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The *Aristolochia* (Aristolochiaceae) genus: therapeutic properties, biological effects and toxicity

O gênero *Aristolochia* (Aristolochiaceae): propriedades terapêuticas, efeitos biológicos e toxicidade

El género *Aristolochia* (Aristolochiaceae): propiedades terapéuticas, efectos biológicos y toxicidad

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Larissa Pires Mueller
ORCID: https://orcid.org/0000-0003-0134-7033
Federal University of Grande Dourados, Brazil
E-mail: larissapiresmueller@gmail.com
Dioelen Virgínia Borges Souza de Aquino Coelho
ORCID: https://orcid.org/0000-0001-5916-2993
Federal University of Grande Dourados, Brazil
E-mail: dioaquinocoelho@gmail.com
Laís Chancare Garcia
ORCID: https://orcid.org/0000-0001-9064-0279
Federal University of Grande Dourados, Brazil
E-mail: laisgarcianutri@gmail.com
Lígia Harumi Vilela Bartnick Tanaka
ORCID: https://orcid.org/0000-0002-0149-188X
Federal University of Grande Dourados, Brazil
E-mail: ligia.htanaka@gmail.com
Thais Gimenes Bachega
ORCID: https://orcid.org/0000-0003-2402-6195
Federal University of Grande Dourados, Brazil
E-mail: thais.bachega@hotmail.com
Altair Meirelles de Sousa Maia
ORCID: https://orcid.org/0000-0002-4552-8955
Federal University of Grande Dourados, Brazil
E-mail: altairmeirelles@gmail.com
Vinício Guimarães Freitas
ORCID: https://orcid.org/0000-0002-1923-606X
Federal University of Grande Dourados, Brazil
E-mail: vinicioguimaraes1995@gmail.com
Luiz Fernando Benazet
ORCID: https://orcid.org/0000-0002-0069-4300
Federal University of Grande Dourados, Brazil
E-mail: luiz.benazet@outlook.com
Claúdio Rodrigo Nogueira
ORCID: https://orcid.org/0000-0003-2267-4754
Federal University of Grande Dourados, Brazil
E-mail: claudioRnogueira@ufgd.edu.br
Silvia Aparecida Oesterreich
ORCID: https://orcid.org/0000-0001-5293-6618
Federal University of Grande Dourados, Brazil
E-mail: silviaoesterreich@ufgd.edu.br

Abstract
The Brazilian flora harbors extensive plant biodiversity with the possibility of therapeutic use. In this context, the genus *Aristolochia* is widely used in folk medicine. From this perspective, the study aims to demonstrate important characteristics of these vegetables in the current literature. It was observed that the genus has promising medicinal properties that are directly related to its biological and chemical composition. However, it is notable that more research is needed to guide the safe use and encourage the synthesis of new pharmaceutical products derived from these herbs.
Keywords: Medicinal plants; Safe use; Bioactivities.

Resumo
A flora brasileira abriga ampla biodiversidade vegetal com possibilidade de uso terapêutico. Neste contexto, o gênero *Aristolochia* é amplamente utilizado na medicina popular. Nesta perspectiva, o estudo visa demonstrar características importantes destes vegetais encontradas na literatura atual. Foi observado que o gênero possui propriedades medicinais promissoras que estão diretamente relacionadas à sua composição biológica e química. No entanto é

notável que há necessidade de mais pesquisas para nortear o uso seguro e incentivar síntese de novos produtos farmacêuticos derivados destas ervas.
Palavras-chave: Plantas medicinais; Uso seguro; Bioatividades.

Resumen
La flora brasileña tiene una extensa biodiversidad vegetal con posibilidad de uso terapéutico. En este contexto, el género *Aristolochia* es ampliamente utilizado en la medicina popular. En esta perspectiva, el estudio tiene como objetivo demostrar características importantes de estos vegetales que se encuentran en la literatura actual. Se observó que el género tiene propiedades medicinales prometedoras que están directamente relacionadas con su composición biológica y química. Sin embargo, es notable que se necesita más investigación para guiar el uso seguro y fomentar la síntesis de nuevos productos farmacéuticos derivados de estas hierbas.
Palabras clave: Plantas medicinales; Uso seguro; Bioactividades.

1. Introduction

The World Health Organization (WHO) estimates that about 80% of the rural population in developing countries still enjoy practices related to traditional medicine. That is, they use medicinal plants (Tesser; Sousa & Nascimento, 2018). The medicalization of society is intrinsically linked to normality-pathology thinking, which refers to Western medicine in the 20th century based on scientific ideas. In the USA, medicinal plants were assimilated through chemical syntheses, and a chemical revolution was established. The rescue and appreciation of this practice are essential for current health, notably concerning the Complementary Therapies of the SUS (Corell-Doménech, 2019).

Herbs and their derivatives have accompanied humanity over the centuries, whether for manufacturing inputs, work materials, ornamental, therapeutic, or food use (Almeida Rodrigues et al., 2020). The pharmaceutical industry uses medicinal species to develop commercial products (Brandão et al., 2010). This fact demonstrates how much human beings have always depended on natural resources for survival (Marmitti et al., 2015).

In this context, the monophyletic botanical genus belongs to the Aristolochiaceae Juss family (Piperales). Around 400 plants are distributed in the tropical regions of South America, Asia, and Africa. In the flora of Brazil 2020, the genus *Aristolochia* is represented by 83 species, highlighting the Atlantic Forest, with 39 species, the Cerrado, with 36 species, and the Amazon, with 35 species. Most are popularly known as “liana-thousand-men” or “jar”. Its stems, leaves, and roots are used for stomach ailments, convulsions, gout, asthma, and fever, as they have medicinal properties (Lorenzi & Matos, 2008; Freitas et al., 2020).

Different species of this family have different chemical compounds. Some of the therapeutic interests such as terpenoids, alkaloids, flavonoids, lignins, and fatty acids, among others (Navickiene & Lopes, 2001; Pacheco et al., 2009). These vegetables have phytochemical properties that can benefit pathologies and are used in traditional medicine in countries such as China and India (Latha et al., 2015; Sati et al., 2011).

The widespread use of these plants is based on ethnopharmacological information, and 16 species have documented efficacy (Latha et al., 2015). Among them, *Aristolochia* is studied for its wide application in folk medicine, anti-inflammatory, and antidiabetic effects, and treating snake bites (Babu et al., 2021); the species *Aristolochia albida* has anti-malarial activity (Khan et al., 2012). However, some *Aristolochia* species have proven nephrotoxicities, such as *A. fructus*, *A. gigantea*, and *A. melastoma* (Zhou et al., 2011; Holzbach et al., 2010 & Nogueira et al., 2012).

Medicinal plants can provide both therapeutic and toxic, and even lethal effects that are linked to their phytochemical compounds, which is why they must be subjected to toxicological tests, including genotoxicity and cytotoxicity (Badrie & Schauss, 2010). Although scientific knowledge about the species of the genus *Aristolochia* is still scarce, it is known that many are native to Brazilian biomes and have promising ethnopharmacological potential, which makes them a target for further studies aimed at elucidating their toxicological potential and pharmacological effects.

In this way, safe use through investigation of the toxicity of *Aristolochia* and further studies related to their bioactivities and respective therapeutic effects are of utmost importance. In this context, this study addresses the phytochemical and ethnopharmacological characteristics, medicinal properties, and toxicity of the genus *Aristolochia* found in the literature.

2. Methodology

For the elaboration of this study, exploratory research of a qualitative narrative nature was carried out, built from the search in the following databases: Latin American and Caribbean Literature on Health Sciences (LILACS), Scientific Electronic Library Online (Scielo), and Sistema Online Search and Analysis of Medical Literature (MEDLINE/PUBMED). Descriptors were used: *Aristolochia*, Ethnopharmacology, Phytochemistry, Bioactivities, and Therapeutic properties.

The descriptors were crossed using the Boolean operator “and” as follows: *Aristolochia* AND Ethnopharmacology AND Phytochemistry AND Bioactivities AND Therapeutic properties. The guiding research question of the study was: What are the phytochemical, ethnopharmacological, therapeutic properties, and toxicity of the genus *Aristolochia*?

The inclusion criteria were studies available online, with free access, full text in English, Portuguese and Spanish, published between 2005 to 2021, related to the proposed theme, and answered the guiding question. Theses, dissertations, congress abstracts, proceedings, incomplete articles, duplicate articles, and articles not available in full were excluded.

3. Results and Discussion

The search in the databases resulted in 129 articles, of which 38 were excluded because they were not published in the defined period, and 91 articles were selected. Of these, 63 were chosen by reading the title, excluding articles not available in full and with other methodologies. Forty-two were selected by reading the abstract, of which 07 were excluded because they were duplicates, 35 of which were read in full and included in this review.

It was possible to observe that the scientific community has used *Aristolochia* spp. to unveil some of its pharmacological and therapeutic properties. In this sense, different secondary metabolites with biological effects are described, and such information is listed in Frame 1.

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Frame 1. Sample campus of the articles found.

AUTHOR/YEAR	SPECIES	BIOLOGICAL ACTIVITY / SECONDARY METABOLITE	USED PART/ WAY OF PREPARATION
Machado et al, 2005.	*Aristolochia ridicula*	Flavonoids, dimers of chalcones, and flavones, as well as biflavones, were isolated. The studies are: two new biflavones (ridiculuflavone A and B); a new chalcone-flavone tetramer (ridiculuflavonylchalcone A); a well-known cyclitol (proto-quercitol). Concerning biological activity, they are used in traditional Brazilian medicine for stomach problems, anti-inflammatory, anti-asthmatic, as well as androphilic and anticarcinogenic.	Stems and leaves. The preparation of the extract of the leaves had ethyl acetate as solvent.
Machado et al, 2010.	*Aristolochia elegans* *Aristolochia gigantea* *Aristolochia debilis* *Aristolochia fangchi* *Aristolochia contorta* *Aristolochia ridicula.*	It contains benzylisoquinoline bialkaloids, biflavonoids and 11 tetraflavonoids have been described, 10 of which were isolated from Angiosperms: three from *A. ridicula*. As its biological activity has been used mainly in traditional culture as abortifacients, for stomach treatments, androphilic, antiasthmatic, expectorant, and also recently, in weight loss therapies without differentiation between them.	Sheets. Extraction with hexane and ethanol, fractionation with shepadex for compound isolation.
Wang et al, 2018.	*Aristolochia manshuriensis*	The stem is used in traditional Chinese medicines for anti-inflammatory, analgesic, antitussive, antiobesity, antibacterial, and antiasthmatic.	Stalk. Percolated with 95% ethanol and analyzed using high performance liquid chromatography (HPLC).
León-Díaz et al, 2010.	*Aristolochia taliscana*	Used in traditional Mexican medicine to treat coughs and snakebites for antimycobacterial activity. *A. taliscana* hexane extract was tested by Alamar blue microdilution assay against Mycobacterium strains, and bio-guided fractionation led to the isolation of the neolignans licarin A, licarin B, and eupomatenoid-7, all of which showed antimycobacterial activities. Lycarin A was the most active compound, with minimal inhibitory concentrations of 3.12 and 12.5 μg/mL against the following M. tuberculosis strains: H37Rv, four monoresistant H37Rv variants, and 12 MDR clinical isolates, as well as against five strains of nontuberculous mycobacteria (NTM).	Roots. Hexanic extract was tested by Alamar blue microdilution assay against Mycobacterium strains and bioguided fractionation.
Battu et al, 2011.	*Aristolochia tagala* *Aristolochia acuminata*	Traditional uses treat rheumatic pains, fever, gastrointestinal complaints such as dyspepsia, flatulence, stomach pains, and snakebites. The root extracts of this plant and a specific active constituent, kaempferol (flavonoid), isolated from ethyl acetate extract, were submitted to in vivo and in vitro tests and showed significant anti-inflammatory activity.	Root. Ethyl acetate extract (isolated compound).
Chung et al, 2011.	*Aristolochia manshuriensis*	They were used as an analgesic, antibacterial, anti-inflammatory, antitussive, antiasthmatic, and antivenom. The main active constituent is aristolochic acid, which induces nephrotoxic and carcinogenic effects when used for long periods. From stem extraction with methanol, a new alkaloid, aristopyridinone A, and new phenanthrene, aristolamide II, were isolated along with eight known phenanthrenes. Compound 2 showed a selective inhibitory effect on elastase release by human neutrophils in response to fMLP with an IC50 value of 4.11 lg/mL. Compound 7 exhibited significant inhibitory effects on superoxide anion generation and elastase release with IC50 values of 0.12 and 0.20 lg/mL, respectively.	Stalk. Extraction with methanol partitioned with dichloromethane.

Pascoli et al, 2006.	*Aristolochia pubescens* *Aristolochia lagesiana*	Studies led to the isolation of 7 lignans, five neolignans, two sesquiterpenes, two diterpenes, eight aristolochic acids and derivatives and three more aristolactams. This study with *A. pubescens* and *Aristolochia lagesian*a (-)-cubebin, a dibenzylbutyrolactone type of lignan, is known to reduce larval viability in *Anticarsia gemmatalis* to give rise to malformed adult insects, it was found that there was an anti-inflammatory activity. -insect pests, in addition to showing anti-inflammatory and analgesic activities.	Tubers and roots. Ethanol extract and acetone extract.
Zhai et al, 2005.	*Aristolochia arcuata*	A comparative study of the neurotrophic and neuroprotective effects of six 2,5-diaryl-3,4-dimethyl-tetrahydrofuran neolignans isolated from the same plant, veraguensin (2), galgravin (3), aristolignin (4), nectandrin A (5), isonectandrin B (6) and nectandrin B (7). Compounds 3 and 7 promoted neuronal survival and neurite outgrowth, among which compounds 6 and 7 showed neutrophilic activity comparable to 1. Compounds 1-7 protected hippocampal neurons against cytotoxicity induced by amyloid b peptide (Ab 25-35), while compounds 1, 4 and 7 protected against neuronal death by toxicity induced by 1-methyl-4-phenylpyridinium (MPP) ion in hippocampal neurons of tested rats.	One hundred seventeen compounds and their analogs were isolated from a methanolic extract of *A. arcuata* root.
Sreeharsha et al, 2021.	*Aristolochia bracteolata*	We analyzed the antimicrobial activity and cytotoxicity of silver nanoparticles biologically synthesized from the leaf extract of *Aristolochia bracteolata* against the A549 cancer cell line. The silver nanoparticle showed better antimicrobial activity when compared to the crude plant extract. Satisfactory cytotoxic effects by nanoparticles derived from plant extract against the A549 cell line, followed by the potential of biologically synthesized silver nanoparticles, can be considered a finding in treating human laryngeal carcinoma and can be categorized as a potent anticancer agent.	Fresh leaves. Extraction with ethyl acetate, methanol, and ethanol until the solvent becomes colorless, then rotoevaporated and resuspended with a specific solvent.
Bolla et al, 2019.	*Aristolochia saccata*	Investigating the healing ability of *Aristolochia saccata* leaf extract using the experimental "scratch assay" model as the primary model, L929, a human fibroblast cell line, was used. The MTT assay revealed that the extract had no cytotoxic effect on the cells and, at a higher concentration, showed mild toxicity against scraping, showing 34.05%, 70.00%, 93.52% wound closure at 12 hours, 24 hours, and 48 hours of incubation, respectively. Cytometry revealed that the expression of collagen-1 MEC remodeling factor was induced.	Leaves. Methanolic extraction using Soxhlet apparatus and the cytotoxicity of the extract was studied by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.
Bourhia et al, 2019.	*Aristolochia baetica*	Qualitative and quantitative analyzes of the roots showed the presence of polyphenols, tannins, alkaloids, flavonoids, and saponins. Acute toxicity was assessed in mice by gavaging single doses of 1, 2, and 4 g/kg body weight for 14 days; subacute toxicity was done using repeated doses of 1, 1.5, and 2 g/kg/day for 28 days. Acute toxicity does not show mortality and signs of toxicity in the groups treated with 1 and 2 g/kg. The mortality rate was estimated to be 16% in the group treated with 4 g/kg. Subacute toxicity showed changes in serum parameters at doses of 1.5 and 2 g/kg/day. Histological changes were at the highest dose of 2 g/kg/day. There was toxicity at repeated doses, but no toxic effects were observed with a single dose below 4g/kg.	Roots. Aqueous extract (decoction 20 minutes at 100°C).
Bourhia et al, 2019.	*Aristolochia baetica* *Aristolochia paucinervis*	Antioxidant activity (by DPPH assay), antiproliferative activity on human cancer cell lines (T-24, HT-29, and Hep G-2), and acute toxicity. The two plants have different classes of metabolites, and total polyphenol	Roots. Soxhlet extraction at 40°C for 2h using methanol as solvent.

		concentrations are expressed in higher concentrations in *A. paucinervis*. DPPH activity with IC50 values of 150 ± 8 μg/ml and 160 ± 10 μg/ml, respectively. Both species have antiproliferative effects on all cancer cell lines tested. Regarding acute toxicity, no signs of toxicity or mortality were observed in mice treated orally with 2000 mg/kg.	
Omari et al, 2019	*Aristolochia longa*	Antioxidant activity (by the DPPH assay) is widely used in Moroccan medicine. Many healers also use a small amount of the rhizome powder with honey or salted butter to treat abdominal pain and upper respiratory tract infections.	Roots. High temperature with solvents of different polarities under magnetic stirring, filtered, and rotaevaporated.
Ahmad et al, 2021	*Aristolochia ringes*	Extracting antihyperglycemic activity on alpha-amylase and alpha-glucosidase activity was compared with the standard drug (acarbose). Inhibition in each case was dose-dependent for extracts and acarbose at all investigated dose levels. By assays, the highest percentage of inhibition occurred at the highest concentration for extract and acarbose with no corresponding significant difference.	Roots. Ethanol extract.
Ji et al, 2020.	*Aristolochia contorta*	Twelve compounds, including two new aristolochic acid analogs with a formyloxy and 10 known derivatives of aristolochic acid. Their structures were elucidated using extensive spectroscopic methods. Its cytotoxic activity on human HK-2 proximal tubular cells was evaluated by the MTT method. Among these molecules, compounds 3 and 9 were shown to be cytotoxic.	Roots.

Source: Authors.

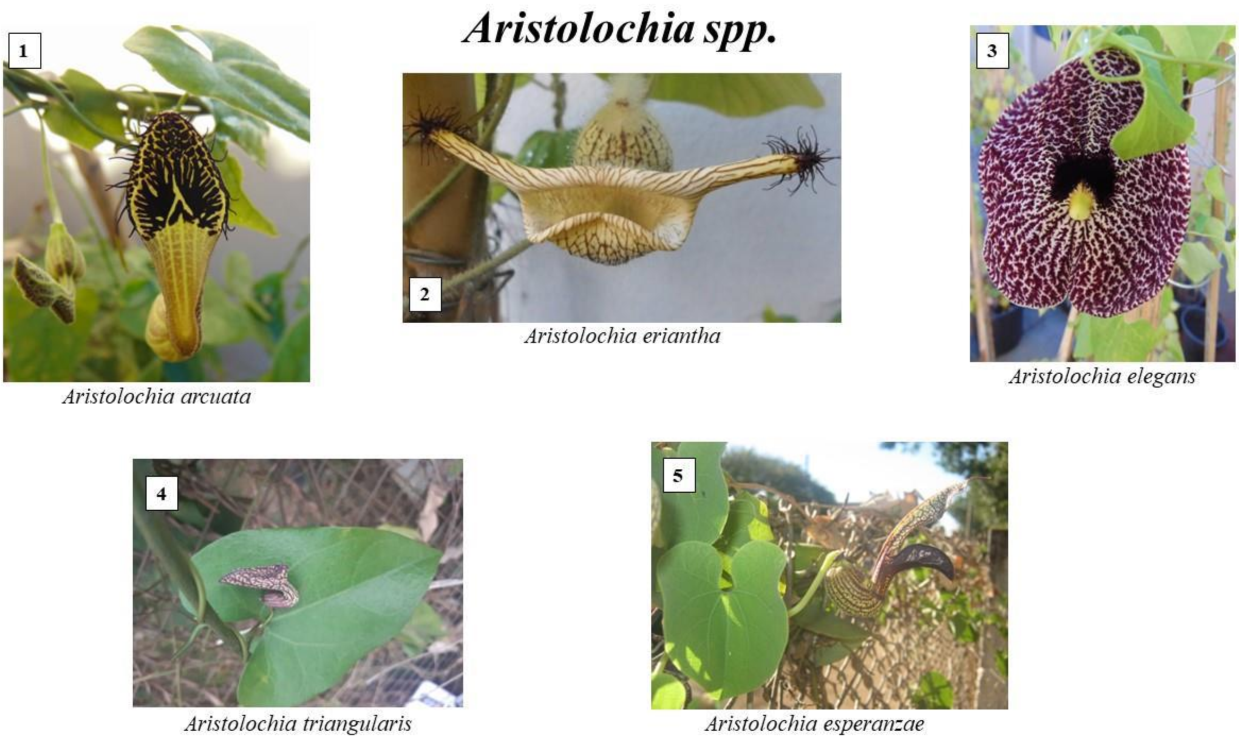
From the analysis of the studies covered in this review, it is possible to perceive that plants of the genus *Aristolochia* have many bioactive compounds of pharmaceutical interest. For example, the antioxidant potential demonstrated by Omari & collaborators (2019) in *A. longa* reminds us of the importance of returning research to plants with such activity since it is known that free radicals are protagonists in the progress of diseases such as cancer and some of the immune system. And in this context, drugs with antioxidant properties are essential to prevent and treat conditions originating from oxidative stress (Asimi et al., 2013; Devasagayam et al., 2004).

In this same scenario, it was observed that some *Aristolochia* have the antihyperglycemic capacity, which is significant bioactivity because currently, in medicine, the drugs used in the treatment of diabetes have several side effects. And therefore, plants that can offer new alternatives to revolutionize the antidiabetic drug market with safer products and economic viability are estimable (Marles & Farnsworth, 1994).

The ability to be involved in the healing processes of some species of the *Aristolochia* species also drew attention in this narrative research, as it identified bioactive compounds from extracts of medicinal plants to search for new therapeutic agents with different mechanisms of action to act in wound repair. It is highly reasonable since the skin, besides being the largest organ of the human body, has a protective function. And the wound healing process is mandatory to maintain lost tissue homeostasis (Bolla et al., 2019). The anti-inflammatory potential of some species of this genus was also evidenced, corroborating the practical use reports (Battu et al., 2011).

The evaluated works suggest that representatives of the genus *Aristolochia* are widely used in traditional medicine in our country and around the world, depending on the geographic distribution of the species. Figure 1 represents some species of the genus *Aristolochia*.

Figure 1. Images of representative species of the genus *Aristolochia spp*.



Source: Personal archives of Cláudio Rodrigo Nogueira and Larissa Pires Mueller.

In addition, herbs of this genus have essential biological effects, such as antidote to snakebite, anti-inflammatory, antiasthmatic, antiproliferative, and abortifacient potential (Lopes et al., 2001). In such a way, they are rich in compounds of therapeutic interest, which are being, little by little, elucidated by the scientific community. However, it is necessary to investigate the true medicinal potential, especially concerning its toxicity profile. Despite the therapeutic reports, harmful effects have already been described and reported for plants of this genus acting as a nephrotoxic, antispermatogenic, and antifertility agent (Dey & De, 2011), in addition to demonstrating toxicity and cytotoxicity in bioassays (Silva et al., 2019).

4. Final Considerations

The use of medicinal plants is a practice that has been around humanity over the centuries, through the manufacture of inputs, work materials, ornamental, therapeutic, and food use, among other purposes. Currently, the pharmaceutical industry uses several medicinal species to synthesize new commercial products. This demonstrates how much human beings have depended on natural resources for survival.

Aristolochies are traditionally used in folk medicine and have numerous pharmacological properties of therapeutic interest, as described in recent research. Thus, although understanding the genus is related to its ethnopharmacological potential, there is essential knowledge to be investigated to understand its true medicinal potential, especially regarding its toxicological profile and, consequently, predictions of safe use.

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