molecules

MDPI

Review

Biological Activities of Organic Extracts of the Genus *Aristolochia*: A Review from 2005 to 2021

Martín A. Lerma-Herrera [1,*], Lidia Beiza-Granados [1], Alejandra Ochoa-Zarzosa [2], Joel E. López-Meza [2], Pedro Navarro-Santos [3], Rafael Herrera-Bucio [1], Judit Aviña-Verduzco [1] and Hugo A. García-Gutiérrez [1,*]

1 Instituto de Investigaciones Químico Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Ciudad Universitaria, Morelia 58030, Michoacán, Mexico; lidia.beiza@umich.mx (L.B.-G.); rafael.herrera.bucio@umich.mx (R.H.-B.); jaavina@umich.mx (J.A.-V.)
2 Centro Multidisciplinario de Estudios en Biotecnología, Facultad de Medicina Veterinaria y Zootecnia, Universidad Michoacana de San Nicolás de Hidalgo, Tarímbaro 58893, Michoacán, Mexico; ochoaz@umich.mx (A.O.-Z.); elmeza@umich.mx (J.E.L.-M.)
3 CONACYT—Universidad Michoacana de San Nicolás de Hidalgo, Edificio B-1, Ciudad Universitaria, Morelia 58030, Michoacán, Mexico; pedro.navarro@umich.mx
* Correspondence: martin.lerma@umich.mx (M.A.L.-H.); hgarcia@umich.mx (H.A.G.-G.)

Abstract: Different ethnomedicinal studies have investigated the relationship between various phytochemicals as well as organic extracts and their bioactive aspects. Studies on biological effects are attributed to secondary metabolites such as alkaloids, phenolic compounds, and terpenes. Since there have been no reviews in the literature on the traditional, phytochemical, and ethnomedicinal uses of the genus *Aristolochia* so far, this article systematically reviews 141 published studies that analyze the associations between secondary metabolites present in organic extracts and their beneficial effects. Most studies found associations between individual secondary metabolites and beneficial effects such as anticancer activity, antibacterial, antioxidant activity, snake anti-venom and anti-inflammatory activity. The aim of this review was to analyze studies carried out in the period 2005–2021 to update the existing knowledge on different species of the genus *Aristolochia* for ethnomedicinal uses, as well as pharmacological aspects and therapeutic uses.

Keywords: *Aristolochia*; bioactivity; phytochemistry; ethnomedicinal

Citation: Lerma-Herrera, M.A.; Beiza-Granados, L.; Ochoa-Zarzosa, A.; López-Meza, J.E.; Navarro-Santos, P.; Herrera-Bucio, R.; Aviña-Verduzco, J.; García-Gutiérrez, H.A. Biological Activities of Organic Extracts of the Genus *Aristolochia*: A Review from 2005 to 2021. *Molecules* **2022**, *27*, 3937. https://doi.org/10.3390/molecules27123937

Academic Editor: Jolanta Mierzejewska

Received: 21 May 2022
Accepted: 12 June 2022
Published: 20 June 2022

1. Introduction

The Aristolochiaceae family is represented by seven genera: *Asarum*, *Saruma*, *Lactoris*, *Hydnora*, *Prosopanche*, *Thottea*, and *Aristolochia* [1]. About 550 species are known, distributed in the tropics and temperate zones of America, Asia, and Australia [2]. Traditionally, the Aristolochiaceae family was located in the Aristolochiales order by Cronquist (1981) and Takhtajan (1997). Recent studies indicate that it belongs to the Piperales order [3]. The genus *Aristolochia* is the most abundant of the Aristolochiaceae family and has been widely used in traditional Chinese medicine mainly [4], the genus is integrated by 550 species, making it the most important genus of the family [5]. Most of the species of this genus are perennial, herbaceous, distributed in bushes, in coiled or liana form, showy flowers, prostrate or tuberous rhizomes, as well as leaves with the presence of essential oils [6]. In the last two decades, the genus *Aristolochia* has generated great interest due to the abundance of mainly secondary metabolites, terpenes, and alkaloids [7–9].

Aristolochias species exist in various parts of the world; however, some species have been identified in Mexico: *A. buntingii* Pfeifer, *A. tresmariae* Ferris, *A. pacifica* Santana Mich. & Paizanni, *A. savannoidea* Paizanni & M. Ramírez, *A. tuitensis* Santana Mich. & Paizanni, *A. manantlanensis* Santana Mich., *A. malacophylla* Standl., *A. odoratissima* L., *A. styloglossa* Pfeifer, *A. foetida* Kunth, *A. tequilana* S. Watson, *A. luzmariana* Santana Mich. and *A. emiliae* Santana Mich. & Solís for which there are no phytochemical or biological studies showing

the presence of active compounds [10–12]. Other species such as *A. cardiantha* Pfeifer, *A. flexuosa* Duch., *A. glossa* Pfeifer, *A. malacophylla* Standl., *A. mutabilis* Pfeifer, *A. mycteria* Pfeifer, and *A. tentaculata* O. C. Schmidt, have also been identified in the state of Michoacán, in localities near the Bajío area, in Mexico [13–15].

Some of the species of the genus *Aristolochia* are characterized by having compounds such as aristolochic acids that are attributed to adverse health effects. However, these compounds can be related to other lower-risk applications. Otherwise, there are also phenolic and terpene compounds that show beneficial effects in different biological aspects, which is why it is important to know which ones are related to the different species for subsequent studies. Therefore, this systematic review examined the published pharmacological and ethnomedicinal literature of different *Aristolochias* species for possible studies associated with phytochemicals from organic extracts and beneficial effects.

2. Beneficial Effects of *Aristolochia* Genus

The secondary metabolites responsible for the biological effects of the species of the *Aristolochia* genus generally are usually aristolochic acids and their derivatives, as well as monoterpenes such as thujene, camphene, and carene, kaurene-type diterpenes, triterpenes such as lupeol, among others. Likewise, alkaloid metabolites derived from aristolactams and phenolic compounds of the lignan type are involved in these functions [9,16–18].

Aristolochia is the most abundant genus in the Aristolochiaceae family. The species of this genus are used ornamentally and in traditional medicine as a source of abortifacients, emmenagogues, sedatives, analgesics, anti-cancers, anti-inflammatories, muscle relaxants, antihistamines, antiparasitics, to treat cholera, abdominal pain, rheumatism, antimalarial, skin problems, and different types of bites and stings from animals and insects [9].

The use of plant extracts in traditional medicine is profitable because no elaborate procedures are required to obtain them, production costs are low, and the materials to obtain them are accessible [19,20]. For these reasons, several studies have used extracts of different solvents to obtain metabolites using different parts of the plant. The extracts as well as the active compounds that comprise the *Aristolochia* species have been used in pharmacological aspects and in traditional medicine frequently in recent years.

2.1. Ethnomedicinal Use

A variety of traditional uses for species of the genus *Aristolochia* were found in the literature. Of the traditional uses cited, the most common uses are anticancer (33 articles) [21–53], antibacterial (31 articles) [23,25,29,30,38,39,45,49,54–76], antioxidants (18 articles) [22,25,29,33,34,46,55,60,61,70,73,74,77–82], snake anti-venom (13 articles) [21,22,39,40,76,83–90], anti-inflammatory (11 articles) [22,40,46,47,74,86,91–95], abdominal pain (11 articles) [17,21–23,39,40,48,76,96–98], antiparasitic (7 articles) [18,39,75,83,99–101], insecticide an predator protection (7 articles) [40,102–107], anti-malarial (5 articles) [21,40,48,108,109], skin diseases (5 articles) [22,23,40,76,86], fever (4 articles) [7,21,22,48], headache (4 articles) [21,22,48,85]. Other beneficial effects such as, antifungal activities [45,62,110], antinociceptive [94,111,112], changes in the estrous cycle [113,114], antifibrosis [115,116], hepatoprotection, nephroprotection [117], neuroprotective effect [118], antiurcer [119], antiallergic [120], immune effect [121], angiogenic [122], osteogenic differentiation of gingival mesenchymal stem cells [123], antidiabetic [22,124,125], control of melanogenesis [126], antihemorrhagic [127], antispasmodic [97], antitoxin [128], liver protector [100], bronchitis, constipation, rheumatism and bladder diseases [129], heart protector [130], antidyslipidemic [82], healing of wounds [98], acaricide [131], expectorant, antitussive, antihistamine and pain reliever [89].

Also, traditional uses include mainly the root of the plant (42 articles), the leaves (31 articles), the stems (17 articles), aerial parts (15 articles), and the whole plant (15 articles). Some forms of use of *Aristolochia* plants for ethnomedicinal use in snakebites are drinking whole plant juice and leaves, aqueous extract (AE) orally and applying a root paste to the wound and giving a root paste orally. In skin diseases, the shade-dried root powder is

taken orally for 48 days. In fever, the leaves are chewed during the illness. The headache is treated with the formation of a paste placed on the forehead. In abdominal pain, the use of a decoction of the roots is used. In the treatment of malaria, the plant is used in decoction [21,22,108].

2.2. Phytochemical Studies

The review of the literature allowed knowing phytochemicals that have a higher prevalence such as phenanthrene derivatives, phenolic compounds, fatty acids, and isoprenoid derivatives. Extracted and polar roots showed a higher prevalence of phenanthrene derivatives and phenolic compounds. The roots and aerial parts of the medium and low-polarity extracts showed a higher presence of fatty acids and derived isoprenoids. The most prominent phytochemicals are shown in Table 1.

Table 1. Main phytochemicals of species of the genus *Aristolochia*, using different solvents.

Phytochemicals	Species	Plant Part [1]	Extract/ Solvent	References
Polyphenols, alkaloids, flavonoids, saponins, tannins	*A. baetica* L.	RT	ME	[33]
Aristolochic acid I	*A. baetica* L.	RT	CE	[26]
Saponins, alkaloids, flavonoids, sterols, carbohydrates	*A. bracteolata* Lam.	RT	EE	[34]
Aristolactam I	*A. brevipes* Benth.	RT	DCME	[76]
Aristchamic-A	*A. championii* Merr. & Chun.	RZ	EE	[36]
β-caryophyllene, *iso*-caryophyllene, Bicyclogermacrene	*A. elegans* Mast.	LV	N/A	[54]
Fargesin, (8*R*,8′*R*,9*R*)-cubebin, eupomatenoid-1	*A. elegans* Mast.	RZ	HXE	[39]
Methylhexadecanoate; hexadecanoic acid; 2-butoxyethyl dodecanoate; ethylhexadecanoate; methyl octadeca-9,12,15-trienoate, (9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trienoic acid	*A. foetida* Kunth.	LV, S	DCME	[24]
β-caryophyllene, limonene, linalool	*A. fordiana* Hemsl.	AP	Et_2O	[29]
Benzofuranneolignans, (−)-licarin-B, parakmerin A, perseal G, (+)-conocarpan, (7*R*,8*R*)-3,4-methylenedioxy-4′,7-epoxy-8,3′-neolignan-7′-[*E*]-ene, (+)-*trans*-dehydrodiisoeugenol, decurrenal, (2*R*,3*R*)-2,3-dihydro-2-(4-hydroxyphenyl)-7-methoxy-3-methyl-5-(*E*)-propenylbenzofuran, eupomatenoid-13, eupomatenoid-7, eupomatenoid-6, eupomatenoid-5	*A. fordiana* Hemsl.	AP	EE	[37]
Dihydrobenzofuran neolignans, 2-aryldihydrobenzofurans, 8-*O*-4′-neolignan and analogs	*A. fordiana* Hemsl.	S	EE	[118]
Flavonoids, steroids, and triterpenes	*A. galeata* Mart.	RZ	EE	[38]
Aristolic acid	*A. indica* L.	RT	CE	[22]
Aristolochic acid I	*A. indica* L.	RT	EE	
Aristolochicacid II	*A. indica* L.	LV	ME	
Aristolochicacid D	*A. indica* L.	RT	ME	
Aristololactam-I *N*-*β*-*D*-glucoside	*A. indica* L.	RT	Et_2O	
(12*S*)-7,12-secoishwaran-12-ol	*A. indica* L.	RT	Et_2O	
β-sitosterol	*A. indica* L.	RT	EE	
(−)-hinokinin	*A. indica* L.	AP	DCME	
Aristolactam I	*A. indica* L.	AP	EAE	
β-caryophyllene and *α*-humulene	*A. indica* L.	AP	N/A	[114]
Flavonoids, tannins, glycosides, phenol, saponins, terpenoids, amino acid	*A. indica* L.	LV	CE	[27]
Alkaloid, anthraquinone, coumarin, flavonoid, phenol, quinone, saponin, steroid, tannin, terpenoid, sugar, glycoside, xanthoprotein	*A. krisagathra* Sivar. & Pradeep.	WP	EE	[95]
Linoleic acid chloride	*A. longa* L.	AP	HXE	[23]
Oleic acid	*A. longa* L.	AP	HXE	

Table 1. *Cont.*

Phytochemicals	Species	Plant Part [1]	Extract/ Solvent	References
Limonene-6-ol, pivalate	*A. longa* L.	AP	HXE	
Starch, tannins	*A. longa* L.	RT	H_2O	
Tannins, flavonoids, coumarins, anthocyans	*A. longa* L.	RT	ME	[25]
Polyphenols, flavonoids	*A. longa* L.	RT	HXE	
Flavonols, flavones, and/or flavonoid glycosides	*A. longa* L.	RT	H_2O	[50]
Polyphenols, flavonoids	*A. longa* L.	RT	H_2O	[51]
Aristolochic acid I	*A. maurorum* L.	RT	ME	
Aristolochic acid II	*A. maurorum* L.	RT	ME	[53]
Aristolochic acid IIIa	*A. maurorum* L.	RT	ME	
2,2,7,7-tetramethyltricyclo [6.2.1.0(1,6)]undec-4-en-3-one, (*E*)-*β*-santalolacetate, camphene, spathulenol, *β*-caryophyllene, *α*-humulene	*A. mollissima Hance.*	RZ	N/A	[30]
Alkaloids, flavonoids, steroids, anthraquinones	*A. ringens* Vahl.	AP	CE	[28]
Aristolochiaside, aristolactam AIIIa	*A. tadungensis* T. V. Do & Luu.	S, LV	ME	[35]
(±)-licarin-A and -B, eupomatenoid-1 and -7	*A. taliscana* Hook. & Arn.	RZ	HXE	[55]
(−)-licarin-A	*A. taliscana* Hook. & Arn.	RT	HXE	[56]
(+)-*iso*-bicyclogermacrenal	*A. yunnanensis* Franch.	S	EAE	[116]
Spatulenol	*A. yunnanensis* Franch.	S	EAE	

[1] AP = aerial parts, LV = leaves, RT = roots, RZ = rhizomes, S = stems, WP = whole plant. N/A = not applicable. CE = chloroformic extract, DCME = dichloromethane extract, EAE = ethyl acetate extract, EE = ethanol extract, HXE = hexanic extract, ME = methanol extract, Et_2O = ether.

2.3. Pharmacological Activity

Pharmacological studies have been carried out using crude extracts and bioactive compounds from different species of *Aristolochia*. The beneficial effects that most prevailed in this review were: anticancer activity, antibacterial, antiparasitic and antiviral activity, antiplatelet activity, antioxidant activity, neuroprotective activity, changes in the estrous cycle, antidiabetic potential, anti-inflammatory activity, and antifibrotic activity. Table 2 shows the common beneficial and ethnomedicinal effects of *Aristolochia* species in traditional medicine.

Table 2. Ethnomedicinal uses and biological activities of *Aristolochia* species.

Species	Plant Part [1]	Beneficial Effects	References
A. acuminata Lam.	FT, LV, RT, and S	Abdominal pain, abortifacient, analeptic, antipyretic, anti-inflammatory, bone fracture, bilious disorders, carminative, diarrhea, dysentery, emmenagogue, health tonic, loss of appetite, antimalarial, muscle relaxant, rheumatism, regulate menstrual disorders, snake bite, stomachache, swollen limbs, stimulate uterine flow, snake and scorpion poison, tumor, venereal disease	[40]
A. albida Duch.	RT	Larvicide, antiparasitic, snake antivenom	[83]
A. arcuata Mast.	LV	Hepatoprotection, nephroprotection	[117]
	LV	Protection against insects	[102]
	WP	Antimicrobial	[57]
A. argentina Griseb.	WP	Antiseptic, diuretic, emmenagogue, antioxidant	[77]
	AP	Insecticide	[103]

Table 2. *Cont.*

Species	Plant Part [1]	Beneficial Effects	References
A. baetica L.	RT	Antioxidant, antiproliferative	[33]
	RT and LV	Antiproliferative	[26]
A. birostris Duch.	AP	Antimicrobial	[58]
A. bracteata Retz.	RT	Antimicrobial	[59]
	WP	Antiulcer	[119]
	WP and RT	Antioxidant	[60,78]
	WP	Antiallergic	[120]
	FT, LV and RT	Insecticide	[104]
	WP	Antioxidant, antimicrobial	[73]
	AP	Anti-inflammatory	[91]
	LV	Immune effect	[121]
	AP	Angiogenic	[122]
A. bracteolata Lam.	AP	Osteogenic differentiation of gingival mesenchymal stem cells	[123]
	LV	Antidiabetic	[124]
	RT	Cytotoxic, antioxidant	[34]
	AP	Control of melanogenesis	[126]
	WP, RT and LV	Gastric stimulant treatment, cancer treatment, lungs inflammation dysentery, and snake bite, treatment of malaria, convulsions, abdominal pain, scorpion stings, flu, vomiting, pneumonia, polymenorrhea and edema, fever, headache, general body pain, stomachache, diarrhea, and flu	[21]
A. brevipes Benth.	RZ	Antimycobacterial, antidiarrheal, arthritis, wound cleaner, and snake antivenom	[76]
A. bodamae Dingler.	RZ	Antimycobacterial	[60]
	RT	Antibacterial, antioxidant	[61]
A. cathcartii Hook.	LV, RZ, RT, and S	Food poisoning, insect repellent, liver disorders, promotes flow of urine, stomach ailments	[40]
A. championii Merr. & Chun.	RZ	Cytotoxic	[36]
A. chilensis Bridges ex Lindl.	S and LV	Antihemorrhagic	[127]
A. clematitis L.	RZ	Antibacterial, antifungal	[62]
	AP	Antioxidant	[79]
A. constricta Griseb.	AP	Antispasmodic	[97]
A. cordigera Willd. Ex Klotzsch.	S, LV, and RT	Antiprotozoal	[99]
A. cymbifera Mart.	LV, RT	Antitrypanosomal, antischistosomal	[18]
A. debilis Siebold & Zucc.	RT	Anti-inflammatory	[92]
	RT	Cytotoxic	[41]
A. delavayi Franch.	AP	Antibacterial	[63]
A. elegans Mast.	RZ	Antiparasitic and antimycobacterial, antibacterial, antitumor, antidiarrheal, antipyretic, snake bites	[39]
	RT	Antitoxin	[128]
	LV	Antifungal	[110]
	LV	Antiviral, antibacterial	[54]
	RT	Scorpion antivenom	[84]
A. esperanzae Kuntze.	RT	Antibacterial	[64,65]
A. fangchi Y. C. Wu ex L. D. Chou & S. M. Hwang.	RT	Cytotoxic	[42]
A. foetida Kunth.	WP	Snake bite, headache	[85]
	RT	Fever, colds, chills, asthma treatment	[7]
	LV and S	Cytotoxic	[24]

Table 2. *Cont.*

Species	Plant Part [1]	Beneficial Effects	References
	WP	Cytotoxic	[37]
A. fordiana Hemsl.	WP	Antibacterial, cytotoxic and antioxidant	[29]
	S	Neuroprotective effect	[118]
A. galeata Mart.	RZ	Antibacterial and cytotoxic	[38]
A. gehrtii Hoehne.	LV	Liver protector and antiparasitic	[100]
A. griffithii Hook.f. & Thomson ex Duch.	RT	Antimalarial	[108]
A. gigantea Mart.	RT	Antitrypanosomal	[75]
	RT	Fertility regulator	[114]
	RT	Antidiarrheal	[17]
	RT	Cytotoxic	[43]
	LV	Antibacterial	[66]
	S and LV	Antibacterial	[67]
	LV	Anti-inflammatory, poisonous bites, gastric stimulator, skin problems, antidiarrheal, antipyretic, antitussive	[86]
A. indica L.	LV	Snake bites	[87]
	WP	Antibacterial	[68]
	WP, RT, L, FR	Antidote for snake bite, scorpion bite, bee bite, spider bite, blood clotting, leukoderma, skin infection, emollient, headache, leucorrhoea, dandruff, fever, constipation and abdominal colic, abortifacient, blood purifier, cholera, dryness of tongue, dysmenorrhea, watering of eye, gangrene, swelling in leg, stomach burning, pulmonary problems, arthritis, mastitis in animals, hemiplegia, anti-inflammatory, anti-oxidant, antidiabetic, larvicidal, antitumor	[22]
A. krisagathra Sivar. & Pradeep.	WP	Anti-inflammatory	[95]
	WP	Antiulcer	[119]
A. kwangsiensis Chun & F. C. How ex C. F. Liang.	LV	Antimicrobial, antioxidant, anti-inflammatory	[74]
A. longa L.	T	Antibacterial, cytotoxic, skin problems, gastrointestinal disorders	[23]
	S	Bronchitis, constipation, rheumatism, bladder diseases	[129]
	RT	Heart protector	[130]
	RT and AP	Antibacterial	[69]
	RT	Antioxidant	[80]
	RT and AP	Antibacterial, antioxidant	[70]
	RT	Antioxidant, antibacterial, cytotoxic	[25]
A. macroura Gomes.	LV	Cytotoxic	[32]
	AP	Antioxidant	[81]
A. malmeana Hoehne.	RT and LV	Insecticide	[105]
A. maurorum L.	RT and AP	Antiplatelet	[53]
A. mollissima Hance.	RZ and AP	Antibacterial,	[30]
	WP	Cytotoxic	[44]
A. manshuriensis Kom.	S	Anti-inflammatory	[93]
	LV	Antibacterial	[71]
A. paucinervis Pomel.	RT	Antiproliferative	[33]
A. petersiana Klotzsch.	RT	Antimalarial	[109]
A. pubescens Will. ex Duch.	RT and S	Insecticide	[106]
A. odoratissima L.	LV	Snake antivenom	[88]
	S	Antinociceptive	[111]
A. orbicularis Duch.	RT	Antibacterial	[72]
A. ringens Vahl.	RT	Cytotoxic	[31]
	SB	Antidiarrheal	[96]
	AP	Antibacterial, antifungal, cytotoxic	[28,45]
	RT	Antidiabetic	[82]
	RT	Antioxidant, antidyslipidemic	[82]

Table 2. *Cont.*

Species	Plant Part [1]	Beneficial Effects	References
A. saccata Wall.	LV, RT, S, and T	Healing of wounds, body pain, diarrhea, dysentery, hemorrhage, jaundice, tonsil	[40,98]
A. tadungensis T. V. Do & Luu.	S and LV	Cytotoxic	[35]
	RT and LV	Insecticide	[107]
A. tagala Cham.	RT	Antioxidant, anti-inflammatory, anti-cancer	[46]
	RT	Anti-inflammatory, anti-cancer	[47]
	RT, LV, and WP	Stomach pain, chest pain, fever, poultice in abdomen, skin disease, snake bite, antimalarial, dyspepsia, flatulent, diarrhea, vomiting, headache, gynecological disorders, stimulate the menstrual flow, bone fracture, treatment of cancer	[48]
A. taliscana Hook. & Arn.	RZ	Antioxidant, antimicrobial	[52,55]
	RT	Antimycobacterial	[56,60]
A. triangularis Cham.	S	Antiproliferative, antibacterial	[49]
	LV	Acaricide	[131]
A. trilobata L.	S	Antinociceptive	[112]
	S	Antinociceptive, anti-inflammatory	[94]
A. tuberosa C. F. Liang & S. M. Hwang.	FT	Antinematode	[101]
A. yunnanensis Franch.	S	Antifibrosis	[115,116]
A. zollingeriana Miq.	FT and RT	Expectorant, antitussive, antihistamine, pain reliever, treatment of snake bites	[89]

[1] AP = aerial parts, FT = fruits, LV = leaves, FR = fresh root, RT = roots, RZ = rhizomes, S = stems, SB = stem bark, T = tuber, WP = whole plant.

2.3.1. Anticancer Activity

In aerial parts of *A. longa* L., a greater in vitro cytotoxic effect was determined on RD (embryonal rhabdomyosarcoma cells) (IC_{50} = 0.015 mg/mL) of a dichloromethane extract (DCME), followed by the hexane extract (HXE) on BSR (kidney adenocarcinoma of hamster cells) (IC_{50} = 0.018 mg/mL). The least cytotoxic effect was shown in the HXE and DCME analyzed in Vero (monkey kidney cancer cells) cells (IC_{50} = 0.250 mg/mL) as well as in the methanolic extract (ME) of RD (IC_{50} = 0.200 mg/mL) and BSR (IC_{50} = 0.350 mg/mL). The compounds implicated in this beneficial activity are attributed to linoleic acid chloride, oleic acid, and limonene-6-ol, pivalate [23]. The possible mechanisms of cytotoxicity of the compounds characterized in the HXE and DCME could be related to the cleavage of the plasma membrane and the release of its content into the extracellular medium [24]. *A. longa* L. exhibited an in vitro cytotoxic effect of HXE of the root on RD cells (IC_{50} = 0.0151 mg/mL) showing a relationship of its activity to flavonoids (76.41 ± 8.74 mg GAE/g), while the HXE the cytotoxicity in healthy PBMC (human peripheral blood mononuclear) cells was lower (IC_{50} = 0.0625 mg/mL) [25]. The chloroform extract (CE) from the roots of *A. baetica* L. showed cytotoxic activity (IC_{50} = 0.2160 mg/mL) in vitro against MCF-7 (breast cancer cells) by means of the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric assay. Aristolochic acid I was identified and contributed to the cytotoxicity of the extract [26].

A study of the CE of leaves of *A. indica* L. was carried out and cytotoxicity was obtained with the MTT assay at 48 h after treatment in MCF-7 cells (IC_{50} = 0.347 mg/mL) using Taxol™ (IC_{50} = 1.17 × 10^{-8} M) as a standard control. The compounds identified in the CE of the leaves were flavonoids, tannins, glycosides, phenols, saponins, terpenoids, and amino acids [27].

Compounds such as alkaloids, flavonoids, steroids, and anthraquinones from the aerial parts of the CE of *A. ringens* Vahl. caused a cytotoxic effect against HepG-2 (human liver cancer cells) (IC_{50} = 0.0164 mg/mL) and on MCF-7 cells (IC_{50} = 0.0816 mg/mL) [28].

In DCME collected in 2018 from *A. foetida* Kunth, IC_{50} values were determined for leaves of 0.0473 mg/mL and for stems with IC_{50} values of 0.0459 mg/mL in MCF-7 cells. Components in the extracts can cause late apoptotic cell death through the intrinsic pathway in the cancer cell line. The main compounds identified were methyl hexadecanoate; hexadecanoic acid; 2-butoxyethyl dodecanoate; ethyl hexadecanoate; methyl octadeca-9,12,15-trienoate; and (9*Z*,12*Z*,15*Z*)-octadeca-9,12,15-trienoic acid that allow cytotoxic activity [24].

Essential oils from the aerial parts of *A. fordiana* Hemsl. were evaluated against HepG-2 cells (IC_{50} = 0.69 mg/mL) and the MCF-7 cell line (IC_{50} = 0.22 mg/mL) for 72 h attributing its effect to the compounds β-caryophyllene, limonene, and linalool. Doxorubicin was used as a positive control in HepG-2 (IC_{50} = 0.00049 mg/mL) and MCF-7 (IC_{50} = 0.00022 mg/mL) [29]. The sesquiterpene 2,2,7,7-tetramethyltricyclo[6.2.1.0(1,6)] undec-4-en-3-one has been identified and characterized as the main compound in essential oils of *A. mollissima* Hance. Essential oils from rhizomes showed cytotoxic activity in ACHN (kidney adenocarcinoma cells) (IC_{50} = 0.0223 mg/mL), MCF-7 (IC_{50} = 0.0206 mg/mL), Bel-7402 (human liver carcinoma cells) (IC_{50} = 0.0331 mg/mL), HepG-2 (IC_{50} = 0.0332 mg/mL), and HeLa (human cervix carcinoma cells) (IC_{50} = 0.0386 mg/mL) compared to aerial parts with the exception of MDA-MB-435S (melanoma cells) (IC_{50} = 0.0203 mg/mL) [30].

The cytotoxic effect of an AE of the root of *A. longa* L. on breast cancer cell lines was evaluated in vitro by means of the MTT assay, whose activity may be related to flavonols, flavones, and/or flavonoid glycosides [50]. On the other hand, tests were carried out on human red blood cells with an AE of aerial parts of *A. longa* L. collected in Algeria in March 2018. The AE did not show high percentages of hemolysis (68.75 $\pm$ 6.11%; 200 mg/mL). The concentration of polyphenols [283.68 $\pm$ 0.60 mg GAE (gallic acid equivalent)/g] and flavonoids (10.50 $\pm$ 0.03 mg QE (quercetin equivalent)/g) could influence hemolysis, which is important to consider the dose of the AE in traditional cancer medicine [51].

Ethanol extract (EE) and DCME:ME from *A. ringens* Vahl. roots were evaluated in vitro and in vivo and compared with 5-fluorouracil. However, the study lacked the characterization of the bioactive compounds to corroborate their anticancer therapeutic approach [31]. Likewise, in the ME of leaves of the species *A. macroura* Gomes., the active components were not specifically mentioned and their cytotoxic activity against HepG-2 cells (IC_{50} = 0.513 mg/mL) was higher compared to other species such as *Schinus molle* L. (IC_{50} = 0.050 mg/mL) [32].

In a chemical and biological study of *A. maurorum* L., the main components of roots and aerial parts of ME were aristolochic acid I, II, and IIIa. However, the compound that showed the greatest cytotoxic effect was aristolochic acid I ($IC_{50} = 1.43 \times 10^{-8}$ M, in *Artemia salina*); it is worth mentioning that the biological evaluation of the cytotoxic activity was not carried out in cancer cells [53]. The ME of the roots of *A. baetica* L. demonstrated antiproliferative effect against T-24 (human bladder cancer cells) IC_{50} = 0.048 mg/mL and HT-29 (human colon cancer cells) IC_{50} = 0.100 mg/mL relative to HepG-2 (IC_{50} = 0.380 mg/mL). The antiproliferative effect can be attributed to phytochemicals identified mostly as polyphenols, alkaloids, flavonoids, saponins, and tannins and their possible mechanism of action against cancer cells via intrinsic apoptosis [33]. The polar extracts such as the ME ones mentioned above, as well as the EE one from the roots of *A. bracteolata* Lam. have shown highly effective cytotoxic activity against MCF-7 cells (IC_{50} = 0.0191 mg/mL), where saponins, alkaloids, flavonoids, sterols, and carbohydrates were identified as major components [34]. The mechanism of cell death against cancer cells that phenolic compounds can present involves the inhibition of enzymes compromising the cell cycle [132]. The ME of stems and leaves of *A. tadungensis* T. V. Do & Luu. was evaluated in HeLa (IC_{50} = 0.0083 mg/mL), PANC-1 (human pancreas cell line) IC_{50} = 0.0826 mg/mL, and A-549 (human lung cell line) IC_{50} = 0.0755 mg/mL. The aristolochiaside compounds with cytotoxic effect on HeLa ($IC_{50} = 7.59 \times 10^{-6}$ M) and on PANC-1 ($IC_{50} = 5.47 \times 10^{-5}$ M) were characterized and identified. Only in the PANC-1 cell line the IC_{50} values were $> 2.5 \times 10^{-5}$ M [133]. Aristolactam AIIIa showed cytotoxicity against A-549 cells ($IC_{50} = 2.40 \times 10^{-5}$ M). Camptothecin (1.35×10^{-6} M) was used as a control [35]. Aristolactam AIIIa can induce apoptosis and cell

cycle arrest in the G2/M phase in cancer cells [134]. In particular, in the EE of the rhizomes of *A. championii* Merr. & Chun. The aristolochic acid derivative aristchamic-A showed higher cytotoxic activity against HCT-116 (human colon cancer cells) $IC_{50} = 5.00 \times 10^{-7}$ M, HepG-2 ($IC_{50} = 7.37 \times 10^{-6}$ M), BGC-823 (human gastric carcinoma cells) $IC_{50} = 2.66 \times 10^{-6}$ M and NCI-H1650 (human lung cancer cell line) $IC_{50} = 7.50 \times 10^{-7}$ M. The activity of aristolochic acid derivatives could be associated with the 9,10-dihydroaristolochic acid skeleton [36]. From an EE of roots, aristolochic acid I was identified in *A. indica* L., which showed antitumor action in adenocarcinoma 755 in mice at a dose of 2 mg/kg [22]. At low doses, aristolochic acids can arrest the G2/M phase of the cell cycle and cause DNA damage by increasing reactive oxygen species (4.0×10^{-6} M) as well as activating apoptosis in higher doses (4.0×10^{-5} M) [135]. Despite the controversy over the nephrotoxicity and carcinogenic effects of aristolochic acids and their derivatives, they can be focused on cytotoxic treatments [136].

The cytotoxic effect on MG-63 (human osteosarcoma cells) was determined with eupomatenoid-7 ($IC_{50} = 1.19 \times 10^{-5}$ M) and HepG-2 with eupomatenoid-5 ($IC_{50} = 9.15 \times 10^{-6}$ M) isolated from the EE of aerial parts of *A. fordiana* Hemsl. Cisplatin was used as a positive control against MG-63 ($IC_{50} = 5.31 \times 10^{-6}$ M) and HepG-2 ($IC_{50} = 5.21 \times 10^{-6}$ M) [37].

On the other hand, in the species *A. galeata* Mart., a cytotoxic effect was found against HeLa cells of the ethanolic extract (IC_{50} = 0.369 mg/mL) and by partitioning the dichloromethane fraction (IC_{50} = 0.09 mg/mL) was obtained whose cytotoxic effect was greater with respect to the fractions of hexane, ethyl acetate, and hydroethanolic. The secondary metabolites determined in the EE and the dichloromethane fraction were flavonoids, steroids, and triterpenes [38].

In HK-2 (renal cells), 28 ME from different species of the genus *Aristolochia* were tested, so that aristolactam BI, aristolochic acid D, and aristolactam IIIa may be responsible for the genotoxic and cytotoxic activity. The possible mechanism of action of aristolochic acids and their derivatives causes apoptosis and arrest of the G2/M phase of the cell cycle [137]. Of the 68 extracts tested on cancer cells, 31 extracts had an $IC_{50} < 0.1$ mg/mL [133]. Table 3 shows different cancer cell lines against organic extracts of different species of the genus *Aristolochia*.

Table 3. IC_{50} values of crude extracts of the genus *Aristolochia*.

Cell Line	IC_{50} (mg/mL)	Species	Plant Part [1]	Extract/Solvent [2]	Reference
A431	0.0280	*A. ringens* Vahl.	RT	DCME:ME	[31]
A-549	0.0200	*A. ringens* Vahl.	RT	EE	[31]
	0.0260	*A. ringens* Vahl.	RT	DCME:ME	
	0.0755	*A. tadungensis* T. V. Do & Luu.	S and LV	ME	[35]
BSR	0.0600	*A. longa* L.	AP	DCM	[23]
	0.0180	*A. longa* L.	AP	HXE	
	0.3500 ‡	*A. longa* L.	AP	ME	
HBL-100	0.0400	*A. longa* L.	RT	H_2O	[50]
HCT-116	0.0220	*A. ringens* Vahl.	RT	EE	[31]
	0.0195	*A. ringens* Vahl.	RT	DCME:ME	
HeLa	0.369 ‡	*A. galeata* Mart.	RZ	EE	[38]
	0.0300	*A. ringens* Vahl.	RT	DCME:ME	[31]
	0.0083	*A. tadungensis* T. V. Do & Luu.	S and LV	ME	[35]
Hep G-2	0.3800 ‡	*A. baetica* L.	RT	ME	[33]
	0.0164	*A. ringens* Vahl.	AP	CE	[28]
	0.5130 ‡	*A. macroura* Gomes.	LV	ME	[32]

Table 3. *Cont.*

Cell Line	IC_{50} (mg/mL)	Species	Plant Part [1]	Extract/Solvent [2]	Reference
HK-2	0.1826 ‡	*A. acumiata* Lam.	RT	ME	[137]
	>0.2000 ‡	*A. acuminata* Lam.	F		
	0.1574 ‡	*A. argentina* Griseb.	S		
	>0.2000 ‡	*A. baetica* L.	LV		
	>0.2000 ‡	*A. californica* Torr.	S		
	>0.2000 ‡	*A. chamissonis* Duch.	LV		
	0.0478	*A. clematitis* L.	SD		
	0.1633 ‡	*A. clematitis* L.	RT		
	>0.2000 ‡	*A. cymbifera* Mart.	S		
	>0.2000 ‡	*A. debilis* Siebold & Zucc.	S		
	>0.2000 ‡	*A. elegans* Mast.	LV		
	0.0911	*A. elegans* Mast.	RT		
	0.1881 ‡	*A. fangchi* Y.C. Wu ex L.D. Chow & S.M. Hwang.	S		
	0.1272 ‡	*A. grandiflora* Sw.	LV		
	>0.2000 ‡	*A. guentheri* O.C. Schmidt.	LV		
	0.0854	*A. guentheri* O.C. Schmidt.	S		
	0.1197 ‡	*A. labiata* Willd.	LV		
	>0.2000 ‡	*A. manshuriensis* Kom.	S		
	>0.2000 ‡	*A. maurorum* L.	LV		
	>0.2000 ‡	*A. maxima* Jacq.	RT		
	>0.2000 ‡	*A. odoratissima* L.	LV		
	>0.2000 ‡	*A. paucinervis* Pomel.	SD		
	0.1060 ‡	*A. ringens* Vahl.	RT		
	>0.2000 ‡	*A. rotunda* L.	RT		
	>0.2000 ‡	*A. tomentosa* Sims.	S		
	>0.2000 ‡	*A. trilobata* L.	LV		
	0.1424 ‡	*A. westlandii* Hemsl.	S		
	>0.2000 ‡	*A. zollingeriana* Miq.	LV		
HT-29	0.1000 ‡	*A. baetica* L.	RT	ME	[33]
	0.2160 ‡	*A. baetica* L.	RT	CE	[26]
MCF-7	0.0191	*A. bracteolata* Lam.	RT	EE	[34]
	0.3470 ‡	*A. indica* L.	LV	CE	[27]
	0.0816	*A. ringens* Vahl.	AP	CE	[28]
	0.0473	*A. foetida* Kunth	LV	DCME	[24]
	0.0459	*A. foetida* Kunth	S	DCME	
MDA-MB-231	0.0970	*A. longa* L.	RT	H_2O	[50]
PANC-1	0.0826	*A. tadungensis* T. V. Do & Luu.	S and LV	ME	[35]
PC-3	0.0030	*A. ringens* Vahl.	RT	EE	[31]
	0.0120	*A. ringens* Vahl.	RT	DCME:ME	
RD	0.1254 ‡	*A. longa* L.	RT	DCME	[25]
	0.0625	*A. longa* L.	RT	ME	
	0.0151	*A. longa* L.	RT	HXE	
	0.0150	*A. longa* L.	AP	DCME	[23]
	0.2000 ‡	*A. longa* L.	AP	ME	
T-24	0.0480	*A. baetica* L.	RT	ME	[33]
THP-1	0.0240	*A. ringens* Vahl.	RT	EE	[31]
	0.0220	*A. ringens* Vahl.	RT	DCME:ME	
Vero	0.2500 ‡	*A. longa* L.	AP	DCME	[23]
	0.2500 ‡	*A. longa* L.	AP	HXE	
	0.0151	*A. longa* L.	RT	HXE	[25]
	0.0312	*A. longa* L.	RT	DCME	
	0.1253 ‡	*A. longa* L.	RT	ME	

[1] AP = aerial parts, F = flower, LV = leaves, RT = roots, RZ = rhizomes, S = stems. [2] CE = chloroformic extract, DCME = dichloromethane extract, EE = ethanol extract, HXE = hexanic extract, ME = methanol extract. ‡ Shows concentrations > 0.1 mg/mL.

2.3.2. Antibacterial, Antiparasitic and Antiviral Activity

Mohanraj et al., (2009) identified from essential oils of leaves of *A. elegans* Mast. sesquiterpenes β-caryophyllene and *iso*-caryophyllene with antibacterial activity against *Klebsiella pneumoniae, Vibrio cholerae, Salmonella typhi*, and *S. paratyphi* A. The aforementioned compounds, as well as bicyclogermacrene, are attributed to antiviral activity against the HIV-1 antigen p24 with an inhibition of 35.6–14.9% [54]. Phenolic compounds such as fargesin, (8*R*,8′*R*,9*R*)-cubebin and eupomatenoid-1 were identified in HXE from the rhizomes of *A. elegans* Mast. which favored the inhibition of *M. tuberculosis* at a minimum inhibitory concentration (MIC) of 50 µg/mL. Eupomatenoid-1 showed antiparasitic activity ($IC_{50} < 1.93 \times 10^{-9}$ M) against *E. histolytica* and *G. lamblia* [39]. Navarro-García et al., (2011) determined that in the DCME from *A. brevipes* Benth. roots collected in Mexico, the aristolactam I presented greater antibacterial activity against *Mycobacterium tuberculosis* H37Rv with an MIC between 8.52×10^{-8} and 4.26×10^{-8} M [76]. Likewise, in *A. taliscana* Hook. & Arn., the rhizome HXE exhibited antibacterial activity (MIC = 0.7 mg/mL) as well as the isolated compound eupomatenoid-7 (MIC = 2.15×10^{-6} M) inhibiting the growth of *Escherichia coli, Pseudomona fluorescens*, and *Listeria monocytogenesis* [55]. In the research carried out by León-Díaz et al. (2013), the HXE root of *A. taliscana* Hook. & Arn. (−)-licarin-A was isolated whose concentration of 5 mg/kg reduced pneumonia in mice infected with *M. tuberculosis* [56]. The linoleic acid chloride, oleic acid, and limonene-6-ol, pivalate were isolated from DCME from the tubers of the *A. longa* L. species, the present activity was evident against *Rhodococcus* sp: *R. equi,* GK1, and GK3 (with an inhibition zone of 30 mm at 50 mg/mL) [23]. The HXE of *A. longa* L. exhibited antibacterial activity (10 mg/mL) against *Staphylococcus aureus*, determining a total inhibitory effect with a zone of inhibition of 8.5 mm. The antibacterial activity may be related to the amount of polyphenols and flavonoids in the organic extract of *A. longa* L. [25]. Essential oils promote the loss of the integrity of the cell membrane by releasing the cell material to the external environment, in addition to the inhibition of proteins and biofilms [138]. It is worth mentioning that the extracts of *A. longa* L. mentioned above exceed 0.1 mg/mL, so they would not be suitable for use as antibacterials [133].

2.3.3. Antiplatelet Activity

In *A. maurorum* L., the main components of the roots and aerial parts of the ME were aristolochic acid I (1.17×10^{-6} M), II (1.28×10^{-6} M), and IIIa (1.22×10^{-6} M). These components showed an antiplatelet activity of 100% and the assay was compared with the standard acetylsalicylic acid (3.05×10^{-5} M) showing an inhibition of platelet aggregation of 100%. Compounds were evaluated using an automatic platelet aggregometer and coagulation tracer [53].

2.3.4. Antioxidant Activity

In *A. taliscana* Hook. & Arn. in HXE of rhizomes, the ABTS assay (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) was performed to measure the ability of the compounds to trap the $ABTS^{\bullet+}$ radical. The results obtained were expressed as antioxidant activity of eupomatenoid-7 (151.2 mg GAE/g) and (±)-licarin-A (143.4 mg GAE/g) and were the most active at both points of the determination (minute 1 and 7 of the reaction) [55]. The antioxidant activity is dependent on hydroxyl groups, to which its antioxidant effect is attributed, which is why licarin-B and eupomatenoid-1 did not present this condition.

A. bracteolata Lam. showed activity to chelate iron with an antioxidant capacity of 44 ± 0.01%, whose activity is attributed to phenolic compounds [34]. In the ME of *A. longa* L., it was determined that it has a high amount of polyphenols and flavonoids, and it showed a remarkable antioxidant activity. The total content of phenolic compounds of *A. longa* L. showed that the ME of roots presented the concentrations of polyphenols and flavonoids with 101.4 mg of GAE/g and 54.21 mg of QE/g of extract, respectively [25].

2.3.5. Neuroprotective Activity

Dihydrobenzofuran neolignans, 2-aryldihydrobenzofurans, 8-*O*-4′-neolignan, and analogs (3.0×10^{-5} M) as well as the EE of the stem (0.01 mg/mL) of *A. fordiana* Hemsl. exhibited a neuroprotective effect that prevents cell death in hippocampal cells (HT-22) [118].

2.4. In Vivo Studies on Extracts of the Genus Aristolochia

2.4.1. Changes in the Estrous Cycle

In tubers of the EE of the species *A. indica* L., an application has been found regarding changes in the estrous cycle in vivo with a dose of 150 mg/kg of extract [113]. The compounds involved in the effect of the extract were not shown.

2.4.2. Antidiabetic Potential

From the EE of roots of *A. ringens* Vahl., aristolone was identified and it was shown to have an antidiabetic potential in rats at concentrations of 300–75 mg/kg, so this part of the plant could be used in decoctions for the treatment of diabetes with the approval of more relevant studies [125].

2.4.3. Antifibrotic Activity

The compounds (+)-*iso*-bicyclogermacrenal and spatulenol (3.0×10^{-5} M) present in the ethyl acetate extract (EAE) of *A. yunnanensis* Franch. stems were responsible for promoting antifibrotic concentration effects in vivo [116]. However, the concentrations in which the pure compound was handled under in vivo conditions turned out to be high for antifibrotic activity. The genus *Aristolochia* has extensive traditional and pharmacological uses in various pathological conditions. Therefore, it is an attractive subject for future clinical and experimental research.

2.4.4. Anti-Inflammatory Activity

In particular, in *A. krisagathra* Sivar. & Pradeep., studies of EE of the whole plant have been carried out. An anti-inflammatory activity of 87.1% was obtained with a dose of 400 mg/kg in rats. The compounds that could act in biological activity are alkaloid, anthraquinone, coumarin, flavonoid, phenol, quinone, saponin, steroid, tannin, terpenoid, sugar, glycoside, and xanthoprotein [95].

The anti-inflammatory activity of (−)-hinokinin in tumor necrosis factor-α (TNF-α) IC_{50} = 0.0775 M and interleukin-6 (IL-6) IC_{50} = 0.0205 M and aristolactam I (TNF-α; IC_{50} = 0.1168 M, IL-6; IC_{50} = 0.0520 M) of *A. indica* L. in aerial parts of the DCME and EAE, respectively [22]. In in vivo and in vitro studies, doses greater than 200 mg/kg are not usually recommended, as well as values in pure compounds > 2.5×10^{-5} M [133,139].

2.4.5. Snake Anti-Venom Activity

The hexanic extract from the roots of *A. elegans* Mast. was subjected to an inhibition assay of smooth muscle contraction induced by scorpion venom (*Centruroides limpidus limpidus*) in an isolated guinea pig ileum model with an inhibition of 41.66% (0.4 mg/mL), whose effects are related to neolignan-type compounds [84]. On the other hand, in vivo studies in albino mice using a ME from the whole plant of the species *A. indica* L. demonstrated neutralization against *Daboia russelli* venom at a dose of 0.14 mg. However, no mention is made of the metabolites responsible for the activity [90].

Compounds obtained from polar extracts, especially aristolochic acids, as mentioned above, are not considered safe compounds according to the International Agency for Research on Cancer (WHO), due to their carcinogenic effects. Despite developing these problems, they can be oriented towards their possible use as antivenoms. Likewise, the presence of aristolochic acids, aristolactams, and their derivatives can be used as chemotaxonomic markers in species of the genus *Aristolochia* [22,136,140].

2.4.6. Cancer Treatment

The AE of *A. longa* L. roots (5000 mg/kg) did not show hepatic and renal toxicity in a preclinical assay by oral administration in rats. More studies are warranted on its possible use in breast cancer therapy. The possible compounds responsible for the beneficial activity could be the flavonols, flavones, and/or flavonoid glycosides identified in the extract [50]. In addition to the bioactive compounds mentioned above, the amount of lectin in *A. longa* L. extracts was not favorable for potential cancer treatment in an in vitro immunological activity assay [141]. The use of AE of *A. longa* L. rhizomes as in vivo anticancer treatment in gingival tumorigenesis caused tissue damage as well as pulmonary and toxicity problems. This could be due to the presence of aristolochic acids in the extract [52]. In a preclinical assay against S-180 solid tumors from BALB/c mice, *A. ringens* Vahl. roots from extracts of EE (120 mg/kg) and DCME:ME (110 mg/kg) produced a significant value ($p < 0.05$) in tumor growth over a period of 9–13 days compared to control models. However, the characterization of the polar and moderately polar extracts lacked phytochemical information [31].

3. Materials and Methods

A total of 141 publications were included in this review. SciFinder and EBSCO were used to search for articles that analyzed the beneficial effects of *Aristolochia* in the period from 2005 to 2021. Eighty-eight different species of *Aristolochia* were considered and reviewed by International Plant Names Index and World Flora Online. The inclusion criteria that were retained included: phytochemicals, *Aristolochia*, beneficial effects, extract, pharmacology, and ethnomedicinal. Articles were excluded based on the following criteria: articles that did not address the intervention, articles without adequate *Aristolochia* species theoretical foundations, and articles that did not include *Aristolochia* species.

4. Conclusions

The review in the literature about biological activities allowed identifying studies of different species of the genus *Aristolochia* highlighting phytochemical and pharmacological aspects, and their possible clinical applications. In the roots and leaves, a greater number of beneficial effects were found. From this review, it is concluded that the information detailed the relevant species of the genus *Aristolochia* as promising candidates for natural uses in human health of greater relevance in extracts and pure compounds in anticancer activities. More selective studies are suggested in terms of concentration parameters as well as clinical studies for higher quality.

Author Contributions: Conceptualization, M.A.L.-H., L.B.-G. and H.A.G.-G.; writing—original draft preparation, M.A.L.-H. and H.A.G.-G.; writing—review and editing, L.B.-G., A.O.-Z., J.E.L.-M., P.N.-S., R.H.-B. and J.A.-V. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by CIC-UMSNH and CONACYT-México (Grant Nos. A1-S-47352 and 287210).

Acknowledgments: We thank CIC-UMSNH and CONACYT-México (Grant Nos. A1-S-47352 and 287210) for partial financial support. M.A.L.-H. is grateful to CONACYT-México for the scholarship (722997). We are grateful to Bryan L. Fourman, for revision of manuscript.

Conflicts of Interest: The authors declare that there are no conflict of interest.

References

1. Wagner, S.T.; Hesse, L.; Isnard, S.; Samain, M.-S.; Bolin, J.; Maass, E.; Neinhuis, C.; Rowe, N.P.; Wanke, S. Major trends in stem anatomy and growth forms in the perianth-bearing piperales, with special focus on *Aristolochia*. *Ann. Bot.* **2014**, *113*, 1139–1154. [CrossRef] [PubMed]
2. Xin-Xin, Z.; Guo-Bin, J.; Xin-Xin, Z.; Zi-Yue, L.; Yi, H.; Gang-Tao, W.; Rui-Jiang, W. *Isotrema plagiostomum* (Aristolochiaceae), a new species from Guangdong, South China. *Phytotaxa* **2019**, *405*, 221. [CrossRef]
3. Jun-Ho, S.; Yang, S.; Choi, G. Taxonomic implications of leaf micromorphology using microscopic analysis: A tool for identification and authentication of korean piperales. *Plants* **2020**, *9*, 566. [CrossRef]

4. Zhou, J.; Chen, X.; Cui, Y.; Sun, W.; Li, Y.; Wang, Y.; Song, J.; Yao, H. Molecular structure and phylogenetic analyses of complete chloroplast genomes of two *Aristolochia* medicinal species. *Int. J. Mol. Sci.* **2017**, *18*, 1839. [CrossRef] [PubMed]
5. Gonzalez, F.; Pabón Mora, N. Sinopsis actualizada de *Aristolochia* (Aristolochiaceae, Piperales) en Panamá. *Acta Bot Mex.* **2018**, *122*, 109–140. [CrossRef]
6. Ping-Chung, K.; Yue-Chiun, L.; Tian-Shung, W. Chemical constituents and pharmacology of the *Aristolochia* (馬兜鈴 Mădōu Ling) species. *J. Tradit. Complement. Med.* **2012**, *2*, 249–266. [CrossRef]
7. Heinrich, M.; Chan, J.; Wanke, S.; Neinhuis, C.; Simmonds, M.S.J. Local uses of *Aristolochia* species and content of nephrotoxic aristolochic acid 1 and 2—A global assessment based on bibliographic sources. *J. Ethnopharmacol.* **2009**, *125*, 108–144. [CrossRef]
8. Jeude, S.E.; Fordyce, J.A. The effects of qualitative and quantitative variation of aristolochic acids on preference and performance of a generalist herbivore. *Entomol. Exp. Appl.* **2014**, *150*, 232–239. [CrossRef]
9. Pacheco, A.G.; Machado de Oliveira, P.; Piló-Veloso, D.; Flávio de Carvalho Alcântara, A. ^{13}C-NMR data of diterpenes isolated from *Aristolochia* species. *Molecules* **2009**, *14*, 1245–1262. [CrossRef]
10. Santana-Michel, F.J. Una especie nueva de *Aristolochia* L., subsección Pentandrae (Aristolochiaceae) de la reserva de la biosfera sierra de Manantlán, Jalisco, México. *Acta Bot. Mex.* **2007**, *79*, 81–87. [CrossRef]
11. Santana-Michel, F.J.; Solís-Magallanes, J.A. *Aristolochia emiliae* (Aristolochiaceae: Subsección Pentandrae), Una especie nueva de la costa de Jalisco, México. *Acta Bot. Mex.* **2008**, *82*, 7–13. [CrossRef]
12. Paizanni-Guillén, A.; Michel, F.J.S.; Amezcua, J.M.R.; Wagner, S.T.; Müller, S.; Castro, J.C.M.; Wanke, S.; Samain, M.-S. Four new species of *Aristolochia* subsection *Pentandrae* from Western Mexico. *Syst. Bot.* **2016**, *41*, 128–141. [CrossRef]
13. Santana-Michel, F.J. *Aristolochia rzedowskiana* (Aristolochiaceae), una especie nueva para la subsección Pentandrae del estado de Jalisco, México. *Acta Bot. Mex.* **2014**, *106*, 1–7. [CrossRef]
14. Santana-Michel, F.J.; Cuevas-Guzmán, R.; Sánchez-Rodríguez, E.V.; Morales-Arias, J.G. *Aristolochia purhepecha* (Aristolochiaceae: Subsección Pentandrae) una especie nueva de Michoacán, México. *Rev. Mex. Biodivers.* **2017**, *88*, 519–523. [CrossRef]
15. Paizanni-Guillén, A.; Santana-Michel, F.J. *Familia Aristolochiaceae*; Flora Del Bajío y de Regiones Adyacentes: Pátzcuaro, Michoacán, México, 2018. [CrossRef]
16. Al-Barham, M.B.; Al-Jaber, H.I.; Al-Qudah, M.A.; Abu Zarga, M.H. New aristolochic acid and other chemical constituents of *Aristolochia maurorum* growing wild in Jordan. *Nat. Prod. Res.* **2017**, *31*, 245–252. [CrossRef] [PubMed]
17. Dharmalingam, S.; Madhappan, R.; Ramamurthy, S.; Chidambaram, K.; Srikanth, M.; Shanmugham, S.; Kumar, S. Investigation on antidiarrhoeal activity of *Aristolochia indica* Linn. root extracts in mice. *Afr. J. Tradit. Complement. Altern. Med.* **2014**, *11*, 292. [CrossRef]
18. Sartorelli, P.; Salomone Carvalho, C.; Quero Reimão, J.; Lorenzi, H.; Tempone, A. Antitrypanosomal activity of a diterpene and lignans isolated from *Aristolochia cymbifera*. *Planta Med.* **2010**, *76*, 1454–1456. [CrossRef]
19. Dias, D.A.; Urban, S.; Roessner, U. A historical overview of natural products in drug discovery. *Metabolites* **2012**, *2*, 303–336. [CrossRef]
20. Fregene, A.; Newman, L.A. Breast cancer in sub-Saharan Africa: How does it relate to breast cancer in African-American women? *Cancer* **2005**, *103*, 1540–1550. [CrossRef]
21. Mathew, L.S.; Mtewa, A.G.; Ajayi, C.O.; Deyno, S.; Weisheit, A.; Tolo, C.U.; Deng, A.L.; Engeu Ogwang, P. Ethnopharmacology, pharmacology and phytochemistry of *Aristolochia bracteolata* Lam: A review of an antimalarial plant. *East Afr. Sci.* **2020**, *2*, 22–28. [CrossRef]
22. Padhy, G.K. A review of *Aristolochia indica*: Ethnomedicinal uses, phytochemistry, pharmacological and toxicological effects. *Curr. Tradit. Med.* **2021**, *7*, 372–386. [CrossRef]
23. Aneb, M.; Talbaoui, A.; Bouyahya, A.; Boury, H.; Amzazi, S.; Benjouad, A.; Dakka, N.; Bakri, Y. In vitro cytotoxic effects and antibacterial activity of Moroccan medicinal plants *Aristolochia longa* and *Lavandula multifida*. *Eur. J. Med. Plants* **2016**, *16*, 1–13. [CrossRef]
24. Lerma-Herrera, M.A.; Beiza-Granados, L.; Ochoa-Zarzosa, A.; López-Meza, J.E.; Hernández-Hernández, J.D.; Aviña-Verduzco, J.; García-Gutiérrez, H.A. In vitro cytotoxic potential of extracts from *Aristolochia foetida* Kunth against MCF-7 and bMECs cell lines. *Saudi J. Biol. Sci.* **2021**, *28*, 7082–7089. [CrossRef] [PubMed]
25. Idrissi, A.Y.; Khouchlaa, A.; Bouyahya, A.; Bakri, Y.; Tijane, Y.B.M. Phytochemical characterization, in vitro antioxidant, cytotoxic, and antibacterial effects of *Aristolochia longa* L. *Biointerface Res. Appl. Chem.* **2020**, *11*, 8129–8140. [CrossRef]
26. Chaouki, W.; Leger, D.Y.; Eljastimi, J.; Beneytout, J.-L.; Hmamouchi, M. Antiproliferative effect of extracts from *Aristolochia baetica* and *Origanum compactum* on human breast cancer cell line MCF-7. *Pharm. Biol.* **2010**, *48*, 269–274. [CrossRef]
27. Subramaniyan, V.; Saravanan, R.; Baskaran, D.; Ramalalingam, S. In vitro free radical scavenging and anticancer potential of *Aristolochia indica* L. against MCF-7 cell line. *Int. J. Pharm.* **2015**, *7*, 392–396.
28. Owolabi, M.S.; Omowonuola, A.; Lawal, O.A.; Dosoky, N.S.; Collins, J.T.; Ogungbe, I.V.; Setzer, W.N. Phytochemical and bioactivity screening of six Nigerian medicinal plants. *Int. J. Pharmacogn. Phytochem.* **2017**, *6*, 1430–1437.
29. Xiao-dan, S.; Yang, G.; Ying-Xin, X.; Peng-Xiang, L.; Xiang, X. Chemical composition and biological activities of the essential oil from *Aristolochia fordiana* Hemsl. *Rec. Nat. Prod.* **2019**, *13*, 346–354. [CrossRef]
30. Yu, J.Q.; Liao, Z.X.; Cai, X.Q.; Lei, J.C.; Zou, G.L. Composition, antimicrobial activity and cytotoxicity of essential oils from *Aristolochia mollissima*. *Environ. Toxicol. Pharmacol.* **2007**, *23*, 162–167. [CrossRef]

31. Akindele, A.J.; Wani, Z.; Mahajan, G.; Sharma, S.; Aigbe, F.R.; Satti, N.; Adeyemi, O.O.; Mondhe, D.M. Anticancer activity of *Aristolochia ringens* Vahl. (Aristolochiaceae). *J. Tradit. Complement. Med.* **2015**, *5*, 35–41. [CrossRef]
32. Abd El-Hafeez, A.A.; Khalifa, H.O.; Elgawish, R.A.; Shouman, S.A.; Abd El-Twab, M.H.; Kawamoto, S. *Melilotus indicus* extract induces apoptosis in hepatocellular carcinoma cells via a mechanism involving mitochondria-mediated pathways. *Cytotechnology* **2018**, *70*, 831–842. [CrossRef] [PubMed]
33. Bourhia, M.; Laasri, F.E.; Moussa, S.I.; Ullah, R.; Bari, A.; Saeed Ali, S.; Kaoutar, A.; Haj Said, A.A.; El Mzibri, M.; Said, G.; et al. Phytochemistry, antioxidant activity, antiproliferative effect, and acute toxicity testing of two Moroccan *Aristolochia* Species. *Evid. Based Complement. Altern. Med.* **2019**, *2019*, 9710876. [CrossRef] [PubMed]
34. Taha, M.; Parveen, B.; Osman, B.; Abdoon, I.H.; Mohamed, M.S.; Osman, W.J.A.; Ahmad, S. In vitro profiling of plants used in sudanese traditional medicine for antioxidant and anti-breast cancer activities. *Ann. Phytomed. Int. J.* **2019**, *8*, 119–126. [CrossRef]
35. Truong, L.H.; Cuong, N.H.; Dang, T.H.; Hanh, N.T.M.; Thi, V.L.; Tran Thi Hong, H.; Tran Hong, Q.; Nguyen, H.D.; Nguyen Xuan, C.; Nguyen Hoai, N.; et al. Cytotoxic Constituents from *Isotrema tadungense*. *J. Asian Nat. Prod. Res.* **2020**, *23*, 491–497. [CrossRef] [PubMed]
36. Xin, W.; Guo-Ru, S.; Yan-Fei, L.; Li, L.; Ruo-Yun, C.; De-Quan, Y. Aristolochic acid derivatives from the rhizome of *Arisolochia championii*. *Fitoterapia* **2017**, *118*, 63–68. [CrossRef]
37. Zhong-bo, Z.; Jian-guang, L.; Ke, P.; Si-ming, S.; Wei, Z.; Ling-yi, K. Bioactive benzofuran neolignans from *Aristolochia fordiana*. *Planta Med.* **2013**, *79*, 1730–1735. [CrossRef]
38. Aleixo, Á.A.; Vidyleison, N.C.; dos Santos Pereira Andrade, A.C.; Marjorie, K.; Herrera, S.; Iara, R.; Ribeiro, M.; Magalhães Rodrigues, L.A.; Ferreira, J.M. Antibacterial and cytotoxic antibacterial potential of ethanol extract and fractions from *Aristolochia galeata* Mart. Ex Zucc. *J. Med. Plants Res.* **2014**, *8*, 326–330. [CrossRef]
39. Jiménez-Arellanes, A.; León-Díaz, R.; Meckes, M.; Tapia, A.; Molina-Salinas, G.M.; Luna-Herrera, J.; Yépez-Mulia, L. Antiprotozoal and antimycobacterial activities of pure compounds from *Aristolochia elegans* rhizomes. *Evid.-Based Complement. Altern. Med.* **2012**, *2012*, 593403. [CrossRef]
40. Borah, P.J.; Borah, D.; Das, U.; Das, T.J.; Sarma, R. A review on ethnopharmacological utility, traditional knowledge and phytochemistry of *Aristolochia* species in Assam, India. *Not. Sci. Biol.* **2021**, *13*, 11027. [CrossRef]
41. Chunmei, L.; Myeong-Hyeon, W. *Aristolochia debilis* Sieb. *et* Zucc. induces apoptosis and reactive oxygen species in the HT-29 human colon cancer cell line. *Cancer Biother. Radiopharm.* **2013**, *28*, 717–724. [CrossRef]
42. Cai, Y.; Cai, T.-G. Two new aristolochic acid derivatives from the roots of *Aristolochia fangchi* and their cytotoxicities. *Chem. Pharm. Bull.* **2010**, *58*, 1093–1095. [CrossRef] [PubMed]
43. Kangralkar, V.A.; Kulkami, A.R. In vitro cytotoxic activity of alcoholic extract of *Aristolochia indica*. *Res. J. Pharm. Technol.* **2013**, *6*, 1240–1241.
44. Yu, Y.; Bo, Z.; Chao, H.; Minghua, Z. A study on the anticancer activity of ethanol extract of *Aristolochia mollissima* hance on osteosarcoma HOS cells. *Afr. J. Tradit. Complement. Altern. Med.* **2013**, *10*, 551. [CrossRef] [PubMed]
45. Mazadu, E.A.; Misau, M.S.; Gwallameji, L.B. Phytochemical screening and antimicrobial activity of some medicinal trees grown in Bauchi state, north eastern, Nigeria. *Int. J. Pharmacogn. Phytochem.* **2018**, *7*, 3503–3507.
46. Hadem, K.H.; Sharan, R.; Kma, L. Phytochemicals of *Aristolochia tagala* and *Curcuma caesia* exert anticancer effect by tumor necrosis factor-α-mediated decrease in nuclear factor kappaB binding activity. *J. Basic Clin. Pharm.* **2016**, *7*, 1. [CrossRef]
47. Hynniewta-Hadem, K.L.; Sharan, R.N.; Kma, L. Inhibitory potential of methanolic extracts of *Aristolochia tagala* and *Curcuma caesia* on hepatocellular carcinoma induced by diethylnitrosamine in BALB/c mice. *J. Carcinog.* **2014**, *30*, 13–17. [CrossRef]
48. Rajani, M.B.; Raviraja, S.G.; Pooja, D.A. A review on medicinal uses, pharmacology and phytochemistry of *Aristolochia tagala* Cham. An endangered medicinal plant. *J. Pharmacogn. Phytochem.* **2020**, *9*, 580–583.
49. Oliveira, S.Q.; Kratz, J.M.; Chaves, V.C.; Guimarães, T.R.; Costa, D.T.M.; Dimitrakoudi, S.; Vontzalidou, A.; Bordignon, S.A.L.; Simionato, C.P.; Steindel, M.; et al. Chemical constituents and pharmacology properties of *Aristolochia triangularis*: A south Brazilian highly-consumed botanical with multiple bioactivities. *An. Acad. Bras. Ciênc.* **2019**, *91*, e20180621. [CrossRef]
50. Benarba, B.; Pandiella, A.; Elmallah, A. Anticancer activity, phytochemical screening and acute toxicity evaluation of an aqueous extract of *Aristolochia longa* L. *Int. J. Pharm. Phytopharm. Res.* **2017**, *6*, 20. [CrossRef]
51. Gadouche, L.; Zidane, A.; Zerrouki, K.; Azouni, K.; Bouinoune, S. Cytotoxic Effect of *Myrtus communis*, *Aristolochia longa*, and *Calycotome spinosa* on human erythrocyte cells. *Foods Raw Mater.* **2021**, *9*, 379–386. [CrossRef]
52. Benzakour, G.; Amrani, M.; Oudghiri, M. A histopathological analyses of in vivo anti-tumor effect of an aqueous extract of *Aristolochia longa* used in cancer treatment in traditional medicine in Morocco. *Int. J. Plant Res.* **2012**, *2*, 31–35. [CrossRef]
53. Alali, F.Q.; Tawaha, K.; Shehadeh, M.B.; Telfah, S. Phytochemical and biological investigation of *Aristolochia maurorum* L. *Z. Nat. C* **2006**, *61*, 685–691. [CrossRef]
54. Mohanraj, R.; Patil, A.; Rathore, M.; Nobre, M. Anti HIV-1 and anti-bacterial activities of the leaf extracts of *Aristolochia elegans*. *J. Trop. Med. Plants* **2009**, *10*, 9–12.
55. Arellanes, M.A.J.; Cortés, N.R.R.; García, I. Antioxidant and antimicrobial activities of hexane extracts and pure compounds from *Aristolochia taliscana* rhizome. *Rev. Mex. Cienc. Farm.* **2011**, *42*, 35–41.
56. León-Díaz, R.; Meckes-Fischer, M.; Valdovinos-Martínez, L.; Campos, M.G.; Hernández-Pando, R.; Jiménez-Arellanes, M.A. Antitubercular activity and the subacute toxicity of (−)-Licarin A in BALB/c mice: A neolignan isolated from *Aristolochia taliscana*. *Arch. Med. Res.* **2013**, *44*, 99–104. [CrossRef] [PubMed]

57. Salinas Ibáñez, A.G.; Arismendi Sosa, A.C.; Ferramola, F.F.; Paredes, J.; Wendel, G.; Maria, A.O.; Vega, A.E. Inhibition of *Helicobacter pylori* and its associated urease by two regional plants of San Luis Argentina. *Int. J. Curr. Microbiol. Appl. Sci.* **2017**, *6*, 2097–2106. [CrossRef]
58. França, V.C.; Vieira, K.V.M.; Lima, E.O.; Barbosa-Filho, J.M.; da-Cunha, E.V.L.; Silva, M.S. da Estudo fitoquímico das partes aéreas de *Aristolochia birostris* Ducht. (Aristolochiaceae). *Rev. Bras. Farmacogn.* **2005**, *15*, 326–330. [CrossRef]
59. Angalaparameswari, S.; Saleem, T.S.M.; Alagusundaram, M.; Ramkanth, S.; Thiruvengadarajan, V.S.; Gnanaprakash, K.; Chetty, C.M.; Pratheesh, G. Anti-microbial activity of aristolochic acid from root of *Aristolochia bracteata* Retz. *Int. J. Med. Med. Health Sci.* **2011**, *5*, 462–464.
60. Gómez-Cansino, R.; Guzmán-Gutiérrez, S.L.; Campos-Lara, M.G.; Espitia-Pinzón, C.I.; Reyes-Chilpa, R. Natural compounds from Mexican medicinal plants as potential drug leads for anti-tuberculosis drugs. *An. Acad. Bras. Ciênc.* **2017**, *89*, 31–43. [CrossRef]
61. Ozen, T.; Bora, N.; Yenigun, S.; Korkmaz, H. An investigation of chemical content, enzyme inhibitory propert, antioxidant and antibacterial activity of *Aristolochia bodamae* Dingler (Develiotu) (Aristolochiaceae) root extracts from Samsun, Turkey. *Flavour Fragr. J.* **2020**, *35*, 270–283. [CrossRef]
62. Abbouyi, A.E.; Maliki, S.E.; Filali-Ansari, N.; Khyari, S.E. Antibacterial and antifungal activities of rhizomes extract from *Aristolochia clematitis*. *Int. J. Pharm. Chem. Biol. Sci.* **2016**, *6*, 72–75.
63. Zhi-Jian, L.; Guy, S.S.N.; Wen-Jia, H.; Hong-Xia, Z.; Jian-Long, G.; Shan-Na, C.; Zhi-Zhi, D. Chemical composition and antimicrobial activity of the essential oil from the edible aromatic plant *Aristolochia delavayi*. *Chem. Biodivers.* **2013**, *10*, 2032–2041. [CrossRef]
64. Pacheco, A.G.; Silva, T.M.; Manfrini, R.M.; Sallum, W.S.T.; Duarte, L.P.; Piló-Veloso, D.; Alcântara, A.F.C.; Knupp, V.F. Estudo químico e atividade antibacteriana do caule de *Aristolochia esperanzae* Kuntze (Aristolochiaceae). *Quím. Nova.* **2010**, *33*, 1649–1652. [CrossRef]
65. Botelho-Filho, C.R.; Izumi, G.K.; Vieira, J.C.; Palva-Bertoil, F.M.; Ricomini-Filho, A.P.; Maranho, L.T.; Baratto-Filho, F.; Leão-Gabardo, M.C. Anatomical description and in vitro evaluation of the antibacterial potential of *Aristolochia esperanzae* Kuntze (Aristolochiaceae) extract on oral micro-organisms. *Phcog. Res.* **2020**, *12*, 424. [CrossRef]
66. Pugazharasi, G.; Christy, R.; Jaganathan, J.; Shree Devi, M.S.; Karthik, L. A novel approach on herbal water to reduce water contaminant *Salmonella typhi*—An in vitro study. *Malaya J. Biosci.* **2015**, *2*, 166–176.
67. Murugan, M.; Mohan, V.R. Efficacy of different solvent extracts of *Vitex trifolia* L. and *Aristolochia indica* L. for potential antibacterial activity. *Sci. Res. Rep.* **2012**, *2*, 110–114.
68. Venkatadri, B.; Arunagirinathan, N.; Rameshkumar, M.R.; Ramesh, L.; Dhanasezhian, A.; Agastian, P. In vitro antibacterial activity of aqueous and ethanol extracts of *Aristolochia indica* and *Toddalia asiatica* against multidrug-resistant bacteria. *Indian J. Pharm. Sci.* **2015**, *77*, 788–791. [CrossRef]
69. Dhouioui, M.; Boulila, A.; Jemli, M.; Schiets, F.; Casabianca, H.; Zina, M.S. Fatty acids composition and antibacterial activity of *Aristolochia longa* L. and *Bryonia dioïca* Jacq. growing wild in Tunisia. *J. Oleo Sci.* **2016**, *65*, 655–661. [CrossRef]
70. Merouani, N.; Belhattab, R.; Sahli, F. Evaluation of the biological activity of *Aristolochia longa* L. extracts. *Int. J. Pharm. Sci.* **2017**, *8*, 15.
71. Zazharskyi, V.V.; Davydenko, P.O.; Kulishenko, O.M.; Borovik, I.V.; Zazharska, N.M.; Brygadyrenko, V.V. Antibacterial and fungicidal activities of ethanol extracts of 38 species of plants. *Biosyst. Divers.* **2020**, *28*, 281–289. [CrossRef]
72. Rios, M.Y.; Navarro, V.; Ramírez-Cisneros, M.Á.; Salazar-Rios, E. Sulfur-containing aristoloxazines and other constituents of the roots of *Aristolochia orbicularis*. *J. Nat. Prod.* **2017**, *80*, 3112–3119. [CrossRef] [PubMed]
73. Eltayeb, I.M.; Nari, F.H.M. Phytochemical screening, antioxidant and antimicrobial activities of some sudanese medicinal plants against standard and isolated microorganisms. *Int. J. Pharmacogn. Phytochem.* **2017**, *6*, 97–100.
74. Hoi, T.M.; Dai, D.N.; Ha, C.T.T.; Anh, H.V.; Ogunwande, I.A. Essential oil constituents from the leaves of *Anoectochilus setaceus*, *Codonopsis javanica* and *Aristolochia kwangsiensis* from Vietnam. *Rec. Nat. Prod.* **2019**, *13*, 281–286. [CrossRef]
75. Vahekeni, N.; Neto, P.M.; Kayimbo, M.K.; Mäser, P.; Josenando, T.; da Costa, E.; Falquet, J.; van Eeuwijk, P. Use of herbal remedies in the management of sleeping sickness in four northern provinces of Angola. *J. Ethnopharmacol.* **2020**, *256*, 112382. [CrossRef]
76. Navarro-García, V.M.; Luna-Herrera, J.; Rojas-Bribiesca, M.G.; Álvarez-Fitz, P.; Ríos, M.Y. Antibacterial activity of *Aristolochia brevipes* against multidrug-resistant *Mycobacterium tuberculosis*. *Molecules* **2011**, *16*, 7357–7364. [CrossRef]
77. Borneo, R.; León, A.E.; Aguirre, A.; Ribotta, P.; Cantero, J.J. Antioxidant capacity of medicinal plants from the province of Córdoba (Argentina) and their in vitro testing in a model food system. *Food Chem.* **2009**, *112*, 664–670. [CrossRef]
78. Jegadeeswari, P.; Daffodil, E.; Mohan, V.R. Quantification of total phenolics, flavonoid and in vitro antioxidant activity of *Aristolochia bracteata* Retz. *Int. J. Pharm. Pharm.* **2014**, *6*, 747–752.
79. Papuc, C.; Crivineanu, M.; Goran, G.; Nicorescu, V.; Durdun, N. Free radicals scavenging and antioxidant activity of european mistletoe (Viscum Album) and European birthwort (*Aristolochia clematitis*). *Rev. Chim.* **2010**, *61*, 619–622.
80. El Omari, N.; Sayah, K.; Fettach, S.; El Blidi, O.; Bouyahya, A.; Faouzi, M.E.A.; Kamal, R.; Barkiyou, M. Evaluation of in vitro antioxidant and antidiabetic activities of *Aristolochia longa* extracts. *Evid. Based Complement. Altern. Med.* **2019**, *2019*, 7384735. [CrossRef]
81. Dade, M.M.; Fioravanti, D.E.; Schinella, G.R.; Tournier, H.A. Total antioxidant capacity and polyphenol content of 21 aqueous extracts obtained from native plants of Traslasierra valley (Argentina). *Boletín Latinoam. Caribe Plantas Med. Aromát.* **2009**, *8*, 529–539.

82. Sulyman, A.O.; Akolade, J.O.; Aladodo, R.A.; Ibrahim, R.B.; Na'Allah, A.; Abdulazeez, A.T. *Aristolochia ringens* extract ameliorates oxidative stress and dyslipidaemia associated with streptozotocin-induced hyperglycaemia in rats. *J. Ethnopharmacol.* **2018**, *182*, 122–128. [CrossRef] [PubMed]
83. Usman, H.S.; Sallau, A.B.; Salihu, A.; Nok, A.J. Larvicidal assessment of fractions of *Aristolochia albida* rhizome on culex quinquefasciatus. *Trop. J. Nat. Prod. Res.* **2018**, *2*, 227–234. [CrossRef]
84. Zamilpa, A.; Abarca-Vargas, R.; Ventura-Zapata, E.; Osuna-Torres, L.; Zavala, M.A.; Herrera-Ruiz, M.; Jiménez-Ferrer, E.; González-Cortazar, M. Neolignans from *Aristolochia elegans* as antagonists of the neurotropic effect of scorpion venom. *J. Ethnopharmacol.* **2014**, *157*, 156–160. [CrossRef] [PubMed]
85. Alonso-Castro, A.J.; Domínguez, F.; Ruiz-Padilla, A.J.; Campos-Xolalpa, N.; Zapata-Morales, J.R.; Carranza-Alvarez, C.; Maldonado-Miranda, J.J. Medicinal plants from North and Central America and the Caribbean considered toxic for humans: The other side of the coin. *Evid.-Based Complment. Altern. Med.* **2017**, *2017*, 9439868. [CrossRef]
86. Naz, R.; Ayub, H.; Nawaz, S.; Islam, Z.U.; Yasmin, T.; Bano, A.; Wakeel, A.; Zia, S.; Roberts, T.H. Antimicrobial activity, toxicity and anti-inflammatory potential of methanolic extracts of four ethnomedicinal plant species from Punjab, Pakistan. *BMC Complement. Altern. Med.* **2017**, *17*, 302. [CrossRef]
87. Samy, R.P.; Thwin, M.M.; Gopalakrishnakone, P.; Ignacimuthu, S. Ethnobotanical survey of folk plants for the treatment of snakebites in southern part of Tamilnadu, India. *J. Ethnopharmacol.* **2008**, *115*, 302–312. [CrossRef]
88. Usubillaga, A.; Khouri, N.; Cedillo-Vaz, S.; Yibirin, E. Anti-snake venom effect of *Aristolochia odoratissima* L. aqueous extract on mice. *Acta Hortic.* **2005**, *3*, 85–89. [CrossRef]
89. Wu, T.-S.; Damu, A.G.; Kuo, P.-C. Chemical constituents and pharmacology of *Aristolochia* species. *Stud. Nat. Prod. Chem.* **2005**, *32*, 855–1018. [CrossRef]
90. Meenatchisundaram, S.; Parameswari, G.; Michael, A. Studies on antivenom activity of *Andrographis paniculata* and *Aristolochia indica* plant extracts against *Daboia russelli* venom by in vivo and in vitro methods. *Indian J. Sci. Technol.* **2009**, *2*, 76–79. [CrossRef]
91. Girija, D.M.; Kalachaveedu, M.; Subbarayan, R.; Jenifer, P.; Rao, S.R. *Aristolochia bracteolata* enhances wound healing in vitro through anti-inflammatory and proliferative effect on human dermal fibroblasts and keratinocytes. *Pharmacogn. J.* **2017**, *9*, s129–s136. [CrossRef]
92. Wang, X.; Jin, M.; Jin, C.; Sun, J.; Zhou, W.; Li, G. A new sesquiterpene, a new monoterpene and other constituents with anti-inflammatory activities from the roots of *Aristolochia debilis*. *Nat. Prod. Res.* **2020**, *34*, 351–358. [CrossRef] [PubMed]
93. Chung, Y.-M.; Chang, F.-R.; Tseng, T.-F.; Hwang, T.-L.; Chen, L.-C.; Wu, S.-F.; Lee, C.-L.; Lin, Z.-Y.; Chuang, L.-Y.; Su, J.-H.; et al. A novel alkaloid, aristopyridinone A and anti-inflammatory phenanthrenes isolated from *Aristolochia manshuriensis*. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1792–1794. [CrossRef] [PubMed]
94. Salomé, D.C.; Cordeiro, N.; Valério, T.S.; Santos, D.; Alves, P.B.; Alviano, C.S.; Moreno, D.S.A.; Fernandes, P.D. *Aristolochia trilobata*: Identification of the anti-inflammatory and antinociceptive effects. *Biomedicines* **2020**, *8*, 111. [CrossRef] [PubMed]
95. Paulpriya, K.; Tresina, P.S.; Mohan, V.R. Investigation of anti-inflammatory activity of *Aristolochia krisagathra* Sivarajan and Pradeep. *Int. J. Pharm.* **2016**, *5*, 132–135.
96. Bamisaye, F.A.; Sulyman, A.O.; Ibrahim, R.B.; Yusuf, B.L. Antidiarrhoeal activities of ethanolic extract of *Aristolochia ringens* stem bark in castor oil-induced diarrhoeal albino rats. *Fountain J. Nat. Appl. Sci.* **2018**, *7*, 20–28.
97. Zhang, G.; Shimokawa, S.; Mochizuki, M.; Kumamoto, T.; Nakanishi, W.; Watanabe, T.; Ishikawa, T.; Matsumoto, K.; Tashima, K.; Horie, S.; et al. Chemical constituents of *Aristolochia constricta*: Antispasmodic effects of its constituents in guinea-pig ileum and isolation of a diterpeno−lignan hybrid. *J. Nat. Prod.* **2008**, *71*, 1167–1172. [CrossRef]
98. Bolla, S.R.; Mohammed Al-Subaie, A.; Yousuf Al-Jindan, R.; Papayya Balakrishna, J.; Kanchi Ravi, P.; Veeraraghavan, V.P.; Arumugam Pillai, A.; Gollapalli, S.S.R.; Palpath Joseph, J.; Surapaneni, K.M. In vitro wound healing potency of methanolic leaf extract of *Aristolochia saccata* is possibly mediated by its stimulatory effect on collagen-1 expression. *Heliyon* **2019**, *5*, e01648. [CrossRef]
99. Pereira, M.; da Silva, T.; Aguiar, A.; Oliva, G.; Guido, R.; Yokoyama-Yasunaka, J.; Uliana, S.; Lopes, L. Chemical composition, antiprotozoal and cytotoxic activities of indole alkaloids and benzofuran neolignan of *Aristolochia cordigera*. *Planta Med.* **2017**, *83*, 912–920. [CrossRef]
100. Koriem, K.M.M.; Shahabudin, R.E.; Jamaludin, R.Z. *Aristolochia gehrtii* inhibits liver toxicity and apoptosis in *Schistosoma malayensis* infection. *Asian Pac. J. Trop. Med.* **2014**, *7*, 685–692. [CrossRef]
101. Miao-Miao, B.; De-Jian, H.; Cun-Zhu, D. Nematicidal activity of chemical compositions from *Aristolochia tuberosa* fruits against root-knot nematode. *Redai Yaredai Zhiwu Xuebao* **2018**, *26*, 197–201.
102. Morais, A.B.B.; Brown, K.S.; Stanton, M.A.; Massuda, K.F.; Trigo, J.R. Are aristolochic acids responsible for the chemical defence of aposematic larvae of *Battus polydamas* (L.) (Lepidoptera: Papilionidae)? *Neotrop. Entomol.* **2013**, *42*, 558–564. [CrossRef] [PubMed]
103. Defagó, M.T.; Nolli, L.; Díaz Napal, G.; Palacios, S.M. Can the extract of *Aristolochia argentina* Griseb. affect the foraging decisions of the leaf cutting ant *Acromyrmex lundi* (Guérin)? Preliminary assays. *Int. J. Pest Manag.* **2017**, *63*, 207–212. [CrossRef]
104. Elamin, M.M.; Satti, A.A. Insecticidal and repellent effects of *Aristolochia bracteolata* Lam. against *Trogoderma granarium* Everts. *Int. J. Sci. Innov. Discov.* **2012**, *2*, 9.
105. Messiano, G.B.; Vieira, L.; Machado, M.B.; Lopes, L.M.X.; de Bortoli, S.A.; Zukerman-Schpector, J. Evaluation of insecticidal activity of diterpenes and lignans from *Aristolochia malmeana* against *Anticarsia gemmatalis*. *J. Agric. Food Chem.* **2008**, *56*, 2655–2659. [CrossRef] [PubMed]

106. De Pascoli, I.; Nascimento, I.; Lopes, L. Configurational analysis of cubebins and bicubebin from *Aristolochia lagesiana* and *Aristolochia pubescens*. *Phytochemistry* **2006**, *67*, 735–742. [CrossRef] [PubMed]
107. Baskar, K.; Sasikumar, S.; Muthu, C.; Kingsley, S.; Ignacimuthu, S. Bioefficacy of *Aristolochia tagala* Cham. against *Spodoptera litura* Fab. (Lepidoptera: Noctuidae). *Saudi J. Biol. Sci.* **2011**, *18*, 23–27. [CrossRef]
108. Das, N.G.; Rabha, B.; Talukdar, P.K.; Goswami, D.; Dhiman, S. Preliminary in vitro antiplasmodial activity of *Aristolochia griffithii* and *Thalictrum foliolosum* DC extracts against malaria parasite *Plasmodium falciparum*. *BMC Res. Notes* **2016**, *9*, 51. [CrossRef]
109. Kazembe, T.; Munyarari, E. Effect of *Aristolochia petersiana* on the efficacy of fansidar. *Cent. Afr. J. Med.* **2006**, *52*, 11–16.
110. Meela, M.M.; Mdee, L.K.; Masoko, P.; Eloff, J.N. Acetone leaf extracts of seven invasive weeds have promising activity against eight important plant fungal pathogens. *S. Afr. J. Bot.* **2019**, *121*, 442–446. [CrossRef]
111. Montiel-Ruiz, R.M.; Córdova-de la Cruz, M.; González-Cortázar, M.; Zamilpa, A.; Gómez-Rivera, A.; López-Rodríguez, R.; Lobato-García, C.E.; Blé-González, E.A. Antinociceptive effect of hinokinin and kaurenoic acid isolated from *Aristolochia odoratissima* L. *Molecules* **2020**, *25*, 1454. [CrossRef]
112. Quintans, J.S.S.; Alves, R.S.; Santos, D.A.; Serafini, M.R.; Alves, P.B.; Costa, E.V.; Zengin, G.; Quintans-Júnior, L.J.; Guimarães, A.G. Antinociceptive effect of *Aristolochia trilobata* stem essential oil and 6-methyl-5-hepten-2yl acetate, its main compound, in rodents. *Z. Nat. C* **2017**, *72*, 93–97. [CrossRef] [PubMed]
113. Dar, N.A.; Mittal, D.K. Effect of Ethanolic extract of *Aristolochia indica* on the oestrous cycle of adult rats. *Int. J. Pharm. Sci. Rev. Res.* **2019**, *57*, 105–107.
114. Abhijit, D.; Jitendra, N.D. *Aristolochia indica* L.: A review. *Asian J. Plant Sci.* **2011**, *10*, 108–116. [CrossRef]
115. Shao, W.; Li, D.; Peng, J.; Chen, S.; Zhou, C.; Cheng, Z.; Yu, Y.; Li, H.; Li, C.; You, Y.; et al. Inhibitory effect of ethyl acetate extract of *Aristolochia yunnanensis* on cardiac fibrosis through extracellular signal-regulated kinases 1/2 and transforming growth factor β/small mother against decapentaplegic signaling pathways. *Transl. Res.* **2014**, *163*, 160–170. [CrossRef] [PubMed]
116. Lan-Lan, L.; Wei, L.; Bin-Hua, Z.; Li, C.; Han-Zhuang, W.; Yin-Hong, Z.; Gui-Hua, T.; Xian-Zhang, B.; Sheng, Y. (+)-Isobicyclogermacrenal and spathulenol from *Aristolochia yunnanensis* alleviate cardiac fibrosis by inhibiting transforming growth factor β/small mother against decapentaplegic signaling pathway: Anti-cardiac fibrosis sesquiterpenoids from *Aristolochia yunnanensis*. *Phytother. Res.* **2019**, *33*, 214–223. [CrossRef]
117. Guinnin, F.D.F.; Sangare, M.M.; Ategbo, J.M.; Sacramento, I.T.; Issotina, Z.A.; Klotoe, J.R.; Attakpa, E. Dramane Evaluation of hepatoprotective and nephroprotective activities of ethanolic extract leaves of *Aristolochia albida* Duch. against CCl_4-induced hepatic and renal dysfunction. *J. Pharm. Biomed. Sci.* **2017**, *7*, 264–269. [CrossRef]
118. Gui-Hua, T.; Zi-Wei, C.; Ting-Ting, L.; Min, T.; Xiao-Yun, G.; Jing-Mei, B.; Zhong-Bin, C.; Zhang-Hua, S.; Gang, H.; Sheng, Y. Neolignans from *Aristolochia fordiana* prevent oxidative stress-induced neuronal death through maintaining the Nrf2/HO-1 pathway in HT22 cells. *J. Nat. Prod.* **2015**, *78*, 1894–1903. [CrossRef]
119. Tresina, P.S.; Paulpriya, K.; Mohan, V.R. Evaluation of antiulcer activity of ethanol extracts of *Aristolochia krisagathra* Sivarajan and Pradeep and *Aristolochia bracteata* Retz. whole plants in experimental rats. *Res. J. Pharm. Biol. Chem. Sci.* **2016**, *7*, 1165–1170.
120. Chitme, H.R.; Malipatil, M.; Chandrashekhar, V.M.; Prashant, P.M. Antiallergic activity of *Aristolochia bracteolata* Lank in animal model. *Indian J. Exp. Biol.* **2010**, *48*, 46–52.
121. Gupta, A.; Prakash, J.; Shinde, B. Immunopharmacological activity of medicinal plants against *Aristolochia bracteolate* and *Phallus impudicus*. *J. Biomed. Pharm. Res.* **2016**, *5*, 9–15.
122. Jenifer, P.; Kalachaveedu, M.; Dinesh, G. Wound healing mechanism by the standardized extracts of *Acalypha indica* and *Aristolochia bracteolata* on human cell lines. *Int. J. Pharm. Biol. Sci.* **2019**, *9*, 450–458.
123. Murugan Girija, D.; Ranga Rao, S.Y.; Kalachaveedu, M.; Subbarayan, R. Osteogenic differentiation of human gingival mesenchymal stem cells by *Aristolochia bracteolata* supplementation through enhanced Runx2 expression. *J. Cell. Physiol.* **2017**, *232*, 1591–1595. [CrossRef] [PubMed]
124. Sivakkumar, S.; Iyswarya, S.; Juliet, L.; Ganapathy, G. A review on ingredients of anti-diabetic siddha preparation *Naaval Kottai Mathirai*. *Int. J. Pharm. Sci. Rev. Res.* **2019**, *55*, 69–76.
125. Sulyman, A.O.; Akolade, J.O.; Sabiu, S.A.; Aladodo, R.A.; Muritala, H.F. Antidiabetic potentials of ethanolic extract of *Aristolochia ringens* (Vahl.) roots. *J. Ethnopharmacol.* **2016**, *182*, 122–128. [CrossRef] [PubMed]
126. Yamauchi, K.; Mitsunaga, T.; Muddathir, A.M. Screening for melanogenesis-controlled agents using sudanese medicinal plants and identification of active compounds in the methanol extract of *Terminalia brownii* Bark. *J. Wood Sci.* **2016**, *62*, 285–293. [CrossRef]
127. Urzúa, A.; Espinoza, J.; Olguín, Á.; Santander, R. Phenolic aristolactams from leaves and stems of *Aristolochia chilensis*. *Boletín Latinoam. Caribe Plantas Med. Aromát.* **2013**, *12*, 537–542.
128. Jiménez-Ferrer, J.E.; Pérez-Terán, Y.Y.; Román-Ramos, R.; Tortoriello, J. Antitoxin activity of plants used in Mexican traditional medicine against scorpion poisoning. *Phytomedicine* **2005**, *12*, 116–122. [CrossRef]
129. Daoudi, A.; Aarab, L.; Abdel-Sattar, E. Screening of immunomodulatory activity of total and protein extracts of some Moroccan medicinal plants. *Toxicol. Ind. Health.* **2013**, *29*, 245–253. [CrossRef]
130. Derouiche, S.; Khaoula, Z.; Safa, G.; Khelef, Y. Beneficial effects of *Aristolochia longa* and *Aquilaria malaccensis* on lead-induced hematological alterations and heart oxidative stress in rats. *J. Chem. Pharm. Res.* **2018**, *10*, 8–15.
131. Melo, J.P.R.; da Carmara, C.A.G.; Lima, G.S.; Moraes, M.M.; Alves, P.B. Acaricidal properties of the essential oil from *Aristolochia trilobata* and its major constituents against the twospotted spider mite (*Tetranychus urticae*). *Can. J. Plant Sci.* **2018**, *98*, 1342–1348. [CrossRef]

132. Sylvie, D.D.; Anatole, P.C.; Cabral, B.P.; Veronique, P.B. Comparison of in vitro antioxidant properties of extracts from three plants used for medical purpose in Cameroon: *Acalypha racemosa*, *Garcinia lucida* and *Hymenocardia lyrata*. *Asian Pac. J. Trop. Biomed.* **2014**, *4*, S625–S632. [CrossRef]
133. Cos, P.; Vlietinck, A.J.; Berghe, D.V.; Maes, L. Anti-infective potential of natural products: How to develop a stronger in vitro 'proof-of-concept'. *J. Ethnopharmacol.* **2006**, *106*, 290–302. [CrossRef] [PubMed]
134. Li, L.; Wang, X.; Chen, J.; Ding, H.; Zhang, Y.; Hu, T.; Hu, L.; Jiang, H.; Shen, X. The natural product aristolactam AIIIa as a new ligand targeting the polo-box domain of polo-like kinase 1 potently inhibits cancer cell proliferation. *Acta Pharmacol. Sin.* **2009**, *30*, 1443–1453. [CrossRef]
135. Romanov, V.; Whyard, T.C.; Waltzer, W.C.; Grollman, A.P.; Rosenquist, T. Aristolochic acid-induced apoptosis and G2 cell cycle arrest depends on ROS generation and MAP kinases activation. *Arch. Toxicol.* **2015**, *89*, 47–56. [CrossRef]
136. Zhou, Q.; Pei, J.; Poon, J.; Lau, A.Y.; Zhang, L.; Wang, Y.; Liu, C.; Huang, L. Worldwide research trends on aristolochic acids (1957–2017): Suggestions for researchers. *PLoS ONE* **2019**, *14*, e0216135. [CrossRef]
137. Michl, J.; Kite, G.C.; Wanke, S.; Zierau, O.; Vollmer, G.; Neinhuis, C.; Simmonds, M.S.J.; Heinrich, M. LC-MS- and ^{1}H NMR-based metabolomic analysis and in vitro toxicological assessment of 43 *Aristolochia* species. *J. Nat. Prod.* **2016**, *79*, 30–37. [CrossRef] [PubMed]
138. Tang, C.; Chen, J.; Zhang, L.; Zhang, R.; Zhang, S.; Ye, S.; Zhao, Z.; Yang, D. Exploring the antibacterial mechanism of essential oils by membrane permeability, apoptosis and biofilm formation combination with proteomics analysis against methicillin-resistant *Staphylococcus aureus*. *Int. J. Med. Microbiol.* **2020**, *310*, 151435. [CrossRef]
139. Gertsch, J. How scientific is the science in ethnopharmacology? Historical perspectives and epistemological problems. *J. Ethnopharmacol.* **2009**, *122*, 177–183. [CrossRef]
140. Rui, L.; Hong-Chi, Z. Chemical constituents from *Aristolochia tagala* and their chemotaxonomic significance. *Biochem. Syst. Ecol.* **2020**, *90*, 104037. [CrossRef]
141. Daoudi, A.; Abdel-Satter, E.; Aarab, L. The relationship between lectin compounds and immunomodulatory activities of protein extracted from plants. *J. Plant Stud.* **2013**, *3*, 56. [CrossRef]