as vismiaquinone A). In other study, the benzene extract from the stem barks of *Vismia reichardtiana* (syn. *Vismia guaramirangae* Huber), afforded physcion (**2**), madagascin (**3**), 2-prenylemodin (**4**) and chrysophanic acid (**5**) (Camele et al. 1982). *Vismia laurentii*, an African species, was the subject of several phytochemical studies. From lipophilic extracts of roots and stems, vismiaquinone (**1**), physcion (**2**), vismiaquinone B (**6**), vismiaquinone C (**7**) and 3-*O*-geranyloxyemodin (**8**) were isolated (Nguemeving et al. 2006; Kuete et al. 2007; Noungoue et al. 2009; Kemegne et al. 2017). The seeds of *Vismia laurentii* were studied, and provided physcion (**2**), together with the novels laurenquinones A (**9**) and B (**10**) (Wabo et al. 2007). From the fruits of the same species, a new anthraquinone, named as laurentiquinone C (**11**), with the previously known laurenquinone A (**9**), laurenquinone B (**10**), isoxanthorin (**12**) and emodin (**13**) were isolated (Noungoue et al. 2008; Tchamo et al. 2008).

The compound 3-*O*-geranyloxyemodin (**8**) was isolated from the root barks of *Vismia guineensis* (Botta et al. 1986a). The roots of this species, studied by Bilia et al. (2000), afforded four new anthraquinones, 3-*O*-(2-hydroxy-3-methyl-3-enyl)-emodin (**14**), 3-*O*-(2-methoxy-3-methyl-3-enyl)-emodin (**15**), 3-*O*-(*E*-hydroxymethylbut-2-enyl)-emodin (**16**) and 3-*O*-(3-hydroxymethyl-4-hydroxybut-2-enyl)-emodin (**17**), as well as the known madagascin (**3**), 3-*O*-geranyloxyemodin (**8**), emodin (**13**), 3-(18,19-dihydro-18,19-dihydroxygeranyloxy-1,8-dihydroxy-6-methylanthraquinone (**18**) and 3-(19-hydroxygeranyloxy)-6-methyl-1,8-dihydroxyanthraquinone (**19**). From the seeds of this plant, vismiaquinone (**1**), laurenquinone A (**9**), laurenquinone B (**10**) and laurentiquinone C (**11**) were identified (Tala et al. 2013).

Phytochemical studies carried out with the Brazilian native species *Vismia japurensis* allowed the isolation of vismiaquinone (**1**) and vismiaquinone B (**6**) (Miraglia et al. 1981). The leaves and fruits of *Vismia baccifera* (syn. *Vismia mexicana* Schltdl.) afforded vismiaquinone (**1**), physcion (**2**) and vismiaquinone C (**7**) (Pinheiro et al. 1984; Hussein et al. 2003; Reyes-Chilpa et al. 2014). Additionally, the compound **1** was also isolated from the leaves of *Vismia baccifera* subsp. *dealbata* (Kunth) Ewan (Hussein et al. 2003) and *Vismia guianensis* (Lins et al. 2016).

A study published by Nagem and Faria (1990) reported the isolation of anthraquinones from the leaves of *Vismia martiana* Reichardt. The compounds were identified as vismiaquinone (**1**), chrysophanic acid (**5**), vismiaquinone B (**6**) and vismiaquinone C (**7**). The stems of *Vismia parviflora* Schltdl. & Cham. was also studied showing the presence of vismiaquinone (**1**), madagascin (**3**), chrysophanic acid (**5**), and vismiaquinone C (**7**) (Nagem and de Oliveira 1997). Ethanolic extract (80%) of stem barks of *Vismia orientalis* Engl. afforded the compounds 3-*O*-geranyloxyemodin (**8**) and emodin (**13**) (Mbwambo et al. 2004).

Studies with *Vismia cayennensis*, *Vismia latifolia* (Aubl.) Choisy and *Vismia rubescens* resulted in the isolation of physcion (**2**) and chrysophanic acid (**5**) (Pinheiro et al. 1984; dos Santos et al. 2000a; Tamokou et al. 2009).

Some anthraquinones were identified in species of the genus *Psorospermum*. The roots and fruits of *Psorospermum febrifugum* afforded the compounds 2-prenylemodin (**4**), chrysophanic acid (**5**), 3-*O*-geranyloxyemodin (**8**) (Botta et al. 1983, 1985, 1986b) and the novel 3-(19-hydroxygeranyloxy)-6-methyl-1,8-dihydroxyanthraquinone (**19**) (Marston et al. 1986). The roots of *Psorospermum tenuifolium* Hook.f. were studied by Delle Monache et al. (1987), resulting in the isolation of the anthraquinones 3-*O*-geranyloxyemodin (**8**) and emodin (**13**), 3-(18,19-dihydro-18,19-dihydrogeranyloxy)-1,8-dihydroxy-6-methylanthraquinone (**18**), 3-(19-hydroxygeranyloxy)-6-methyl-1,8-dihydroxyanthraquinone (**19**). The compound **8** was also isolated from the root barks of *Psorospermum corymbiferum* Hochr. (Zubair et al. 2011).

From *Psorospermum adamauense* Engl. and *Psorospermum glaberrimum* Hochr. physcion (**2**), 2-prenylemodin (**4**), 3-*O*-geranylemodin (**8**), emodin (**13**), and 2- geranylemodin (**20**) have been isolated (Delle Monache et al. 1985; Lenta et al. 2008; Tsaffack et al. 2009). Additionally, vismiaquinone (**1**) and physcion (**2**) were obtained from the stem barks and leaves of *Psorospermum androsaemifolium* Baker (Poumale et al. 2008, 2011). In a study performed by Tanemossu et al. (2015) with the stems of *Psorospermum densipunctatum* Engl. three known anthraquinones were isolated, vismiaquinone (**1**), 3-*O*-geranyloxyemodin (**8**) and 2-geranylemodin (**20**). The leaves of *Psorospermum auranticum* Engl. afforded vismiaquinone (**1**), physcion (**2**) and 3-*O*-geranyloxyemodin (**8**) (Tchakam et al. 2012).

The roots and stems of *Harungana madagascariensis* were submitted to several phytochemical studies resulting in the isolation of vismiaquinone (**1**), physcion (**2**), madagascin (**3**), chrysophanic acid (**5**), vismiaquinone B (**6**), aloe-emodin acetate (**21**) and madagascol (**22**) (Ritchie and Taylor 1964; Iinuma et al. 1995; Kouam et al. 2006; Tih et al. 2006).

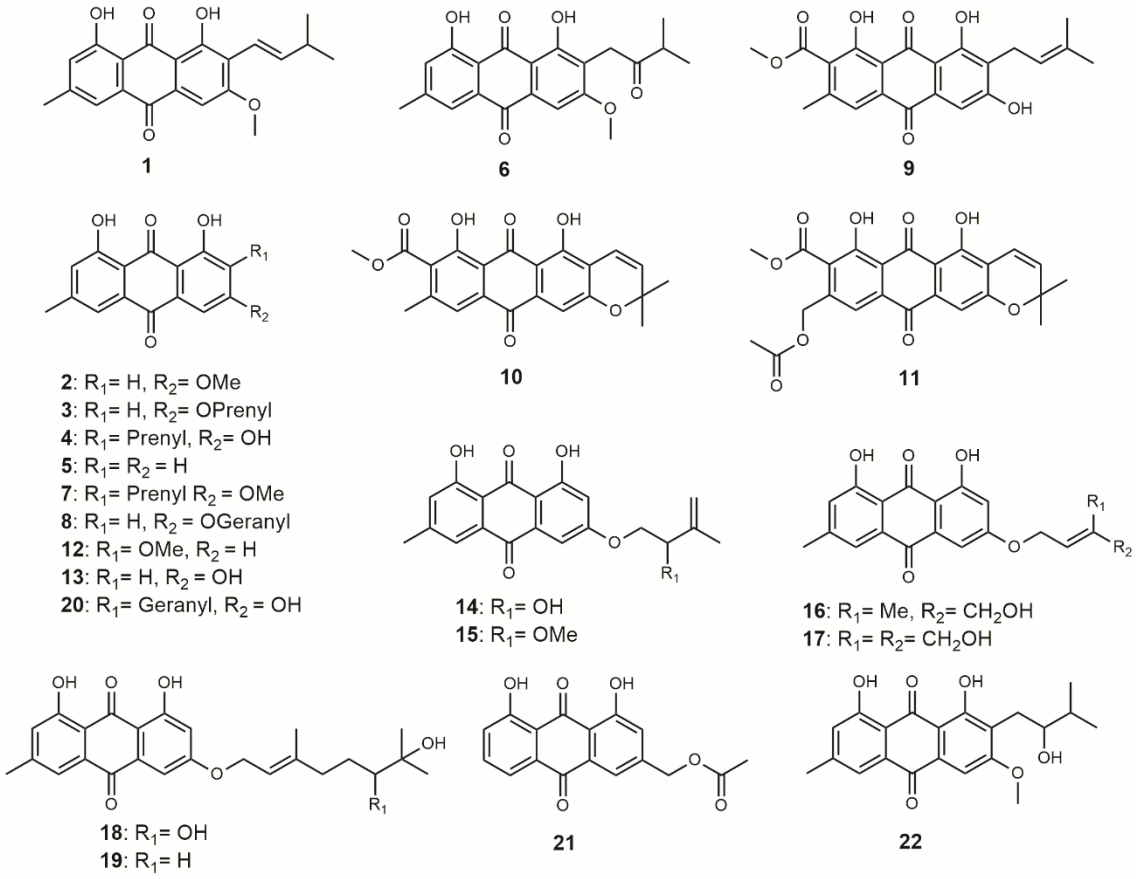

Fig. 1 Anthraquinones (**1 - 22**) from Vismieae species.

Anthrones

The prenylated anthrones ferruanthrone (**23**), ferruginin A (**24**), ferruginin B (**25**) and ferruginin C (**26**) were isolated from the chloroformic extract from the fruits of *Vismia baccifera* subsp. *ferruginea* (Kunth) Ewan (Delle Monache et al. 1979). The fruits and leaves of *Vismia macrophylla* Kunth presented the same compounds reported to *Vismia baccifera* subsp. *ferruginea*. Additionally, the new anthrone vismin (**27**) was identified in *Vismia macrophylla* (Delle Monache et al. 1980a; Hussein et al. 2003).

The fruits of *Vismia pentagyna* (Spreng.) Swan (syn. *Vismia decipiens* Schltdl. & Cham.) afforded ferruginin A (**24**) and the novels *γ*-hydroxyferruginin A (**28**) and *γ*,*γ*′-dihydroxyferruginin A (**29**) (Delle Monache et al. 1980b, c). Pinheiro et al. (1984) isolated ferruginin A (**24**), *cis*-*γ*-hydroxy-ferruginin A (**30**), vismione A (**31**) and vismione B (**32**) from the fruits of *Vismia baccifera* (syn. *Vismia mexicana*). More recently, the bioguided fractionation of methanolic extracts from the leaves of the same species lead to the isolation of deacetylvismione A (**33**) and deacetylvismione H (**34**) (Hussein et al. 2003).

A series of studies were focused in the phytochemical analysis of the roots and fruits of *Vismia guineensis*, resulting in the isolation of ferruginin A (**24**), *γ*-hydroxyferruginin A (**28**), *γ*,*γ*′-dihydroxyferruginin A (**29**), vismione H (**35**) and madagascin anthrone (**36**) (Delle Monache et al. 1980b; Botta et al. 1986a; François et al. 1999; Bilia et al. 2000). Vismione D (**37**) was isolated from the stem barks of *Vismia orientalis* (Mbwambo et al. 2004).

Furthermore, the fruits of *Vismia japurensis* accumulate the anthrones γ-hydroxyferruginin A (**28**), vismione A (**31**), acetylvismione B (**38**) and γ-hydroxyanthrone B (**39**) (Pinheiro et al. 1984; Cassinelli et al. 1986). Studies by Delle Monache et al. (1980a) and Cassinelli et al. (1986), demonstrated that the fruits of *Vismia laxiflora* Rchb.f. (syn. *Vismia falcata* Rusby) and *Vismia lindeniana* Decne. ex Turcz. are a source of ferruginin A (**24**), vismione A (**31**), vismione B (**32**) and deacetylvismione A (**33**).

From *Vismia reichardtiana* (syn. *Vismia guaramirangae*) anthrones such as ferruginin A (**24**), γ-hydroxyferruginin A (**28**), γ,γ′-dihydroxyferruginin A (**29**) and γ-hydroxyanthrone A_3 (**40**) were isolated (Delle Monache et al. 1983). Two new compounds were reported for the *n*-hexane extract from the roots of *Vismia latifolia*, named as vismianol A (**41**) and vismianol B (**42**) (dos Santos et al. 2000a). *Vismia baccifera* subsp. *dealbata* was a source of vismione A (**31**) and vismione B (**32**) (Cassinelli et al. 1986). Additionally, the leaves of *Vismia guianensis* afforded vismione A (**31**) (Gonzales Gonzales et al. 1980). Deacetylvismione A (**33**) and deacetylvismione H (**34**) were isolated from the leaves of *Vismia jefensis* N.Robson (Hussein et al. 2003).

Five species from the genus *Psorospermum* were studied until now, and several anthrones have been isolated. From the fruits and roots of *Psorospermum febrifugum* the compounds ferruginin B (**25**), vismione A (**31**), vismione D (**37**), vismione C (**43**), acetylvismione D (**44**), vismione E (**45**), vismione F (**46**) and 3-geranyloxyemodin anthrone (**47**) were obtained (Amonkar et al. 1981; Botta et al. 1983, 1985, 1986b; Cassinelli et al. 1986; Marston et al. 1986; Abou-Shoer et al. 1993; Tsaffack et al. 2009).

The species *Psorospermum glaberrimum* was also studied over the years. From the roots of this plant, Delle Monache et al. (1985) isolated a new compound named as vismione G (**48**), together with the known vismione C (**43**), vismione D (**37**) and vismione F (**46**). The same research group identified six new anthrones from the fruits of this species, named as psorolactone A (**49**), psorolactone B (**50**), homoferruginin B (**51**), 2-prenylphyscion anthrone (**52**), 6-*O*-acetyltorosachrysone (**53**) and 6-*O*-prenylvismione E (**54**). The compounds **49** and **50** possess a lactone ring in the anthracene moiety (Botta et al. 1987, 1988). The stem barks of this species also afforded acetylvismione D (**44**), 3-geranyloxyemodin anthrone (**47**) and madagascin anthrone (**36**) (Lenta et al. 2008).

Studies with the roots of *Psorospermum tenuifolium* resulted in the isolation of the new anthranol named as 10-isoprenylemodinanthran-10-ol (**55**), with the known vismione D (**37**), acetylvismione D (**44**), vismione F (**46**), acetylvismione F (**56**) (Cassinelli et al. 1986; Delle Monache et al. 1987). Two new anthrones, acetylvismione F (**56**) and 2-geranylemodin anthrone (**57**), with the previously isolated vismione D (**37**), vismione F (**46**) and vismione G (**48**) were isolated from the roots of *Psorospermum corymbiferum* (Delle Monache et al. 1985; Cassinelli et al. 1986; Zubair et al. 2011). The seeds of *Psorospermum auranticum* also demonstrate the capacity of accumulating these compounds. The novel kenganthranol E (**58**) and kenganthranol F (**59**), as well as the previously isolated ferruginin B (**25**), vismin (**27**), vismione D (**37**), kengaquinone (**60**), kenganthranol B (**61**) and harungin anthrone (**62**) were obtained (Kouam et al. 2010; Tchakam et al. 2012; Tiani et al. 2013).

The species *Harungana madagascariensis* also presented anthrones. The first studies were published in the years 1960, reporting the isolation of harunganin (**63**), madagascin anthrone (**36**) and harungin anthrone (**62**) (Stout et al. 1962; Ritchie and Taylor 1964).

Ferruginin A (**24**) was obtained from the roots, barks and leaves (Lenta et al. 2007a; Johnson et al. 2016; Tankeo et al. 2016). Additionally, kengaquinone (**60**), kenganthranol A (**64**), kenganthranol B (**61**), kenganthranol C (**65**), kenganthranol D (**66**) were identified as new anthrones (Kouam et al. 2006, 2007).

Still from *Harungana madagascariensis*, the new anthrones harunmadagascarins A – D (**67 - 70**), harunganols A (**71**), B (**72**), D (**73**), E (**74**) and F (**75**), 2-(3-methyl-1-butenyl)-1,8-dihydroxy-3-methoxy-6-methylanthrone (**76**) and bazouanthrone (**77**) were obtained from the roots, stem barks and leaves (Iinuma et al. 1995; Kouam et al. 2005, 2007; Lenta et al. 2007a; Johnson et al. 2016). Finally, Onajobi et al. (2016) identified in the stem barks, the compounds madagascenone A (**78**) and madagascenone B (**79**).

Dimeric anthranoids

The compound bianthrone A_1 (**80**) was isolated from the roots and stem barks of several species of the tribe Vismieae, as *Vismia guineensis* (Botta et al. 1986a; Bilia et al. 2000), *Vismia orientalis* (Mbwambo et al. 2004), *Psorospermum febrifugum* (Botta et al. 1985, 1986b; Tsaffack et al. 2009), *Psorospermum tenuifolium* (Delle Monache et al. 1987) and *Psorospermum glaberrimum* (Lenta et al. 2008). Bivismiaquinone (**81**) was isolated from *Vismia baccifera* (Hussein et al. 2003) and *Vismia laurentii* (Nguemeving et al. 2006; Kuete et al. 2007; Tala et al. 2007; Noungoue et al. 2009; Kemegne et al. 2017).

The roots of *Psorospermum febrifugum* afforded the dimeric compounds, named as bianthrone A_{3a} (with the enol-tautomer bianthrone A_{3b}) (**82**) (Botta et al. 1985) and febrifuquinone (**83**) (Tsaffack et al. 2009). The species *Psorospermum tenuifolium* accumulates in the roots the compounds bianthrone A_{2a} (**84**) and bianthrone A_{2b} (**85**) (Delle Monache et al. 1987). Later on, the dimers bianthrone A_{2b} (**85**) and adamabianthrone (**86**) were isolated from the barks of *Psorospermum adamauense* (Tsaffack et al. 2009). The compound **85** and the new glaberianthrone (**87**) were obtained from *Psorospermum glaberrimum* (Lenta et al. 2008). Psorantin (**88**) was isolated from the hexanic extract of *Psorospermum aurianticum* (Kouam et al. 2010). From *Harungana madagascariensis*, the bianthraquinone madagascarin (**89**) was isolated as an orange crystalline compound (Buckley et al. 1972). More recently, this species afforded the compound harunganol C (**90**) (Johnson et al. 2016).

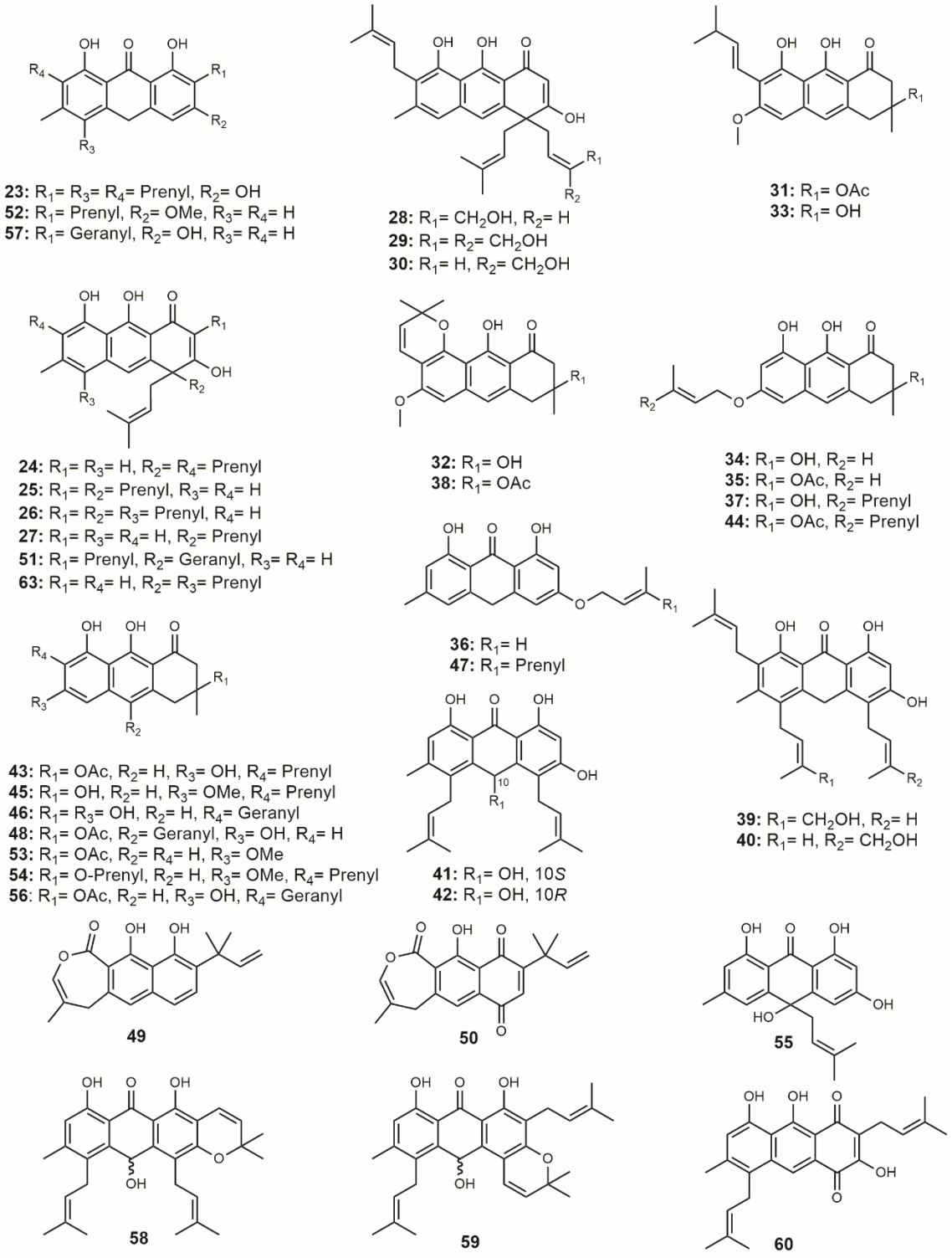

Fig. 2 Anthrones (**23 - 79**) from Vismieae species.

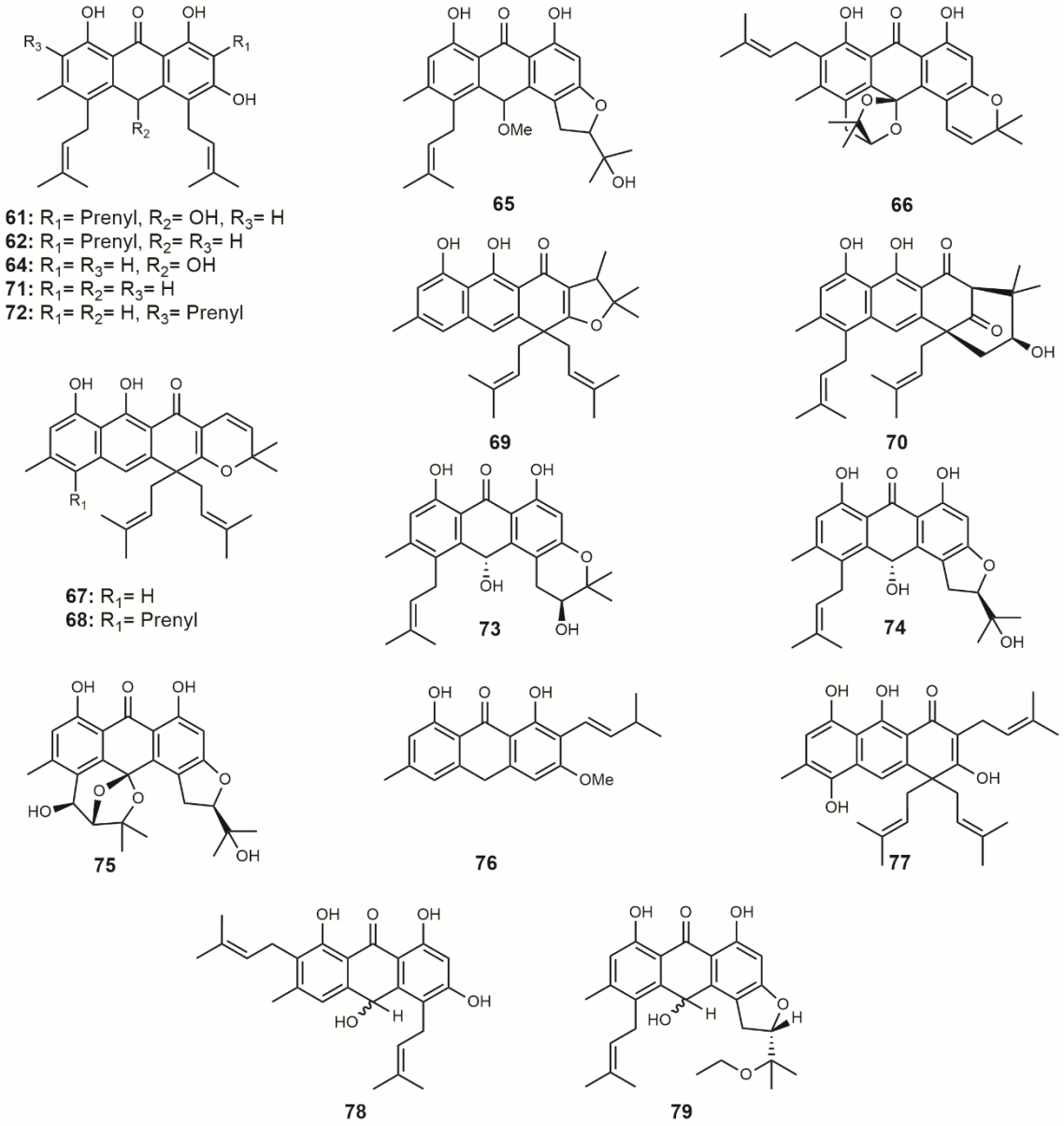

Fig. 2 Continued.

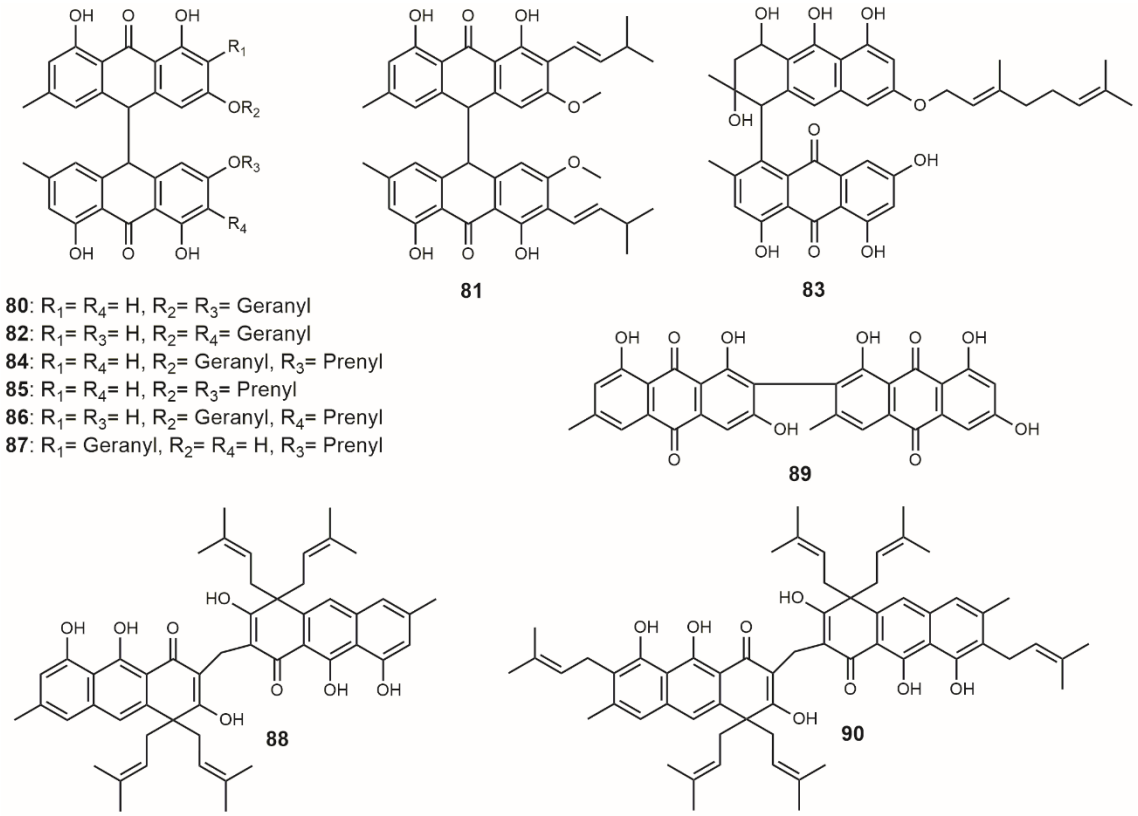

Fig. 3 Dimeric anthranoids (**80 - 90**) from Vismieae species.

Benzophenones

These compounds have been indicated as the natural precursors of xanthones. Interestingly, so far, among species of the tribe Vismieae only the American *Vismia* representatives have afforded benzophenones (Fig. 4). From the fruits of *Vismia pentagyna* (syn. *Vismia decipiens*), the new vismiaphenone A (**91**), vismiaphenone B (**92**) and isovismiaphenone B (**93**) were identified (Delle Monache et al. 1980c). Afterward, the same research group identified vismiaphenone A (**91**) and vismiaphenone C (**94**) in the roots of *Vismia reichardtiana* (syn. *Vismia guaramirangae*) (Delle Monache et al. 1983).

Fuller et al. (1999), through a bioassay-guided fractionation, isolated four new benzophenones from the leaves of *Vismia cayennensis*. These compounds were named as vismiaphenones D – G (**95** – **98**). Additionally, by the same approach, five new benzophenones were obtained from the roots of *Vismia guianensis*, the vismiaguianones A – E (**99** – **103**) (Seo et al. 2000).

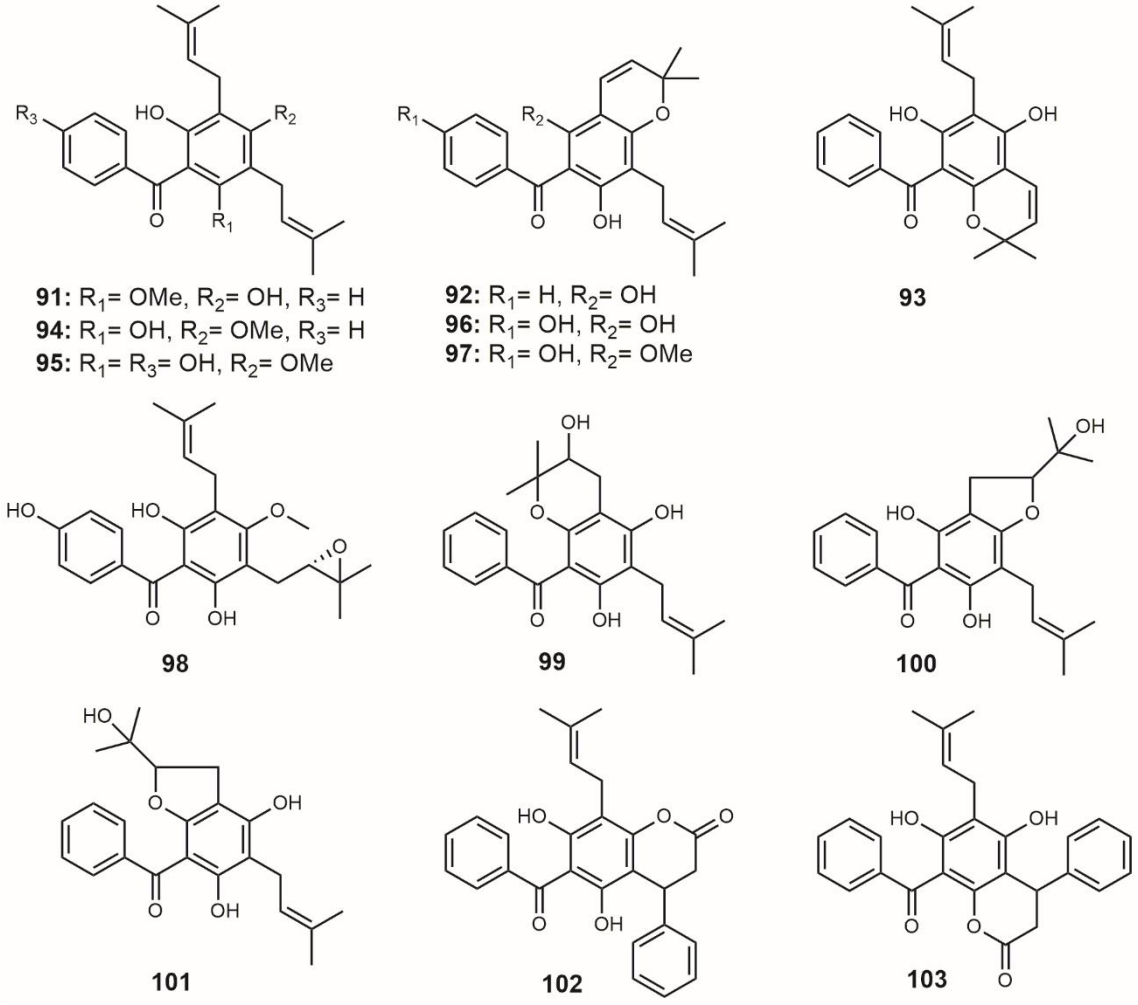

Fig. 4 Benzophenones (**91 - 103**) from Vismieae species.

Xanthones

This class of compounds presents a great diversity of structures. Therefore, it was subdivided into simple oxygenated xanthones, prenylated xanthones and xanthonolignoids (Fig. 5).

Simple oxygenated xanthones

The woody parts of *Vismia reichardtiana* (syn. *Vismia guaramirangae*) afforded a series of xanthones: 1,7-dihydroxyxanthone (also known as euxanthone) (**104**), 2-hydroxyxanthone (**105**), 2-methoxyxanthone (**106**), 2-hydroxy-1-methoxyxanthone (**107**), 1-hydroxy-7-methoxyxanthone (**108**), 1,7-dihydroxy-4-methoxyxanthone (**109**), 1,3-dihydroxy-2-methoxyxanthone (**110**), 3-hydroxy-2-methoxyxanthone (**111**), 1,5-dihydroxy-8-methoxyxanthone (**112**) and 1,5-dihydroxy-3-methoxyxanthone (**113**) (Delle Monache et al. 1983). The compound **104** was also obtained from the stems of *Vismia martiana* (Nagem and Faria 1990). The roots of *Vismia laurentii* afforded the new xanthone 1-hydroxy-5,6,7,8-tetramethoxyxanthone (named as laurentixanthone B) (**114**), along with the known 1,7-dihydroxyxanthone (**104**) (Nguemeving et al. 2006).

A new xanthone was obtained from the roots of *Vismia latifolia* as 1,4,8-trihydroxyxanthone (**115**), together with the known 1,7-dihydroxyxanthone (**104**), 1,5-dihydroxy-8-methoxyxanthone (**112**), 1,6-dihydroxy-7-methoxyxanthone (**116**) and 1,3,5,6-tetrahydroxyxanthone (**117**) (dos Santos et al. 2000b). Furthermore, from the lipophilic extract (benzene) of *Vismia parvifolia* two compounds were isolated and identified as 1,7-dihydroxyxanthone (**104**) and 1,5-dihydroxy-8-methoxyxanthone (**112**) (Nagem and de Oliveira 1997). The fractionation of the methanol extract from the stem barks of *Vismia rubescens* afforded the xanthones 1,7-dihydroxyxanthone (**104**) and 1,4-trihydroxyxanthone (**115**) (Tamokou et al. 2009). Furthermore, a new xanthone lichexanthone (**118**) was isolated from the leaves of *Vismia baccifera* subsp. *dealbata* (Díaz et al. 2010).

Some species of *Psorospermum* are also source of oxygenated xanthones. The roots of *Psorospermum febrifugum* afforded the new xanthones 1,2,4-trimethoxy-3,8-dihydroxyxanthone (**119**) and 1,2,4-trimethoxy-3-hydroxyxanthone (**120**), along with the previously isolated 3-hydroxy-2-methoxyxanthone (**111**) and 1,3,5,6-tetrahydroxyxanthone (**117**) (Habib et al. 1987a; Abou-Shoer et al. 1993). The compound 1,7-dihydroxyxanthone (**104**) was obtained from *Psorospermum aurantiacum* (Kouam et al. 2010) and *Psorospermum molluscum* (Pers.) Hochr. (Leet et al. 2008). Additionally, the last mentioned species also afforded 2-hydroxyxanthone (**105**) (Leet et al. 2008).

Xanthones of this group were also found in *Harungana madagascariensis*. The plant afforded 1,7-dihydroxyxanthone (**104**) (Ritchie and Taylor 1964; Kouam et al. 2006, 2007) and 1,5,6-trihydroxy-7-methoxyxanthone (**121**) (Iinuma et al. 1995).

Prenylated xanthones

The first prenylated xanthones of Viemieae were achieved from the roots of *Vismia guineensis*. Four new compounds were identified and named as xanthone V_1 (**122**), xanthone V_2 (**123**), xanthone V_{1a} (**124**) and xanthone V_{2a} (**125**) (Botta et al. 1986a). Additionally, six novel xanthones, 1,8-dihydroxy-3-(2-methoxy-3-methylbut-3-enyloxy)-6-methylxanthone (**126**), 1,8-dihydroxy-3-geranyloxy-6-methylxanthone (**127**), 1,8-dihydroxy-3-isoprenyloxy-6-methylxanthone (**128**), 1,8-dihydroxy-3-(3,7-dimethyl-7-methoxyoct-2-enyloxy)-6-methyl xanthone (**129**), 1,8-dihydroxy-3-(E-3-hydroxymethylbut-2-enyloxy)-6-methylxanthone (**130**) and 1,8-dihydroxy-3-(3-hydroxymethyl-4-hydroxybut-2-enyloxy)-6-methylxanthone (**131**) were isolated by Bilia et al. (2000).

The studies with the roots and stem barks of *Vismia laurentii* resulted in the isolation of the novel compounds laurentixanthones A (**132**) and C (**133**), with the known xanthone V_1 (**122**), 6-deoxyisojacareubin (**134**) and O^1-demethyl-3′,4′-deoxypsorospermin-3′,4′-diol (**135**) (Nguemeving et al. 2006; Kuete et al. 2007; Tala et al. 2007). The compound 6-deoxyjacareubin (**136**) was isolated from the leaves of *Vismia latifolia* (Doriguetto et al. 2001).

The species *Psorospermum febrifugum* afforded several prenylated xanthones. From the roots, Kupchan et al. (1980) and Pachuta and Cooks (1986) obtained the new dihydrofuranoxanthones psorospermin (**137**) and 3′,4′-deoxypsorospermin-4′-chloro-3′-ol (**138**). Subsequently, novel structures were obtained from the same plant material, and named as 3′,4′-deoxypsorospermin (**139**), 3′,4′-deoxypsorospermin-3′,4′-diol (**140**) and O^5-methyl-3′,4′-deoxypsorospermin-3′-ol (**141**) (Habib et al. 1987b).

The bioassay-guided fractionation of the ethanolic extract from the roots of *Psorospermum febrifugum* lead to a series of new prenylated xanthones, identified as O^1-demethyl-3′,4′-deoxypsorospermin-3′,4′-diol (**135**), O^5-methyl-3′,4′-deoxypsorospermin-3′,4′-diol (**142**), O^4-methyl-3′,4′-deoxypsorospermin-3′,4′-diol (**143**), O^4-ethyl-3′,4′-deoxypsorospermin-3′,4′-diol (**144**), 3′,4′-deoxyisopsorospermin-3′,4′, 5′-triol (**145**), 5′-hydroxypsorospermin (**146**) and 4′-chloro-5-O-methyl-3′,4′-deoxypsorospermin-3′,5′-diol (**147**) (Abou-Shoer et al. 1988). Later on, the same research group isolated more xanthones, identified as psorofebrin (**148**), 5′-hydroxyisopsorofebrin (**149**), 4′-O-acetyl-3′,4′-deoxypsorospermin-3′,4′-diol (**150**) and 3′,4′-deoxypsorospermin-3′,4′,5′-diol (**151**) (Abou-Shoer et al. 1989a, 1993).

The phytochemical analysis of *Psorospermum molluscum* resulted in the isolation of three new xanthones, named as 3′,4′-deoxy-4′-chloropsoroxanthin-(3′,5′-diol) (**152**), psoroxanthin (**153**) and 8-(4′hydroxyprenyl)-1,7-dihydroxyxanthone (**154**) (Leet et al. 2008).

Xanthonolignoids

This type of compounds represents a rare class of natural compounds, with few different structures reported. A study with the extract from the roots of *Psorospermum febrifugum* lead to the isolation of seven xanthonolignoids. These compounds were identified as kielcorin (**155**), cadensin D (**156**), isocadensin D (**157**), isocadensin D monoacetate (**158**), cadensin F (**159**), 6-hydroxyisocadensin F (**160**) and cadensin G (**161**) (Abou-Shoer et al. 1989b). Furthermore, the roots of *Harungana madagascariensis* afforded the compound cadensin C (**162**) (Iinuma et al. 1996).

Terpenes

Sesquiterpenes

This section encompasses compounds that were isolated from extracts of Vismieae species and/or identified by gas - chromatography – mass spectrometry (GC-MS) analysis of essential oils. Only compounds present in amounts greater than 5% are cited (Fig. 6). In the essential oils of *Vismia* and *Harungana*, monoterpenes were not identified. Only one species of *Psosorospermum* presented these compounds, but in very small quantities (Zubair et al. 2010).

The barks of *Vismia reichardtiana* (syn. *Vismia guaramirangae*) were extracted with benzene and afforded *β*-caryoplyllene (**163**), isocaryophyllene (**164**) and humulene (**165**) (Camele et al. 1982). In a study developed by Pinheiro et al. (1984), the fruits of three species of *Vismia* were screened resulting in the isolation of some terpenes. The compounds *α*-selinene (**166**) and *β*-selinene (**167**) were obtained from *Vismia japurensis*. *Vismia cayennnensis* afforded isocaryophyllene (**164**), *β*-selinene (**167**) and *trans*-*α*-farnesene (**168**). Additionally, isocaryophyllene (**164**) and cis-*α*-farnesene (**169**) were isolated from *Vismia baccifera* (syn. *Vismia mexicana*).

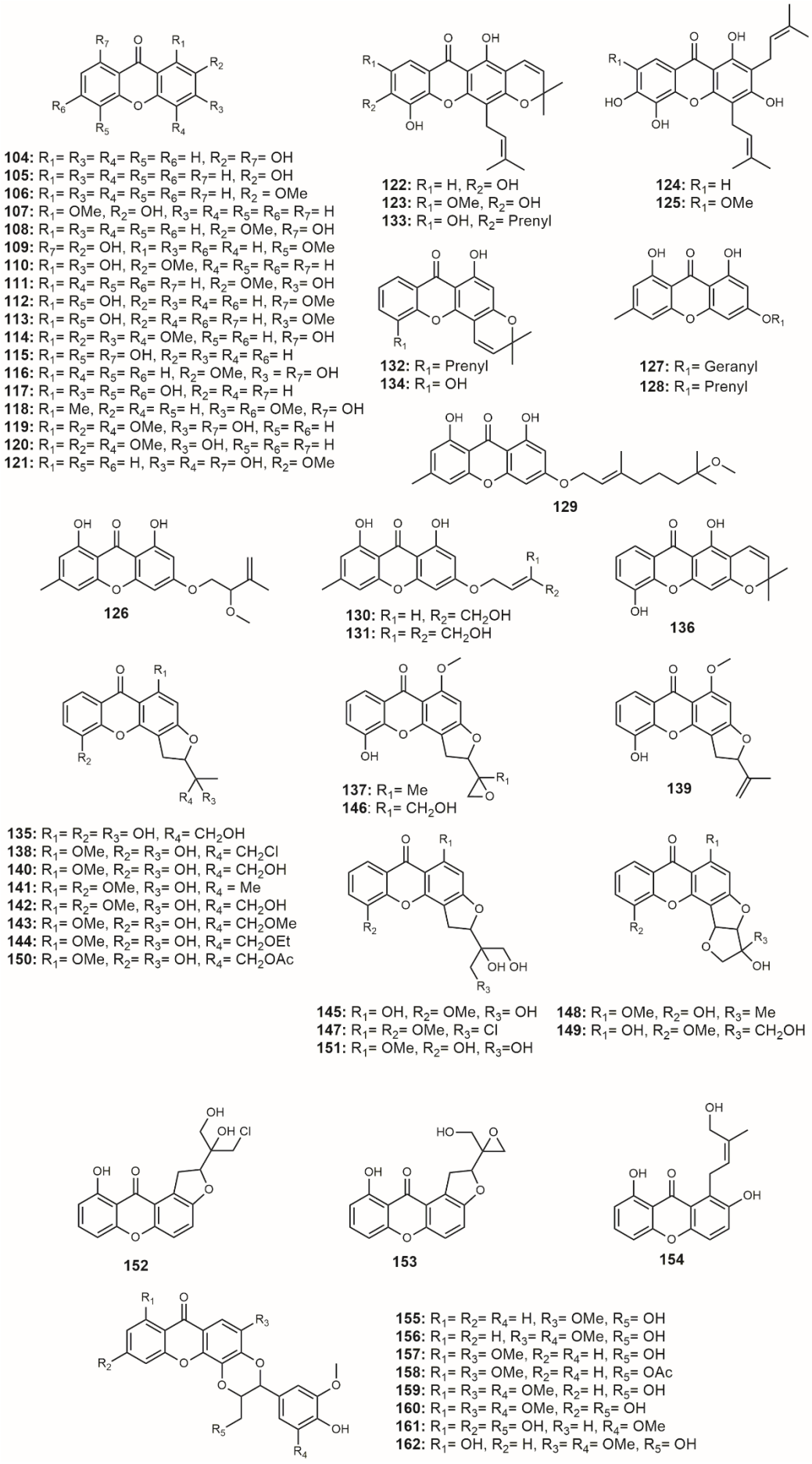

Fig. 5 Xanthones (**104 - 162**) from Vismieae species.

The essential oil from the fruits of *Vismia baccifera* presented, as main compounds, *β*-caryophyllene (**163**), *cis*-cadin-1,4-diene (**170**) and *trans*-cadin-1,4-diene (**171**) (Rojas et al. 2011a). Two studies analyzed the essential oils from the leaves and fruits of *Vismia macrophylla*. From the leaves, Rojas et al. (2011b) identified *β*-caryophyllene (**163**), *α*-selinene (**166**), germacrene-D (**172**) and *β*–elemene (**173**) as the main compounds. Subsequently, the oil from fruits and leaves afforded the compounds isocaryophyllene (**164**), *δ*-cadinene (**174**), *γ*-bisabolene (**175**) and *β*-bisabolol (**176**) (Buitrago et al. 2015). Recently, the essential oil from the dried leaves of *Vismia guianensis* was analyzed and caryophyllene oxide (**177**) and humulene epoxide II (**178**), were identified as the main compounds (Costa et al. 2017).

Some sesquiterpenes were identified in *Psorospermum* species. Paradisiol (**179**) was obtained from *Psorospermum aurantiacum*, *α*-selinene (**166**) and *β*-selinene (**167**) from *Psorospermum febrifugum*, and *β*-caryophyllene (**163**) from *Psorospermum corymbiferum* (Botta et al. 1983; Kouam et al. 2010; Zubair et al. 2010). The essential oils from the leaves, fruits and stem barks of *Harungana madagascariensis* were also submitted to GC-MS analyses. The results indicated that *β*-caryophyllene (**163**), humulene (**165**) and *cis*-*α*-farnesene (**169**), were the compounds accumulated in higher amounts (Gbolade et al. 2009).

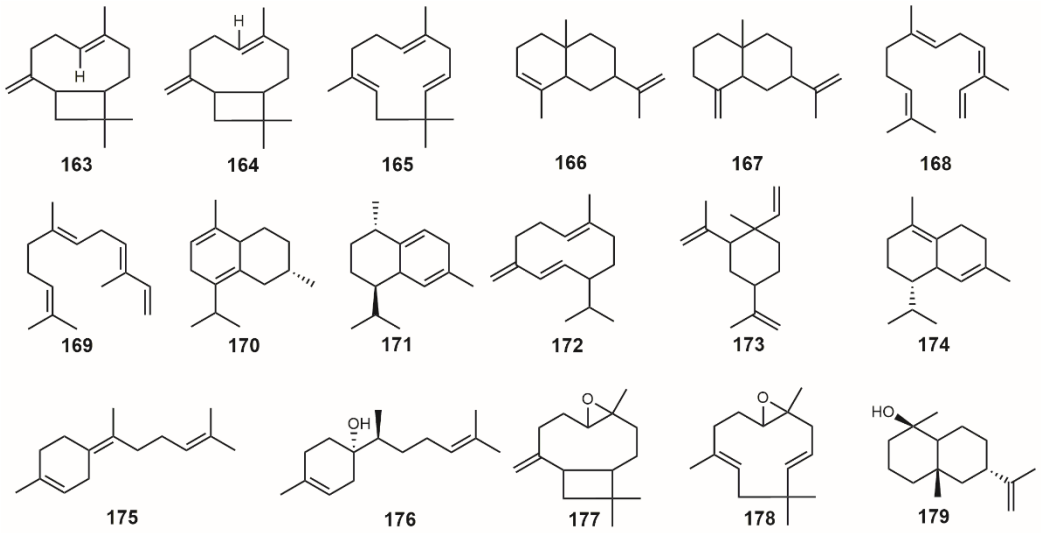

Fig. 6 Sesquiterpenes (**163 - 179**) from Vismieae species.

Triterpenes

The structures of triterpenes (**180** – **196**) isolated from Vismieae are shown in the Fig. 7. The leaves of *Vismia guianensis* were studied and *β*-sitosterol (**180**), *β*-amyrine (**181**) and lupeol (**182**) were obtained (Gonzales Gonzales et al. 1980; Lins et al. 2016). The barks of *Vismia reichardtiana* (syn. *Vismia guaramirangae*) accumulate the compounds *β*-sitosterol (**180**) and dammaradienol (**183**) (Camele et al. 1982). Bilia et al. (2000) and Tala et al. (2013) screened the roots and seeds of *Vismia guineensis*, isolating *β*-sitosterol (**180**), lupeol (**182**), betulinic acid (**184**), ursolic acid (**185**), 2*α*-hydroxyursolic acid (**186**), tormentic acid (**187**), stigma-4-en-3-one (**188**) and stigmasterol (**189**).

A series of studies have been carried out with *Vismia laurentii* along the years. From this plant the triterpenes dammaredienol (**183**) (Tala et al. 2007), betulinic acid (**184**), epifriedelinol (**190**), stigma-7,22-dien-3-ol (**191**) (Noungoue et al. 2009), friedelin (**192**) (Nguemeving et al. 2006; Kuete et al. 2007; Wabo et al. 2007), stigmasterol (**189**) (Noungoue et al. 2008) and tirucalla-7,24-dien-3-one (**193**) (Noungoue et al. 2007, 2009) were identified. The compounds **180**, **183**, **184** and **192** were obtained from the aerial parts of *Vismia martiana* (Nagem and Faria 1990).

From the barks of the Brazilian native species *Vismia cayannensis*, *β*-sitosterol (**180**), *β*-amyrine (**181**) and betulinic acid (**184**) were obtained. Further, in the same study, the wood of *Vismia japurensis* were screened showing the presence of epifriedelinol (**190**) and friedelin (**192**) (Miraglia et al. 1981). The stems of *Vismia parvifolia* afforded *β*-sitosterol (**180**), betulinic acid (**184**), epifriedelinol (**190**) and friedelin (**192**) (Nagem and de Oliveira 1997). The compounds **190** and **192** were also obtained from *Vismia baccifera* subsp. *dealbata* (Salas et al. 2007) and *Vismia rubescens* (Tamokou et al. 2009).

The species *Psorospermum glaberrimum* and *Psorospermum aurantiacum* have a similar triterpenes composition, presenting betulinic acid (**184**), epifriedelinol (**190**), and friedelin (**192**) (Lenta et al. 2008; Kouam et al. 2010). The leaves and stem barks of *Psorospermum androsaemifolium* accumulate *β*-amyrine (**181**), *α*-amyrine (**194**) and lupeol acetate (**195**) (Poumale et al. 2008, 2011). Diosgenin (**196**) was isolated from the roots of *Psorospermum corymbiferum* (Zubair et al. 2011).

Along the years, various research groups investigated *Harungana madagascariensis* and some triterpenes as *β*-sitosterol (**180**), lupeol (**182**), betulinic acid (**184**), friedelin (**192**) were isolated (Ritchie and Taylor 1964; Buckley et al. 1972; Kouam et al. 2005; Lenta et al. 2007a; Tankeo et al. 2016).

Flavonoids

Some flavonoids and anthocyanidins were isolated from species of the tribe Vismieae (Fig. 8). The leaves of *Vismia guianensis* provided the flavanol *epi*-catechin (**197**) and the anthocyanidin procyanidin B_2 (**198**) (Gonzales Gonzales et al. 1980). Apigenin-6*C*-*β*-D-glucopyranoside (**199**) was obtained from the roots of *Vismia guineensis* (Bilia et al. 2000). *Vismia laurentii* and *Vismia parvifolia* afforded kaempferol (**200**) (Nguemeving et al. 2006; Kuete et al. 2007) and quercetin (**201**) (Nagem and de Oliveira 1997), respectively.

The phytochemical analysis of leaves and stem barks of *Psorospermum androsaemifolium* resulted in the identification of new flavonoids, named as 3'-(2",4"-dihydroxybenzyloxy) acanthophorin B (**202**), 3'-(4"'-(3"',4"'-dihydroxyphenoxy)-2""hydroxyphenoxy) acanthophorin B (**203**) and *β*-2,3',4',4',6-hexahydroxy-alpha-(alpha-L-rhamnopyranosyl) dihydrochalcone (**204**), along with the known quercetin (**201**) and acantophorin B (**205**) (Poumale et al. 2008, 2011).

From the stems of *Psorospermum densipunctatum* *epi*-catechin (**197**) and the anthocyanidins, procyanidin B_2 (**198**), procyanidin A_2 (**206**), procyanidin B_1 (**207**) and proanthocyanidin C_1 (**208**) were obtained (Tanemossu et al. 2015). Astilbin (**209**) and

kaempferol-3-*O*-*β*-glucopyranoside (**210**) were identified from *Harungana madagascariensis* (Iinuma et al. 1995; Moulari et al. 2006; Tankeo et al. 2016).

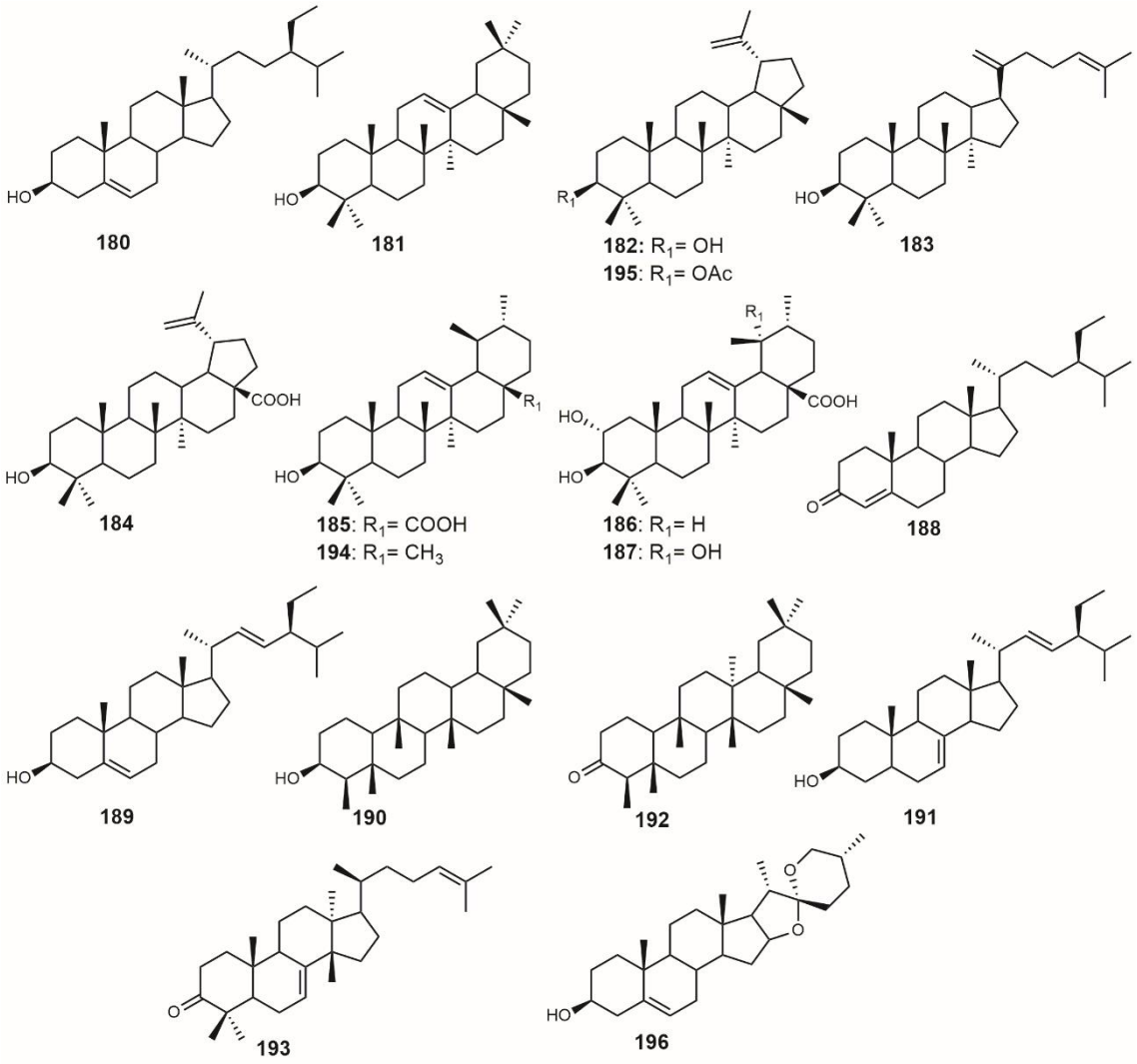

Fig. 7 Triterpenes (**180 - 196**) from Vismieae species.

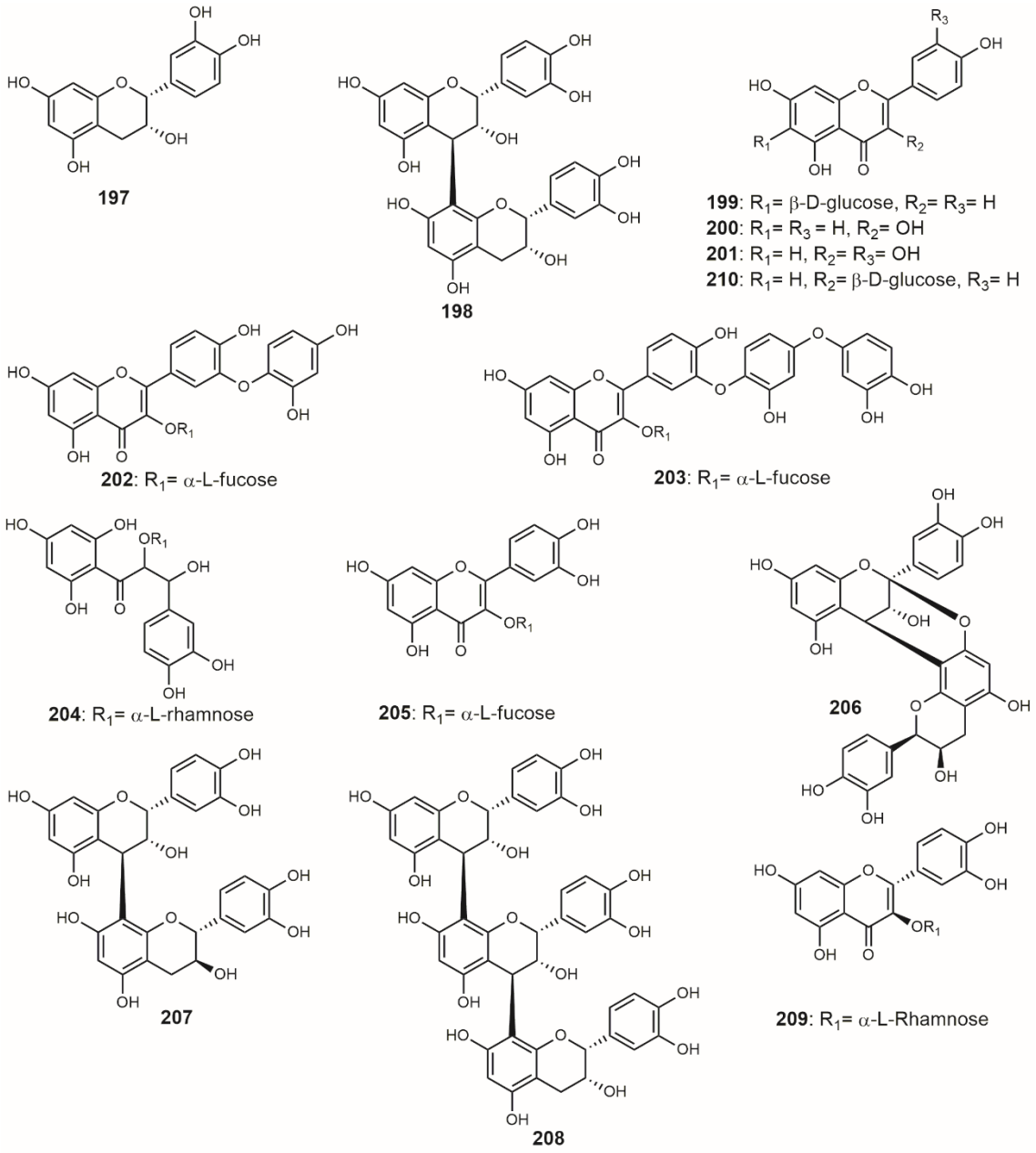

Fig. 8 Flavonoids (**197 - 210**) from Vismieae species.

Miscellaneous compounds

Compounds from other classes have also been found in Vismieae species. Their structures are presented in fig. 9.

The woods and barks of *Vismia reichardtiana* (syn. *Vismia guaramirangae*) afforded three lignan compounds that were identified as sesamin (**211**), 5,5′-methoxy-sesamin (**212**) and syringaresinol (**213**) (Camele et al. 1982; Delle Monache et al. 1983). The compound **211** was also obtained from *Vismia baccifera* subsp. *Dealbata* (Salas et al. 2007).

In the study by Seo et al. (2000), the chloroformic extract of the roots were screened affording two new coumarins, named as vismiaguianin A (**214**) and vismiaguianin B (**215**). The phenolic acids 3,4-dihydroxy-benzoic acid (**216**) and shikimic acid (**217**) were obtained from *Vismia parvifolia* (Nagem and de Oliveira 1997).

The long-chain fatty compounds 12-hentricontanol (**218**) and hentricontane (**219**) were isolated from the leaves of *Psorospermum androsaemifolium* (Poumale et al. 2008). Octacosanol (**220**) was afforded from the leaves of *Psorospermum auranticum* (Tchakam et al. 2012). From the stem barks of *Harungana madagascariensis*, the phenolic acid methyl-3-formyl-2,4-dihydroxy-6-methyl-benzoate (**221**) was obtained (Kouam et al. 2005).

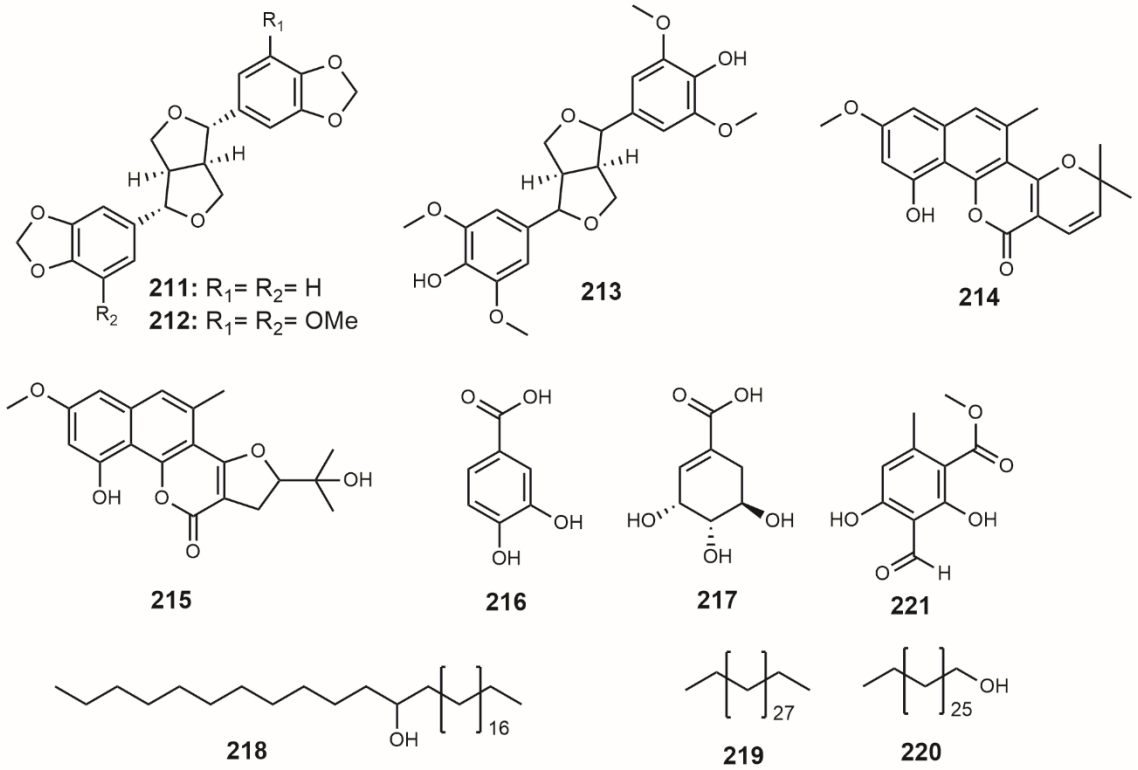

Fig. 9 Miscellaneous compounds (**211 -221**) from Vismieae species.

Biological properties

Along the years, extracts of species from the tribe Vismieae, as well as isolated compounds have been evaluated concerning their biological properties, such as cytotoxic and anti-proliferative, antimicrobial, anti-diabetic, among others. The main outcomes are described in the following section.

Cytotoxic and anti-proliferative activities

Cancer is one of the main causes of morbidity and mortality all over the world (Lozano et al. 2012). The treatment of this disease is currently performed with tumor surgery, when recommended, radiotherapy and chemotherapy. The major disadvantages of chemotherapy are the drug resistance and the side effects which can limit the treatment. Thus, new alternatives to medicines currently available are needed. In this regard, natural products emerge as excellent options, since most of anticancer drugs that are in clinical practice are originated from compounds isolated from plants, marine organisms and microorganisms (Rayan et al. 2017). In order to verify the anticancer activity, the compounds are tested on cells (cancer and normal cell lines) and experimental animals prior to be analyzed in clinical trials.

Regarding the species of the tribe Vismieae, several extracts and isolated compounds have been evaluated for the cytotoxicity in cancer cell lineages. In this sense, methanolic extracts from young leaves of *Vismia baccifera*, *Vismia jefensis* and *Vismia macrophylla* demonstrated cytotoxic effects on MCF-7 (breast cancer) (GI_{50} 2.4, < 1 and 0.5 µg/mL, respectively), H-460 (lung cancer) (GI_{50} 4.4, 1.3 and 0.5 µg/mL, respectively) and SF-268 (central nervous system cancer) (GI_{50} 3.7, 2.3 and 0.4 µg/mL, respectively) lineages (Hussein et al. 2003). Additionally, aqueous extracts from stems and fruits of the American *Vismia guianensis* demonstrated 80 - 100% of lethality (at 100 µg/mL) in MCF-7 and KM-12 (human adenocarcinoma colon cancer) cell lines (Suffredini et al. 2007a, b). The methanolic extracts from stems and root barks of other *Vismia* species, the African *Vismia guineensis*, showed cytotoxicity against MRC-5 (human lung fibroblast cancer) lineage (CC_{50} 8.6 and 5.2 µg/mL, respectively) (Traore et al. 2013). Still addressing this genus, Lizcano et al. (2015) reported the activity of an aqueous extract from the leaves of *Vismia baccifera* against HepG2 (human liver cancer) (LC_{50} 35 µg/mL), that may be related to the deregulation of the antioxidant status and accumulation of reactive oxygen species, especially hydrogen peroxide (Trepiana et al. 2018).

Two studies investigating the cytotoxic activity of *Harungana madagascariensis* extracts were found in literature. In the first, an aqueous extract from the stems was effective in MRC-5 cells (CC_{50} 20.06 µg/mL) (Muganza et al. 2012). The last report assessed the cytotoxicity of a dichloromethane : methanol (1:1) extract from stem barks of this plant in a panel of drug-sensitive and multidrug-resistant cells, presenting better results against CCRF-CEM (leukemic lymphoblasts) cells (IC_{50} 9.11 ± 0.63 µg/mL) (Ochwang'i et al. 2018).

Among the compounds isolated from species of the tribe Vismieae to which cytotoxic activity has been attributed, xanthones and anthracenic derivatives, in particular, may become interesting scaffolds to the development of new anticancer drugs. In this context, Abou-Shoer et al. (1988) reported the activity of 4′-chloro-5-O-methyl-3′,4′-deoxypsorospermin-3′,5′-diol (**147**) ($ED_{50} < 10^{-5}$ µg/mL) in addition to 5′-hydroxypsorospermin (**146**) (ED_{50} 7 x 10^{-5}µg/mL), O^4-methyl-3′,4′-deoxypsorospermin-3′,4′-diol (**143**) (ED_{50} 2 x 10^{-4} µg/mL), O^4-ethyl-3′,4′-deoxypsorospermin-3′, 4′-diol (**144**) (ED_{50} 3 x 10^{-3}µg/mL) and psorospermin (**137**) (ED_{50} 1 x 10^{-4}µg/mL), obtained from the root barks of *Psorospermum febrifugum*, against 9PS cancer cell lines. The activity of the compound **137** had already been demonstrated in a model of mouse leukemia (P388) (8 mg/kg), as well as in a cytotoxicity assay against KB (keratin-forming tumor) cells line (ED_{50} 1 x 10^{-1}µg/mL) (Kupchan et al. 1980). A study by Nguyen et al. (2009) indicated that psorospermin (**137**) and its derivatives can bind to the N-7 position of guanine units in the presence of topoisomerase II to exert the anticancer effect.

In 2008, Leet et al. described the cytotoxic effect of 3′,4′-deoxy-4′-chloropsoroxanthin-(3′,5′-diol) (**152**) and psoroxanthin (**153**) obtained from *Psorospermum molluscum* in three

cancer cell lineages (A2780, ovarian carcinoma; HCT-116, human colon cancer and ABAE, bovine endothelial cell). The best results were found for compound **152**, which was active against all cell lines (ABAE, IC_{50} 0.004 µM; A2780, IC_{50} 0.042 µM; HCT-116, IC_{50} 0.068 µM). Other compound, xanthone V_1 (**122**), isolated from the seeds of *Vismia laurentii* presented doxorubicin-like cytotoxic effect in MCF-7 (breast cancer), HeLa and Caski (cervix cancer) lines (Kuete et al. 2011).

Along with xanthones, the anthracenic derivatives represent good structural scaffolds aiming at discovering new anticancer drugs. The first study conducted with compounds of this class dated from 1981, in which the activity of 3-*O*-geranyloxyemodin (**8**), obtained from the roots of *Psorospermum febrifugum* was verified in the P-388 mouse leukemia system (Amonkar et al. 1981). After that, Marston et al. (1986) demonstrated the cytotoxicity of acetylvismione D (**44**) and vismione D (**37**), also from the root barks of *Psorospermum febrifugum*, in Co-115 (human colon carcinoma) cell cultures (IC_{50} 0.38 and 0.15 µg/mL, respectively). In the same year, a survey carried out with *Psorospermum* and *Vismia* species identified a series of compounds endowed with cytotoxic activity in cancer cell lines. Acetylvismione D (**44**), also isolated from fruits of *Vismia japuresis*, was active in KB (IC_{50} 5 µg/mL) and P388s (murine leukemic sensitive cells) (IC_{50} 1.8 µg/mL) lines. From the fruits of *Vismia baccifera*, vismione A (**31**) demonstrated cytotoxicity against KB (IC_{50} 0.25 µg/mL), P388s (IC_{50} 0.45 µg/mL) and P388r (murine leukemic resistant cells) (IC_{50} 1.1 µg/mL) lineages, whereas vismione C (**43**), from the leaves, was active only in KB cells (IC_{50} 2.1 µg/mL). Still searching cytotoxic compounds in *Vismia* species, deacetylvismione A (**33**), obtained from the fruits of *Vismia lindeniana*, presented activity in all cell lines tested (KB, IC_{50} 0.7 µg/mL; P388s, IC_{50} 0.40 µg/mL; P388r, IC_{50} 0.30 µg/mL). Finally, acetylvismione F (**56**) from the roots of *Psorospermum corymbiferum* showed cytotoxicity against KB (IC_{50} 2.8 µg/mL) and P388s (IC_{50} 2 µg/mL) cells (Cassinelli et al. 1986).

In 2003, Hussein et al. demonstrated the cytotoxic activity of ferrugin C (**26**), ferruginin A (**24**), ferruginin B (**25**), vismin (**27**) and harunganin (**63**) isolated from the young leaves of *Vismia macrophylla* against three cancer cell lines, MCF-7, H-460 and SF-268 presenting a range of GI_{50} from 4 to 7.3 µg/mL. In the same study, vismione B (**32**), deacetylvismione A (**33**) and deacetylvismione H (**34**) obtained from young leaves of *Vismia baccifera* were also tested against the cell lineages described above, showing a range of GI_{50} from 0.4 to 2.8 µg/mL.

Antioxidant activity

The oxidative stress results from the disequilibrium between the reactive oxygen species production and the endogenous antioxidant defenses. This stress is one of the main factors to the development of chronic and degenerative ailments such as cancer, cardiovascular and neurodegenerative diseases. Many natural products, for example the phenolic compounds, are potential antioxidants that can be used in the prevention and therapy of disorders related to oxidative stress (Chen et al. 2016).

Extracts and compounds obtained from different parts of species belonging to the tribe Vismieae have been assessed for their antioxidant potential and some of these natural products present significant free radical scavenging activities. Antioxidant assays including DPPH, ABTS, FRAP, ORAC, among others, were carried out *in vivo* and *in vitro*.

Most of the studies were performed aiming at evaluating the potential of polar extracts, although some of them have reported the activity of isolated compounds. In a research performed by Alvarez et al. (2008), extracts obtained from the berries of *Vismia baccifera* subsp. *ferruginea* and *Vismia guianensis* using solvents of different polarities (petroleum ether, ethyl acetate and methanol) were subjected to antioxidant activity assays (DPPH and ABTS). Ethyl acetate extracts, of both species, presented the best results (IC_{50} 4.46 ± 0.19 and 3.72 ± 0.13 μg/mL in DPPH; IC_{50} 4.16 ± 0.07 and 5.86 ± 0.72 μg/mL in ABTS) using butylated hydroxytoluene (BHT) as positive control (IC_{50} 7.00 ± 0.50 μg/mL in DPPH; IC_{50} 2.00 ± 0.20 μg/mL in ABTS).

The aqueous extracts of the stems (IC_{50} 7.9 ± 1.7 μg/mL) and leaves (IC_{50} 5.5 ± 1.7 μg/mL) of *Vismia baccifera* were able to inhibit the lipid peroxidation, which was evidenced in the TBARS assay. These results are relevant since the values were comparable to gallic acid (IC_{50} 8.8 μg/mL), a known antioxidant molecule (Lizcano et al. 2012). In 2016, the activity of different extracts (hexane, chloroform, ethyl acetate, ethanol and methanol : water (1:1)) from aerial parts of *Vismia guianensis* was evaluated using DPPH and ABTS methodologies. It was observed that ethyl acetate (EC_{50} 6.61 ± 0.03 and EC_{50} 6.82 ± 0.11 μg/mL in DPPH and ABTS, respectively) and ethanolic extracts (EC_{50} 6.76 ± 0.05 and EC_{50} 8.07 ± 0.11 μg/mL in DPPH and ABTS, respectively) presented better results in comparison to the less polar extracts, probably due to the high content of phenolic compounds (Lins et al. 2016). Furthermore, aqueous extracts of *Vismia japurensis* also presented antioxidant activity employing DPPH test (EC_{50} 4.8 ± 0.2 μg/mL) (Santana et al. 2015).

Still addressing the genus *Vismia*, ethanolic extracts from distinct parts (leaves, stems, stem barks, flowers or whole fruits) of *Visma cauliflora* were tested concerning their antioxidant potential. All extracts efficiently scavenged superoxide radicals ($O_2^{\cdot-}$) at concentrations ranged from 10.3 to 53.8 μg/mL. The stems (IC_{50} 10.3 ± 0.4 μg/mL), stem barks (IC_{50} 11.2 ± 0.4 μg/mL) and flowers (IC_{50} 10.2 ± 0.4 μg/mL) presented results comparable to quercetin (IC_{50} 14 ± 1 μg/mL). Regarding the activity against hydrogen peroxide radical ($H_2O_2^{\cdot-}$), the flowers extract seems to be the most active (IC_{50} 106.4 ± 0.3 μg/mL) showing higher efficiency than ascorbic acid (IC_{50} 116.50 ± 0.05 μg/mL). As verified in the experiment with $H_2O_2^{\cdot-}$, the best result against the hypochlorous acid radical ($HOCl^{\cdot-}$) was obtained with the flowers extract (IC_{50} 2.6 ± 0.2 μg/mL). The activities of all extracts *versus* the other radicals tested (singlet oxygen ($O_2^{\cdot-}$), nitric oxide ($NO^{\cdot-}$) and peroxynitrite ($ONOO^{\cdot-}$)) were only moderated. This is the first report on the antioxidant activity inherent to *Vismia cauliflora* extracts, with flowers and stem barks exhibiting the most prominent radical scavenging capacity which may be related to the high amount of phenolic constituents present in these samples (Ribeiro et al. 2015a).

In another study carried out with ethanolic extracts from stem barks and flowers of *Vismia cauliflora*, the modulation of neutrophil's oxidative burst was determined by the oxidation of specific probes by reactive species. In this work, the potential of inhibition of the oxidative damage in human erythrocytes was also assessed. The results showed that the extracts were capable to prevent the oxidative burst in activated human neutrophils (IC_{50} < 15 μg/mL). Regarding the oxidative damage in human erythrocytes, the extracts succeeded in minimize the hemoglobin oxidation and lipid peroxidation, provoked by tert-butyl hydroperoxide (IC_{50} 2.7 to 18 μg/mL) (Ribeiro et al. 2015b). Altogether, these studies with *Vismia cauliflora* reinforce the popular use of the stem barks and flowers by indigenous population from Amazonian forest to heal topical skin diseases which may be related to oxidative damage (Chisté et al. 2014).

Psorospermum species also present compounds endowed with antioxidant capacity. In this context, an ethyl acetate extract from the leaves of *Psorospermum aurianticum* was tested against DPPH radical and showed an IC_{50} of 6.35 ± 0.10 μg/mL. In addition, the compound kenganthranol B (**61**) isolated from this extract, also demonstrated antioxidant action (IC_{50} of 21.93 ± 5.98 μg/mL) using the same methodology. The higher value of IC_{50} achieved with the isolated compound indicates that the activity of the extract may be related to the action of other compounds alone or in a relation of addition/synergism (Tchakam et al. 2012). Further studies with the same species, demonstrated that a dichlorometane : methanol (1:1) extract from the stems and barks was able in scavenging hydroxyl radicals (OH^-) (IC_{50} 29.70 ± 5.37 μg/mL) in the same level of ascorbic acid (IC_{50} 30.80 ± 0.0 μg/mL). The reducing power ability of this extract (IC_{50} 1.43 ± 0.02 μg/mL) was also compared with the standard molecule (IC_{50} 1.41 ± 0.05 μg/mL). Interestingly, the effect of the extract on inhibition of lipid peroxidation (IC_{50} 10.8 ± 0.0 μg/mL) was better than that obtained with ascorbic acid (IC_{50} 19.5 ± 2.12 μg/mL). In addition to antioxidant activity, the extract presented a considerable elastase inhibitory effect (77.58 ± 0.23%) at 100 μg/mL. These results provide evidence on skin anti-aging potential of *Psorospermum aurianticum* corroborating with the use in folk medicine (Manjia et al. 2019). Aiming at evaluating the antioxidant potential of a methanolic extract of *Psorospermum febrifugum*, Konan et al. (2014) performed the DPPH methodology and found an IC_{50} of 2.3 ± 0.1 μg/mL, which was comparable to ascorbic acid (IC_{50} 2.9 ± 0.2 μg/mL).

Concerning *Harungana madagascariensis*, the literature brings several studies into antioxidant properties of extracts and isolated compounds. In 2005, Kouam et al. demonstrated that harunmadagascarin A (**67**) and harunganol B (**72**), obtained from stem barks, exhibited moderated antioxidant activity against DPPH radical (IC_{50} of 60.97 ± 3.2 and 64.76 ± 5.5 μM, respectively) (Kouam et al. 2005). In addition, an aqueous extract from the leaves submitted to acid hydrolysis, presented a high scavenging capacity on DPPH (90.15% of inhibition) and FRAP (306.24 ± 31.14 mg/g) assays (Agbor et al. 2007).

A study using ethanolic extract from the stem barks of *Harungana madagascariensis* was performed regarding the prevention of oxidative parameters on diabetic rats. First, an *in vitro* experiment using DPPH radical presented good results (IC_{50} 5.33 μg/mL in comparison to IC_{50} 4 μg/mL of ascorbic acid). After that, the oxidative parameters on diabetic rats were evaluated, and interesting results such as increase of glutathione levels (from 12.52 ± 0.95 to 28.471 ± 1.08 nmol/g) and decrease of lipid oxidation (from 1.30 ± 0.54 to 0.12 ±0.05 MDA/mg protein) were obtained (Iwalewa et al. 2008a). In a similar direction, the same type of extract (5 μg/mL) demonstrated 96.7 ± 1.1% of inhibition using DPPH radical, as well as a Fe (II) chelating ability of 86.2 ± 0.5%. Furthermore, the extract was capable to maintain the levels of malondialdehyde, aspartate aminotransferase, alanine amino transferase and total bilirubin compared with basal in rats stressed with cyclophosphamide (Oboh et al. 2010).

A survey of a dichlorometane : methanol (1:1) extract from the stems and barks of *Harungana madagascariensis* at 100 μg/mL was accomplished to verify its antioxidant potential. The results demonstrated a radical scavenging activity against DPPH (IC_{50} of 3.2 μg/mL) and hydroxyl (OH^-) (IC_{50} 31.3 μg/mL) radicals. The reducing power ability of the extract (IC_{50} 1.48 μg/mL) was in the same level of ascorbic acid (IC_{50} 1.41 μg/mL) and the capacity of preventing the lipid oxidation was superior (IC_{50} 9.35 μg/mL) to that demonstrated by the standard (IC_{50} 19.5 μg/mL). Additionally, the extract presented a considerable elastase inhibitory effect (100 ± 0.01%) (Manjia et al. 2019).

Nwaehujor et al. (2013) described the antioxidant activity of a methanolic extract from stem barks of *Harungana madagascariensis* (80% DPPH inhibition). More recently, Llorent Martinez et al. (2020) compared the radical scavenging and reduction power of aqueous and methanolic extracts from the leaves and stem bark. The best results were found to methanolic extracts of both leaves (DPPH: 1.87 ± 0.02 mmol trolox/g; ABTS: 3.38 ± 0.04 mmol trolox/g) and stem barks (DPPH: 1.87 ± 0.02 mmol trolox/g; ABTS: 2.86 ± 0.19 mmol trolox/g). Likewise, the reducing power was higher of the aqueous (leaves: 4.97 ± 0.03 mmol trolox/g (CUPRAC); 3.06 ± 0.09 mmol trolox/g (FRAP); stem bark: 3.41 ± 0.13 mmol trolox/g (CUPRAC); 2.03 ± 0.12 mmol trolox/g (FRAP)) and methanolic extracts (leaves: 3.92 ± 0.16 mmol trolox/g (CUPRAC); 2.28 ± 0.12 mmol trolox/g (FRAP); stem bark: 3.36 ± 0.09 mmol trolox/g (CUPRAC); 2.04 ± 0.06 mmol trolox/g (FRAP)).

Antimicrobial activity

Essential oils, extracts, and isolated compounds from species of Vismieae demonstrated significant antibacterial, antifungal, antiviral and antiprotozoal effects. Actually, notable antibacterial potential of 1,7-dihydroxyxanthone (**104**), antifungal effects of laurentixanthone B (**114**) and antimalarial properties of acetylvismione D (**44**) and vismione H (**35**) were observed.

Antibacterial activity

Bacteria are ubiquitous microorganisms that play an important role in maintaining the environment where they live either in the soil or associated with live organisms. Only a small percentage of them is capable to cause diseases, that are commonly treated with antibacterial drugs. However, over the years, drug resistance has increased to dangerous high levels, because the microorganisms are acquiring new defense mechanisms. Some infections such as pneumonia, tuberculosis and gonorrhea are becoming harder to treat considering that the drugs available are losing their effectiveness (WHO 2020). Therefore, new treatments that may overcome the bacterial resistance mechanism are needed.

Faced this scenario, the essential oil from leaves and fruits of *Vismia macrophylla* demonstrated to be active against *Staphylococcus aureus* (MIC 100 and 150 μL/mL, respectively) (Buitrago et al. 2015), which may be related with their popular use for the treatment of skin infections (Hussein et al. 2003; Mbwambo et al. 2004). Still working with essential oils, samples obtained from fruits of *Vismia baccifera* were effective against strains of *Staphylococcus aureus* (MIC 37 ± 0.7 μg/mL), *Enterococcus faecalis* (MIC 18 ± 0.5 μg/mL), *Escherichia coli* (MIC 18 ± 0.6 μg/mL), *Klebsiella pneumoniae* (MIC 9 ± 0.8 μg/mL) and *Pseudomonas aeruginosa* (MIC 9 ± 0.4 μg/mL) (Rojas et al. 2011a).

Vismia laurentii afforded several compounds endowed with antibacterial activity. Vismiaquinone (**1**) and 3-*O*-geranyloxyemodin (**8**) isolated from the twigs revealed antibacterial effect against *Pseudomonas aeruginosa* (MIC 2.44 and 4.88 μg/mL, respectively) and *Bacillus subtilis* (MIC 2.44 and 4.88 μg/mL, respectively), whereas bivismiaquinone (**81**) was active only on *Bacillus subtilis* strain (MIC 2.44 μg/mL). The compounds physcion (**2**) and 6-deoxyisojacareubin (**134**), isolated from the roots of the same species, revealed a good action against *Bacillus subtilis* (MIC 1.22 and 4.88 μg/mL). The compound **2** also showed activity

against *Shigella dysenteriae* (MIC 4.88 µg/mL). The leaves of *Vismia laurentii* also presented active compounds such as O^1-demethyl-3′,4′-deoxypsorospermin-3′,4′-diol (**135**), friedelin (**175**) and kaempferol (**200**). Among them, compounds **135** and **200** were effective in inhibiting the growth of *Bacilus subtilis* strains (MIC 1.22 and 2.44 µg/mL), whereas friedelin (**175**) exerted activity against *Pseudomonas aeruginosa* (MIC 2.44 µg/mL) and *Shigella dysenteriae* (MIC 2.44 µg/mL) (Kuete et al. 2007). The compound **175,** also reported in stem barks of *Vismia rubescens*, exhibited a moderated effect on the etiological agent of typhoid fever, *Salmonella typhy* (MIC 25 µg/mL) (Tamokou et al. 2009).

Still referring *Vismia laurentii*, Nguemeving et al. (2006) demonstrated the activity of laurentixanthones A (**132**) and B (**114**) against *Bacillus subtilis* (MIC 4.88 and 2.44 µg/mL). Besides that, compound **132** showed antibacterial effect against *Shigella dysenteriae* (MIC 4.88 µg/mL), whereas **114** inhibited the growth of *Pseudomonas aeruginosa* (MIC 4.88 µg/mL). Altogether, these results (Nguemeving et al. 2006; Kuete et al. 2007) may explain the use of different parts of this species to treat infected wounds (Kerharo and Adam 1974).

A study performed by Tamokou et al. (2009) revealed the antibacterial activity of the methanolic extract from the stem barks of *Vismia rubescens* and isolated compounds. The extract was effective mainly against *Staphylococcus aureus* (MIC 125 µg/mL). The compounds 1,4,8-trihydroxyxanthone (**115**) and 1,7-dihydroxyxanthone (**104**), in turn, besides the action on *Staphylococcus aureus* (MIC 12.5 and 6.25 µg/mL, respectively), also inhibited the growth of *Pseudomonas aeruginosa* (MIC 50 and 6.25 µg/mL, respectively), being compound **104** more effective than gentamycin (MIC 12.5 µg/mL). Physcion (**2**) and epifriedelinol (**173**), isolated from the stem barks, presented antibacterial activity with equal MIC values of 12.5 µg/mL against *Pseudomonas aeruginosa* and *Salmonella typhy*.

Tsaffack et al. (2009) reported the antibacterial action of febrifuquinone (**83**) and adamabianthrone (**86**) isolated from the roots of *Psorospermum febrifugum* and stem barks of *Psorospermum adamauense*, respectively. Both compounds exhibited effect against *E. faecalis* (MIC 9.76 and 19.53 µg/mL, respectively), whereas compound **83** demonstrated activity against *Salmonella typhi* (MIC 19.53 µg/mL), in the same level of gentamycin. The ethyl acetate extract of *Psorospermum aurantiacum* leaves was slightly active against *Klebsiella pneumoniae* (MIC 250 µg/mL). On the other hand, compounds isolated from this extract, such as vismiaquinone (**1**) and octacosanol (**220**) presented interesting activities against *Klebsiella pneumoniae* (MIC 4 and 8 µg/mL, respectively), and *Sighella flexneri* (MIC 8 and 16 µg/mL, respectively) strains. Besides that, compound **220** demonstrated effectiveness against *Salmonella typhi* (MIC 2 µg/mL) and vismiaquinone (**1**) was active on *Pseudomonas aeruginosa* (MIC 8 µg/mL), as stated before (Tchakam et al. 2012).

A methanolic extract from the root barks of *Harungana madagascariensis* was active against bacteria such as *Escherichia coli* (MIC < 8 µg/mL), *Enterobacter aerogenes* (MIC 32 µg/mL), *Pseudomonas aeruginosa* (MIC 32 µg/mL) and *Klebsiella pneumoniae* (MIC 16 µg/mL). In a subsequent step, ferruginin A (**24**), isolated from this extract, demonstrated activity on *Escherichia coli* (MIC 4 µg/mL), *Enterobacter aerogenes* (MIC 8 µg/mL), *Pseudomonas aeruginosa* (MIC 8 µg/mL) and *Klebsiella pneumoniae* (MIC 4 µg/mL) (Tankeo et al. 2016).

In 2016, Kengni et al. evaluated the antityphoid properties of the aqueous extract from the leaves of *Harungana madagascariensis*. The *in vivo* study demonstrated that this extract (25 mg/kg) was able to reduce the number of *Salmonella typhi* recovered from faeces of rats and

thus, stop the salmonellosis. This result could sustain the popular use of the leaves for treating typhoid fever in Cameroon (Kengni et al. 2013).

Antifungal activity

Fungal infections affect more than one billion of individuals worldwide, causing over 1.5 million of deaths per year (Bongomin et al. 2017). Although these infections are very occasional in healthy people, the incidence of superficial and invasive infections has risen in recent years. This increase could be related to the growing number of immunocompromised individuals, as well as to the high incidence of drug-resistant fungi. Thus, the research of new therapeutic alternatives is required. Studies with species from the tribe Vismieae have demonstrated that some of them present relevant antifungal activity against both dermatophytes and leveduriform fungi.

The essential oil from the roots of *Vismia baccifera* subsp. *dealbata* was able to hinder the growth of *Candida krusei*, presenting a MIC value (MIC 1.6 µg/mL) lower than fluconazole (MIC 8 µg/mL) (Vizcaya et al., 2014). In another study, Costa et al. (2017) reported the activity of the essential oil of *Vismia guianensis* against a spectrum of leveduriform fungi species, *Candida albicans* (MIC 0.62 µL/mL), *Candida glabrata* (MIC 1.25 µL/mL), *Candida krusei* (MIC 0.62 µL/mL) *Candida parapsilosis* (MIC 1.25 µL/mL) and *Candida tropicalis* (MIC 1.25 µL/mL). The ethanol : water (1:1) extract of the leaves and stem barks of the same plant have also exhibited antifungal activities (MIC of 3.9 µg/mL) on *Sporothrix schenckii* strains. The last-mentioned species is traditionally used in north and northeast of Brazil for treating dermatomycoses (Oliveira et al. 2017).

Besides the documented antibacterial activity, *Vismia laurentii* produces several compounds with antifungal action. Vismiaquinone (**1**) and bivismiaquinone (**81**) obtained from the twigs were active against *Candida albicans* and *Candida glabrata* presenting the same MIC of 2.44 µg/mL. Furthermore, the leaves of the same species afforded O^1-demethyl-3′,4′-deoxypsorospermin-3′,4′-diol (**135**), friedelin (**175**) and kaempferol (**200**). All compounds demonstrated antifungal effect against *Candida glabrata* (MIC 1.22, 4.88 and 2.44 µg/mL, respectively), whereas friedelin (**175**) was also active on *Candida albicans* strains (MIC 2.44 µg/mL) (Kuete et al., 2007). Still addressing *Vismia laurentii*, a study by Nguemeving et al. (2006) showed the notable antifungal effect of laurentixanthones A (**132**) and B (**114**) against *Candida glabrata* strains (MIC 2.44 and 0.61 µg/mL, respectively), superior to nystatin in terms of efficacy (MIC 4.88 µg/mL). These results corroborate the popular use of this species to treat wounds which could be infected by *Candida* species (Kerharo and Adam 1974; Kuete et al. 2007).

The compounds 1,4,8-trihydroxyxanthone (**115**), 1,7-dihydroxyxanthone (**104**) and physcion (**2**), isolated from stem barks of *Vismia rubescens*, revealed antifungal activity against *Candida parapsilosis* and *Cryptococcus neoformans*. Except for the effect of compound **104** against *Candida parapilosis* strains (MIC 6.25 µg/mL), the other presented moderate antifungal potential (Tamokou et al. 2009).

Isolated from the leaves of *Psorospermum aurianticum*, kenganthranol B (**61**) was effective against the dermatophytes fungi *Trichophyton ajelloi* (MIC 4 µg/mL) and *Trichophyton rubrum* (MIC 16 µg/mL), whereas octacosanol (**220**) was active only on

Trichophyton ajelloi strain (MIC 4 µg/mL). Moreover, vismiaquinone (**1**) demonstrated action on *Candida lusiataneae* (MIC 4 µg/mL), *Trichophyton ajelloi* (MIC 4 µg/mL) and *Trichophyton rubrum* (MIC 8 µg/mL) (Tchakam et al. 2012).

Iwalewa et al. (2009a) evaluated the activity of different extracts (hexane, dichloromethane, chloroform and acetone) from the stem barks of *Harungana madagascariensis* against *Microsporum canis.* All extracts showed moderate activity with slightly better results demonstrated by the hexane extract (MIC 50 µg/mL).

Antiviral activity

Few reports were found in literature concerning the antiviral activity of species belonging to tribe Vismieae. Lopez et al. (2001) investigated the effect of a methanolic resin from *Vismia macrophylla* against herpes Simplex Virus type 1 (HSV-1) founding a MIC of 5.5 µg/mL. Furthermore, extracts from *Vismia camparaguey* and *Vismia baccifera* (syn. *Vismia mexicana*) (50 µg/mL) were able to inhibit reverse transcriptase (HIV-1) at levels of 70.8 ± 1.5 and 72.9 ± 1.1%, respectively (Huerta-Reyes et al. 2004). In the same line, a dichloromethane : methanol (1:1) extract from leaves of *Vismia baccifera* was also active in inhibiting reverse transcriptase (HIV-1) (IC_{50} 31.75 ± 1.34) (Gómez-Cansino et al. 2015).

Antiprotozoal activity

Protozoa are single celled eukaryotic organisms. Most species are free-living and motile, but some of them have parasitic relationships and when transmitted to humans (commonly via insect vectors) cause serious infectious diseases, such as malaria, Chagas disease and leishmaniasis. In absence of vaccines, the control of these parasites depends on chemotherapy. In this sense, natural products play a key role in the treatment of protozoal infections, mainly in malaria disease (Aronson and Magill 2020). It is noteworthy that almost all antimalarial drugs available, in fact, can be traced to a natural product structure.

The popular use of species of Vismieae to treat malaria cases is well-established (Kupchan et al. 1980; Ménan et al. 2006; Traore et al. 2014). Therefore, several studies have been performed to justify this use by the population and find the active compound. The first study is dated from 1999, when François et al. reported the activity of different extracts and isolated compounds from the roots and leaves of *Vismia guineesis*. The results demonstrated that the petroleum ether and dichloromethane extracts obtained from the roots were effective in asexual erythrocytic stages of *Plasmodium falciparum*, presenting IC_{50} values around 2 µg/mL. Noteworthy, vismione H (**35**), isolated from the petroleum ether extract, exhibited a remarkable IC_{50} of 0.088 µg/mL. Besides that, the petroleum ether extract obtained from leaves of the same species presented an anti-*Plasmodium* activity at an IC_{50} of 3.2 µg/mL.

Other studies evaluating the potential anti-malaria of *Vismia* species were conducted. The activity of ethanolic and aqueous extracts from the leaves of *Vismia guineensis* was showed in *Plasmodium falciparum* chloroquine sensitive and resistant strains. The activity of both extracts was moderate, with better results being obtained with the ethanolic extract (IC_{50} 40 ± 3 and 21 ± 11 µg/mL to sensitive and resistant strains, respectively) (Ménan et al. 2006). Furthermore,

hexane : ethyl acetate (1:1) extract from stem barks of *Vismia laurentii* presented IC_{50} of 4.6 ± 0.09 µg/mL against *Plasmodium falciparum* chloroquine resistant, whereas the compounds vismiaquinone (**1**) and tirucalla-7,24-dien-3-one (**193**) were more effective, presenting IC_{50} values of 1.43 ± 0.03 and 1.18 ± 0.05 µM, respectively (Noungoue et al. 2009). Finally, Mbwambo et al. (2004) reported the antimalarial effects of emodin (**13**) (IC_{50} of 9.7 ± 1.16 µg/mL), 3-*O*-geranyloxyemodin (**8**) (IC_{50} of 21.6 ± 1.42 µg/mL) and vismione D (**37**) (IC_{50} of 1.01 ± 0.13 µg/mL) isolated from stem barks of *Vismia orientalis*.

Although plants of the genus *Psorospermum* have been used in folk medicine as antimalarial agents, there is only one study investigating this activity. The effect of a hexane extract from stem barks of *Psorospermum glaberrimum* (IC_{50} 0.87 µg/mL) and its main compounds epifriedelinol (**173**) (IC_{50} 1.68 µM) and acetylvismione D (**44**) (IC_{50} 0.12 µM) is reported (Lenta et al. 2008). It is important to mention that the activity of the compound **44** was comparable of the antimalarial drug chloroquine (IC_{50} 0.11 µM). In another study, the same authors demonstrated the effect of a methanolic extract from the seeds of *Harungana madagascariensis* (IC_{50} 3.6 ± 0.03 µg/mL) (Lenta et al. 2007b), in addition to harunganin (**63**) (IC_{50} 2.7 µM) and bazouanthrone (**77**) (IC_{50} 1.8 µM) (Lenta et al. 2007a). Moreover, Iwalewa et al. (2008b) showed the effect of an ethanolic extract from the root barks of *Harungana madagascariensis* in a range of IC_{50} 0.052-0.517 µg/mL.

Trypanosomes are unicellular parasites that belong to *Trypanosoma* genus. Distinct species, such as *Trypanosoma brucei brucei* and *Trypanosoma cruzi*, can infect different vertebrates, including animals and humans. The human African trypanosomiasis (or sleeping sickness) is a disease that only occurs in sub-saharian Africa and can be caused by two species of *Trypanosoma brucei brucei*, namely *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense.* In contrast, *Trypanosoma cruzi*, the etiological agent of Chagas disease (or American trypanosomiasis), occurs only in Americas (CDC 2020).

In this context, the activity of different extracts (chloroform and methanol) of distinct parts (leaves and root barks) of *Vismia guineensis* was assessed against *Trypanosoma brucei brucei* and *Trypanosoma cruzi*. Both extracts of root barks and the chloroform fraction of leaves presented promising trypanocide activities with IC_{50} values around 2 µg/mL (Traore et al. 2014). Furthermore, Mbwambo et al. (2004) evaluated the potential of the anthranoids emodin (**13**), 3-*O*-geranyloxyemodin (**8**) and vismione D (**37**) from *Vismia orientalis* against *Trypanosoma brucei rhodesiense*. The compounds presented activity against the parasite, being vismione D (**37**) the most active (IC_{50} 9.0 ± 3.5 µg/mL). These anthranoids were also tested against *Trypanosoma cruzi*, exhibiting similar results with an IC_{50} 4.6 ± 1.6 µg/mL to the compound **37**. Besides these studies, a methanolic extract from the seeds of *Harungana madagascariensis* demonstrated activity against *Trypanosoma brucei brucei* (IC_{50} of 7.8 ± 0.3 µg/mL) (IC_{50} of 7.8 ± 0.3 µg/mL) (Lenta et al. 2007b). Finally, Muganza et al. (2012) reported the effect of an aqueous extract from stem barks of this plant against the same parasite (IC_{50} 8.64 µg/mL).

Leishmaniasis is caused by protozoa parasites that belong to at least 20 *Leishmania* species. There are two studies, involving species from the tribe Vismieae, on the combat of *Leishmania donovani*, the etiological agent of visceral leishmaniasis. Mbwambo et al. (2004) described the activity of emodin (**13**) (IC_{50} 2.05 ± 0.45 µg/mL), 3-*O*-geranyloxyemodin (**8**) (IC_{50} 12.0 ± 1.00 µg/mL) and vismione D (**37**) (IC_{50} 0.37 ± 0.03 µg/mL) from *Vismia orientalis*. The other study was performed with the methanolic extract from seeds of *Harungana*

madagascariensis, that showed an IC_{50} of 1.6 ± 0.6 µg/mL against this parasite (Lenta et al. 2007b).

Although conducted with an agent of viceral leishmaniasis, these results should encourage the study of the anti-*Leishmania* activity of some Brazilian species of *Vismia*. The resins of these plants, known as "lacre" or "pau-de-lacre", are used by inhabitants of regions of the Amazon rainforest for the treatment of wounds, including those resulting from cutaneous leishmaniasis (Fundação Rede Amazônica 2012; Viza Junior et al. 2019).

Antiprotozoal activity has also been investigated against *Entamoeba histolytica*. Tona et al. performed two studies concerning amoebicidal activities of the stem barks of *Harungana madagascariensis*. In the former, a MIC value of 62.5 µg/mL was found for the aqueous extract, whereas in the last, a *n*-butanol extract presented the MIC value of 4.7 µg/mL (Tona et al. 1998, 2000).

Antidiabetic activity

Diabetes mellitus is a chronic metabolic disorder that affects about 422 million people worldwide. This disease is characterized by high blood glucose levels which in course of time could lead to several problems such as damage in heart, blood vessels, eyes, among others. There are two types of diabetes, insulin-dependent (type 1) in which the pancreas produces little or no insulin itself, and the most common, that occurs when body becomes resistant to insulin (type 2) (WHO 2020). The treatment of this condition in imperative to patient's survival, however, the access of medicines is irregular according to the people's location. In many developing countries, herbal medicines have a larger importance in the primary health care, for example, 80% of African populations use some form of traditional herbal medicine (Gurib-Fakim 2006).

In this sense, extensive studies on the antidiabetic properties of *Harungana madagascariensis* have been conducted. Olagunju et al. (2004) reported that a saline solution extract from the leaves could reduce the blood cell glucose (14.4%), as well as an ethanolic extract prepared using the stem barks (Iwalewa et al. 2008a). Additionally, the compounds kenganthranol B (**61**), kenganthranol C (**65**), harunganin (**63**), physcion (**2**) and harunganol B (**72**) were able to inhibit the *α*-glucosidase enzyme, which is responsible for the final step of carbohydrates digestion, generating glucose (IC_{50} from 6 to 19.3 µM). Among them, compounds **63** and **61** stood out by the low values of IC_{50} (6 ± 0.09 and 6.3 ± 0.23 µM)(Kouam et al. 2006). Furthermore, the anthrones madagascenone A (**78**) and madagascenone B (**79**) also demonstrated ability to inhibit the *α*-glucosidase enzyme, with IC_{50} values of 69.9 ± 4.21 and 122.3 ± 1.13 µM, respectively (Onajobi et al. 2016).

Still evaluating the *α*-glucosidase inhibition, Johnson et al. (2016) reported the capacity of prenylated anthrones from the leaves of *Harungana madagascariensis* in inhibiting the enzyme. The results demonstrated that harunganol C (**90**) had a higher potency (IC_{50} 1.2 ± 0.05 µM), compared with acarbose (IC_{50} 119.7 ± 0.44 µM), Harunganol D (**73**) (IC_{50} 36.9 ± 1.73 µM), harunganol F (**75**) (IC_{50} 116.7 ± 7.03 µM), kenganthranol A (**64**) (IC_{50} 44.1 ± 5.83 µM) and harunganin (**63**) (IC_{50} 37.7 ± 4.65 µM), also presented this activity.

Rodriguez et al. (2008) performed the only study, so far, that explores the antidiabetic properties of *Vismia* species. The authors reported the effect of an aqueous extract obtained from the fresh leaves and twigs of *Visma japurensis* in the inhibition of glucose-6-phosphatase, enzyme that plays a critical role in blood glucose homeostase (Madsen and Westergaard 2001). The finding demonstrated that this extract was capable to inhibit the microsomal enzymatic activity (89.9%) in a level superior to the positive control phloridzin (59.2%).

Antianemic activity

Anaemia is a condition characterized by a decrease in the number of red blood cells or hemoglobin concentration inside of them. Hemoglobin performs a key role on the transportation of oxygen to the body´s tissues. This disorder is considered a global public health problem which mainly affects young children and pregnant women. An estimative from WHO reported that around 40% of children under 5 years old and pregnant women worldwide are anaemic (WHO 2020).

In this context, some studies with *Harungana madagascariensis* have been performed. This is a plant species commonly used to treat anaemia cases in Cameroonian popular medicine (Biapa et al. 2007). Aiming to prove scientifically the value of this use, Iwalewa et al. (2009b) demonstrated that the hydroethanolic extract from the stem barks was capable to reverse the anemia caused by *Plasmodium yoelli nigeriensis* (rodent malaria parasite) in rats. Likewise, the extract increased, rapidly, the content of hemoglobin, red cell bloods and hematocrit in rats with induced anemia by phenylhydrazin (Biapa et al. 2011). These findings could be explained by the high content of iron in this extract, as previously reported (Biapa et al. 2007; Iwalewa et al. 2009b). In another study by the same group, the ability of the same extract in protecting the membrane of red blood cells was assessed. The authors demonstrated that the previous administration of the extract prevents the lipid oxidation and alterations on membrane fluidity of red blood cells, probably due to its antioxidant effect (Biapa et al. 2013).

Anti-inflammatory activity

Practitioners of traditional system of medicine use Vismieae species as folk remedies to treat inflammatory problems (Chisté et al. 2014; Ribeiro et al. 2014, 2015a; Trepiana et al. 2018). Thus, some studies have been performed in order to validate this use. The first was dated from 1989, in which Nwodo reported the ability of a methanolic extract obtained from stem barks of *Harungana madagascariesis* to inhibit carrageenan induced rat-paw oedema (150 mg/kg), a widely used test to determine anti-inflammatory activity. Likewise, an ethanolic extract from the same part of the plant also reduced the oedema in right paw of rats (43.4% of inhibition in a doses of 100 mg/kg) (Iwalewa et al. 2008a).

Finally, an ethanolic extract obtained from the leaves of *Vismia guianensis* presented anti-inflammatory effect, evidenced by a reduction in the production of nitric oxide and pro-inflammatory cytokines, except TNF-α (100 µg/mL) (Oliveira et al. 2017). The results of this study help to understand the use of *Vismia guianensis* extracts in the traditional medicine for treating inflammatory disorders such as rheumatism (Vizcaya et al. 2012).

Miscellaneous bioactivities

Some Vismieae have been assessed for other bioactivities such as abortifacient, anti-acetyl and butyryl cholinesterase, antipsoriatic, immunomodulatory, anti- hepatotoxic and nephroprotection.

An aqueous extract of *Harungana madagascariensis* demonstrated abortifacient effect on pregnant rats, causing initial hyperactivity that was followed by inability to move. In addition, the animals suffered mild purgation, vaginal bleeding, as well as placental discharge, aborting in 48 hours. This plant is extensively used in Nigerian traditional medicine to induce or accelerate labor, end unwanted pregnancy, and expel retained placenta (Akah 1994).

Extracts and isolated compounds obtained from the stem barks of *Psorospermum glaberrimum* were evaluated concerning their acetyl (AchE) and butyrylcholinesterase (BchE) activities. The inhibition of these enzymes has been related to the treatment of Alzheimer´s dementia, myasthenia gravis and glaucoma (Ballard 2002). The results demonstrated that the hexane extract was able to inhibit both enzymes (AchE, 65.5%; BchE, 98.2%) whereas the isolated compounds were active only against BchE. The most prominent compound was bianthrone A_1 (**80**) (IC_{50} 9.25 ± 0.25 µM) followed by madagascin anthrone (**36**) (IC_{50} 10.1 ± 0.20 µM), acetylvismione D (**44**) (IC_{50} 10.1 ± 0.50 µM), 2-geranylemodin (**20**) (IC_{50} 11.3 ± 0.23 µM), 3-geranyloxyemodin anthrone (**47**) (IC_{50} 11.6 ± 0.20 µM) and physcion (**2**) (IC_{50} 13.3 ± 1.1 µM). This was the first time that cholinesterase inhibiting properties of anthranoids were demonstrated (Lenta et al. 2008).

Recently, Asogwa et al. (2020) reported the antipsoriatic and immunomodulatory properties of the ethanolic extract from the stem barks of *Psorospermum febrifugum*. The findings demonstrated antipsoriatic effect of the extract (93.15% in 400 mg/kg) with reduction of the parameters evaluated (epidermal thickness, ear weight and ear thickness) to values comparable to retinol A (positive control). Furthermore, a dichloromethane fraction obtained from the ethanol extract also exhibited antipsoriatic effect (93.11% in 400 mg/kg). In addition, the immunosuppressive effect was evidenced by the increase of pack cell volume, hemoglobin, red blood cells and a decrease in total white blood cell thorough 21 days of treatment. These results corroborate the extensive popular use of this species by the African populations to treat skin problems (Amonkar et al. 1981; Hamill et al. 2003; Kisangau et al. 2007).

The ethanolic extract from the leaves of *Harungana madagascariensis* was capable to reduce significantly the pentobarbitone-induced sleep in carbone tetrachloride (CCl_4) poisoned rats (70 mg/kg), as well as to attenuate the elevation in glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels provoked by CCl_4, showing an anti-hepatotoxic effect (Madubunyi et al. 1995). Further studies with this species demonstrated the nephroprotective ability of an aqueous extract from the roots, since pretreatments with graded oral doses (100, 200 and 500 mg/kg) attenuated elevations in serum concentration of urea, uric acid and creatinine. In addition, the extract improved diffuse tubular necrosis in models of acetaminophen toxicity (Adeneye et al. 2008a). It is interesting to mention that a sub-acute treatment, with the aim of evaluating the toxicity of a methanolic extract of this species, revealed urinary tract and liver vascular constriction, kidney expansion and necrosis of cardiac muscle and sexual organs in rodents (Etame et al. 2017). These results indicate that further studies must be performed to confirm the safety of use.

Discussion on general aspects of Vismieae species

The tribe Vismieae includes species that have a strong phylogenetic relationship, but whose delimitations in the genera have been controversial. According to Stevens (2007), the species have many characteristics in common, among them the presence of glands and channels. These structures, sometimes, are abundant in flowers, as can be seen in Fig. 10 (A, B and C). All species of the tribe contain dense, unicellular hairs on the adaxial face of the corolla, as it is quite evident in *Vismia pentagyna* (Fig. 10B).

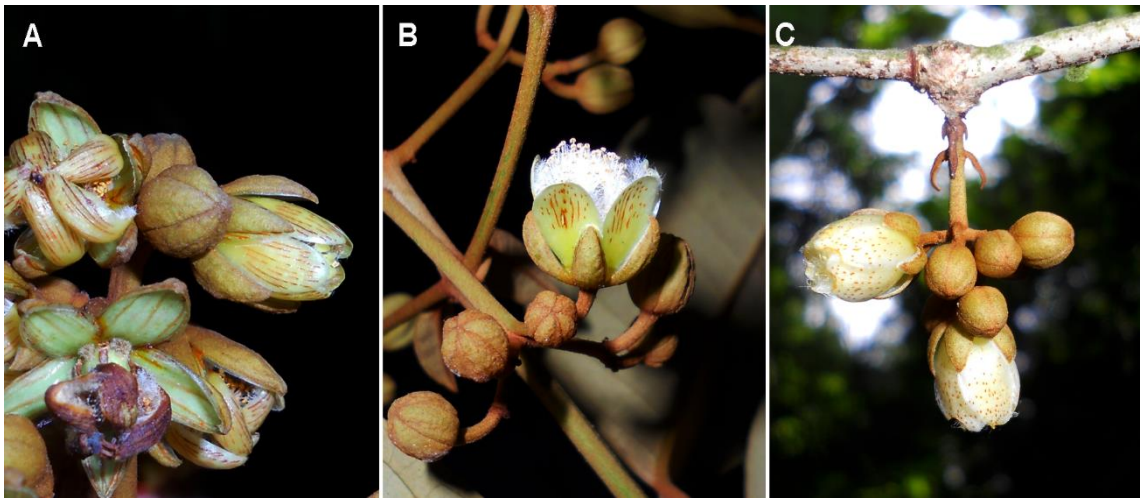

Fig. 10 Photographs highlighting the presence of glands and channels in the petals. (A) *Vismia martiana*; (B) *Vismia pentagyna*; (C) *Vismia obtusa* (Photographs by Lucas Cardoso Marinho – Federal University of Maranhão).

Traditionally, the species have been distributed in the genera *Vismia*, *Psorospermum* and *Harungana*. *Vismia* species occur in both the Americas and Africa. In Americas, species are more prevalent in tropical regions, being often present in degraded areas (Martins et al. 2018a). Actually, as some species of *Vismia* are able of re-sprouting after fires, they are frequently found with high dominance, in large gaps in the forest, resulting from abandoned pastures (Mesquita et al. 2015).

In species of *Vismia* a yellow to red exudate is excreted after incisions in many parts of the plant. The exudate of ***Vismia*** *guianensis* (Gutta-**gum** tree or American gamboga), for example, was known as "American Gum Guttae" in the 19th century. The product was used as a substitute for real gummi guttae obtained from Asian *Garcinia* species (Gonçalves and Mors 1981). Species of *Psorospermum* and *Harungana* also produce exudates of yellow and red colors, respectively. As in other Vismieae species, the adaxial surface of the corolla is densely covered with unicellular hairs (Figure 11).

Fig. 11 Photographs representing *Psorospermum* sp. (A) (by Heritiana Ranarivelo) and *Harungana madagascariensis* (B) (by Matthew Walters, in Dressler et al., 2014).

The same behavior of *Vismia* species is verified with *Psorospermum* spp., which can be found in secondary forest (Ranarivelo 2017), and *Harungana madagascariensis* that easily grows in disturbed evergreen forests (Monteiro et al. 2011). It has been said that because *Harungana madagascariensis* can establish wide stands it can result in an ecological trouble, eliminating native plants and destroying wildlife habitat (Baider and Florens 2011).

While this vast distribution may represent an ecological problem, it makes the plant easily accessible to the population that use the different parts as a remedy for the most varied purposes, as it can be seen in Table 3. *Vismia* and *Psorospermum* species also have widespread use. Some uses are similar to those of *Harungana madagascariensis*, which would be expected since the species have several compounds in common, as will be discussed below.

Chemical investigations were conducted with 30 species of *Vismia*, *Psorospermum* and *Harungana* and 221 specialized metabolites have been identified. Anthracenic derivatives and xanthones represent the majority of the compounds isolated from the species of this tribe. Some of them have an interesting distribution and may have a taxonomic significance.

Anthracenic derivatives have often been found in taxa of Hypericaceae family. Examples are naphthodianthrones present in species of tribe Hypericeae, and anthraquinones and anthrones, produced by species of the tribes Cratoxyleae and Vismieae. The distribution of these compounds in the tribe Vismiaeae is show in Table 4.

Simple anthraquinones were found in several species of the tribe. Prenylated and oxyprenylated anthraquinones also occur in all genera, but a higher number of them were found in *Afrovismia* species. A diversity of prenylated anthrones were found in *Psorospermum*, *Harungana* and American *Vismia* but, curiously, they were not isolated so far from *Afrovismia*. It is worth to cite the occurrence of furanoanthrones (**65**, **66**, **69**, **70**, **74**, **75** and **79**) exclusively in *Harungana*.

Table 4. Distribution of the anthracenic derivatives in Vismieae.

Compounds class		**American *Vismia***	***Afrovismia***	***Psorospermum***	***Harungana madagascariensis***
Anthraquinones	Simple	**3** compounds (in 6 species)	**3** compounds (in 4 species)	**4** compounds (in 5 species)	3 compounds
	Prenylated	**3** compounds (in 6 species)	**6** compounds (in 2 species)	**2** compounds (in 4 species)	**3** compounds
	Oxyprenylated	**1** compound (in 4 species)	**8** compounds (in 2 species)	**3** compounds (in 6 species)	**1** compound
	Pyranoanthraquinone	**0**	**2** compounds (in 2 species)	**0**	**0**
Anthranoids	Prenylated	**13** compounds (in 10 species)	**0**	**21** compounds (in 5 species)	**10** compounds
	Oxyprenylated	**1** compound (in 2 species)	**2** compounds (in 2 species)	**3** compounds (in 5 species)	**0**
	Pyranoanthranoid	**2** compounds (in 6 species)	**0**	**2** compounds (in 1 species)	**4** compounds
	Furanoanthranoid	**0**	**0**	**0**	**7** compounds
Dimeric anthranoids	Prenylated	**1** compound (in 1 species)	**1** compound (in 2 species)	**1** compound (in 1 species)	**2** compounds
	Oxyprenylated	**1** compound (in 1 species)	**1** compound (in 2 species)	**7** compounds (in 4 species)	**0**

Table 5: Distribution of the xanthones and derivatives in Vismiaeae.

Compounds class		American *Vismia*	*Afrovismia*	*Psorospermum*	*Harungana madagascariensis*
Xanthones	Simple oxygenated	**14** compounds (in 5 species)	**3** compounds (in 2 species)	**6** compounds (in 3 species)	**2** compounds
	Prenylated	**0**	**4** compounds (in 2 species)	**1** compound (in 1 species)	**0**
	Oxyprenylated	**0**	**6** compounds (in 1 species)	**0**	**0**
	Pyranoxanthones	**1** compound (in 1 species)	**3** compounds (in 2 species)	**0**	**0**
	Furanoxanthones	**0**	**1** compounds (in 1 species)	**18** compounds (in 2 species)	**0**
Xanthonolignoids		**0**	**0**	**7** compounds (in 1 species)	**1** compound

Prenyloxy (or geranyloxy) anthraquinones, anthrones anthranoids or dianthrones are not frequently found in nature. A review published by Epifano et al. (2007) cited the occurrence of these compounds only in species of the family Hypericaceae (*Psorospermum febrifugum*, *Vismia guineensis*, *Vismia orientalis* and *Cratoxylum arborescens* (Vahl.) Blume, tribe Cratoxyleae). As stated before, further studies reported their occurrence in *Vismia baccifera, Vismia guianensis, Vismia jefensis Vismia martiana, Vismia parvifolia, Vismia reichardtiana, Vismia laurentii, Psorospermum aurantiacum, Psorospermum adamauense, Psorospermum corymbiferum, Psorospermum densipunctatum, Psorospermum glaberrimum, Psorospermum tenuifolium* and *Harungana madagascariensis.*

These compounds, of restricted occurrence, were found in representatives of all taxons included in the Vismieae. In the future, when more species of Vismieae are examined and more oxyprenylated anthracenic derivatives are found, the possibility of defining these compounds as chemotaxonomic markers of the tribe could be considered.

As observed with the anthracenic derivatives, **xanthones** having a variety of **substitution patterns** are present in several members of Vismieae, as shown subsequently (Table 5). Xanthones are oxygenated heterocycles that display diverse biological activities that have been frequently associated to prenyl groups often linked to their skeleton. Since several decades, researchers realized that due to the variation in the oxygenation and prenylation patterns, these compounds have potential chemotaxonomic value (Bennett and Lee 1989).

The species included in the tribe Vismieae afforded, to date, 59 xanthones, some of them co-occurring in the different genera. Eighteen simple oxygenated xanthones, with a diverse degree of oxygenation, were isolated (**104** - **121**), presenting a great diversity in the American *Vismia*, and rarely found in the other members of the tribe. The compounds differ in the number and positions of the hydroxyl or methoxy substituents (Fig. 5). In contrast, prenylated xanthones occur in *Afrovismia*, with only one exception of a pyranoxanthone (**136**) in the American *Vismia latifolia*.

The Vismieae xanthones present one or two prenylations. The prenyl groups can be free or undergo cyclization with a vicinal hydroxyl group, giving rise to pyranoxanthones or furanoxanthones. In the xanthones that present *O*-prenylation the substitution (isopentenyloxy or geranyloxy) is seen always in same position (**126**, **127**, **128**, **129**, **130** and **131**). All the compounds with this substitution pattern were isolated from the African species *Vismia guineensis.*

It is important to note the occurrence of furanoxanthones, remarkably in the genus *Psorospermum*. These compounds were originated from the cyclization of the prenyl groups with the hydroxyl group subjacent (**135**, **137** – **153**). The compound **154** could be inferred as biosynthetic precursor of the compounds **152** and **153**.

In summary, the American *Vismia* accumulate principally simple oxygenated xanthones, except for a pyranoxanthone (**136**) isolated from *Vismia latifolia*. *Afrovismia* species biosynthesize prenylated xanthones and only one furanoxanthone (**135**), found in *V. laurentii*. Interestingly, a diversity of furanoxanthones has been found in *Psorospermum*, where the xanthonolignoids identified so far are also concentrated. *Harungana* is not characterized by the production of xanthones, with only two simple oxygenated xanthones reported up to now. Another fact to highlight with respect to the distribution of the metabolites is the occurrence of

benzophenones. To date, twelve prenylated benzophenones were isolated, all of them from four species of American *Vismia*.

The phytochemical studies also provided other classes of compounds, such as sesquiterpenes, triterpenes and flavonoids. However, these compounds are widely found in the vegetal kingdom and do not present a characteristic distribution in the tribe Vismieae.

As stated before, species from Vismieae are widely used in traditional preparations by the African and South American populations. The phytochemical investigations led to the isolation of several bioactive compounds. Among all the classes of compounds obtained to date from species of Vismieae, anthracenic derivatives are those that have the greatest diversity of compounds.

The ethnobotanical reports cited in this review underline the extensive use of species from the tribe Vismieae for the treatment of skin diseases and the anthracenic derivatives could be responsible for their usefulness. The wound healing effect of these compounds has already been demonstrated (Radha et al. 2008; Gundogdu et al. 2019). In addition, it was recently demonstrated the potential of anthraquinones against cutaneous leishmaniasis (Dimmer et al. 2019) and the healing effect of anthraquinones and anthrones in other diseases that manifest on the skin, such as fungal infections (Kuete et al. 2007; Tchakam et al. 2012) and psoriasis (Wiegrebe and Müller 1995) is known since decades.

Other activity that may be related to the use of these species in skin treatments is the inhibition of tyrosinase, that have already been demonstrated by anthracenic derivatives. Tyrosinase is a key enzyme involved in the metabolism of melanin and the compounds that are able to inhibit it are important in cosmeceuticals products used to treat hyperpigmentation cases of diverse causes (Li et al. 2004). The literature reports the anthraquinone physcion (**2**), for example, as a potent inhibitor of tyrosinase (Leu et al. 2008). This compound was isolated from species belonging from all genus that compose the tribe Vismieae.

The reputation of these plants sparked the interest of industries and patents in this regard were filed. An extract of *Harungana madagascariensis* for example, is commercialized as an active in anti-aging cosmetics by the well-established brand Clarins®. The technology behind those products is described in patents deposited in countries as France (FR1562006A), China (CN201611122612A), among others, in addition to the World Intellectual Property Organization (WIPO) (2014/009874 A2). The patent is related to cosmetic and/or dermatological use of extracts from this plant to inhibit the growth of hair follicles and/or skin depigmentation. It is worth to mention that the patent relates to the use of the extract in many medical conditions such as lentigo, melasma, melanoderma linked to Addison disease, Cushing´s syndrome and hypothyroidism. Interestingly, the LVMH Moët Hennessy Louis Vuitton SE that contains in its portfolio many famous brands is owner of a patent that describes the use of an extract from *Vismia cayennensis* as a promoter of collagen synthesis (WIPO number WO1994015626A1). As far as is known, there is no product involving this technology in the cosmeceutical market.

Beyond all the effects cited above, some anthraquinones present significant cytotoxic activity in cells. In spite of these compounds are structurally similar to the anticancer drug doxorubicin and those isolated from *Psorospermum* genus presented suitable values of IC_{50} against different cancer cell lines, the potential of these molecules remain partially explored.

The xanthones from Vismieae, in addition to the antimicrobial effect, have demonstrated cytotoxic and anti-proliferative activities in the same level of the anthraquinones from *Psorospermum* spp. Indeed, the furanoxanthones, as the psorospermin derivatives (**137**, **143**, **144**, **146**, **147**, **152** and **153)** demonstrated noteworthy activities, as cytotoxicity against cancer cell lines (*in vitro* activities at concentrations < 0.003 µg/mL). A patent behind the activity of these molecules were deposited in the United States of America with number US8263644B2, and assigned by the pharmaceutical company Bristol Myers Squibb Co. However, until now, these technologies did not result into a commercial product.

Conclusions

This work provides a comprehensive review concerning the literature information about species of the tribe Vismieae. Aspects as taxonomy, traditional uses, chemical composition and biological properties were approached. As stated before, this tribe shows some issues regarding taxonomic delimitations. At this point, the compilation of information presented in this article intends to help a better understanding on this subject although several gaps still need to be filled.

From the chemical point of view, there is a certain uniformity in the classes of compounds that occur in the species of the three genera, traditionally accommodated in Vismieae, being the anthracenic derivatives and the xanthones the most representative, occurring in all taxa of the tribe.

In spite of this trend of uniformity in the distribution of compounds, when looking at substitution patterns within each class, differences can be seen. For example, prenylated anthrones, that are widespread in American *Vismia*, *Psorospermum* and *Harungana*, were not found in *Afrovismia.* Furanoanthrones, anthrones in which the prenyl group undergo cyclization in a furan ring, up to now, are restrict to *Harungana madagascariensis*, and species of *Psorospermum* exhibit a higher diversity of dimeric antranoid compounds.

Concerning the distribution of xanthones, the simple oxygenated compounds are common in American *Vismia* (with two exception in *Harungana madagascariensis*). By contrast, oxyprenylated xanthones were obtained only from the African *Vismia guineensis.* Several furanoxanthones were isolated from *Psorospermum*, except for one occurrence in the African *Vismia laurentii*. Xanthonolignoids are almost exclusive of *Psorospermum*, with one exception in *Harungana madagascariensis.* Benzophenones, structures closely related to xanthones, have wide occurrence in Hypericaceae, but in Vismieae were found only in American *Vismia.*

Looking at the distribution of these compounds, it seems reasonable to suppose that, from a chemical perspective, instead of merging some of these groups of plants, it would be appropriate to preserve the three genera and still, maintain *Afrovismia* as a separate genus. Undoubtedly, as a relatively small number of species has been chemically studied, it is premature to propose such a change. However, in the future, with more available information, to include the chemical data in the taxonomic revision of these taxa would be helpful.

The data collected show that this group of Hypericaceae produces compounds with relevant pharmacological activities, highlighting antiproliferative and antimicrobial, deserving further studies. It should be remembered that these plants naturally occur only in South

America, with few exceptions in North and Central America, and in mainland Africa and Madagascar, usually in remote regions, such as in the interior of forests. Therefore, in order to preserve and better exploit the potential of these valuable plants, research projects must be encouraged by the development agencies of the respective countries where they occur.

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Authors' Contribution

Kriptsan Abdon Poletto Diel, Henrique Bridi and Gabriela de Carvalho Meirelles contributed to literature searching and data collection in addition to the manuscript preparation and revision. Gilsane Lino von Poser contributed to the study concepts and design, as well as manuscript preparation and revision. All the authors discussed, edited and approved the final version.

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3.3 Discussão

Este trabalho fornece uma revisão abrangente sobre as informações da literatura envolvendo as espécies da tribo Vismieae. Aspectos como taxonomia, usos tradicionais, composição química e propriedades biológicas foram abordados. Como afirmado anteriormente, esta tribo apresenta alguns problemas com relação às delimitações taxonômicas. Neste ponto, a compilação das informações apresentadas neste artigo pretende auxiliar um melhor entendimento sobre o assunto, embora várias lacunas ainda precisem ser preenchidas.

Do ponto de vista químico, há certa uniformidade nas classes de compostos que ocorrem nas espécies dos três gêneros, tradicionalmente acomodadas em Vismieae, sendo os derivados antracênicos e as xantonas os mais representativos, ocorrendo em todos os táxons da tribo.

Apesar dessa tendência de uniformidade na distribuição dos compostos, ao observar os padrões de substituição dentro de cada classe, diferenças podem ser observadas. Por exemplo, antronas preniladas, que são comuns em *Vismia* americanas, *Psorospermum* e *Harungana*, não foram encontradas em *Vismia* africanas. Furanoantronas, antronas em que o grupo prenil sofre ciclização em um anel furano, até agora, são restritas a *Harungana madagascariensis*, e espécies de *Psorospermum* exibem uma maior diversidade de antranoides diméricos.

Com relação à distribuição das xantonas, os compostos oxigenados simples são comuns em *Vismia* americanas (com duas exceções em *Harungana madagascariensis*). Em contraste, as xantonas oxipreniladas foram obtidas apenas na *Vismia guineensis*, nativa da África. Várias furanoxantonas foram isoladas de *Psorospermum*, exceto por uma ocorrência em *Vismia laurentii,* espécie africana. Os xantonolignoides são quase exclusivos de *Psorospermum*, com uma exceção em *Harungana madagascariensis*. Benzofenonas, estruturas intimamente relacionadas às xantonas, têm ampla ocorrência em Hypericaceae, mas em Vismieae foram encontradas apenas em *Vismia* americanas.

Observando a distribuição desses compostos, parece razoável supor que, do ponto de vista químico, em vez de fundir alguns desses grupos de plantas, seria apropriado preservar os três gêneros e ainda, manter *Vismia* africanas como um gênero separado.

Sem dúvida, como um número relativamente pequeno de espécies foi estudado quimicamente, é prematuro propor tal mudança. Porém, no futuro, com mais informações disponíveis, seria útil incluir os dados químicos nas revisões taxonômicas deste grupo de plantas.

Os dados coletados mostram que este grupo de Hypericaceae produz compostos com atividades farmacológicas relevantes, destacando-se a antiproliferativa e a antimicrobiana, merecendo estudos mais aprofundados. Deve-se lembrar que essas plantas ocorrem naturalmente apenas na América do Sul, com poucas exceções na América do Norte e Central, e na África continental e Madagascar, geralmente em regiões remotas, como no interior de florestas. Portanto, a fim de preservar e explorar melhor o potencial dessas valiosas plantas, projetos de pesquisa devem ser incentivados pelas agências de fomento dos respectivos países onde ocorrem.

4. CONSIDERAÇÕES FINAIS

Hypericeae, Cratoxyleae e Vismieae são as três tribos, bem sustentadas, da família Hypericaceae (Ruhfel *et al*., 2011, 2013; Robson, 2012). No Brasil, esta família é representada por dois gêneros: *Hypericum* L. (tribo Hypericeae), e *Vismia* Vand. (tribo Vismieae) (Martins *et al*., 2018; Vogel Ely *et al*., 2020b).

A partir da metade da década de 1990 foram publicados estudos com espécies de *Hypericum* nativas do sul do Brasil e, desde então, sete espécies foram estudadas mais detalhadamente do ponto de vista químico – *H. austrobrasiliense, H. brasiliense, H. caprifoliatum, H. carinatum, H. denudatum, H. myrianthum* e *H. polyanthemum.* Destas espécies foi possível o isolamento de 12 floroglucinois diméricos (Rocha *et al*., 1995, 1996; Ferraz *et al*., 2002; Nör *et al*., 2004; Bridi *et al*., 2016, 2018) e seis derivados monoméricos, sendo duas benzofenonas (Bernardi *et al*., 2005) e quatro benzopiranos (Ferraz *et al*., 2001; Bridi *et al*., 2018).

Os dados disponíveis até então indicam que apenas cerca de 10% das 500 espécies do gênero *Hypericum* foram estudadas, havendo, então, muito mais a ser descoberto (Bridi *et al*., 2018).

No presente trabalho foi possível realizar o isolamento de um acilfloroglucinol dimérico, sendo identificado através de técnicas de RMN, como hiperbrasilol B, presente em outras espécies do gênero. Este foi o primeiro relato da identificação para *H. pedersenii*, sendo uma nova fonte de obtenção deste composto.

Em relação aos flavonoides, grande parte das espécies analisadas apresenta o hiperosídeo como o componente majoritário, o que já se observou também em diversas espécies de *Hypericum.* Importante salientar a ausência deste flavonoide em *H. teretiusculum.* Com pesquisas mais avançadas sobre as propriedades químicas e também farmacológicas do gênero *Hypericum* novas moléculas bioativas podem ser obtidas.

Um grupo bem estabelecido é tribo Vismieae mas, mesmo assim, a delimitação taxonômica dos gêneros ainda não está bem resolvida (Ruhfel *et al*., 2011, 2013). Analisando do ponto de vista químico, os derivados antracênicos e as xantonas são as classes de compostos que estão presentes de forma mais expressiva, ocorrendo em todos

os táxons, sendo observada uma certa uniformidade nos três gêneros de Vismieae (*Harungana*, *Psorospermum* e *Vismia*). Porém, diferenças também podem ser observadas. Por exemplo, antronas preniladas não foram encontradas em *Vismia* africanas, mas são comuns em *Vismia* americanas, *Psorospermum* e *Harungana*. Furanoantronas, até então, são restritas a *Harungana madagascariensis*, e uma grande variedade de antranoides diméricos são encontrados em espécies de *Psorospermum*.

É possível supor que, do ponto de vista químico, seria adequado preservar os três gêneros e manter *Vismia* africanas como um gênero separado, ao invés de unir este grupo de plantas. Porém ainda é cedo para propor alguma mudança, já que um número pequeno de espécies foi estudado quimicamente. Mas os dados químicos serão úteis, junto com mais informações, nas revisões taxonômicas que podem ser realizadas no futuro.

Os dados obtidos neste trabalho reforçam a importância do estudo de plantas, tanto em relação aos constituintes químicos das diversas espécies e suas atividades biológicas, quanto ao papel que podem ter em reavaliações de classificações taxonômicas. Estudos estes que contribuem, principalmente, para o conhecimento acerca da biodiversidade brasileira.

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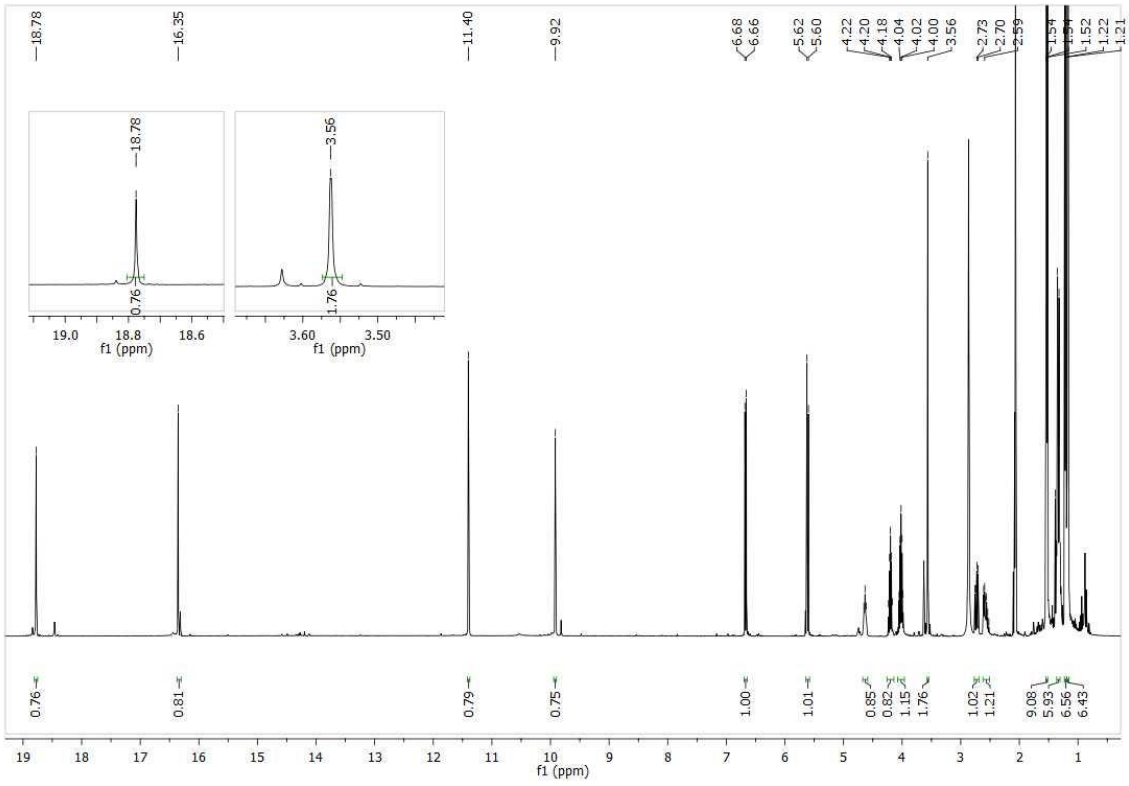
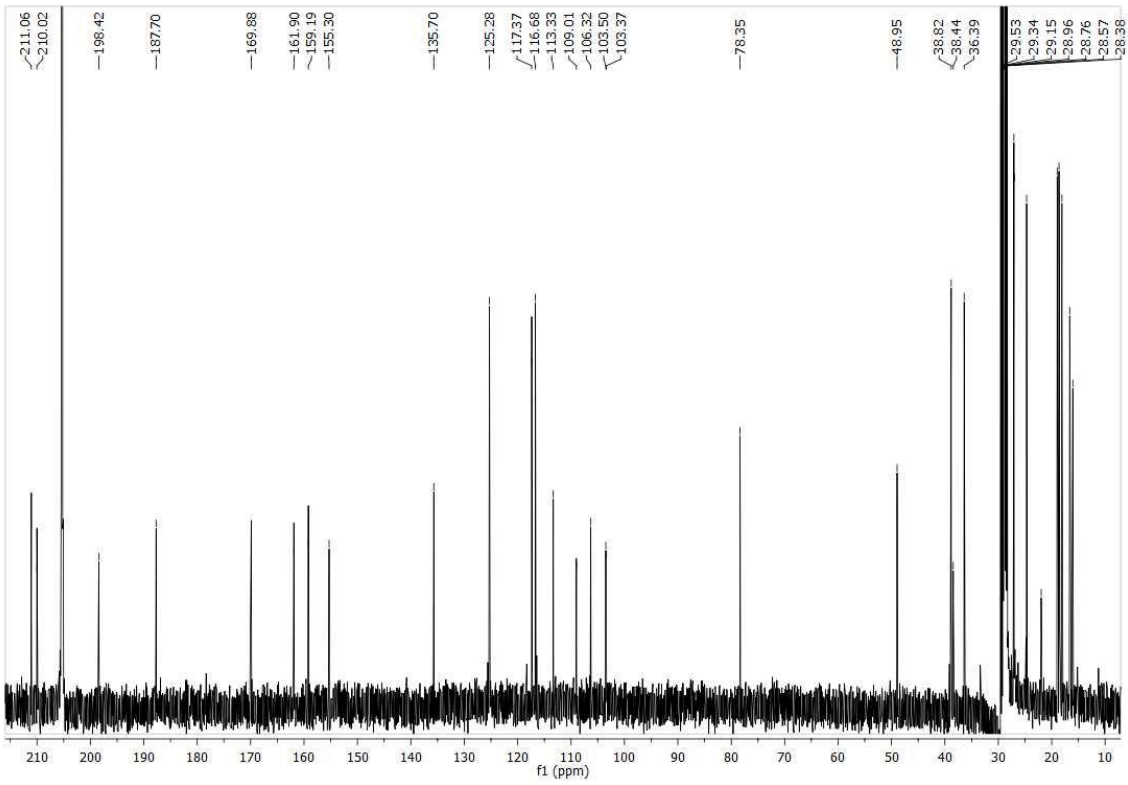
6. ANEXOS

I. Espectros de RMN – Hiperbrasilol B

Espectro de ^{1}H RMN (acetona-d_6, 400 MHz).

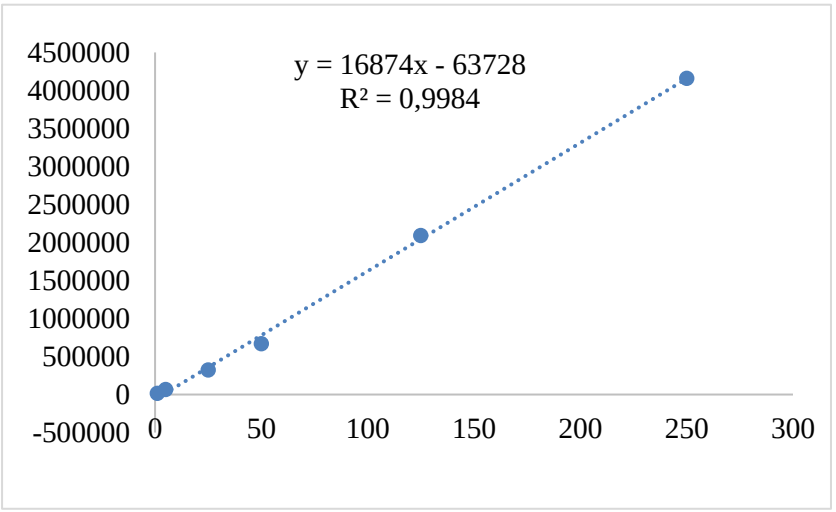


Espectro de ^{13}C RMN (acetona-d_6, 100 MHz).



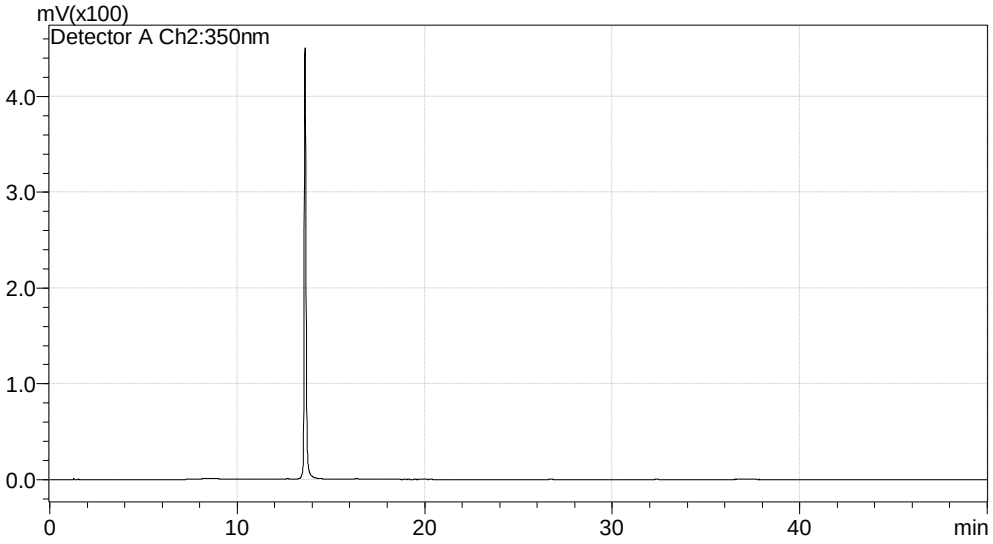
II. Curva padrão - Hiperosídeo

Concentração (µg/mL)	Área
1	13544
5	63868
25	320428
50	666919
125	2089092
250	4158103

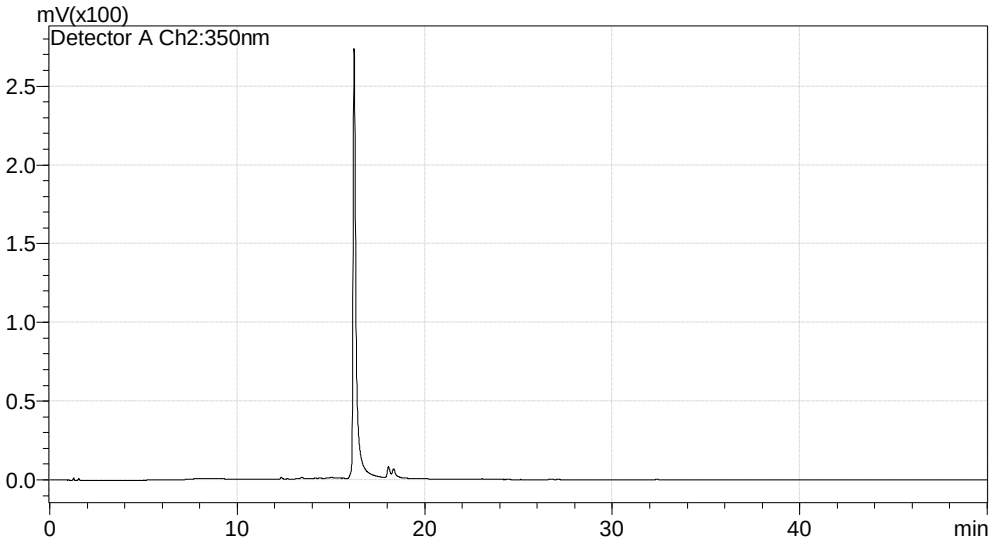


III. Cromatogramas dos padrões analisados

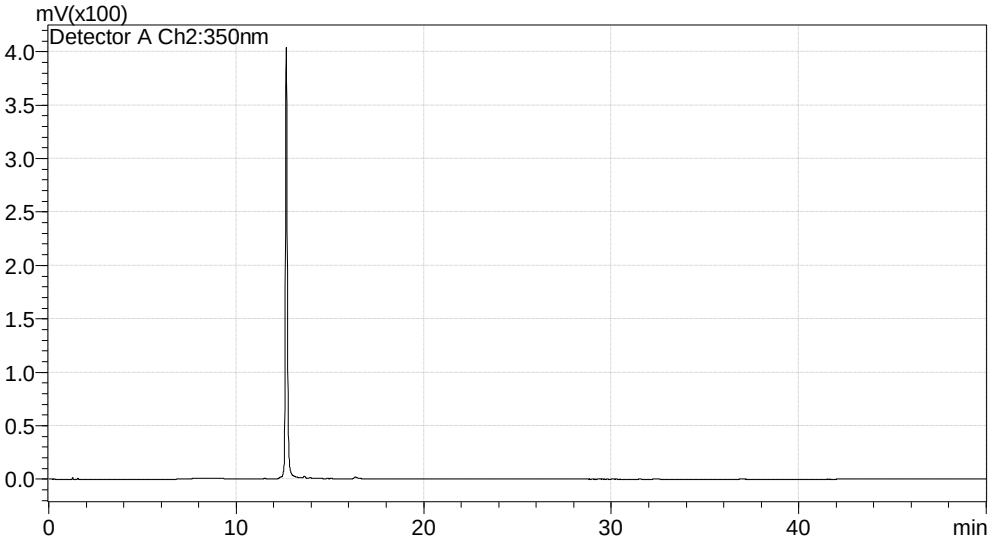
Quercitrina



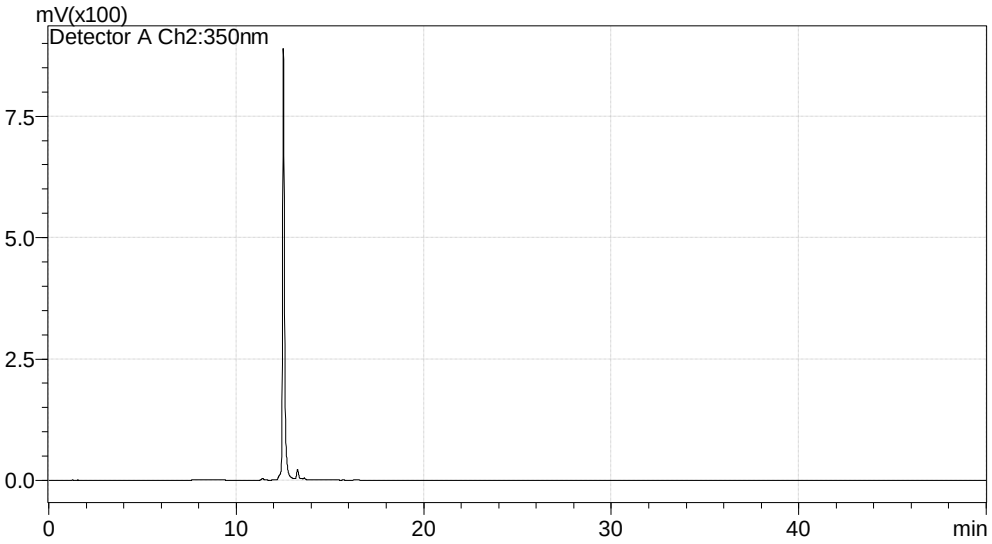
Quercetina



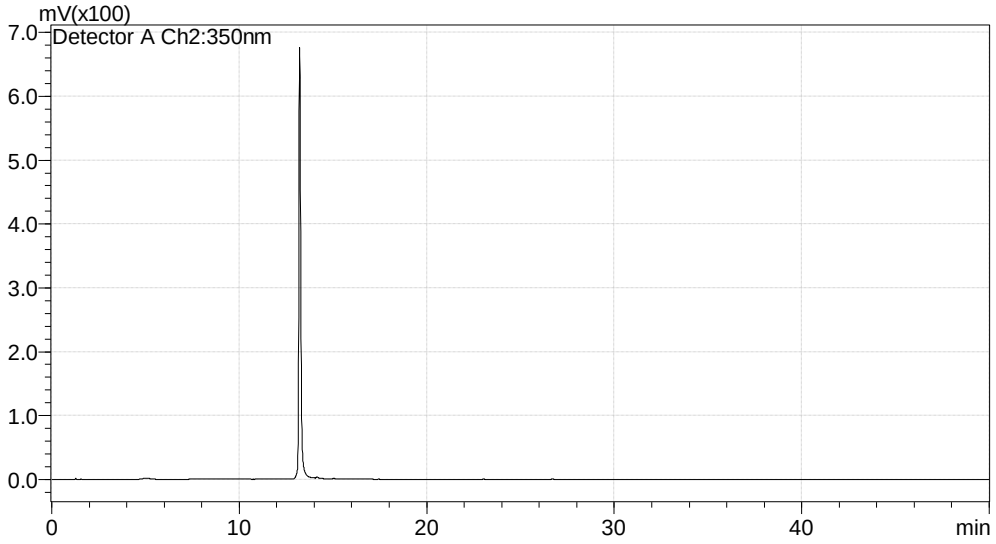
Isoquercitrina



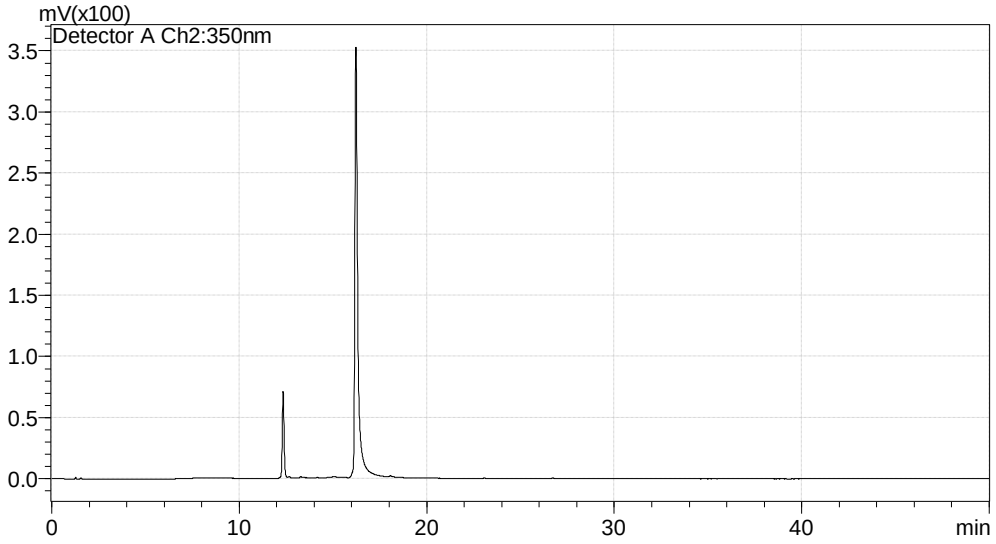
Hiperosídeo



Guajaverina



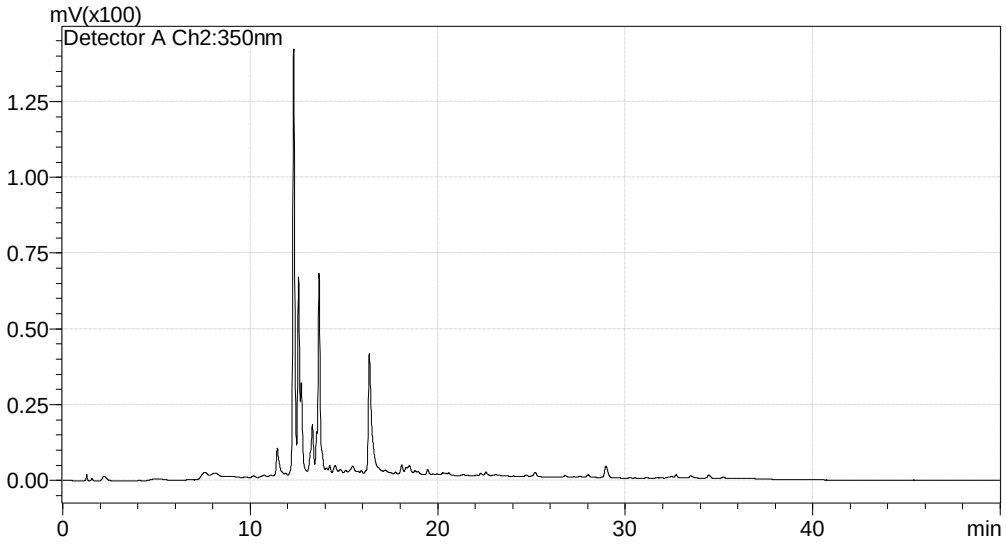
Rutina



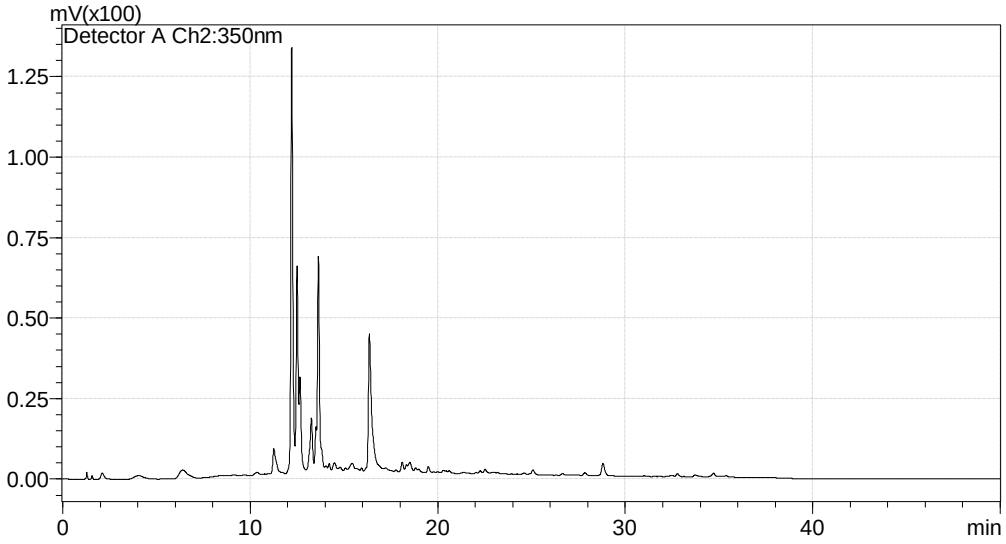
IV. Cromatogramas das amostras analisadas em triplicata

H. caprifoliatum – Acetato de etila

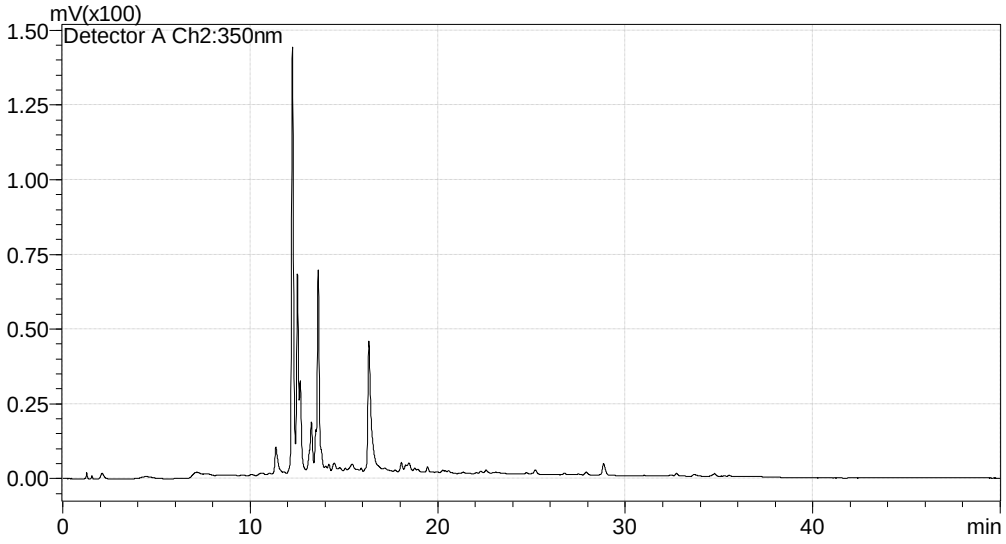
1



2

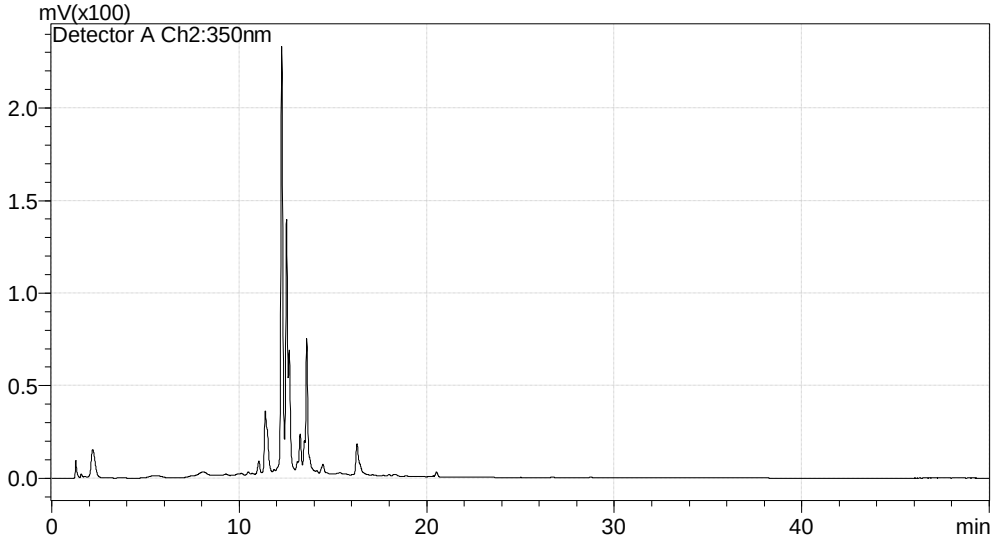


3

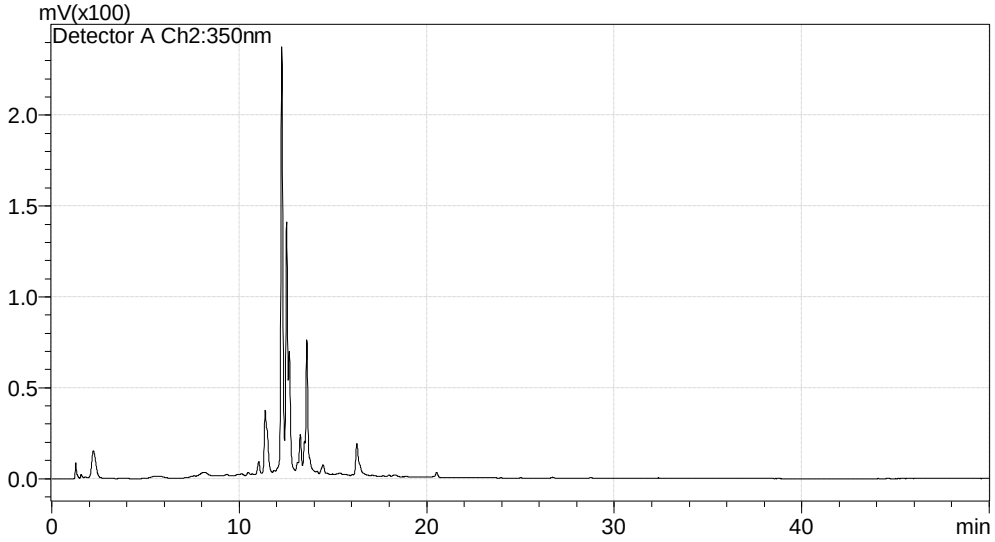


H. caprifoliatum – Metanol

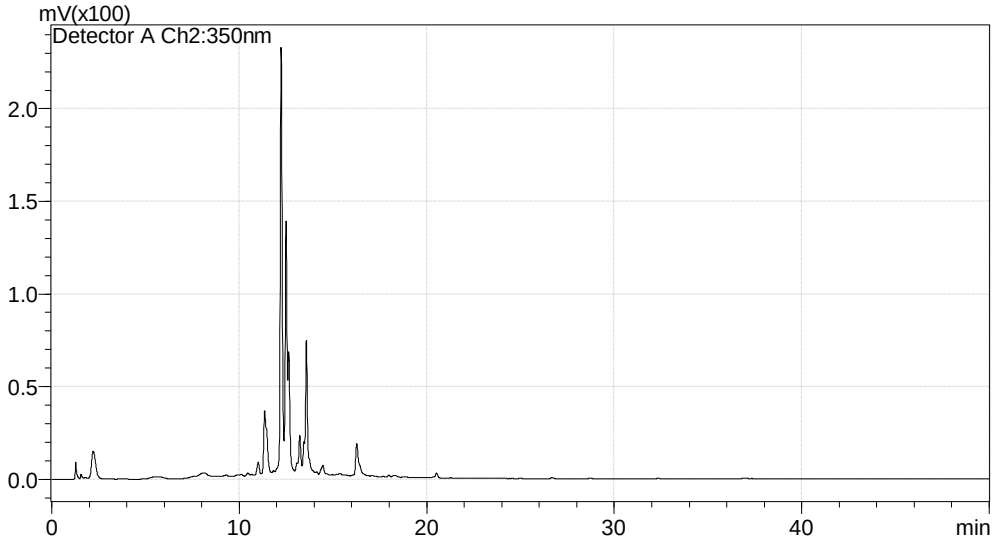
1



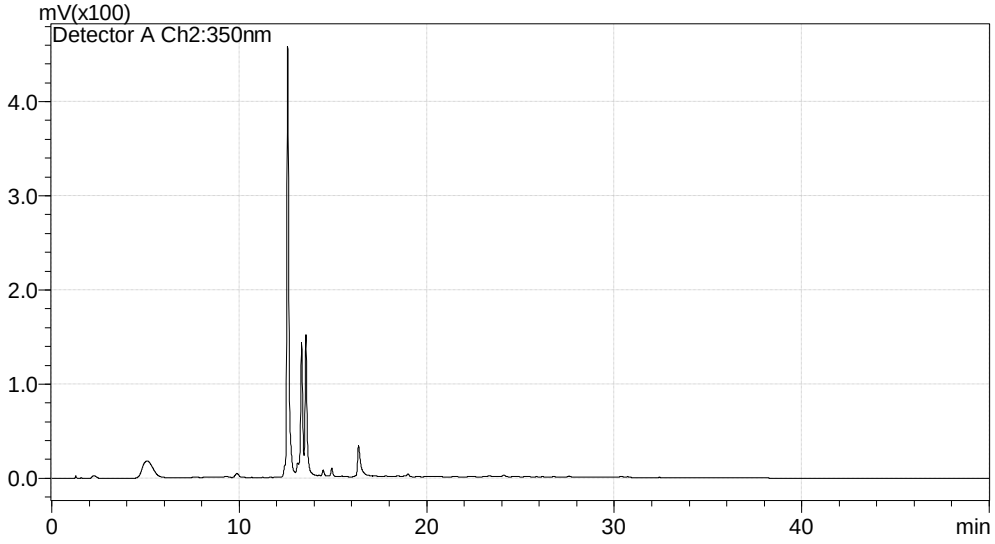
2



3



H. carinatum– Acetato de etila



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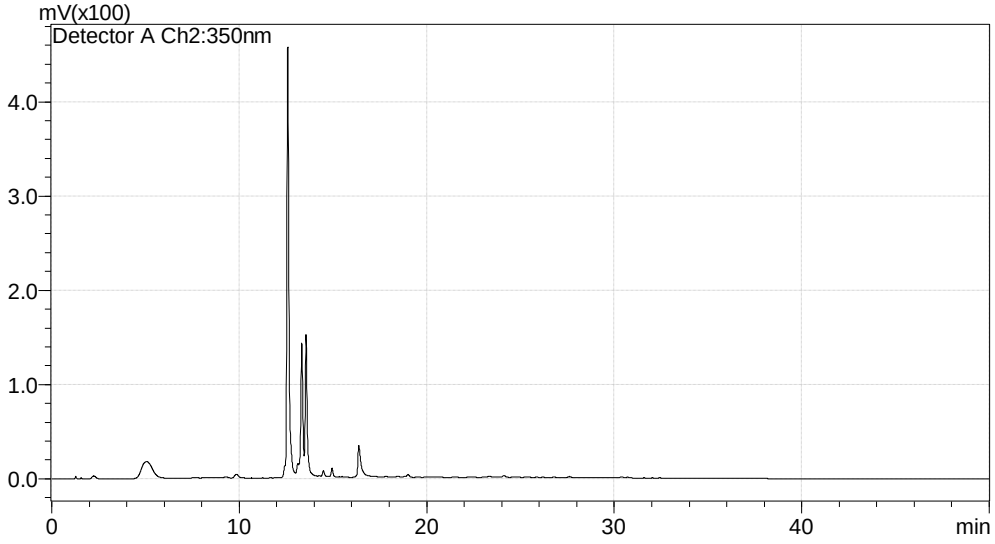

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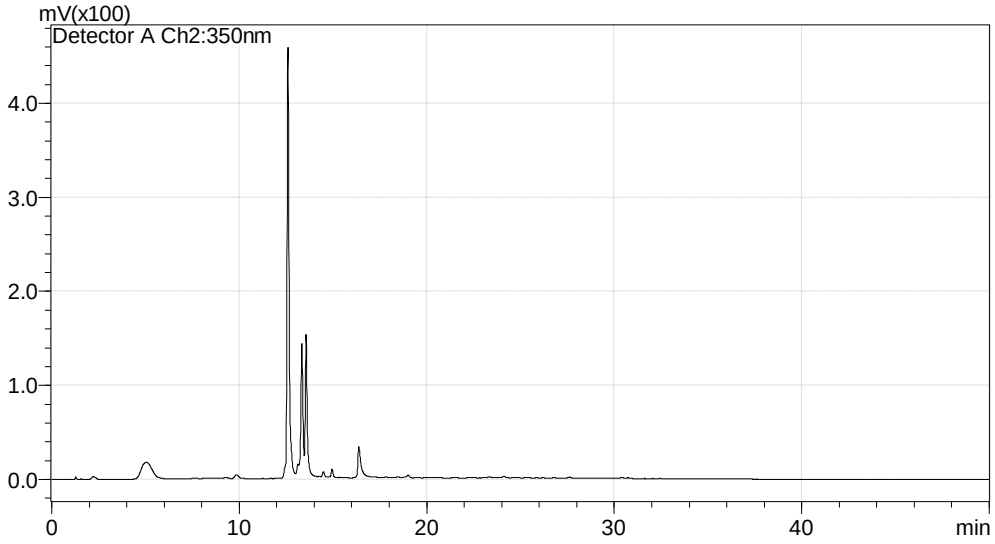
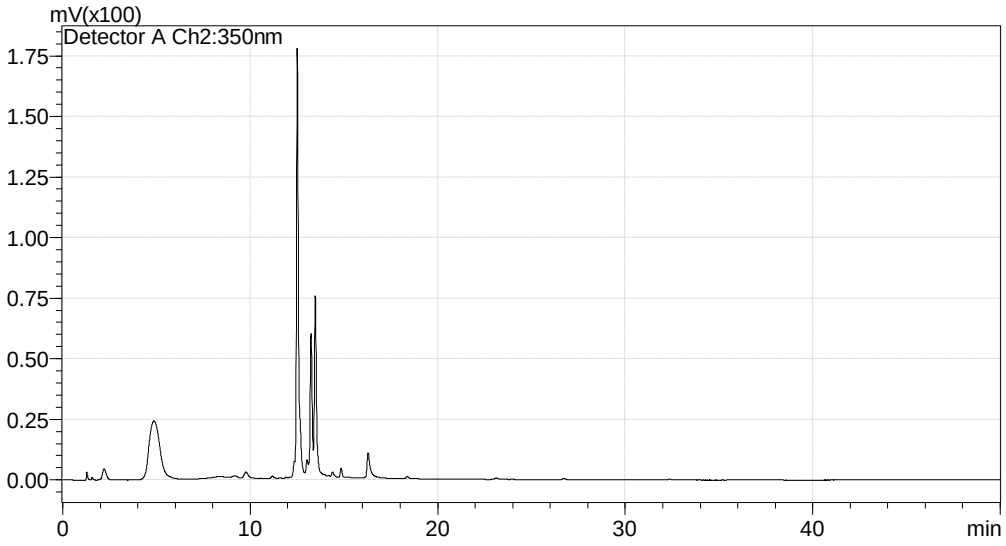


3

H. carinatum – Metanol

1



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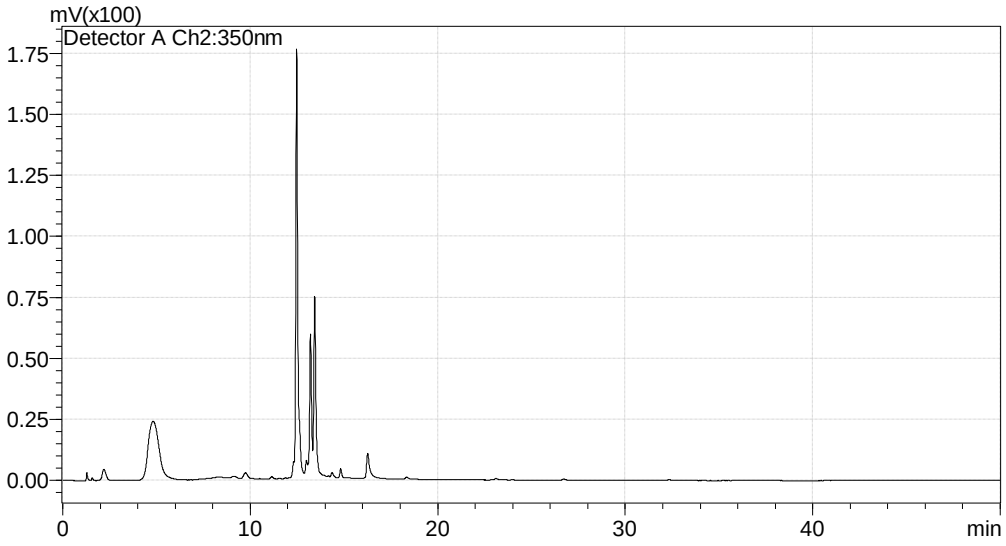

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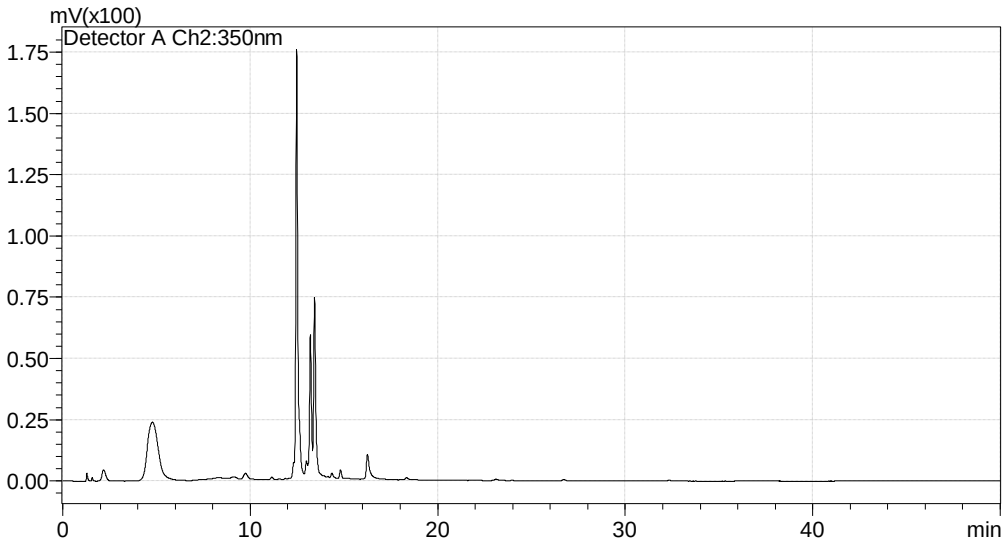
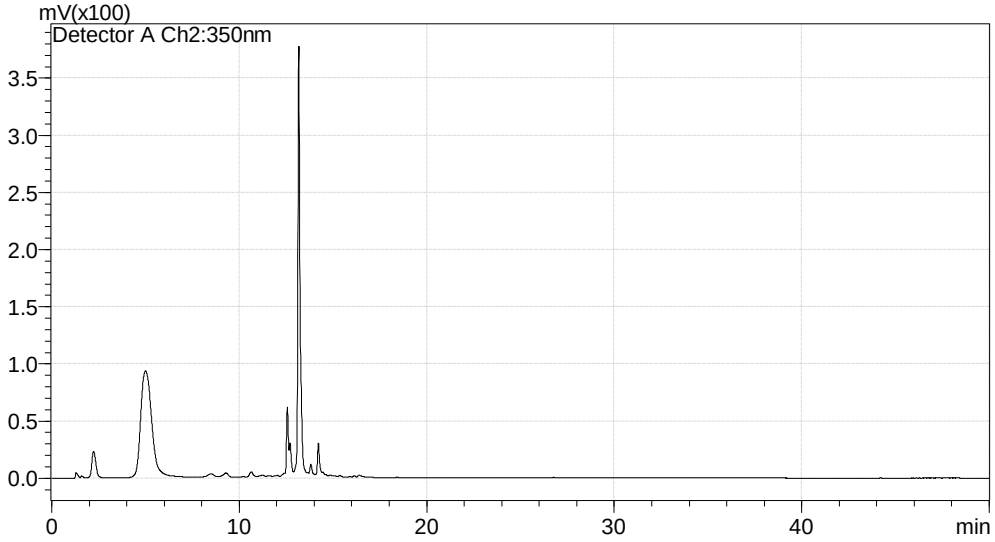


H. cavernicola– Acetato de etila

1



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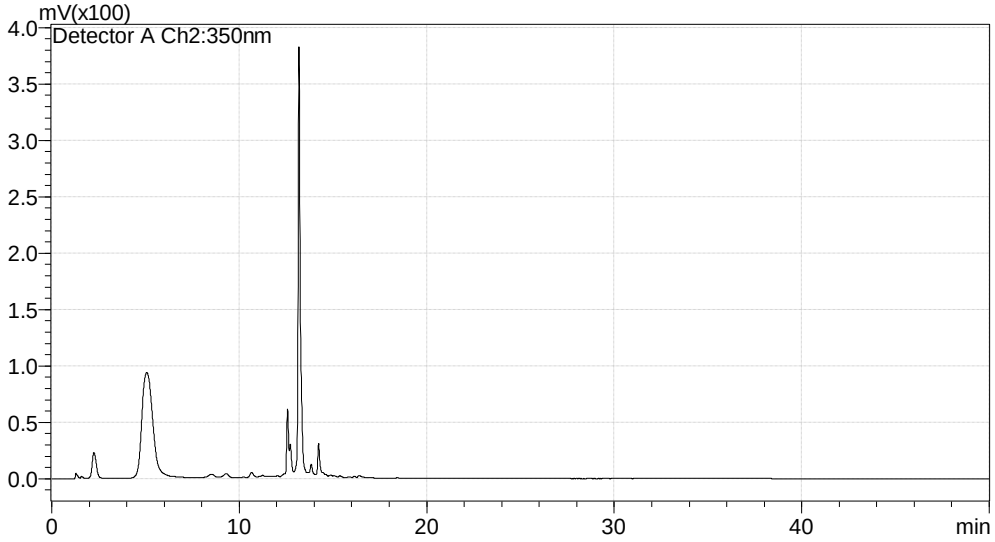

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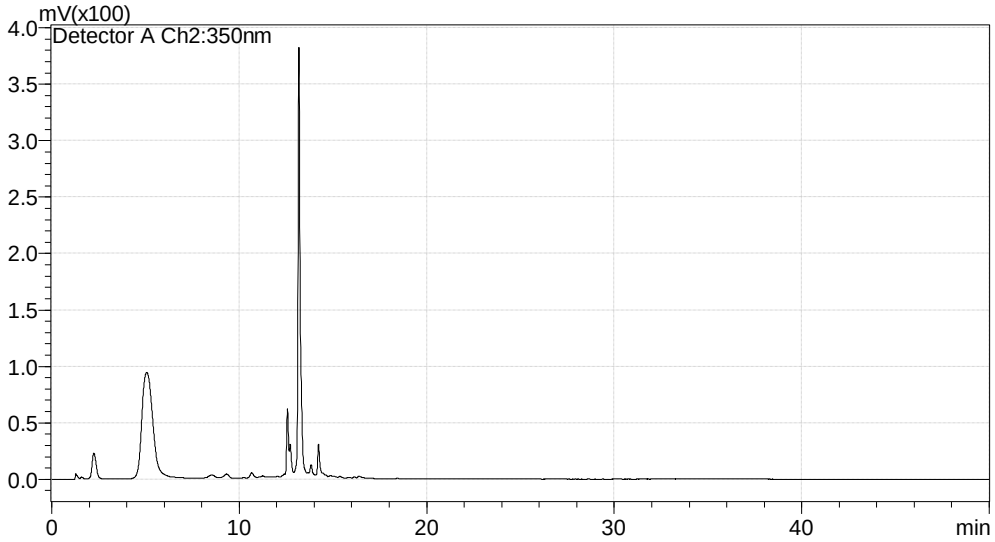
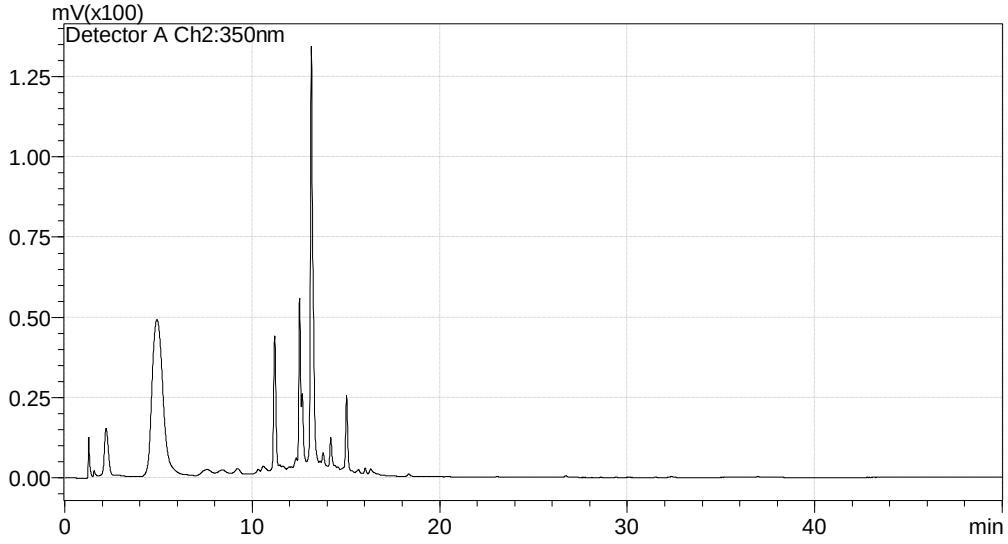


H. cavernicola – Metanol



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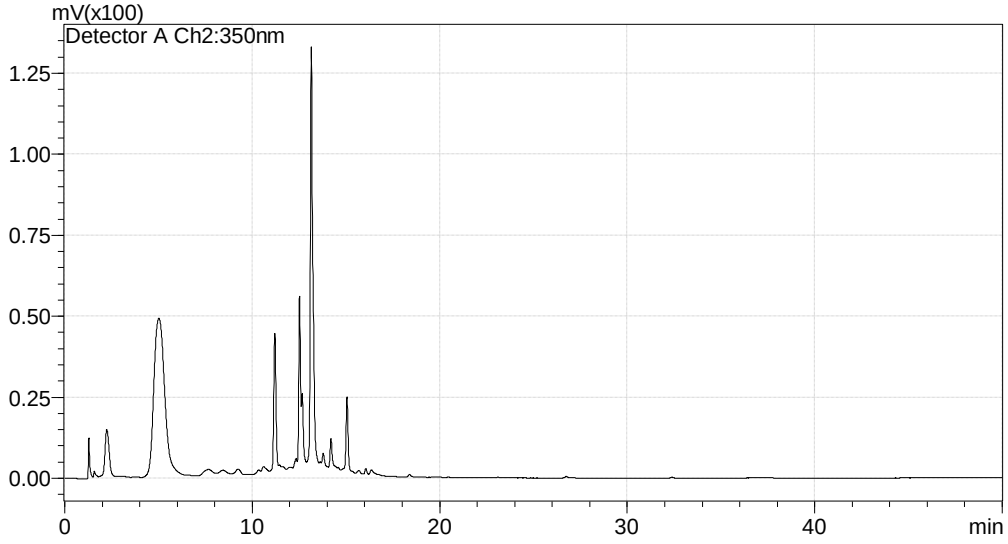

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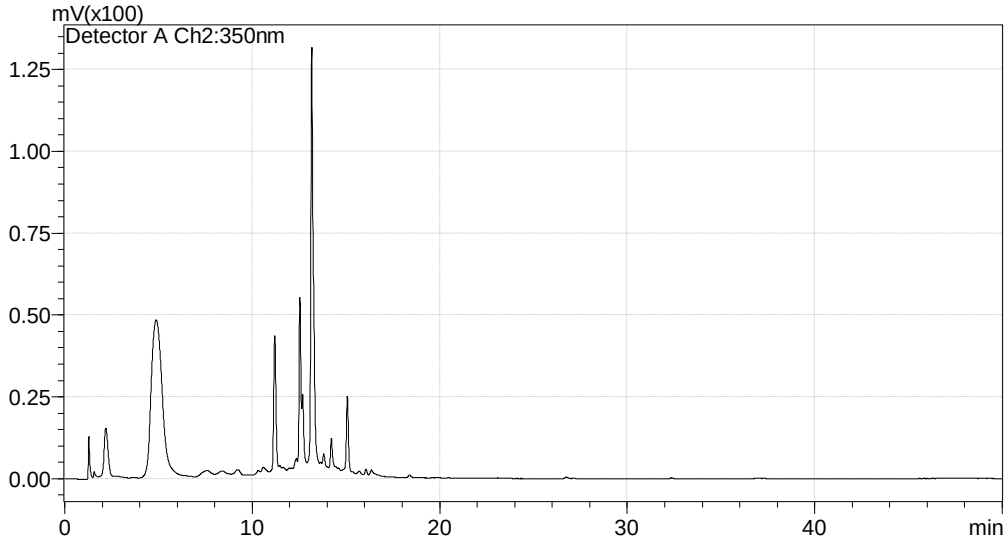
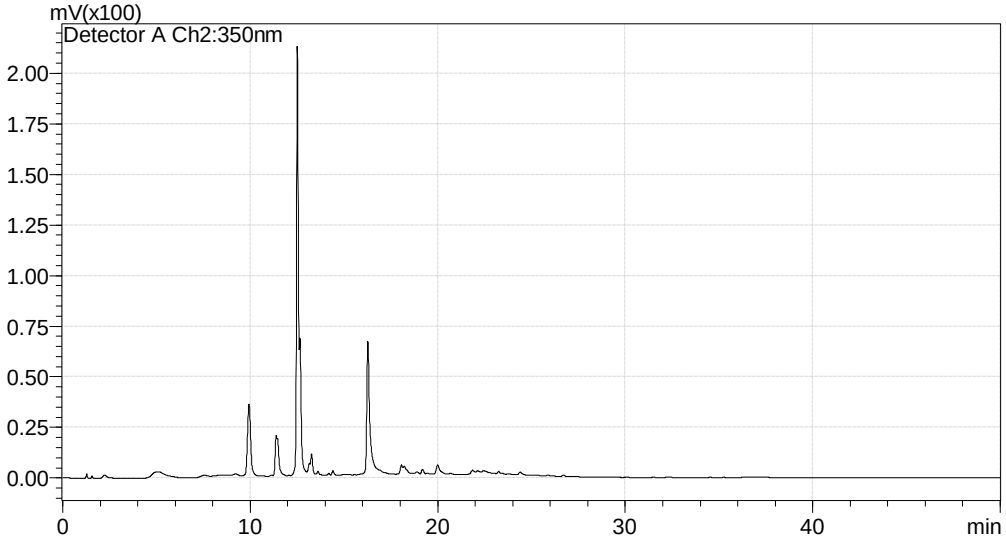


3

H. gentianoides– Acetato de etila

1



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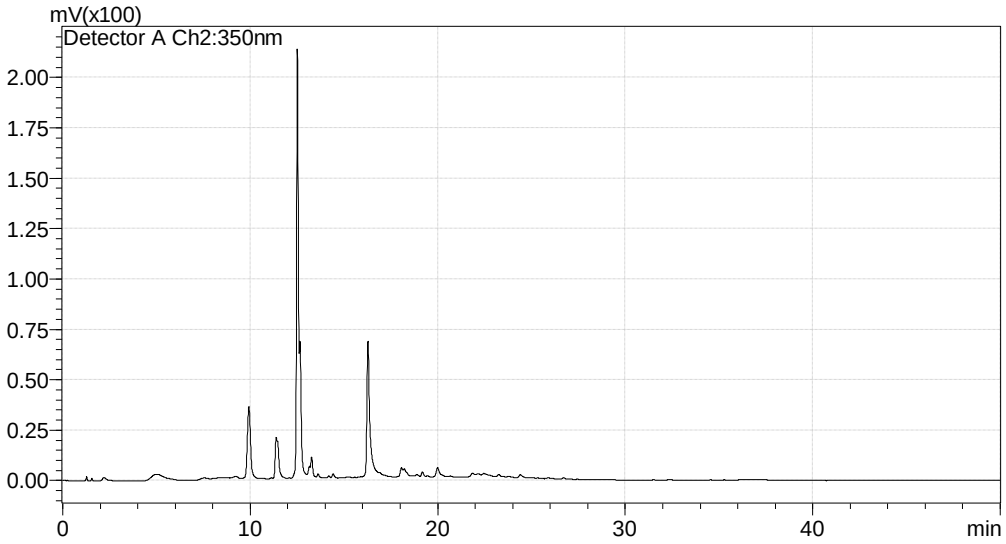

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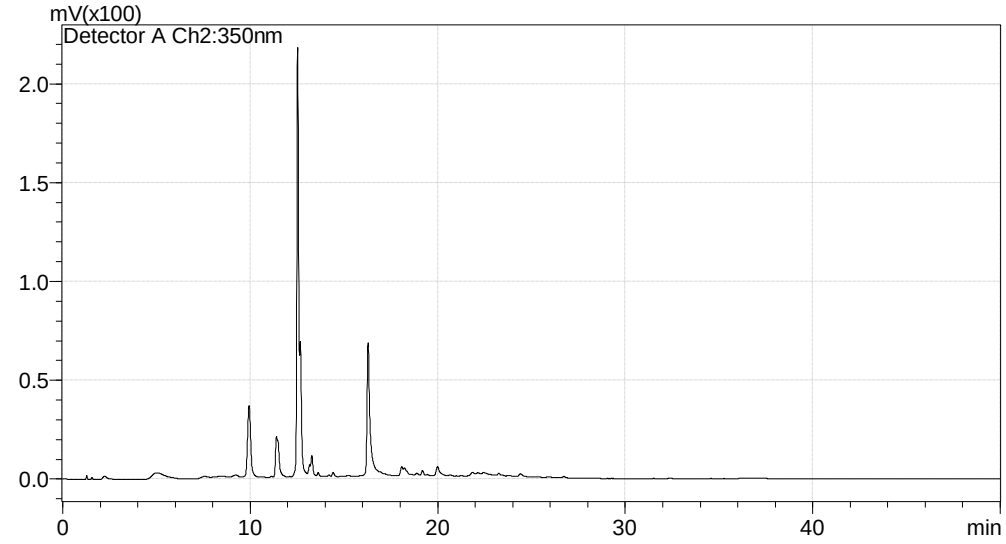
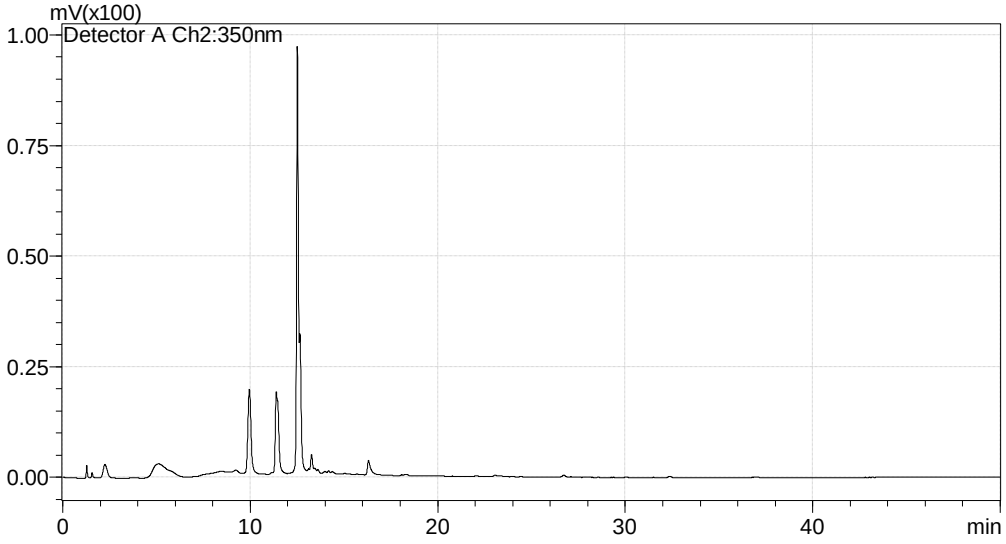


H. gentianoides – Metanol



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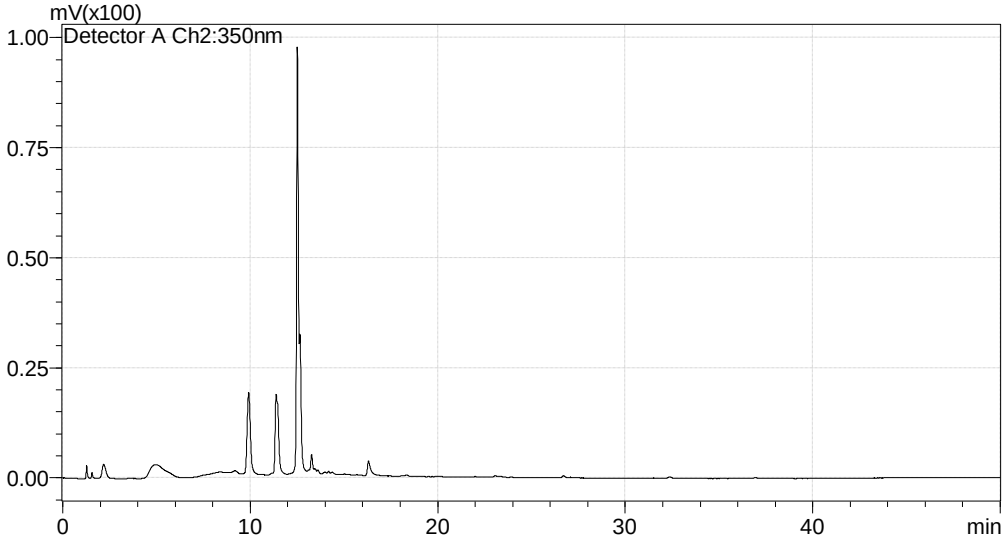

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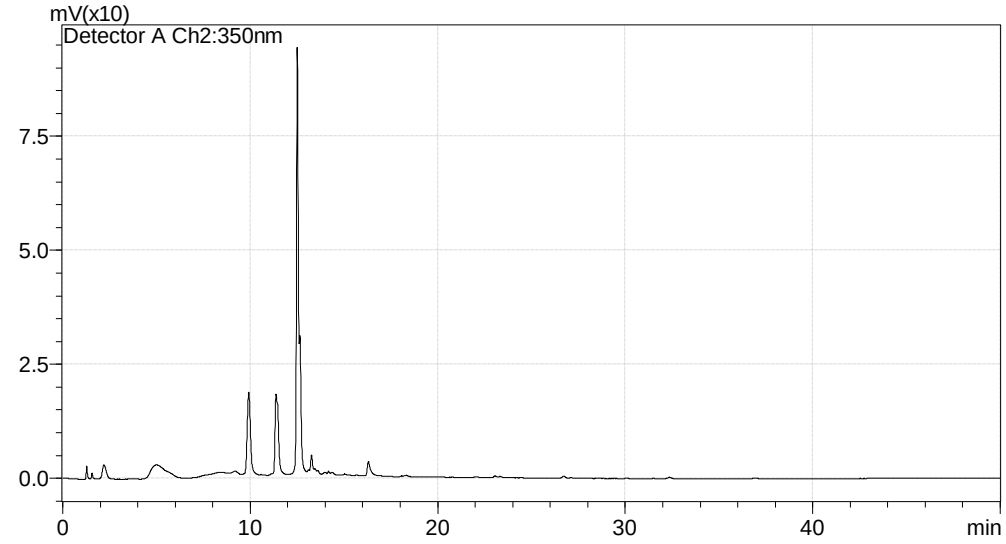
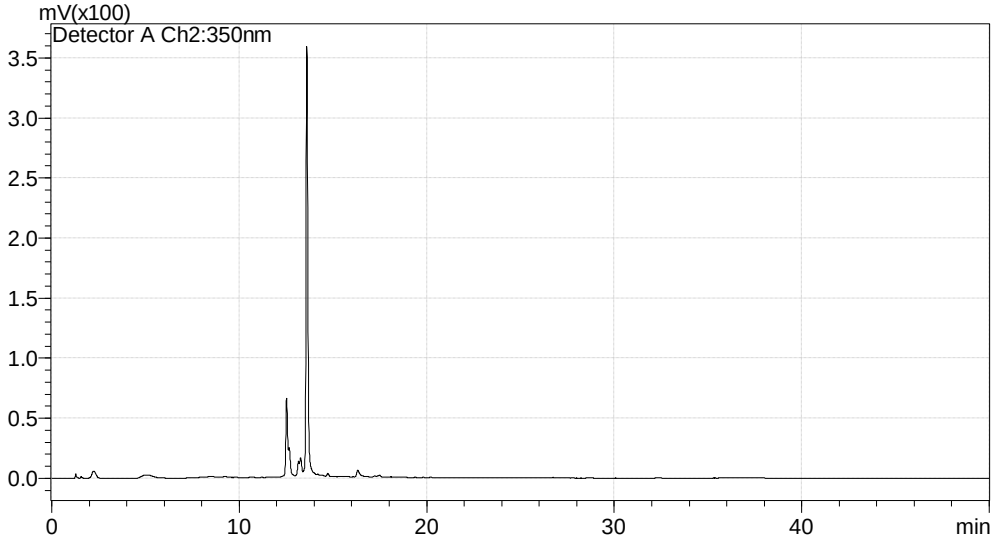


3

H. mutilum– Acetato de etila

1



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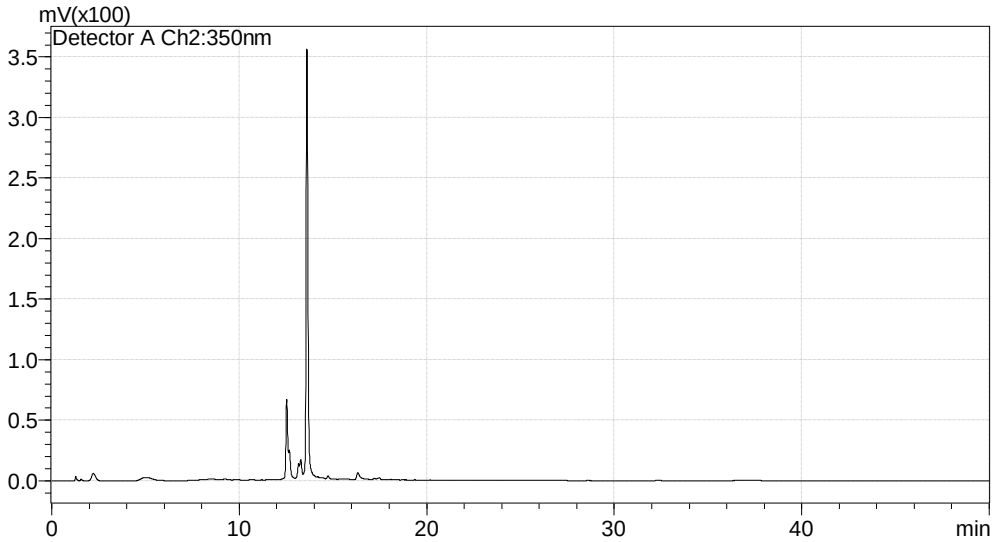

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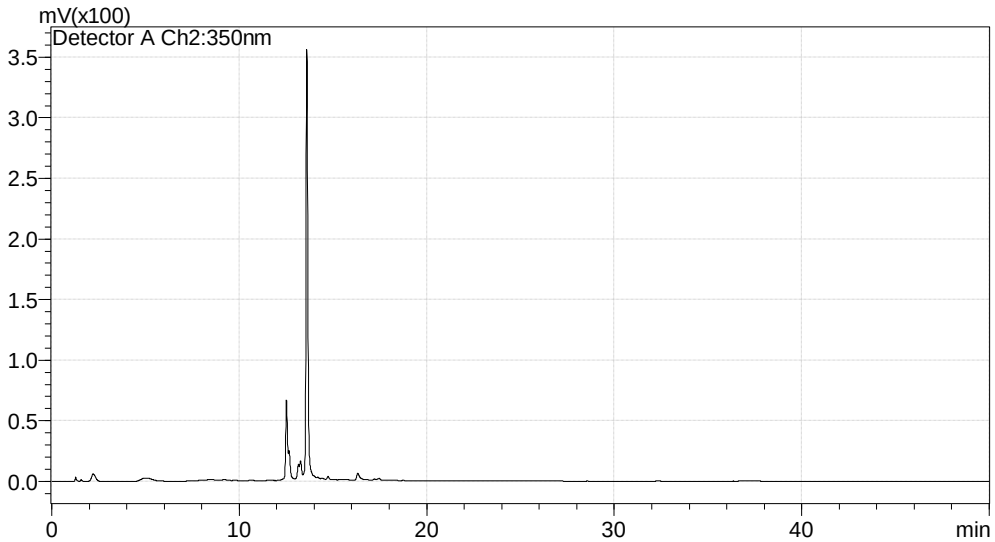

H. mutilum – Metanol

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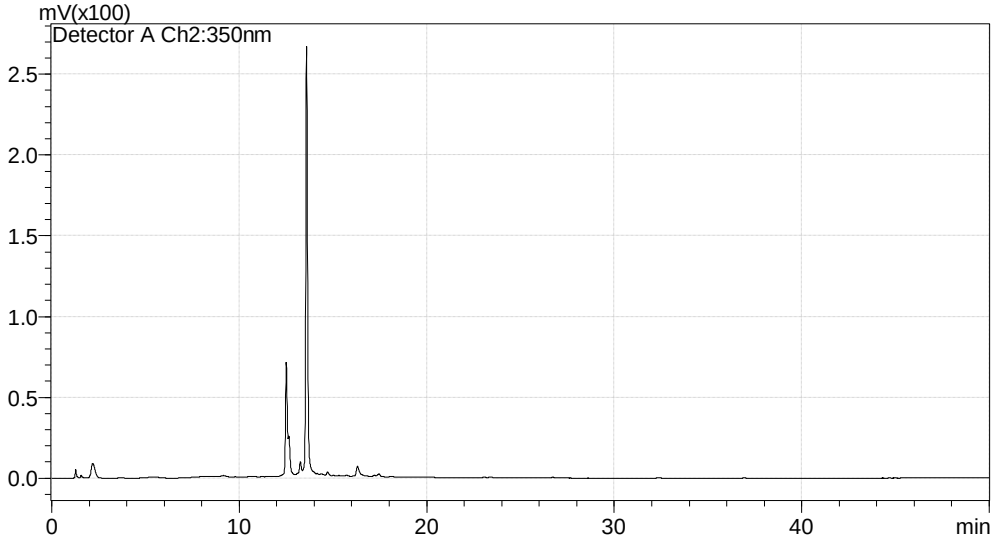

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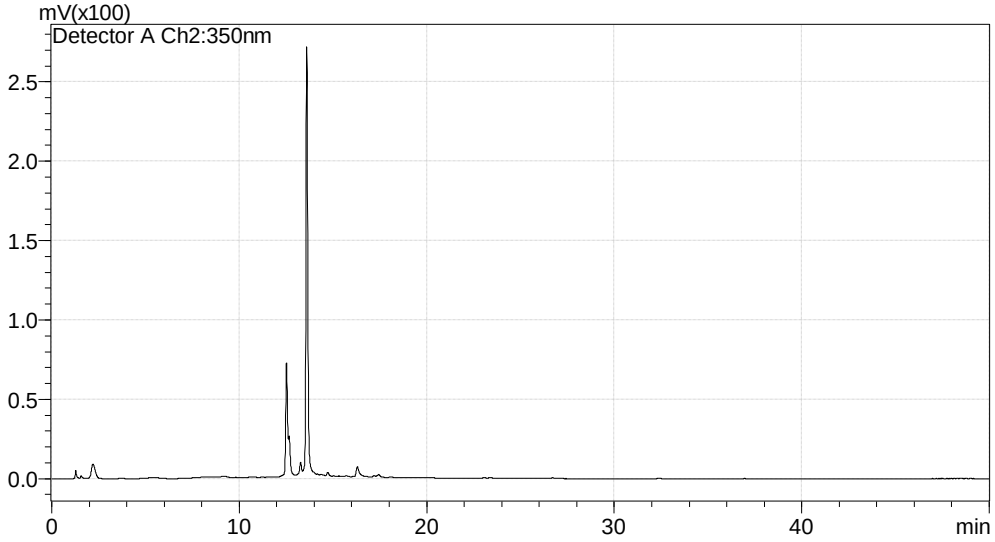

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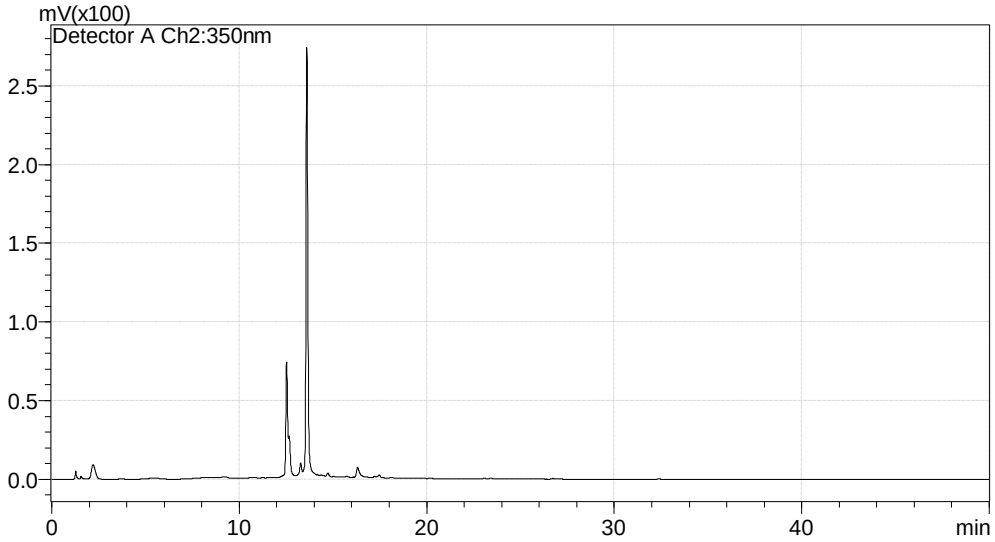
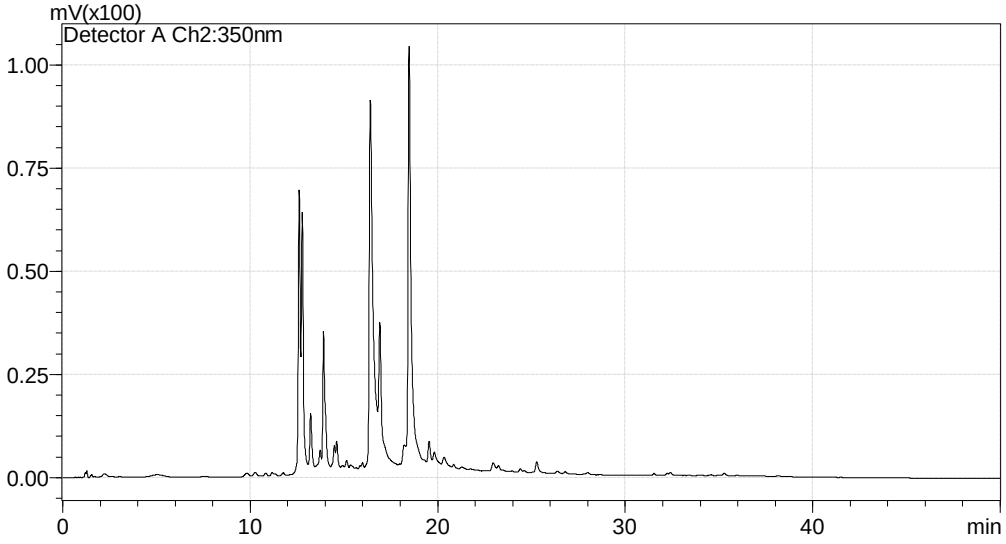


H. pedersenii– Acetato de etila



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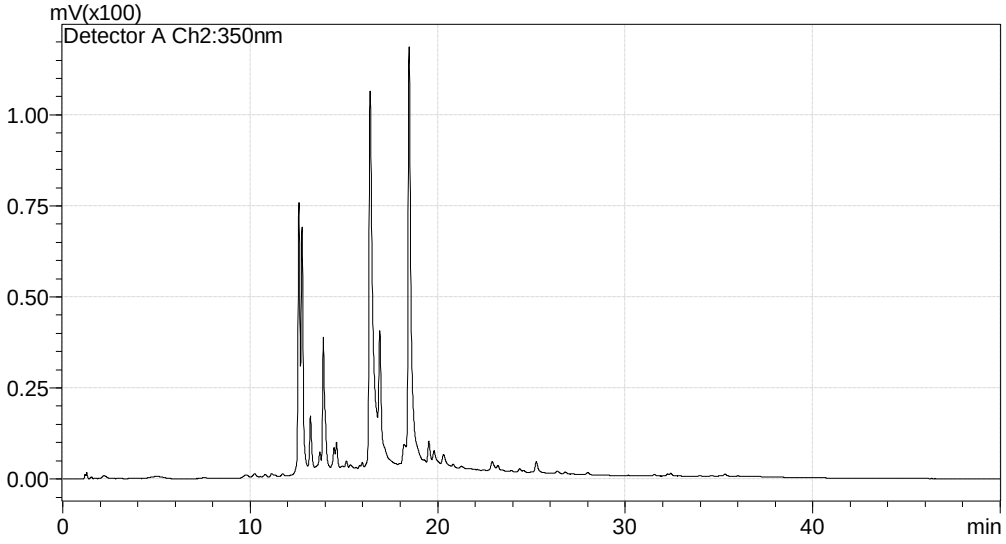

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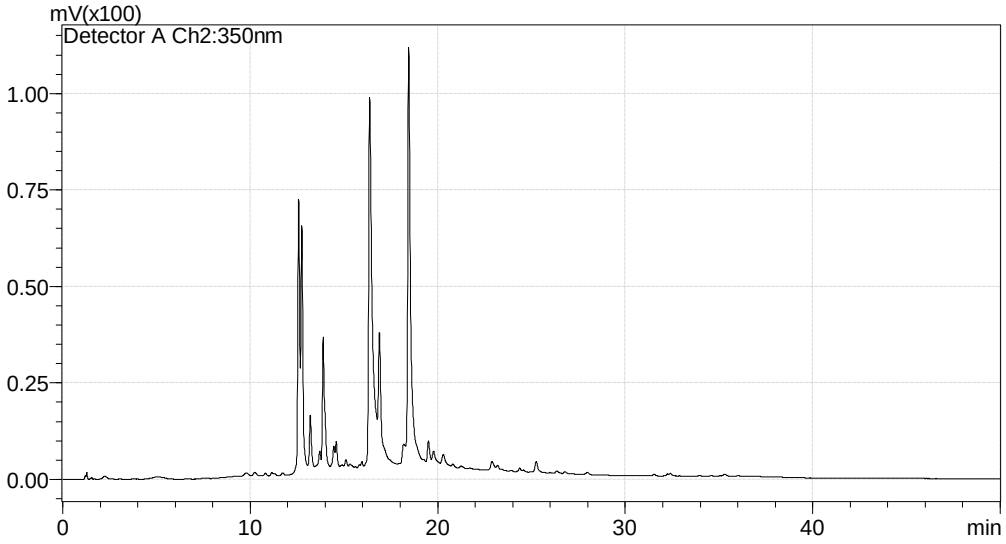

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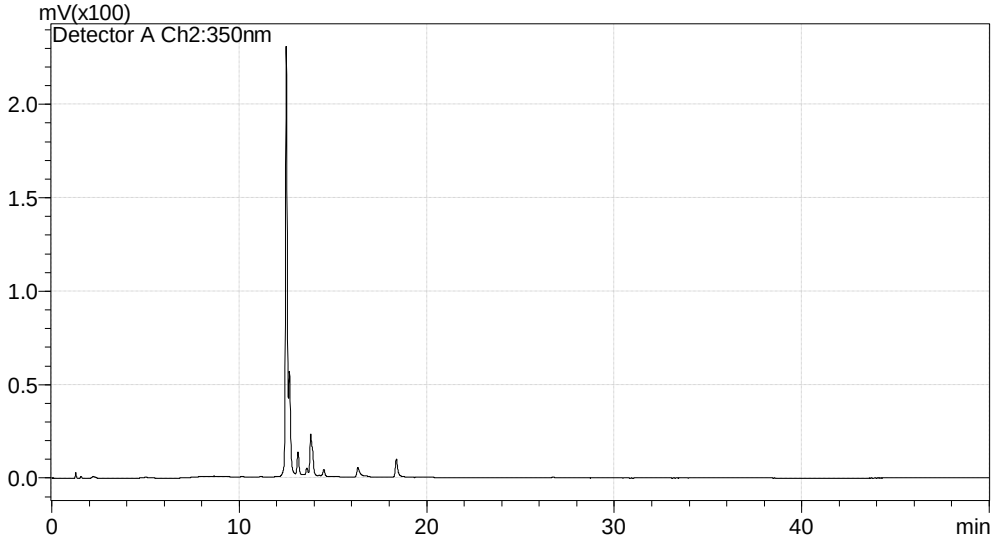
H. pedersenii – Metanol

1



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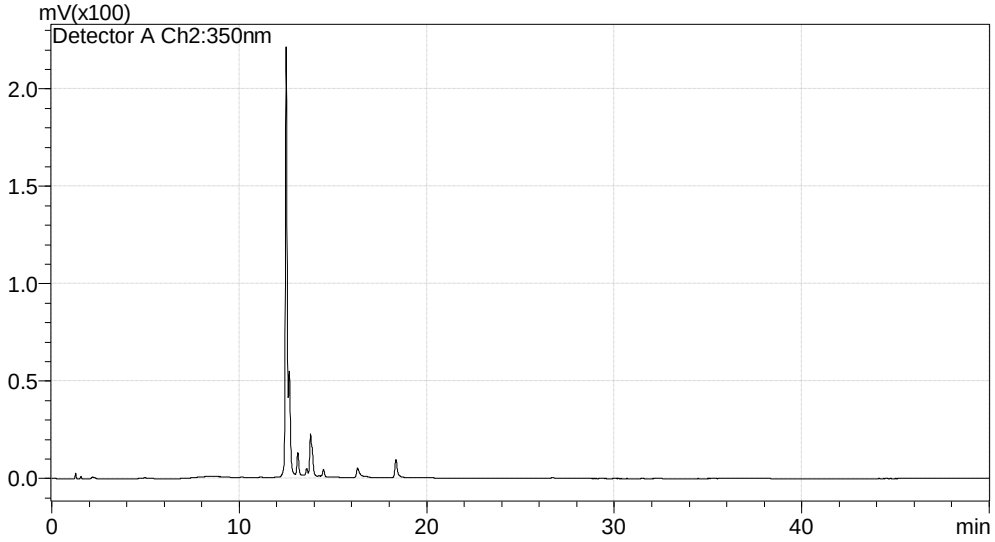

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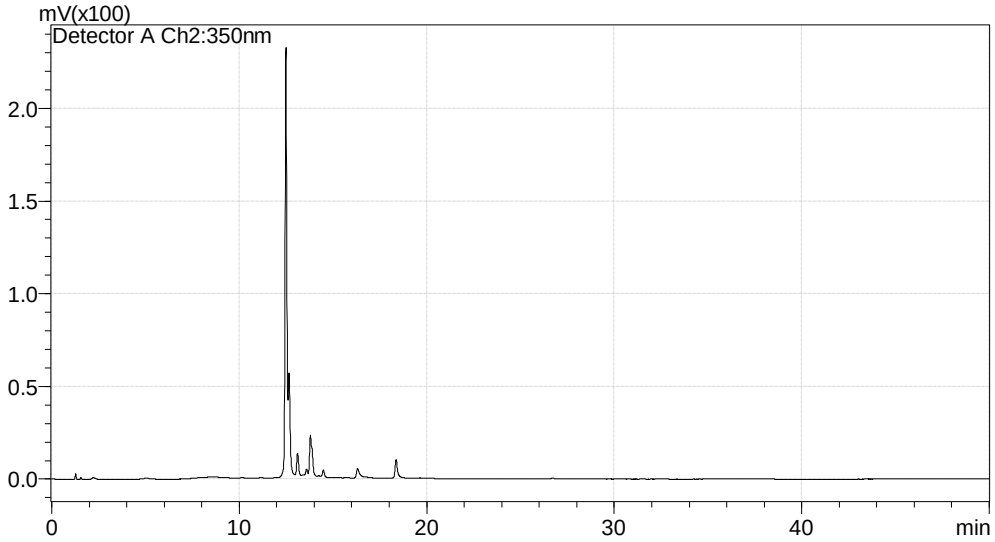
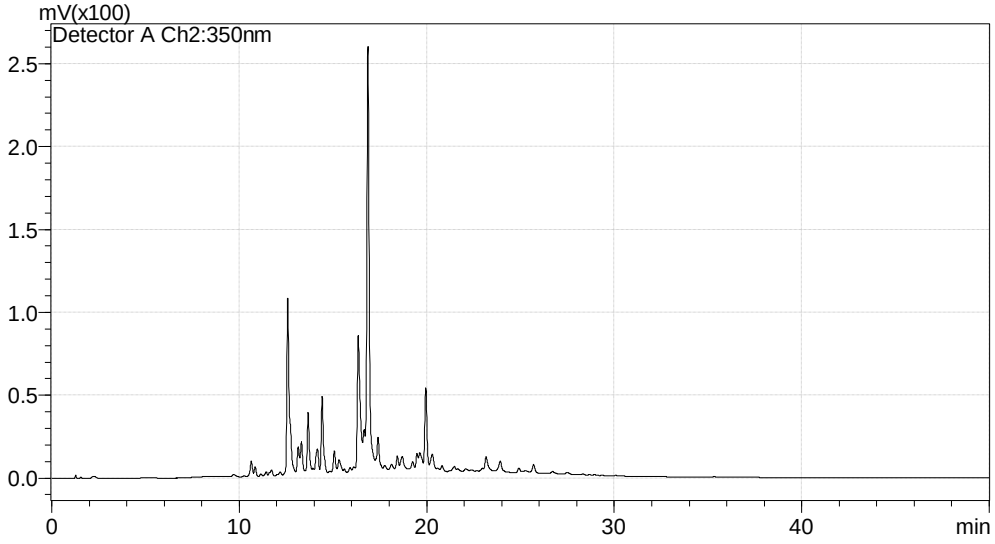


H. polyanthemum– Acetato de etila



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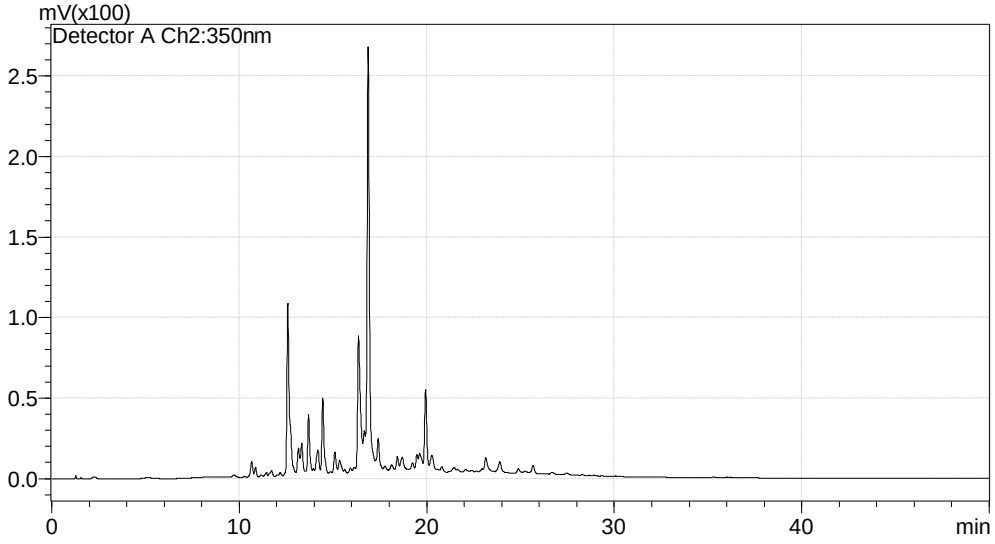

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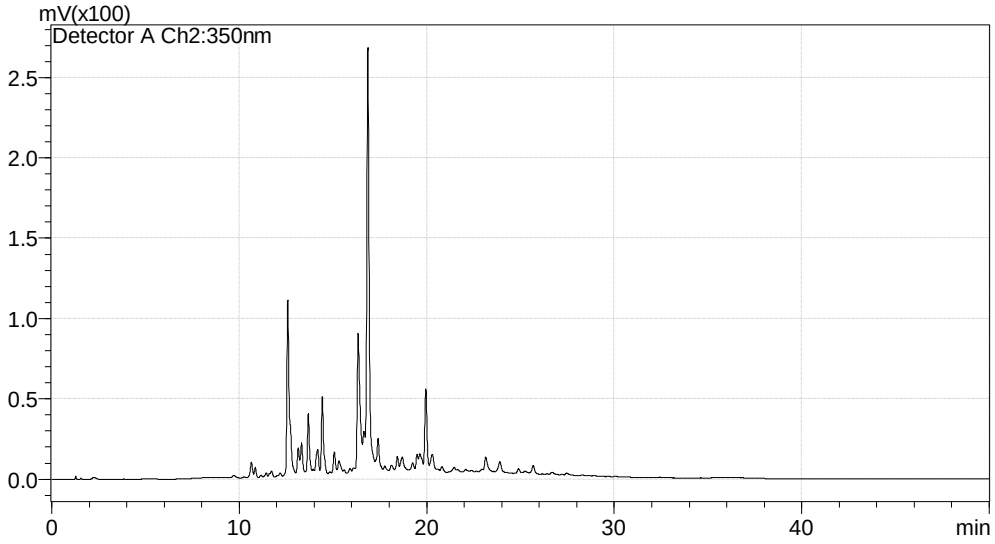

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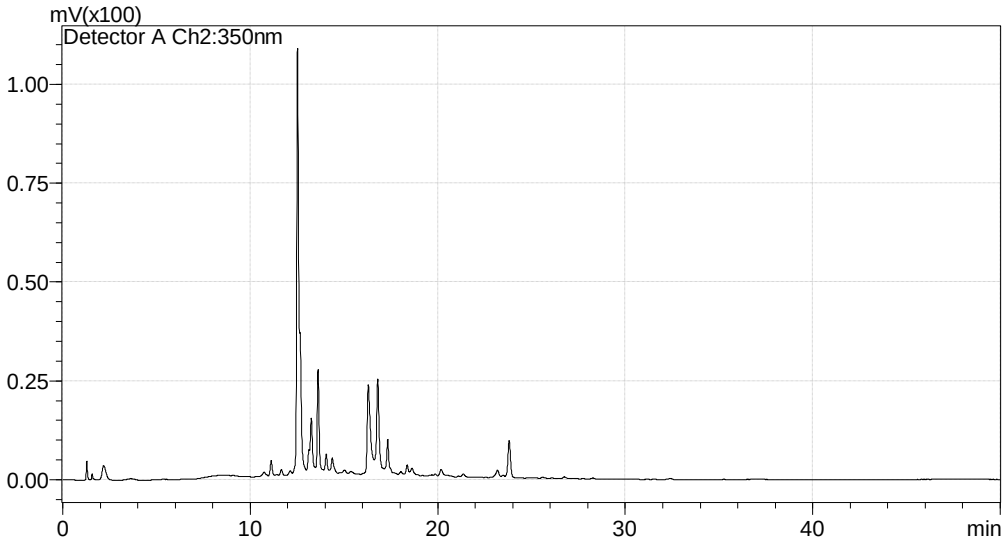
H. polyanthemum – Metanol

1



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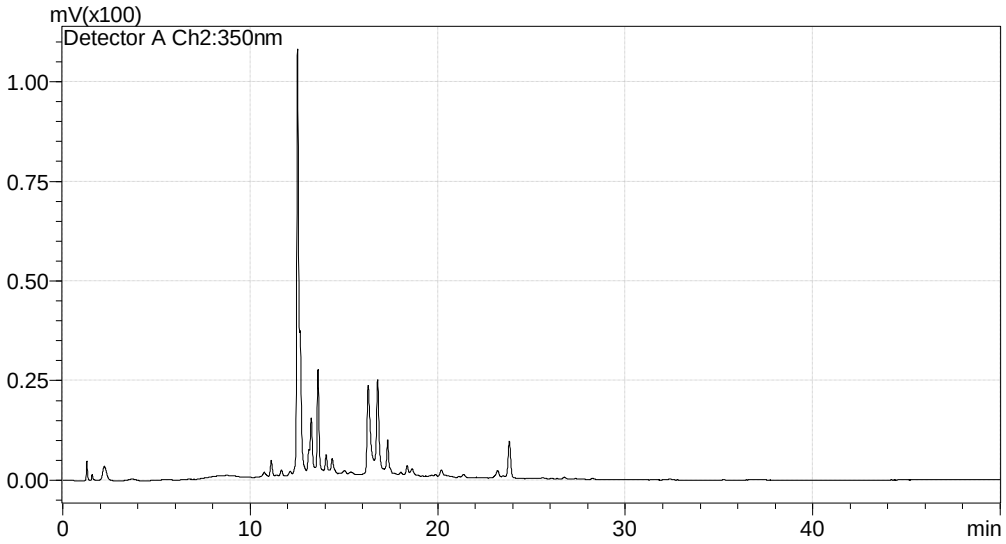

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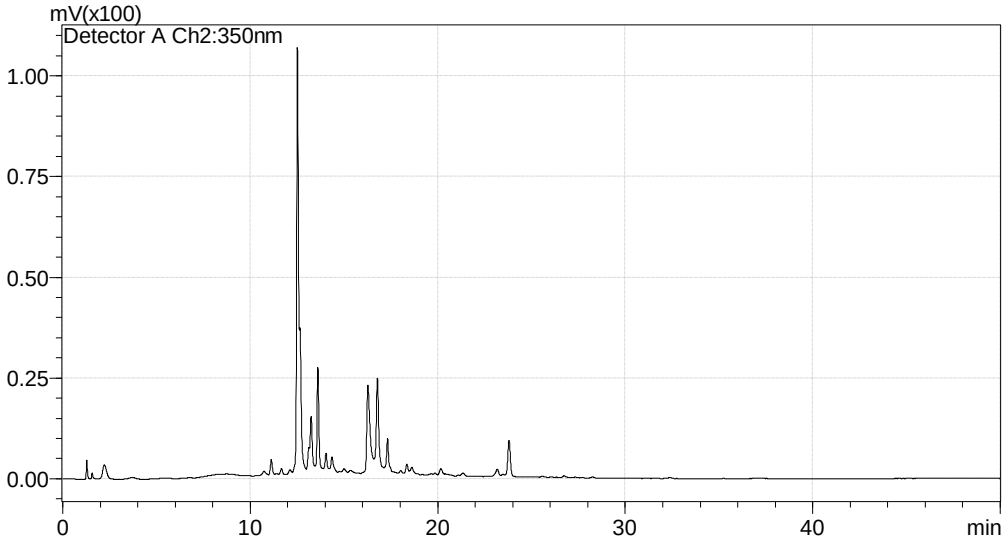
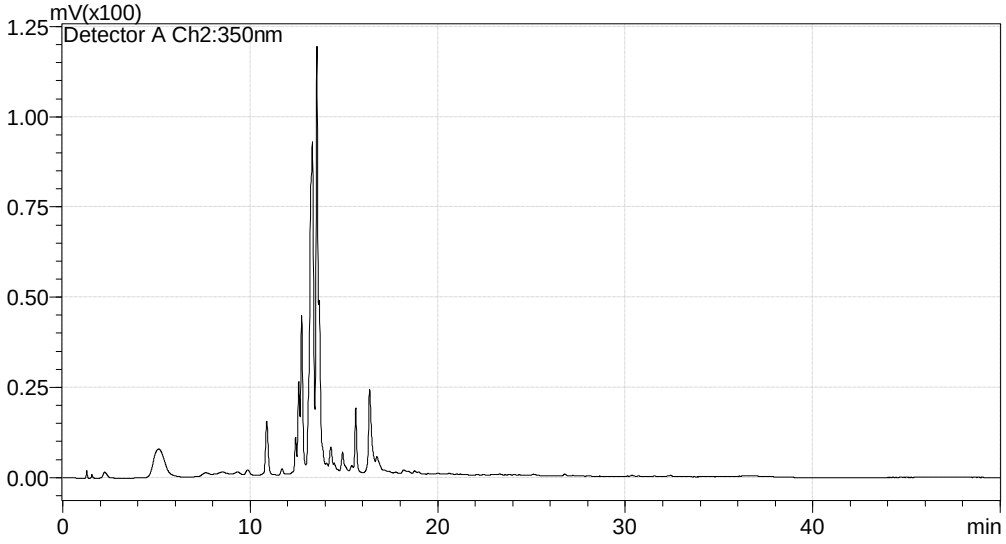


H. rigidum– Acetato de etila



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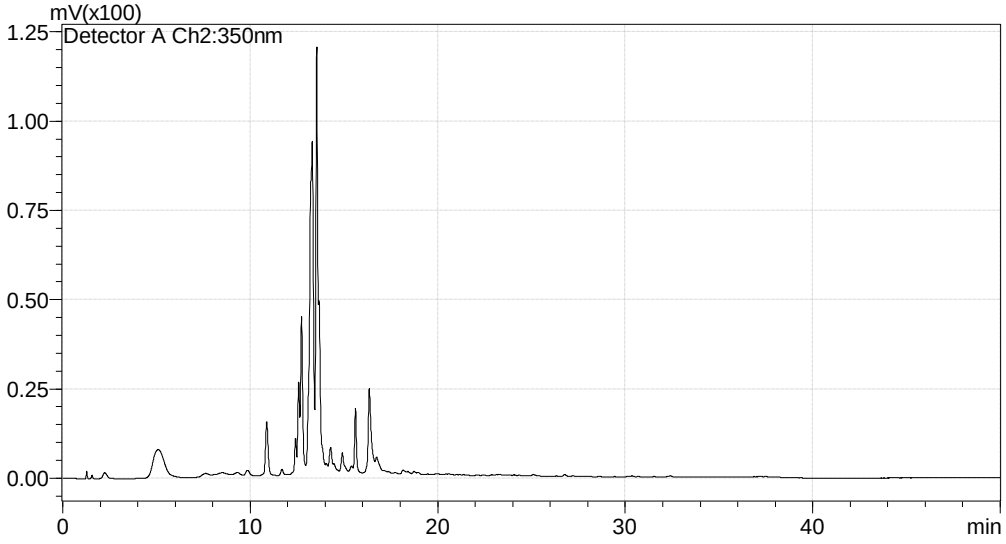

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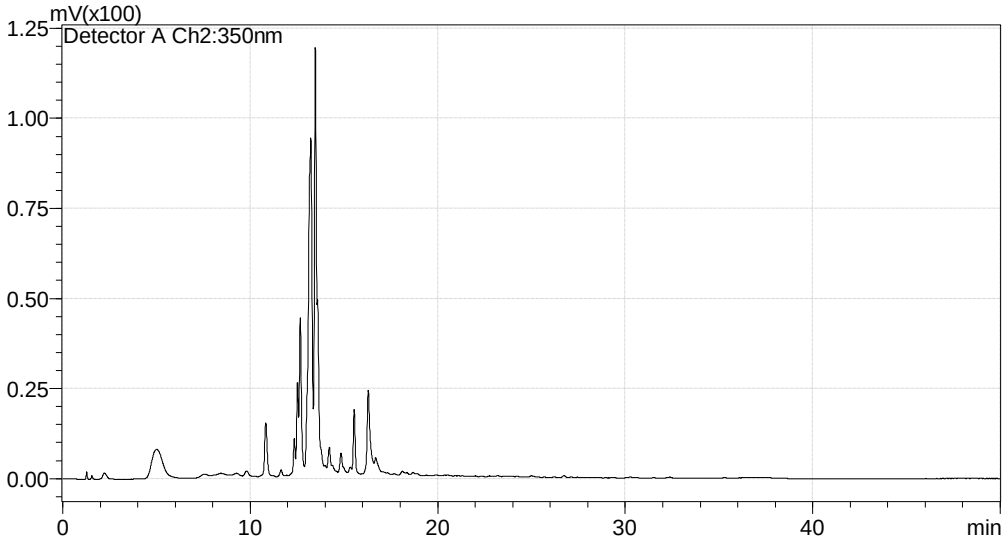

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H. rigidum – Metanol

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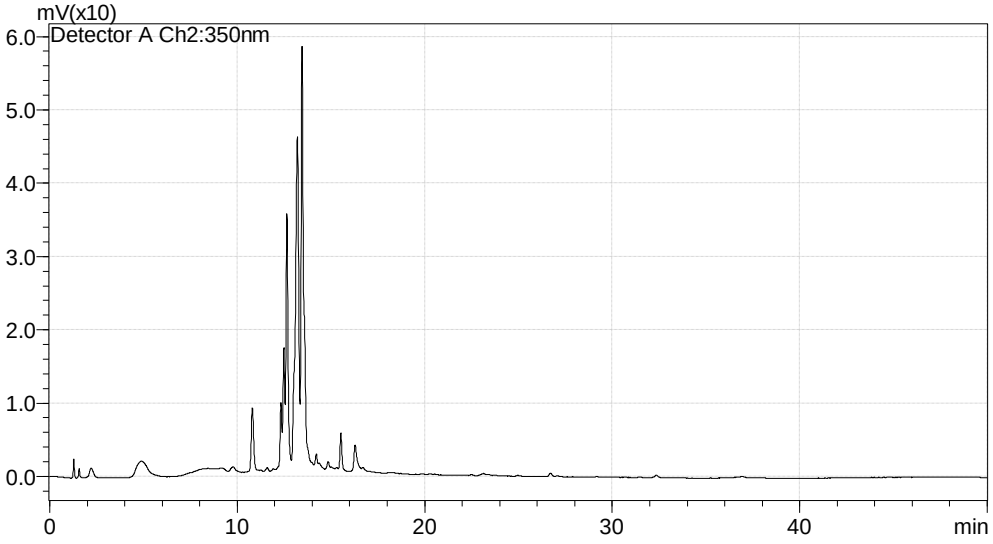

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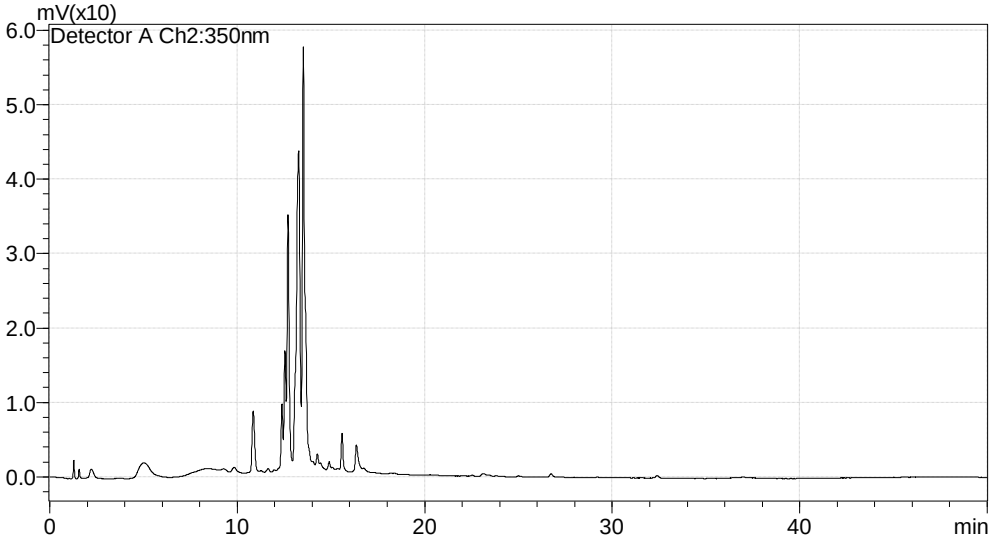

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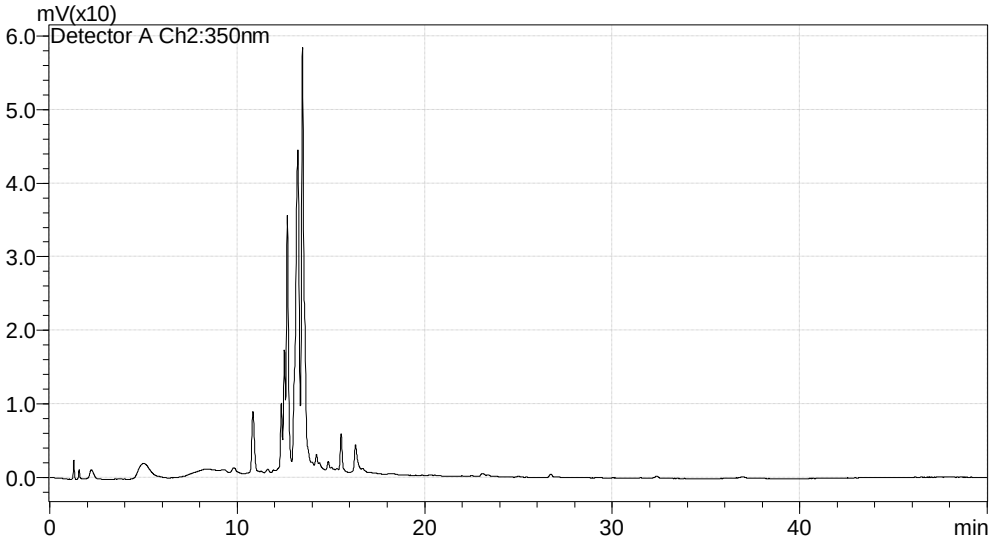
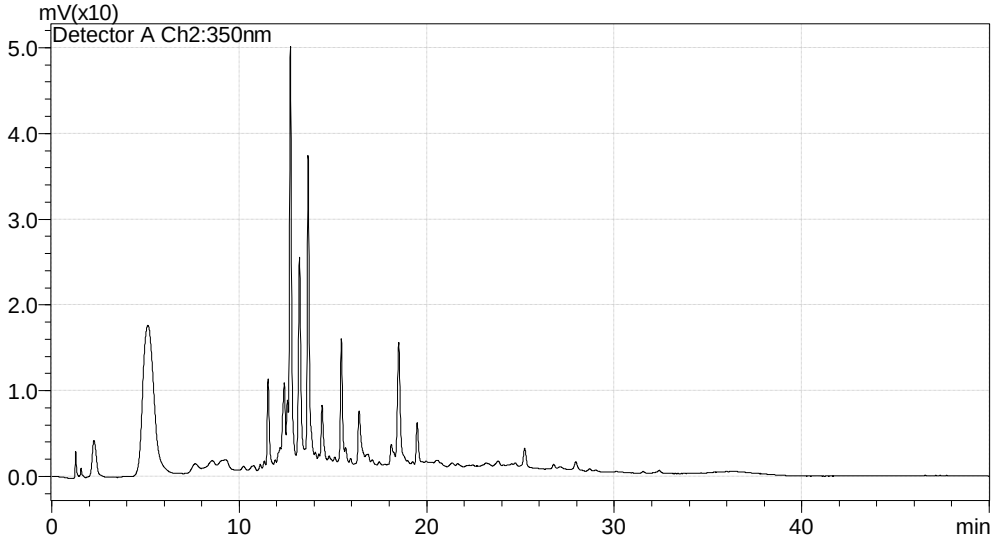


H. teretiusculum– Acetato de etila



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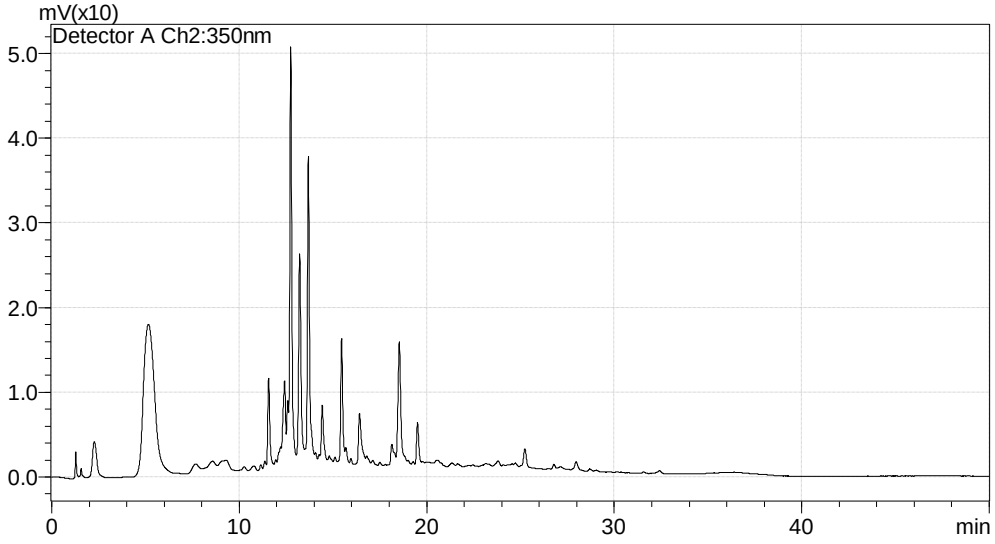

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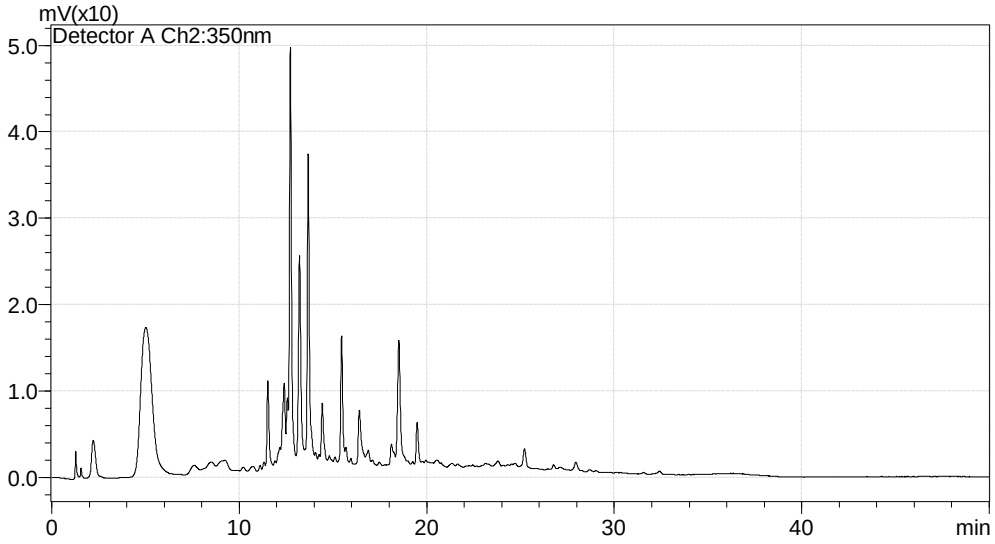

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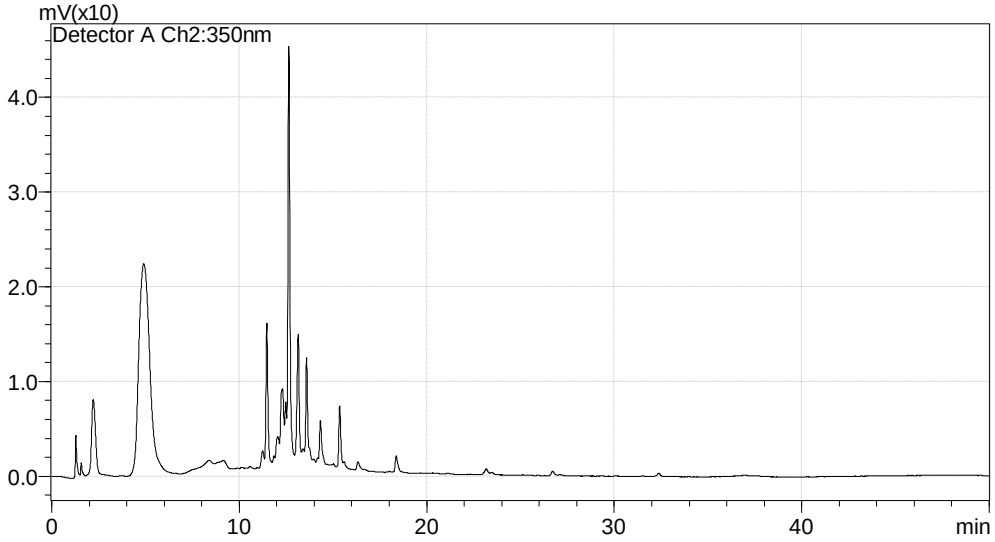
H. teretiusculum – Metanol

1



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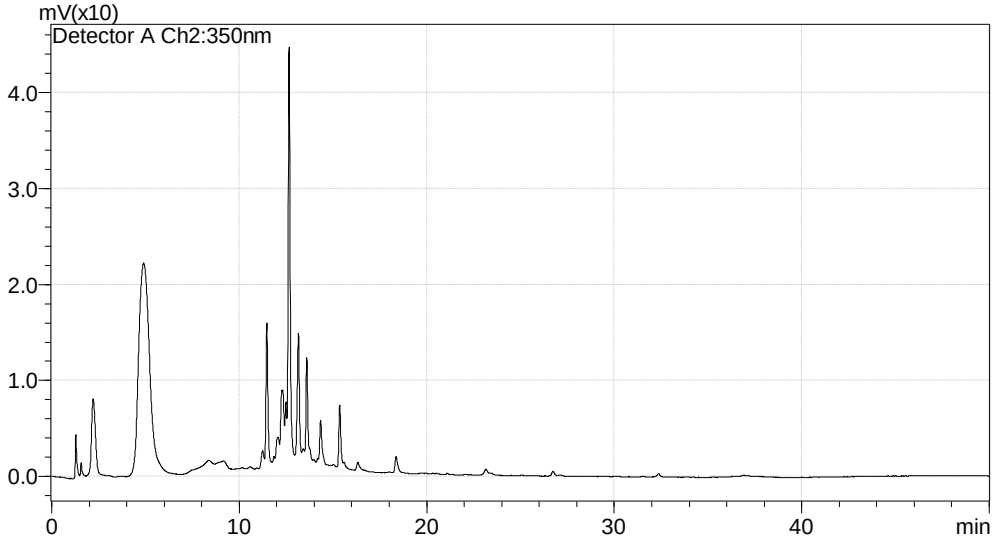

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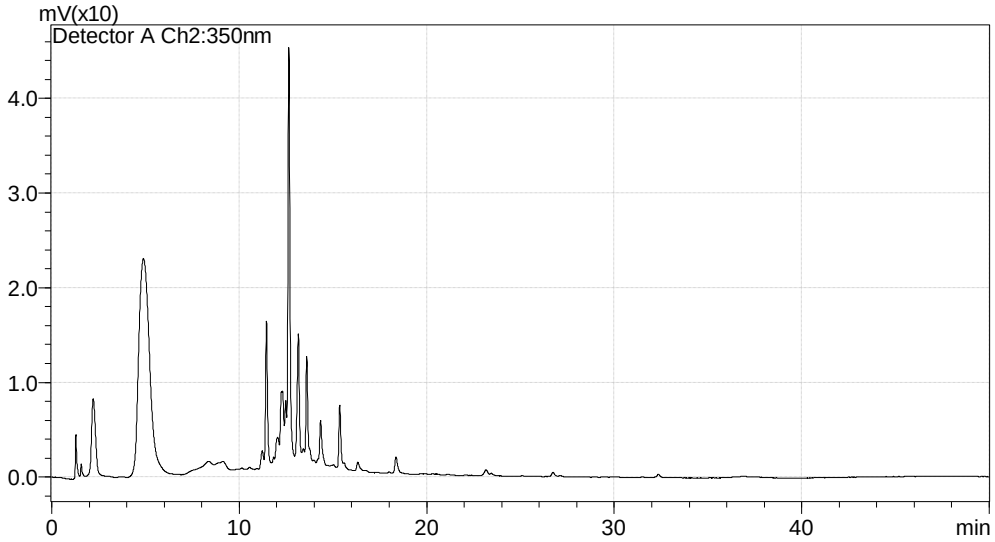

V. Quantificação das amostras analisadas em triplicata

H. caprifoliatum									
Acetato de etila									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12575	339077	23,87134	24,51	0,57		2,387134	2,45	0,06
2	12493	357808	24,98139				2,498139		
3	12515	352473	24,66522				2,466522		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13717	131727	11,5832	11,87	0,28		1,15832	1,19	0,03
2	12649	141048	12,13559				1,213559		
3	12660	137071	11,89991				1,189991		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13311	57323	7,173818	7,28	0,10		0,717382	0,73	0,01
2	13259	60705	7,374244				0,737424		
3	13259	59273	7,28938				0,728938		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13667	313593	22,36109	22,75	0,34		2,236109	2,28	0,03
2	13633	324251	22,99271				2,299271		
3	13623	322742	22,90328				2,290328		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16349	456968	30,85789	31,03	0,50		3,085789	3,10	0,05
2	16353	453348	30,64336				3,064336		
3	16324	469331	31,59055				3,159055		

H. caprifoliatum									
Metanol									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12521	749597	48,19989	47,87	0,29		4,819989	4,79	0,03
2	12525	741985	47,74879				4,774879		
3	12493	740486	47,65995				4,765995		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12662	349423	24,48447	23,10	1,21		2,448447	2,31	0,12
2	12666	311797	22,25465				2,225465		
3	12636	316912	22,55778				2,255778		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13247	93015	9,289025	9,32	0,04		0,928902	0,93	0,00
2	13253	94193	9,358836				0,935884		
3	13225	93166	9,297973				0,929797		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13597	329870	23,32571	23,33	0,09		2,332571	2,33	0,01
2	13603	331533	23,42426				2,342426		
3	13578	328412	23,2393				2,32393		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16273	183609	14,65788	14,58	0,10		1,465788	1,46	0,01
2	16264	182962	14,61953				1,461953		
3	16259	180332	14,46367				1,446367		

H. carinatum									
Acetato de etila									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12582	3122880	188,8472	191,52	2,46		18,88472	19,15	0,25
2	12584	3204402	193,6784				19,36784		
3	12594	3176681	192,0356				19,20356		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12725	216606	16,61337	15,51	0,96		1,661337	1,55	0,10
2	12742	190246	15,0512				1,50512		
3	12750	186987	14,85807				1,485807		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13323	770190	49,42029	49,54	0,13		4,942029	4,95	0,01
2	13331	771742	49,51227				4,951227		
3	13334	774670	49,68579				4,968579		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16361	352997	24,69628	24,90	0,25		2,469628	2,49	0,03
2	16378	361219	25,18354				2,518354		
3	16378	355265	24,83069				2,483069		

H. carinatum									
Metanol									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12505	1215535	75,81267	75,83	0,63		7,581267	7,58	0,06
2	12469	1226706	76,47469				7,647469		
3	12471	1205380	75,21086				7,521086		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12633	142304	12,21003	11,77	0,50		1,221003	1,18	0,05
2	12608	125847	11,23474				1,123474		
3	12600	136640	11,87436				1,187436		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13242	314264	22,40085	22,26	0,19		2,240085	2,23	0,02
2	13211	313182	22,33673				2,233673		
3	13205	308146	22,03828				2,203828		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16280	123060	11,06957	11,15	0,07		1,106957	1,11	0,01
2	16255	124625	11,16232				1,116232		
3	16245	125438	11,2105				1,12105		

H. cavernicola									
Acetato de etila									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12564	377236	26,13275	26,24	0,19		2,613275	2,62	0,02
2	12575	377104	26,12493				2,612493		
3	12571	382739	26,45887				2,645887		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12705	168795	13,77996	13,94	0,17		1,377996	1,39	0,02
2	12716	174373	14,11053				1,411053		
3	12712	171335	13,93048				1,393048		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13169	3028417	183,2491	185,05	1,57		18,32491	18,51	0,16
2	13182	3076061	186,0726				18,60726		
3	13178	3072169	185,8419				18,58419		

H. cavernicola									
Metanol									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12524	325762	23,08226	23,24	0,14		2,308226	2,32	0,01
2	12520	330187	23,34449				2,334449		
3	12539	329442	23,30034				2,330034		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12663	133006	11,659	11,56	0,13		1,1659	1,16	0,01
2	12659	128778	11,40844				1,140844		
3	12681	132128	11,60697				1,160697		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13146	1176877	73,52169	73,77	0,24		7,352169	7,38	0,02
2	13142	1184902	73,99727				7,399727		
3	13168	1181590	73,801				7,3801		

H. gentianoides									
Acetato de etila									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12508	1447583	89,56448	90,14	1,08		8,956448	9,01	0,11
2	12510	1478251	91,38195				9,138195		
3	12525	1445862	89,46249				8,946249		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12646	456165	30,8103	30,28	0,72		3,08103	3,03	0,07
2	12649	433245	29,452				2,9452		
3	12664	452003	30,56365				3,056365		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13269	68298	7,824227	7,87	0,04		0,782423	0,79	0,00
2	13273	69144	7,874363				0,787436		
3	13283	69548	7,898305				0,789831		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16265	775362	49,7268	50,30	0,71		4,97268	5,03	0,07
2	16270	781297	50,07852				5,007852		
3	16278	798501	51,09808				5,109808		

H. gentianoides									
Metanol									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12510	669852	43,47398	43,37	0,59		4,347398	4,34	0,06
2	12510	677168	43,90755				4,390755		
3	12506	657352	42,7332				4,27332		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12645	188698	14,95946	14,93	0,49		1,495946	1,49	0,05
2	12646	196362	15,41365				1,541365		
3	12642	179696	14,42598				1,442598		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13269	19087	4,907846	4,90	0,03		0,490785	0,49	0,00
2	13271	19257	4,917921				0,491792		
3	13267	18340	4,863577				0,486358		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16304	37921	6,024001	6,08	0,05		0,6024	0,61	0,01
2	16303	39473	6,115977				0,611598		
3	16294	39446	6,114377				0,611438		

H. mutilum									
Acetato de etila									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12524	466972	31,45075	31,54	0,19		3,145075	3,15	0,02
2	12530	472149	31,75756				3,175756		
3	12514	466341	31,41336				3,141336		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12659	158111	13,14679	13,14	0,08		1,314679	1,31	0,01
2	12665	156498	13,0512				1,30512		
3	12651	159322	13,21856				1,321856		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13273	90694	9,151476	9,10	0,16		0,915148	0,91	0,02
2	13277	86782	8,91964				0,891964		
3	13268	91909	9,22348				0,922348		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13603	2381772	144,9271	144,79	0,41		14,49271	14,48	0,04
2	13608	2371627	144,3259				14,43259		
3	13602	2384753	145,1038				14,51038		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16314	68046	7,809292	7,87	0,07		0,780929	0,79	0,01
2	16320	70480	7,953538				0,795354		
3	16316	68887	7,859132				0,785913		

H. mutilum									
Metanol									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12506	512446	34,14567	34,45	0,31		3,414567	3,44	0,03
2	12518	517377	34,43789				3,443789		
3	12525	522833	34,76123				3,476123		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12641	170063	13,8551	13,98	0,17		1,38551	1,40	0,02
2	12653	175490	14,17672				1,417672		
3	12658	170914	13,90554				1,390554		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13259	32912	5,727154	5,80	0,08		0,572715	0,58	0,01
2	13269	35638	5,888705				0,58887		
3	13273	34047	5,794417				0,579442		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13587	1799379	110,4129	111,86	1,64		11,04129	11,19	0,16
2	13597	1818427	111,5417				11,15417		
3	13601	1853820	113,6392				11,36392		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16298	63238	7,524357	7,73	0,19		0,752436	0,77	0,02
2	16290	67497	7,776757				0,777676		
3	16307	69570	7,899609				0,789961		

H. pedersenii

Acetato de etila

HIPEROSÍDEO

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	12608	486351	32,59921	33,69	1,14		3,259921	3,37	0,11
2	12594	524676	34,87045				3,487045		
3	12581	503224	33,59915				3,359915		

ISOQUERCITRINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	12769	456797	30,84775	31,82	1,67		3,084775	3,18	0,17
2	12756	505647	33,74274				3,374274		
3	12745	457118	30,86678				3,086678		

GUAJAVERINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	13220	91392	9,192841	9,33	0,30		0,919284	0,93	0,03
2	13209	99506	9,673699				0,96737		
3	13199	90103	9,116451				0,911645		

QUERCITRINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	13726	14079	4,611058	4,63	0,01		0,461106	0,46	0,00
2	13713	14446	4,632808				0,463281		
3	13704	14429	4,6318				0,46318		

QUERCETINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	16403	1181969	73,82346	74,66	10,63		7,382346	7,47	1,06
2	16391	1382167	85,68774				8,568774		
3	16369	1024148	64,47055				6,447055		

H. pedersenii									
Metanol									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12505	1598520	98,50942	96,62	3,61		9,850942	9,66	0,36
2	12498	1496428	92,45917				9,245917		
3	12483	1605128	98,90103				9,890103		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12673	383618	26,51096	26,55	0,14		2,651096	2,65	0,01
2	12664	386781	26,69841				2,669841		
3	12650	382314	26,43368				2,643368		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13126	78155	8,40838	8,33	0,07		0,840838	0,83	0,01
2	13117	76275	8,296966				0,829697		
3	13104	76078	8,285291				0,828529		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13606	17274	4,800403	4,79	0,03		0,48004	0,48	0,00
2	13595	16622	4,761764				0,476176		
3	13585	17449	4,810774				0,481077		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16328	50084	6,744815	6,82	0,07		0,674481	0,68	0,01
2	16308	52172	6,868555				0,686856		
3	16306	51975	6,85688				0,685688		

H. polyanthemum

Acetato de etila

HIPEROSÍDEO

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	12583	758715	48,74025	49,13	1,11		4,874025	4,91	0,11
2	12588	750756	48,26858				4,826858		
3	12585	786534	50,38888				5,038888		

ISOQUERCITRINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	12692	210261	16,23735	16,63	0,57		1,623735	1,66	0,06
2	12692	227965	17,28654				1,728654		
3	12700	212420	16,3653				1,63653		

GUAJAVERINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	13314	128447	11,38882	11,72	0,77		1,138882	1,17	0,08
2	13327	124791	11,17216				1,117216		
3	13319	148980	12,60567				1,260567		

QUERCITRINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	13672	229846	17,39801	17,54	0,16		1,739801	1,75	0,02
2	13692	231698	17,50776				1,750776		
3	13680	235230	17,71708				1,771708		

QUERCETINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	16345	851318	54,22816	55,01	0,85		5,422816	5,50	0,08
2	16361	862521	54,89208				5,489208		
3	16338	879640	55,9066				5,59066		

H. polyanthemum									
Metanol									
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12519	738190	47,52388	47,85	0,74		4,752388	4,79	0,07
2	12520	735002	47,33495				4,733495		
3	12515	758133	48,70576				4,870576		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12625	235924	17,75821	17,55	0,84		1,775821	1,75	0,08
2	12648	244420	18,2617				1,82617		
3	12643	216862	16,62854				1,662854		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13254	95918	9,461064	9,46	0,36		0,946106	0,95	0,04
2	13252	102077	9,826064				0,982606		
3	13246	89882	9,103354				0,910335		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13616	153324	12,8631	12,91	0,05		1,28631	1,29	0,01
2	13611	155152	12,97144				1,297144		
3	13604	154107	12,90951				1,290951		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16289	207904	16,09767	16,10	0,23		1,609767	1,61	0,02
2	16282	204119	15,87336				1,587336		
3	16267	212031	16,34224				1,634224		

H. rigidum

Acetato de etila

RUTINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	12415	64209	7,581901	7,56	0,09		0,75819	0,76	0,01
2	12409	62207	7,463257				0,746326		
3	12344	65294	7,646201				0,76462		

HIPEROSÍDEO

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	12587	172521	14,00077	13,86	0,16		1,400077	1,39	0,02
2	12581	167179	13,68419				1,368419		
3	12517	170510	13,88159				1,388159		

ISOQUERCITRINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	12736	323470	22,94643	23,32	0,40		2,294643	2,33	0,04
2	12730	329019	23,27528				2,327528		
3	12664	337007	23,74867				2,374867		

GUAJAVERINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	13310	1271951	79,15604	79,47	0,47		7,915604	7,95	0,05
2	13302	1286264	80,00427				8,000427		
3	13229	1273407	79,24233				7,924233		

QUERCITRINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	13548	1165845	72,8679	74,30	1,46		7,28679	7,43	0,15
2	13540	1215142	75,78938				7,578938		
3	13465	1189089	74,24541				7,424541		

QUERCETINA

	t_R	Área	ug/ml	Média C ug/mL	±		% Ext	Média % Ext	±
1	16364	208410	16,12765	16,33	0,28		1,612765	1,63	0,03
2	16346	209793	16,20961				1,620961		
3	16287	217216	16,64952				1,664952		

H. rigidum									
Metanol									
RUTINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12328	52494	6,887638	6,94	0,05		0,688764	0,69	0,00
2	12378	53549	6,95016				0,695016		
3	12347	54053	6,980028				0,698003		
HIPEROSÍDEO									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12480	115890	10,64466	10,39	0,24		1,064466	1,04	0,02
2	12543	111070	10,35901				1,035901		
3	12511	107829	10,16694				1,016694		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12645	248139	18,4821	18,36	0,24		1,84821	1,84	0,02
2	12703	241529	18,09038				1,809038		
3	12668	248654	18,51262				1,851262		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13208	556971	36,78434	36,70	0,09		3,678434	3,67	0,01
2	13275	554082	36,61313				3,661313		
3	13233	555526	36,69871				3,669871		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13558	136803	11,88402	11,78	0,12		1,188402	1,18	0,01
2	13617	132812	11,64751				1,164751		
3	13575	135576	11,81131				1,181131		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16279	34428	5,816997	5,76	0,06		0,5817	0,58	0,01
2	16353	33390	5,755482				0,575548		
3	16303	32343	5,693434				0,569343		

H. teretiusculum									
Acetato de etila									
RUTINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12395	50068	6,743866	6,77	0,02		0,674387	0,68	0,00
2	12413	50891	6,79264				0,679264		
3	12391	50611	6,776046				0,677605		
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12722	271230	19,85054	19,92	0,07		1,985054	1,99	0,01
2	12739	272468	19,92391				1,992391		
3	12721	273683	19,99591				1,999591		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13212	188999	14,9773	15,09	0,11		1,49773	1,51	0,01
2	13222	190847	15,08682				1,508682		
3	13214	192610	15,1913				1,51913		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13672	232800	17,57307	17,70	0,11		1,757307	1,77	0,01
2	13681	235733	17,74689				1,774689		
3	13674	236129	17,77036				1,777036		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16390	58314	7,232547	7,19	0,12		0,723255	0,72	0,01
2	16413	55328	7,055588				0,705559		
3	16401	58969	7,271364				0,727136		

H. teretiusculum									
Metanol									
ISOQUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	12641	248002	18,47398	18,28	0,17		1,847398364	1,83	0,02
2	12653	242363	18,1398				1,813980088		
3	12641	243756	18,22235				1,822235392		
GUAJAVERINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13138	95947	9,462783	9,59	0,13		0,946278298	0,96	0,01
2	13151	97709	9,567204				0,956720398		
3	13146	100421	9,727925				0,972792462		
QUERCITRINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	13589	57298	7,172336	7,24	0,14		0,717233614	0,72	0,01
2	13599	56930	7,150527				0,715052744		
3	13598	61192	7,403105				0,740310537		
QUERCETINA									
	t_R	**Área**	**ug/ml**	**Média C ug/mL**	**±**		**% Ext**	**Média % Ext**	**±**
1	16328	8397	4,274327	4,29	0,01		0,427432737	0,43	0,00
2	16320	8584	4,28541				0,428540951		
3	16318	8819	4,299336				0,429933626		