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Ethnopharmacological review, phytochemistry and bioactivity of the genus *Geissospermum* (Apocynaceae)

Revisão etnofarmacológica, fitoquímica e bioatividade do gênero *Geissospermum* (Apocynaceae)

Revisión etnofarmacológica, fitoquímica y bioactividad del género *Geissospermum* (Apocynaceae)

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Abstract
This narrative review aims to update the ethnopharmacology, phytochemistry and biological activities of Geissospermum species described in the literature, in order to contribute to the knowledge of bioactive compounds of therapeutic interest and establish directions for future research with this genus. The term "Geissospermum" was used to perform searches in different databases such as NDLTD (Digital Library Network of Theses and Dissertations), Google Scholar, PubChem, Scifinder, Web of Science, SciELO, PubMed and Science Direct. Google's National Institute of Industrial Property and Patents (INPI) was also consulted. The keywords indole alkaloids, quina-quina, Geissospermum, Geissospermum reticulatum and malaria were used in the search. Publications in Portuguese, French, Spanish and English published between 1950 and 2022 were included. Indole alkaloids are the main secondary metabolites found in this genus, and several molecules have already been isolated, which may be related to the described pharmacological activities. Extracts and isolated compounds showed antitumor, antimalarial, antinociceptive, anti-inflammatory, anticholinesterase, anti-HIV, antimicrobial and antioxidant activity. Plants of the genus Geissospermum are used in Brazil mainly by the Amazonian peoples to treat various pathologies. Biological activities reported for extracts and isolated compounds are consistent with etonopharmacological use against malaria, cancer and other diseases. Future work with Geissospermum species is needed to elucidate the mechanism of action of the isolated alkaloids, as well as their toxicological profile.
Keywords: Indole alkaloids; Quina-quina; Geissospermum; Geissospermum reticulatum; Malaria.

Resumo
Esta revisão narrativa visa atualizar a etnofarmacologia, a fitoquímica e as atividades biológicas das espécies de Geissospermum descritas na literatura, a fim de contribuir para o conhecimento de compostos bioativos de interesse terapêutico e estabelecer direcionamentos para pesquisas futuras com este gênero. O termo "Geissospermum" foi utilizado para realizar buscas em diferentes bases de dados como NDLTD (Biblioteca Digital em Rede de Teses e Dissertações), Google Acadêmico, PubChem, Scifinder, Web of Science, SciELO, PubMed e Science Direct. O Instituto Nacional de Propriedade Industrial e Patentes do Google (INPI) também foi consultado. As palavras-chave alcalóides indólicos, quina-quina, Geissospermum, Geissospermum reticulatum e malaria foram utilizadas na busca. Foram incluídas publicações em português, francês, espanhol e inglês publicadas no período de 1950 a 2022. Alcaloides indólicos são os principais metabólitos secundários encontrados neste gênero, e várias moléculas já foram isoladas, podendo estar relacionadas às atividades farmacológicas descritas. Extratos e compostos isolados apresentaram atividade antitumoral, antimalárica, antinociceptiva, anti-inflamatória, anticolinesterásica, anti-HIV, antimicrobiana e antioxidante. Plantas do gênero Geissospermum são utilizadas no Brasil principalmente pelos povos amazônicos, para tratar diversas patologias. As atividades biológicas relatadas para os extratos e compostos isolados são consistentes com o uso etonofarmacológico contra malária, câncer e outras doenças. Trabalhos futuros com espécies de Geissospermum são necessários para elucidar o mecanismo de ação dos alcaloides isolados, bem como seu perfil toxicológico.
Palavras-chave: Alcaloides indólicos; Quina-quina; Geissospermum; Geissospermum reticulatum; Malária.

Resumen
Esta revisión narrativa pretende actualizar la etnofarmacología, la fitoquímica y las actividades biológicas de las especies de Geissospermum descritas en la literatura, con el fin de contribuir al conocimiento de compuestos bioactivos de interés terapéutico y establecer líneas de investigación futuras con este género. Se utilizó el término "Geissospermum" para realizar búsquedas en diferentes bases de datos como NDLTD (Digital Library Network of Thess and Dissertations), Google Scholar, PubChem, Scifinder, Web of Science, SciELO, PubMed y Science Direct. También se consultó al Instituto Nacional de Propiedad Industrial y Patentes (INPI) de Google. En la búsqueda se utilizaron las palabras clave indole alkaloids, quina-quina, Geissospermum, Geissospermum reticulatum y malaria. Se incluyeron publicaciones en portugués, francés, español e inglés publicadas entre 1950 y 2022. Los alcaloides de indol son los principales metabolitos secundarios encontrados en este género, y ya se han aislado varias moléculas que pueden estar relacionadas con las actividades farmacológicas descritas. Los extractos y compuestos aislados mostraron actividad antitumoral, antipalúdica, antinociceptiva, antiinflamatoria, anticolinesterasa, anti-VIH, antimicrobiana y antioxidante. Las plantas del género Geissospermum son utilizadas en Brasil principalmente por los pueblos amazónicos para tratar diversas patologías. Las actividades biológicas reportadas para extractos y compuestos aislados son consistentes con el uso etonofarmacológico contra la malaria, el cáncer y otras enfermedades. Se necesita trabajo futuro con especies de Geissospermum para dilucidar el mecanismo de acción de los alcaloides aislados, así como su perfil toxicológico.
Palabras clave: Alcaloides de indol; Quinaquina; Geissospermum; Geissospermum reticulatum; Malaria.

1. Introduction

In some communities, like Indians and the riverside populations of the Amazon, the use of medicinal plants is the only way to treat certain pathologies. This traditional knowledge is very important for the discovery of new bioactive molecules and development of pharmaceutical products used as medicines today (Simões et al., 2017).

The Apocynaceae family, for example, has been used in the treatment of inflammation, pain, fever, malaria, diabetes, stomach problems and in the prevention of prostate cancer. These biological activities are probably related to the alkaloids, terpenoids, steroids, flavonoids, glycosides, simple phenols, lactones, and hydrocarbons described in this family (Bhadane et al., 2018; Gordillo-Román et al., 2013).

Apocynaceae is one of the largest and most representative of angiosperm families in Brazil (Viana et al., 2017), with 366 genera grouped in 5 subfamilies, 25 tribes, and 49 subtribes (Barbosa, 2016) occurring preferentially in biomes of tropical and subtropical zones and with some representatives in temperate climates. *Geissospermum* is considered the most relevant genus of this family due to its pharmacological and phytochemical characterization, with predominance of indole-type alkaloids. Pereirin, isolated from the bark of *Geissospermum vellosii*, popularly known as "pau pereira"(Almeida et al., 2009; Simões et al., 2017).

Studies with isolated indole alkaloids, extracts and fractions of different parts of *Geissospermum* spp. have reported antitumor pharmacological (Bastos, 2017; Bemis et al., 2009; Chang et al., 2014; Liu et al., 2019; Sajkowska-Kozielewicz et al., 2016; Yeh et al., 2019; Yu and Chen, 2014), antinociceptive, anti-inflammatory (Lima et al., 2016; Werner et al., 2009), anticholinesterase (Araújo et al., 2011; Lima et al., 2020, 2009), antileishmania, antitrypanosoma(da Silva e Silva et al., 2019; Reina et al., 2012), anti-HIV (Beljanski, 2005), antimicrobial (Camargo, 2011; Correia et al., 2008; Dias, 2012; Saraiva, 2012), cardiovascular (Martins, 2010; Morais, 2012), antioxidant (Sajkowska-Kozielewicz et al., 2016), and antimalarial (Bertania et al., 2005; Camargo, 2011; Mbeunkui et al., 2012; Muñoz et al., 2000; Oliveira, 2018; Steele et al., 2002).

This review aims to update the ethnopharmacology, the phytochemistry and the biological activities of *Geissospermum* species described in the literature in order to contribute to the knowledge of bioactive compounds of therapeutic interest and establish directions for future research with this genus.

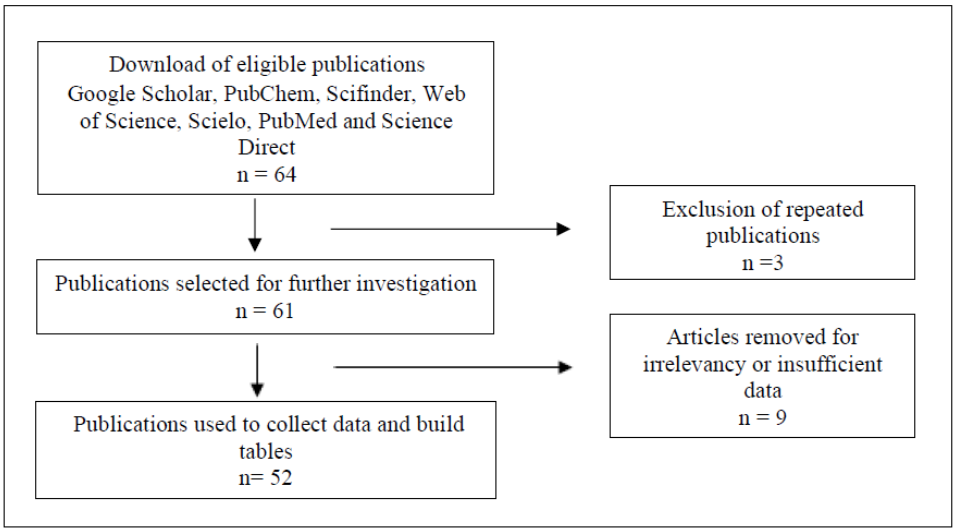
2. Methodology

2.1 Search strategy

The present study aimed to present a comprehensive understanding of the data available in the literature, presenting consolidated topics and new perspectives on the genus Geissospermum. To fulfill this objective, we used the methodology used for a narrative review of the literature. This work was carried out in 7 stages: 1) definition of the theme; 2) elaboration of the research question; 3) establishment of inclusion, exclusion and search criteria in the literature; 4) designation of the information to be extracted from the selected studies; 5) screening of the studies found; 6) exploration of relevant studies included in the review; 7) presentation of the review. Thus, the following central question was defined that guided the study: What is there in the scientific literature about the botanical, phytochemical and bioactivity aspects of the genus Geissospermum?

The keywords indole alkaloids, quina-quina, Geissospermum, Geissospermum reticulatum and malaria were used in Portuguese and English to perform electronic searches in different databases such as: NDLTD (Digital Library Network of Theses and Dissertations), Google Scholar, PubChem, Scifinder, Web of Science, SciELO, PubMed and Science Direct, individually or combined, in order to fully represent and examine the theme chosen in this study. Google's National Institute of Industrial Property and Patents (INPI) was also consulted. The Boolean operators “and” ou/and “or” were used to cross the keywords. Figure 1 presents a workflow with selected publications. To examine the publications, the “content analysis” methodology proposed by Bardin (2010) was used.

Figure 1 - workflow chart with selected publications.



Source: Authors (2023).

2.2 Inclusion and exclusion criteria

Publications (articles, patents, theses and dissertations) published in Portuguese, French, Spanish and English published between 1950 and 2022. This review excluded incomplete articles, abstracts, articles repeated in different databases, editorials, publications that did not contain clear or sufficiently detailed methodology or results, and publications that were not available for free in full.

3. Results and Discussion

In this review, 64 publications related to the proposed theme were initially found in the databases. After the elimination of repeated materials, and the meticulous reading of the documents in their entirety, obeying the inclusion and exclusion criteria, 52 publications were selected entirely according to the proposed theme, which were grouped in summary in Table 1. The results presented to compose the research corpus were organized by year of publication, starting with the oldest work until the most recent publication.

Table 1 - Publications selected to compose the research corpus.

Year	Title	Authors
1958	Alkaloids of *Geissospermum vellosii.*	Rapoport et al.
1962	Alkaloids of *Geissospermum vellosii*. Isolation and structure determinations of vellosimine, vellosiminol, and geissolosimine.	Rapoport & Moore
1973	Geissovelline, a new alkaloid from *Geissospermum vellossi*.	Moore & Rapoport
1978	Alcaloides de *Geissospermum argetum* (Apocynaceae).	Paccioni & Husson
1992	Survey of medicinal plants used as antimalarials in the Amazon.	Brandão et al.
1997	Medicina tradicional antimalárica em Roraima, Brasil.	Milliken
2000	A search for natural bioactive compounds in Bolivia through a multidisciplinary approach.	Muñoz
2000	Plantas de uso medicinal ou ritual numa feira livre no Rio de Janeiro.	Stalcup
2002	Indole and β-carboline alkaloids from *Geissospermum sericeum.*	Steele et al.
2005	Flavopereirine-based pharmaceutical composition and use thereof for treating HIV.	Beljanski
2005	Evaluation of French Guiana traditional antimalarial remedies.	Bertani et al.
2005	Two new indole alkaloids from *Aspidosperma subincanum* and *Geissospermum vellosii.*	Kobayashi et al.
2006	Plantas utilizadas na medicina popular brasileira com potencial atividade antifúngica.	Fenner et al.
2006	Uso de plantas medicinais pela comunidade de Enfarrusca, Bragança, Pará.	Freitas & Fernandes
2007	Plants used traditionally to treat malaria in Brazil: the archives of Flora Medicinal.	Botsaris
2007	Passando da doutrina à prática: Ezequiel Corrêa dos Santos e a farmácia nacional.	Santos
2008	Amazonian plant crude extract screening for activity against multidrug-resistant bacteria.	Correia et al.
2008	Flavopereirine and alstonine combinations in the treatment and prevention of prostate cancer.	Hall et al.
2009	Pereirina: o primeiro alcaloide isolado no Brasil?	Almeida et al.
2009	Beta-carboline alkaloid-enriched extract from the amazonian rain forest tree pao pereira suppresses prostate cancer cells.	Bemis et al.
2009	*Geissospermum vellosii* STEMBARK. Anticholinesterase activity and improvement of scopolamine-induced memory deficits.	Lima et al.
2009	Evidence for a role of 5-HT1A receptor on antinociceptive action from *Geissospermum vellosii*.	Werner et al.
2010	Efeitos dos alcalóides de *Geissospermum urceolatum* A. H. GENTRY (acariquara-branca) na pressão arterial e na contração do músculo liso de ratos.	Martins
2011	Avaliação da atividade antimalárica e antimicrobiana de *Geissospermum argenteum* WOODSON e *Minquartia guianensis* Aubl coletadas em Roraima.	Camargo
2011	Docking of the alkaloid geissospermine into acetylcholinesterase: a natural scaffold targeting the treatment of Alzheimer's disease.	Araújo et al
2012	Fitoquímica e ensaios biológicos do extrato bruto etanólico, frações e substâncias isoladas provenientes das cascas de *Geissospermum vellosii* Allemão.	Dias
2012	In vitro antiplasmodial activity of indole alkaloids from the of *Geissospermum vellosii* STEMBARK.	Mbeunkui et al.
2012	Indole Alkaloids from *Geissospermum reticulatum.*	Reina et al.
2012	Estudo das ações cardiovasculares da fração alcaloídica obtida da espécie nativa amazônica Geissospermum argenteum WOODSON.	Morais
2012	Atividade antibacteriana de plantas medicinais frente á bactérias multirresistentes e a sua interação com drogas antimicrobianas.	Saraiva
2013	Absolute configuration of indoline alkaloids from *Geissospermum reticulatum.*	Gordillo-Román et al.

2013	Chemical composition, ethnopharmacology and biological activity of Geissospermum Allemão species (Apocynaceae Juss.).	Camargo et al.
2014	Pao Pereira extract suppresses castration-resistant prostate cancer cell growth, survival, and invasion through inhibition of NFκB signaling.	Chang et al.
2014	The plant extract of Pao pereira potentiates carboplatin effects against ovarian cancer.	Yu et al.
2015	Plantas utilizadas no tratamento de malária e males associados por comunidades tradicionais de xapuri, AC e Pauini, AM.	Ferreira
2015	Apocynaceae na lista de espécies da flora do Brasil.	Koch et al.
2015	Etnobotânica e medicina popular no tratamento de malária e males associados na comunidade ribeirinha Julião – baixo Rio Negro (Amazônia Central).	Veiga & Scudeller
2016	Revisão taxonomica de *Geissospermum* Allemão (Apocynaceae).	Barbosa
2016	Antinociceptive and anti-inflammatory effects of a *Geissospermum vellosii* STEMBARK fraction.	Lima et al.
2016	Antioxidant, cytotoxic, and antiproliferative activities and total polyphenol contents of the extracts of *Geissospermum reticulatum* BARK.	Sajkowska-Kozielewicz et al.
2016	Estudos farmacognosticos, fitoquímicos e atividades antileishmania de espécies Geissospermun (Apocynaceae).	Silva
2017	Avaliação da citotoxicidade e seletividade do extrato, frações e alcaloide de Geissospermum sericeum (Apocynaceae) em linhagens celulares ACP02, HepG2 e VERO.	Bastos
2017	Revisiting previously investigated plants: A molecular networking-based study of Geissospermum laeve.	Fox Ramos et al.
2017	Diversidade taxonômica de Apocynaceae na ilha do Marajó, PA, Brasil.	Viana et al.
2018	Ethnopharmacology, phytochemistry, and biotechnological advances of family Apocynaceae.	Bhadane et al.
2018	Composição química e atividade antimalárica de Geissospermum urceolatum A. H. Gentry (Apocynaceae).	Oliveira
2019	Flavopereirine an alkaloid derived from Geissospermum vellosii presents Leishmanicidal activity in vitro.	da Silva e Silva et al.
2019	Flavopereirine Suppresses the Growth of Colorectal Cancer Cells through P53 Signaling Dependence.	Li et al.
2019	Pao Pereira extract attenuates testosterone-induced benign prostatic hyperplasia in rats by inhibiting 5α-reductase.	Liu et al.
2019	Flavopereirine induces cell cycle arrest and apoptosis via the AKT/p38 MAPK/ERK1/2 signaling pathway in human breast cancer cells.	Yeh et al.
2020	Geissoschizoline, a promising alkaloid for Alzheimer's disease: Inhibition of human cholinesterases, anti-inflammatory effects and molecular docking	Lima et al.
2020	Geissospermiculatine, a New Alkaloid from Geissospermum reticulatum BARK.	Sajkowska-Kozielewicz et al.

Source: Authors (2023).

3.1 Botanical aspects - Taxonomy, classification, morphology and geographic distribution

Geissospermum belongs to the class Equisetopsida C. Agardh; subclass Magnoliidae Novák ex Takht.; superorder Asteranae Takht.; order Gentianales Juss. ex Bercht. and J. Presl; family Apocynaceae Juss.; subfamily Rauvolfioideae Kostel.; tribe Aspidospermeae Miers.

A meticulous taxonomic review of the genus was performed, analyzing all specimens of Geissospermum collected in the Neotropics and deposited in herbaria that have representative collections of the genus in the Neotropics, and the most important morphological characteristics for the identification of the species were listed. They included induments on leaf blades, flower, corolla tube, anthers, gynoecium and fruit, with the indumentum of the leaf blades of the adult leaves being considered to present the highest diagnostic value to distinguish species (Barbosa, 2016).

The species Geissospermum excelsum Kuhlm, Geissospermum martianum Miers, Geissospermum myristicifolium Markgr, Geissospermum ramiflorum, Geissospermum solandri were excluded from the genus. The species G. martianum and G. solandri are not considered validly published and should not be used to recognize any valid species in the genus. Geissospermum ramiflorum, G. myristicifolium and G. excelsum are considered synonyms with Aspidosperma ramiflorum, A. myristicifolium and A. carapanauba, respectively.

Of the seven species described for the genus, only five are considered valid: G. argenteum, G. laeve, G. reticulatum, G.

sericeum and G. urceolatum. The names G. vellosii and G. fuscum are considered synonyms with G. laeve and G. sericeum, respectively (Barbosa, 2016; Forzza & Leitmam, 2010).

Geissospermum species have a shrubby or arboreal life form, reaching up to 30 meters in height. The trunks of the species may be deeply and irregularly fissured in the longitudinal direction with little or no latex when cut. Younger trunks may be thinner and/or less fissured. The branches are cylindrical, brown, white, greenish or greyish, furrowed or slightly furrowed, and may present scabrous, stringy, hirsute or glabrous induments. The presence of whitish latex is observed at the ends of young plants (Barbosa, 2016; Ribeiro et al., 1999).

The leaves are simple and alternate, with leaf blades that can be oval or elliptical, generally cartaceous. The inflorescence of this genus is a lateral thyrsuswith androgynous flowers. The fruits are bacoid, ellipsoid, ovoid, obovoid or lanceolate, with rounded, acute or attenuated apex, rounded base, reticulate or not, pubescent, densely strident, tomentose or sericeous (Barbosa, 2016).

Geissospermum species are found in the Amazon, Cerrado and Atlantic Forest phytogeographic domains with confirmed occurrences in the North (Acre, Amazonas, Amapá, Pará, Rondônia, Roraima), Northeast (Bahia, Maranhão), Midwest (Federal District) and Southeast (Espírito Santo, Minas Gerais, Rio de Janeiro). These plants are found in areas of sandy and/or clayey soil in solid ground forest (Koch et al., 2015).

3.2 Ethnopharmacological use

Ethnopharmacology and ethnobotany can be a start point for the study of medicinal plants, contributing to increase the knowledge about plant species with new active compounds, traditionally used by some populations (Ferreira, 2015).

Geissospermum species are known for the bitterness of their bark, which is used as infusions or aqueous decoctions by indigenous peoples, native communities in the Amazon and other Brazilian regions for the treatment of several diseases (Camargo, 2011; Gordillo-Román et al., 2013). The ethnopharmacological use of each species that has been described in the literature is described in Table 2. Extensive descriptions of traditional use exist for G. laeve (also G. vellossi) and G. sericeum (or G. fuscum) while few literature data was found for G. reticulatum and G. urceolatum.

Table 2 - Ethnopharmacological use of Geissospermum species.

Popular name	Scientific name	Ethnopharmacological use	Reference
Pau-Pereira, Bergibita, Guatambu, Peroba, Quinarana, Quina-quina, Quina-amargosa, Quina de pobre, Camará-de-bilro, Camará-do-mato, Canudo Amarguroso, Pinguaciba, Pereiroá, Pereiro, Ubá-açú, Tringuaaba, Pereiroá, Chapeú-de-sol.	*Geissospermum vellosii* or *Geissospermum leave*	Sexual stimulant, digestive tonic treatment of malaria, fever, stomach disorders, constipation, pain, fungal infections, antiseptic, inappetence, dizziness, prevention and treatment of prostate cancer and erysipelas.	(Lorenzi, 1992) (Muñoz et al., 2000) (Stalcup, 200AD) (Fenner et al., 2006) (Santos, 2007) (Werner et al., 2009) (Almeida et al., 2009) (Saraiva, 2012) (Camargo et al., 2013)
Ariquara-branca, Maria-congo, Quinarana da fruta pequena.	*Geissospermum argenteum*	Treatment of malaria, diabetes, diarrhea, fevers, infections and dewormer.	(Correia et al., 2008) (Morais, 2012)
Acariquara Branca, Acariúba-rana, Acari-rana, Pau-forquilha, Pau-pereira, Pereira, Quina-rana, Acariranha, Quina-quina.	*Geissospermum sericeum* *Geissospermum fuscum*	Treatment of malaria, dermatosis, inflammation, swamp fever (equine infectious anemia), swollen body, painful urination, allergy, digestive tonic, treatment of stomach and gallbladder, venereal diseases, diabetes, diarrhea, worms, itching, abortifacient and fever.	(Brandão et al., 1992) (Milliken, 1997) (Freitas and Fernandes, 2006) (Botsaris, 2007) (Veiga & Scudeller, 2015) (Silva, 2016)
Acariquara-branca, Acariquara, Quinarana, Acariubarana, Acarirana, Pereira, Pau-pereira, Pau-forquilha.	*Geissospermum urceolatum*	Stomach pains, dizziness, vasodepressor, fever and malaria.	(Martins, 2010)
Quina-quina	*Geissospermum reticulatum*	Treatment of malaria and fever.	(Ferreira, 2015)

Source: Authors (2023).

It is important to notice that some species of *Geissospermum* have the same vernacular name, which suggests a difficult characterization of the ethnospecies based on morphological aspects.

3.3 Phytochemistry

Research on the chemical composition of Geissospermum species began at the end of the 19th century. Brazilian pharmacist Ezequiel Corrêa dos Santos, in 1838, isolated the active principle from the bark of Pau-pereira (*G. vellosii* Allemão), describing it as an alkaloid, which he called pereirina, considered the first alkaloid isolated in (Almeida et al., 2009). Several photochemical studies were carried out with species of Geissospermum and indole alkaloids of the β-carboline and bisindole type being the most commonly found secondary metabolites in this genus (Camargo, 2011; Silva, 2016).

Indole alkaloids are produced by a wide variety of organisms both terrestrial and aquatic. In plants they are particularly found in the Apocynaceae, Loganiaceae and Rubiaceae families. This class of alkaloids has enormous economic importance, responsible for the movement of large sums, in the order of billions of dollars. Due to the structural similarity with neurotransmitters, several indole alkaloids have a significant role in the nervous system (Simões et al., 2017). In Table 3 we provide a summary, where we can know the isolated molecules, parts of the plant and the respective species of Geissopermum studied.

Table 3 - Overview of the isolated molecules, parts of the plant and the respective species of Geissopermum studied.

Nº	Compound	Part of the plant	Species	Reference
01	Geissoschizine	Bark	*G. vellosii* *G. laeve*	(Rapoport et al., 1958)
02	Apogeissoschizine	Bark		(Rapoport & Moore, 1962)
03	Geissoschizoline	Bark and trunk		(Lima et al., 2020)
04	Vellosimine	Bark		
05	Vellosiminol	Bark		
06	Geissolosimine	Bark		
07	Geissovelline	Bark		(Moore & Rapoport, 1973)
08	Pausperedina A	Bark		(Kobayashi et al., 2005)
09	12-Me-thoxy-1-methylaspidospermidine	Bark		(Werner et al., 2009)
10	Geissolosimine	Bark		(Fox Ramos et al., 2017)
11	Leuconolam			
12	Geissoleavine			
13	O-Methylgeissolaevine			
14	3',4',5',6'-tetradehidrogeissospermine			
15	Geissolosimine	Bark		(Mbeunkui et al., 2012)
16	Geissospermine	Bark and trunk		(Lima et al., 2020)
17	Geissoschizoline	Bark		
18	Geissoschizone	Bark and trunk		(Lima et al., 2020)
19	Vellosiminol	Bark		
20	3',4',5',6'-tetradehidrogeissospermine	Trunk		(Lima et al., 2020)
21	Desmethoxyaspidospermine	Bark and leaves	*G. argenteum*	(Paccioni & Husson, 1978)
22	Aspidospermine			
23	Aspidoscarpine			
24	Desmethylaspidospermine			
25	Geissoschizoline	Bark	*G. sericeum* *G. fuscum*	(Steele et al., 2002)
26	Geissoschizolina N 4 -oxido	Bark		
27	1,2- Deshidrogeissoschizoline	Bark		

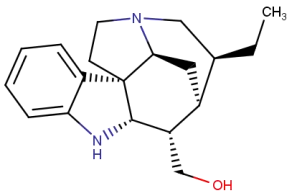
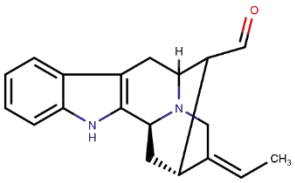
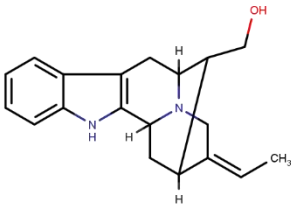
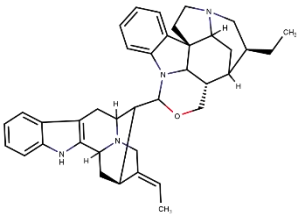
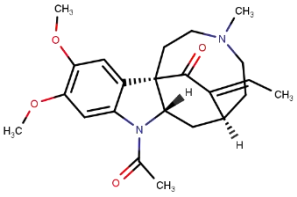
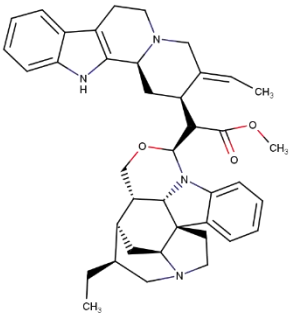
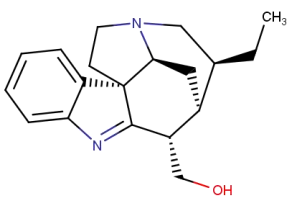
28	Flavopereirine	Bark		
29	10-Demetoxi-12-hidroxi-17,19-epoxigissoveline	Leaf	*G. reticulatum*	(Reina et al., 2012)
30	(Z)-10-Demetoxi-12-hidroxigeissoveline	Leaf		
31	(E) -10-Demetoxi-12-hidroxigissoveline	Leaf		
32	O-Desmetilaspidospermine	Leaf		
33	Geissospermidine	Leaf		
34	10-Metoxigeissospermidine	Leaf		
35	N- Desacetil – N -butanoilgeissospermidine	Leaf		
36	11-Metoxigeissospermidine	Bark		
37	Flavopereirine	Bark		
38	Geissosreticulatine	Bark		
39	Geissospermiculatine	Bark		(Sajkowska-Kozielewicz et al., 2020)
40	Sinapiato de metile	Bark	*G. urceolatum*	(Oliveira, 2018)
41	4-N-metil-akuammicine	Bark		
42	Aspidocarpine	Bark		
43	2- [2-hidroxi-3-metoxi-5-(3-propenooato de metila) fenil]-3-(3-hidroxi-4-metoxi-fenil)propan-1-ol	Bark		

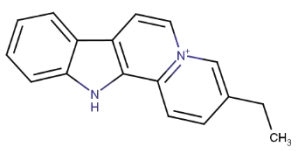
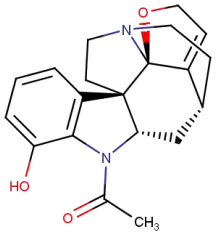
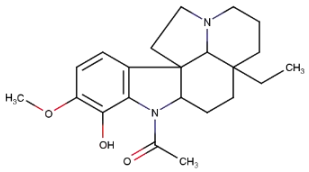
Source: Authors (2023).

In Table 3 it is possible to observe that most of the known molecules belong to the species *G. vellosii* and its synonym *G. laeve*. The species with the fewest isolated molecules is *G. urceolatum*. In general, there are still many molecules to be discovered in this genre.

We provide an overview of the chemical structures of some isolated molecules of the genus *Geissospermum* that can be seen in Table 4.

Table 4 - Chemical structure of some molecules isolated from the genus Geissospermum.

Nº	Compound	CID/ ID Chem Spider	Molecular formula	Molecular Weight	Chemical structure
03	Geissoschizoline	442095	C19H26N2O	298,4	
04	Vellosimine	101348845	C19H20N2O	292,3	
05	Vellosiminol	5318845	C19H22N2O	294,3	
06	Geissolosimine	71594126	C38H44N4O	572,8	
07	Geissovelline	101306829	C23H30N2O4	398.4	
16	Geissospermine	5281401	C40H48N4O3	632,8	
27	1,2-Deshidrogeissoschizoline	15538076	C19H24N2O	296,4	

28	Flavopereirine	65171	C17H15N2 +	247,31	
33	Geissospermidine	70686216	C20H22N2O3	338,4	
42	Aspidocarpine	632854	C 22 H 30 N 2 O 3	370,5	

Source: Authors (2023).

In this table it is possible to observe a structural diversity and a certain chemical complexity in the indole alkaloids found in *Geissospermum* species.

3.4 Biological activities of extracts and isolated compounds

A wide variety of medicinal uses have been attributed to Geissospermum species. Clinical trials have shown pharmacological activity on the cardiovascular system, and anticholinesterase, antinociceptive, antimicrobial, antitrypanosoma, antileishmania, anticancer, anti HIV, and antimalarial activity.

3.4.1 Antitumor activity

Hall and Beljanski (2008) patented a method capable of preventing prostate cancer and/or reducing PSA levels and/or alleviating the symptoms of benign prostatic hyperplasia (BPH) or prostatic intraepithelial neoplasia (PIN) from the administration of a combination of flavopereirine and alstonine. The inventors claim that this composition is ideal for treating low-grade prostate cancer and preventing the onset of metastasis and may reduce the doubling time of PSA levels in men with positive biopsies. Flavopereirine and alstonine can be in the form of natural extracts derived from *G. vellossi* and *Rauwolfia vomitoria*, respectively. Alternatively, these two active compounds can be administered in purified form.

Extracts from the bark of the *G. vellosii* tree enriched with α-carboline alkaloids showed expressive anticancer activities in certain preclinical models. *In vitro* and *in vivo* effects of one of the tree extracts were observed against a human prostate cancer cell line, LNCaP. *Geissospermum vellosii* extract significantly suppressed cell growth in a dose-dependent manner, inducing apoptosis. Tumor growth was suppressed by up to 80% in some groups compared to tumors in vehicle-treated control mice. Doses at the concentration of 10 or 20 mg/kg/day were best for inducing tumor cell apoptosis as opposed to higher doses. The researchers suggested that while the study demonstrated the activity of an extract of the bark of this tree against human prostate cancer, the results of their *in vivo* studies suggest that its potential effectiveness in treating prostate cancer may be limited to a narrow dose range (Bemis et al., 2009).

The anticancer effects of the extract enriched with β-carboline alkaloids from *G. velossi* alone and in combination with carboplatin were investigated. The results showed a selective inhibition of ovarian cancer cell growth with IC_{50} values of 180–235 µg/ml compared to 537 µg/ml in normal cells. The extract induced apoptosis and completely inhibited the formation of

colonies of tumor cells on agar at a concentration of 400 µg/ml. It was observed that the extract of *G. vellosi* was able to highly increase the cytotoxicity of carboplatin, with dose reduction (DRIs) for carboplatin at 1.2–10 fold. *In vivo*, the plant extract without the presence of carboplatin was able to suppress tumor growth by 79% and decrease ascites volume by 55%. When combining the extract and carboplatin, tumor inhibition reached 97%, completely eradicating ascites (Yu and Chen, 2014).

Chang et al. (2014) described in their experiment the activity of *G. vellosi* extract. The extract prevented the growth of metastatic castration-resistant prostate cancer (CRPC) PC3 cells in a dose-time-dependent manner, inducing apoptosis and cell cycle arrest. Treatment with the extract caused the induction of cell cycle inhibitors, p21 and p27, and repressed PCNA, Cyclin A and Cyclin D1. These data suggest that *G. vellosi* extract appears to be beneficial for protection against CRPC.

The antitumor activity and cytotoxicity of the ethanol extract, fractions, subfractions of *G. sericeum* were evaluated through the cell viability assay with MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium]) in primary gastric adenocarcinoma cells (ACP02), human hepatoma cells (HepG2) from Pará and in a normal African green monkey kidney cell line (VERO). The results were positive for antitumor activity with moderate cytotoxic activity (Bastos, 2017).

Sajkowska-Kozielewicz et al. (2016) analyzed the antiproliferative and cytotoxic effects of infusions, tinctures and ethanol extracts of *G. reticulatum* bark in relation to total phenolics and flavonoids content. These extracts showed antiproliferative activities in normal T cells and caused death in malignant cell lines THP-1 and HL-60. Interestingly, the assays showed that the highest concentration of the ethanol extract was not toxic in the zebrafish embryo development assay. These results indicate that *G. reticulatum* is rich in antioxidants and has cytotoxic and antiproliferative properties.

Flavopereirin, a natural alkaloid extracted from *G. vellosii*, significantly reduced and caused intrinsic and extrinsic apoptosis inducing cell cycle arrest in G2/M phase in colorectal cancer (CRC) cells. It was observed that flavopereirin increased the expression and phosphorylation of P53 in CRC cells. Flavopereirin also significantly repressed the growth of CRC cell xenografts *in vivo* by upregulating P53 and P21 and inducing apoptosis. The study suggests that flavopeireirin may be effective in the clinical treatment of CRC since suppression in CRC cells depended on the P53-P21 signaling pathway, but not on the JAKs-STATs-c-Myc signaling pathway (Li et al., 2019).

A study investigated the therapeutic potential of *G. vellosii* bark extract against the development of benign prostatic hyperplasia (BPH) in a model using rats with testosterone-induced BPH. The BPH group treated with *G. vellossi* extract showed a reduction in prostate weight comparable to the control BPH group treated with finasteride. Notably, treatment with the plant extract did not significantly reduce the body weight and number of sperm in the rats, compared to the control group. In addition, extract treatment reduced the proliferative index in the prostate glands as well as testosterone-induced androgen receptor (AR) expression levels and androgen-associated proteins such as SRD5A1 and PSA. Research data reveal that *G. vellossi* extract suppresses testosterone-induced BPH development by inhibiting AR activity and expression and suggest that the plant extract has potential as a promising and relatively safe agent against BPH (Liu et al., 2019).

An investigation was carried out on the effect of flavopereirine, an alkaloid that can be extracted from the bark of trees (*G. sericeum* and *G. laeve*), on cell cycle interruption and on apoptosis signaling in breast cancer cells. The cells were analyzed by flow cytometry and the results showed that flavopereirine caused a disruption of the G0/G1 phase in MCF 7 cells and disrupted the S phase in MDA-MB-231 cells. The authors of the study concluded that flavopereirine induces cell cycle arrest and apoptosis via the AKT/p38 MAPK/ERK1/2 signaling pathway, which contributes to flavopereirine-induced apoptosis in MDA-MB-231 cells (Yeh et al., 2019)

3.4.2 Antinociceptive and anti-inflammatory activity

The study by (Werner et al., 2009) investigated the antinociceptive effects of *G. vellosii* in behavioral models of nociception. The researchers administered the crude extract of *G. vellosii* and a dichloromethane fraction orally at a concentration

of 1-100 mg/kg, inhibiting formalin-induced inflammatory nociception and acetic acid-induced visceral nociception. It was observed that the alkaloid 12-methoxy-1-methyl-aspidospermidine at the concentration of 0.001-1 mg/kg, isolated from the apolar fraction, was able to produce antinociception.

The antinociception caused by the dichloromethane fraction was significantly attenuated by pretreatment of mice with p-chlorophenylalanine methyl ester (PCPA, a serotonin synthesis inhibitor, 100 mg/kg once a day for 4 consecutive days) and WAY-100635 (the 5-HT_{1A} receptor antagonist, 0.3 mg/kg). In contrast, antinociception of the apolar fraction was not affected by pretreatment of animals with ketanserin (a 5-HT2 receptor antagonist, 0.3 mg/kg) or ondansetron (a 5-HT3 receptor antagonist, 0.5 mg/kg). The results suggest that *G. vellosii* produces antinociception through an interaction of the alkaloid 12-methoxy-1-methyl-aspidospermidine with 5-HT1A receptors (Werner et al., 2009).

Lima et al. (2016) evaluated the effects of a stem bark fraction (PPAC fraction) and the ethanol extract (EE) of *G. velossi* in classical murine models of inflammation and pain. The EE and PPAC fractions, both at a dose of 30 mg/kg, significantly reduced acetic acid-induced abdominal constriction by 34.8% and 47.5%, respectively. It was observed that compared to indomethacin, similar doses of EE or PPAC fraction were approximately twice as effective in causing antinociception.

The PPAC fraction was shown to be ineffective in the hot plate test, but it was able to reduce the inflammatory response of carrageenan-induced mouse paw edema. The researchers concluded that the PPAC fraction has anti-inflammatory and antinociceptive activity by a mechanism supposedly unrelated to the activation of the opioid system (Lima et al., 2016)

3.4.3 Anticholinesterase activity

The study by Lima et al. (2009) analyzed the anticholinesterase activity of a concentrated fraction of alkaloids originating from the bark of *G. vellosii* and its impact on memory tests in rats. The extract fraction inhibited rat brain and electric eel acetylcholinesterase as well as serum butyrylcholinesterase of horse in a dose-dependent manner with an IC_{50} of 39.3 µg/mL, 2.9 µg/mL and 1.6 µg/mL, respectively. Geissospermine was the main alkaloid identified in the extract. The fraction significantly reduced scopolamine-induced amnesia in the passive avoidance and morris water maze tests. Through these results it was possible to conclude that compounds present in the stem bark of *G. vellosii* have anticholinesterase activity, being capable of reversing cognitive deficits in a model of cholinergic hypofunction.

Araújo et al. (2011) carried out a study with the objective of elucidating the interaction mode, conformation and orientation of the indole alkaloid geissospermine (GSP), the main alkaloid of the bark extract of *G. vellosii*, reported in the work by Lima et al. [16], against the active site of acetylcholinesterase (AChE). After performing docking simulations, the results suggested a preferential binding mode between GSP and AChE, in which GSP functional groups can perform specific interactions with residues in the enzyme's active site, according to the ligand-protein contacts detected in the simulation.

Four hydrogen bonds were detected between GSP and Tyr121, Ser122, Ser200 and His440, where the last two residues belong to the catalytic triad (Ser200···His440···Glu327). Hydrophobic and stacking interactions were also detected between GSP and Phe330 and Trp84, respectively. The study provided the basis for propositions of structural changes in the structure of the GSP molecule, in order to assist in the design of new potential AChE inhibitors that are significant for the treatment of Alzheimer's disease (Araújo et al., 2011).

In search of new efficient drug options for the treatment of Alzheimer's disease, Lima et al. isolated four indole alkaloids geissoschizoline, geissosquizone, geissospermine and 3',4',5',6'-tetradehydrogeissospermine – from the trunk of the species *G. vellosii* and examined their potential anticholinesterase activity. Geissospermine exclusively inhibited butyrylcholinesterase (BChE) and the other alkaloids behaved as non-selective inhibitors of AChE and BChE. In cell viability assays, geissoschizoline was the only non-cytotoxic substance (Lima et al., 2020).

The actions of geissoschizoline on human cholinesterases were evaluated, showing to be twice as potent as an inhibitor of hBChE (IC_{50} = 10.21 ± 0.01 μM) than hAChE (IC_{50} = 20.40 ± 0.93 μM). In enzyme kinetics studies, geissoschizoline showed a mixed-type inhibition mechanism for both enzymes. Molecular docking analyses showed interactions of geissoschizoline with the active site and peripheral anionic site of hAChE and hBChE, indicating a dual-site inhibition profile. Furthermore, geissoschizoline also exerted a promising anti-inflammatory role, reducing the microglial release of NO and TNF-α. The authors of the study concluded that geissoschizoline is a potential multi-target prototype molecule capable of being very useful in preventing neurodegeneration and with high potential to be evaluated in other targets of Alzheimer's disease (Lima et al., 2020).

3.4.4 Antileishmania and antitrypanosoma activity

Reina et al. (2012) report the isolation of ten indole alkaloids from the species *G. reticulatum* collected in the Peruvian Amazon. Ethanol extracts and isolated compounds were tested against *Trypanosoma cruzi* and *Leishmania infantum*. The extracts generally exhibited selective action and were more active against *Leishmania* than against *Trypanosoma*. The alkaloid demethylaspidospermine was very active against *L. infantum.*

Flavopereirine, an alkaloid isolated from *G. vellosi*, was tested *in vitro* in cultures of *Leishmania amazonensis* promastigotes, and *in silico* for physicochemical characteristics. A greater inhibitory effect of flavopereirine was observed in 24h and 72h (IC_{50} of 0.23 and 0.15 μg/mL, respectively). The extract, fractions and flavopereirine showed low toxicity. The *in silico* test of flavopereirine revealed an interaction with the residue Tyr-499 of oligopeptidase B during molecular dynamics simulations, suggesting an interaction with an inhibitory pathway. Flavopereirine showed potential antileishmanial activity (da Silva e Silva et al., 2019).

3.4.5 Anti HIV activity

Beljanski (2005) registered a pharmaceutical patent developed based on the alkaloid flavopereirine obtained from *G. vellosii* for the treatment of HIV (human immunodeficiency virus). The formulation consists of a solid containing about 250-500 mg of active ingredient, which can be administered orally up to a limit of 1-3 grams per day. This composition can be used to treat humans affected by HIV-1 and people who have already developed AIDS.

3.4.6 Antimicrobial activity

Correia et al. (2008) investigated the antimicrobial activity of ethanol extracts of ten species of plants from the state of Amapá in the Brazilian Amazon, including *G. argenteum*, known by the common name “quinarana da fruta pequena”. The embedded disc assay (Kirby-Bauer method) was used to evaluate the antimicrobial activity.

6-mm diameter paper discs were embedded with the ethanol extract and then left to evaporate, obtaining concentrations ranging ranging from 80 to 1.25 μg in the paper discs. The disks with the extracts were tested against ATCC (Standard American Type Culture Collection) and multidrug-resistant strains obtained from a hospital collection in the city of Brasília (Brazil). The results showed that the extract presented activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both multidrug-resistant, and *S. aureus* ATCC strain. The crude ethanol extract of *G. argenteum* was the only one to show antibacterial activity, at a concentration of 80.0 μg (Correia et al., 2008).

Camargo (2011) examined the antimicrobial activity of the methanol extract of *G. argentum* using the Kirby-Bauer disk diffusion method. The extracts were prepared at concentrations of 10 mg/mL. The minimum inhibitory concentration (MIC) was determined by the microdilution technique using Mueller Hinton broth for the bacteria *E. coli*, *S. aureus*, *S. mutans* and Sabouraud broth for *C. albicans* yeast. The results showed that *G. argenteum* extracts were partially active against *S. aureus*, *S.*

mutans and inactive against *E. coli* and *C. albicans*. The MIC of the methanol/water fraction was 0.63 mg/mL for *S. aureus*, 0.63 mg/mL for *S. mutans*, and 0.63 mg/mL for *C. albicans.*

Dias (2012) carried out a phytochemical and biological study of the ethanol extract, fractions and isolated constituents from the bark of *G. vellosii*, in which the compounds lupeol, sesamin, aspidospermine and a fraction (F14) were identified as a mixture of sesamin and aspidospermine. Antibacterial activity was tested by disk diffusion, MIC, and bioautography. It was found that in the MIC test, the ethanol extract and the butanol fraction inhibited the growth of *S. aureus*. In the bioautographic assay, the dichloromethane fraction inhibited the growth of *S. aureus*, *E. coli*, *S. epidermidis* and *S. typhimurium*, and aspidospermine inhibited the growth of *S. epidermidis* and *S. typhimurium.*

Saraiva (2012) performed antibacterial activity tests of extracts of G. vellosii and other medicinal plants against isolates of Oxacillin-Resistant S. aureus (ORSA) and multidrug-resistant P. aeruginosa from human clinical processes, and the interaction of these plant products with drugs clinically used as antimicrobials. The antibacterial activity was determined by the disk diffusion method in Muller Hinton agar and MIC by the microdilution technique in plates using Muller Hinton broth as the culture medium.

The species *G. vellosii* showed activity against ORSA isolates with MIC of 125 µg/mL. There was synergism with the drugs ciprofloxacin, clindamycin and vancomycin. The results proved the potential of *G. vellosii* to control bacterial infections involving multidrug resistant (MDR) phenotypes and the interaction with antibacterial drugs may represent a new alternative in the treatment of bacterial infections (Saraiva, 2012).

3.4.7 Activity in the cardiovascular system

The effects of the total alkaloids fraction (TAF) obtained from the bark of *G. urceolatum*, popularly known as "acariquara branca", on blood pressure and smooth muscle contraction in rats were tested. In the study fof the blood pressure, the TAF produced rapid and transient hypotension, explained by vasodilation, without altering the hypertensive effect of noradrenaline, or the hypotension produced by acetylcholine. With regard to smooth muscle contraction, TAF relaxed the muscle tone produced by noradrenaline in the rat aorta by two mechanisms of action: via the nitric oxide (NO) cascade and by blocking the influx of calcium ions. The author concluded that some of the observed effects were not well understood and need to be further studied, particularly with purified and isolated TAF constituents (Martins, 2010).

Morais (2012) investigated the cardiovascular effects of G. argenteum in rodents. A chloroform fraction (FCHCl3) containing FAT at the concentration of 10 to 100 mg/kg. Initial experiments carried out with the standardized alkaloid extract of G. argenteum showed many pharmacological actions: hypotensive action, bradycardic action and positive inotropic action in the atrium in vitro, vasodilator action in the aorta, neuromuscular transmission blocking action in the diaphragm, contraction potentiating action muscle in the diaphragm, blocking action of the sympathetic stimulus in the vas deferens, potentiation of the maximum contractile response of noradrenaline and acetylcholine in the vas deferens of rats (Morais, 2012). Morais suggests that future studies should be performed with isolated alkaloids to confirm the mechanisms of action.

3.4.8 Antioxidant activity

Sajkowska-Kozielewicz et al.(2016) determined the antioxidant capacity of the infusion, tincture and ethanol extract of G. reticulatum bark. It was found that the total amount of phenolic compounds in the products studied ranged from 212.40 to 1253.92 mg gallic acid equivalent (GAE)/kg. The values for flavonoids in infusions were significantly lower, ranging from 17.16 to 94.44 mg GAE/kg. The results suggest that flavonoids occurring in G. reticulatum bark are more soluble in 60-70% ethanol than in pure water.

3.4.9 Antimalarial activity

Muñoz et al. (2000) performed a screening of thirty plant extracts used as antimalarials by the native Chacobo community that inhabits the Bolivian Amazon. The extracts were tested in vitro on chloroquine resistant and chloroquine sensitive Plasmodium falciparum (F32) strains provided by the Pasteur Institute. In vivo assays were also performed in rodents infected with Plasmodium berghei NK65 and P. vinckei 279BY. The G. laeve extract showed very good in vitro antimalarial activity against both strains, with IC50 values ranging from 1.7 to 3.1 µg/ml, comparable to the activity of Artemisia annua, and the activity against both strains was corroborated in in vivo analyses.

Steele et al. (2002) conducted assays of antiplasmodic activity and cytotoxicity with methanol-water extracts and compounds isolated from the species G. sericeum in chloroquine-resistant (K1) and chloroquine-sensitive (T9-96) Plasmodium falciparum. Cytotoxicity was evaluated in a human epithelial carcinoma (KB) cell line. The crude extract showed IC_{50} = 1.78 ± 0.047 µg/ mL against the strain K1. The isolated alkaloids geissoschizoline and geissoschizoline oxide were inactive (IC_{50} > 40 µM) against both parasite strains. The 1,2-dehydrogeissochizoline was shown to be inactive against the K1 and T9-96 strains of P. falciparum (IC50 = 27.26 ± 10.9 and 35.37 ± 2.36 µM,) respectively. Flavopereirine, presented IC50 = 11.53 ± 0.54 and 1.83 ± 0.10 µM against the strains K1 e T9-96.

Bertani et al. (2005) carried out a study about the traditional preparations used in the treatment of malaria in French Guiana. Thirty-five remedies were analyzed, involving 23 different plant species. The antimalarial activity of traditional preparation (alcoholic maceration) *with G. laeve* and *G. argenteum* was tested *in vitro* against chloroquine-resistant *P. falciparum* and *in vivo* in rodents infected with *Plasmodium yoelii*. The results showed that the alcoholic preparation of *G. laeve* was inactive (without schizonticidal activity) *in vitro* against chloroquine-resistant *P. falciparum*. However, the same preparation inhibited *in vivo* parasitemia against *P. yoeli*. The *G. argentum* extract was not tested *in vitro*. In the *in vivo* assay, the dose of 324 mg/kg of this drug inhibited *P. yoelii* by 44.3%. Extracts of *G. argenteum* were tested on the hepatic stage of malaria induced by *P. yoelii* and exhibited 83% inhibition of the intrahepatic cycle of the parasite.

Camargo (2011) tested the methano and aqueous extract of *G. argenteum in vitro* for antimalarial activity against a chloroquine-resistant *P. falciparum* strain (K1) at concentrations of 50 and 5 µg/mL. The methanol extract of *G. argentum* bark showed activity, with IC_{50} of 4.6 µg/mL, and the chloroform fraction obtained by partitioning the extract was also considered active with an IC_{50} of 2.0 µg/mL.

Mbeunkui et al. (2012) studied the antiplasmodial activity of indole alkaloids isolated from the crude methanol extract of the bark of G. vellosi. The assay showed that the antiplasmodial activity (IC_{50}) of the crude methanol extract was 2.22 µg/mL, while IC_{50} of the isolated compounds ranged from 0.96 µM to 13.96 µM, except for the compound vellosiminol which showed low activity: 157 µM. In this study, the alkaloid geissolosimine showed the highest antiplasmodic activity: 0.96 µM.

Oliveira (2018) studied the chemical composition through a bioguided study and evaluated the *in vitro* antiplasmodic activity of extracts, fractions and substances isolated from *G. urceolatum*. Nineteen leaf, twig and bark extracts were tested *in vitro* for antimalarial activity (IC_{50}). Three of these bark extracts were found to be active, with IC_{50} values of14.5 µg/mL, 12 µg/mL and 9.7 µg/mL. The extracts considered active were fractionated and subjected to IC_{50} test, NMR and high-resolution mass spectroscopy (HMR). The structural elucidation of the fractions revealed the substances aspidocarpine (IC_{50} = 2.42 µg/mL), 4-N-methyl-akuamycin (IC_{50} = 27.1 µg/mL), and methyl synapiate (IC_{50} = 24.5 µg/mL), both with antiplasmodic activity. The phenyl propanoid dimer 2- [2-hidroxi-3-metoxi-5-(3- methyl propenoate) fenil]-3-(3-hidroxi-4-metoxi-fenil)propan-1-ol showed no activity.

4. Final Considerations

The information presented in this review aims to help direct new studies on *Geissospermum*, which will contribute to

the discovery of new bioactive compounds for medicinal use. Plants of the genus Geissospermum are used in Brazil, mainly by the Amazonian peoples, to treat various pathologies. Biological activities reported for extracts and isolated compounds are consistent with etonopharmacological use against malaria, cancer and other diseases.

There are still many gaps in knowledge about the genus *Geissospermum*. More research can be carried out with Geissospermum species with a focus on elucidating the mechanisms of action of isolated alkaloids, as well as on verifying the toxicological profile of these molecules.

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