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Chemical Constituents and Pharmacology of the *Aristolochia* (馬兜鈴 mădōu ling) species

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Abstract

Aristolochia (馬兜鈴 mă dōu ling) is an important genus widely cultivated and had long been known for their extensive use in traditional Chinese medicine. The genus has attracted so much great interest because of their numerous biological activity reports and unique constituents, aristolochic acids (AAs). In 2004, we reviewed the metabolites of *Aristolochia* species which have appeared in the literature, concerning the isolation, structural elucidation, biological activity and literature references. In addition, the nephrotoxicity of aristolochic acids, biosynthetic studies, ecological adaptation, and chemotaxonomy researches were also covered in the past review. In the present manuscript, we wish to review the various physiologically active compounds of different classes reported from *Aristolochia* species in the period between 2004 and 2011. In regard to the chemical and biological aspects of the constituents from the *Aristolochia* genus, this review would address the continuous development in the phytochemistry and the therapeutic application of the *Aristolochia* species. Moreover, the recent nephrotoxicity studies related to aristolochic acids would be covered in this review and the structure-toxicity relationship would be discussed.

Key words: *Aristolochia*, Aristolochic acid, Alkaloid, Flavonoid, Terpenoid, Bioactivity

Introduction

There are about 500 species in the genus *Aristolochia* and the majority of these species are distributed in the tropical region, with some exceptions range as north as Canada, Scandinavia, and Northern Japan. They may grow as climbing vines, as short creeping herbs and a few are shrub-like (Hutchinson, 1973; Watson and Dallwitz, 1992; Gonzalez, 1999). *Aristolochia* species are herbaceous perennials, undershrubs or shrubs, often scandent, scrambling, twining, sometimes lianas, usually with prostrate or tuberous rhizomes or rootstocks, and alternate, pinnate, polymorphic or lobed leaves bearing essential oils. Species of *Aristolochia* were widely distributed in tropical, subtropical and temperate regions of the world. They are known to occur in Asia, Africa, North and South America and Australia but there is a wide distribution across tropical Asia (Liu and Lai, 1976; How, 1985; Hou, 1996). Various species of *Aristolochia* have been used in the folk and traditional medicines as medicaments and tonics (Andrei, 1977; Correa, 1978; Balbach, 1979; Duke, 1985; Duke and Ayensu, 1985; Simoes et al, 1986; Lopes et al, 2001), especially in the traditional Chinese medicines (Jiangsu New Medicine College, 1977; Li, 1977; Pharmacopeia of China, 1985; Tang and Eisenbrand, 1992; Bensky, 1993). Some species

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have been used in the form of crude drugs as anodynes, antiphlogistics, and detoxicants in Mainland China (Perry, 1980). In our previous review article (Wu et al, 2005), the purification, structural elucidation, and the biological activity of metabolites of *Aristolochia* species have been covered and moreover the nephrotoxicity of aristolochic acids, biosynthetic studies, ecological adaptation, and chemotaxonomy researches were also cited. In this present manuscript, we aimed to address the continuous development regarding the presences of the various metabolites identified from *Aristolochia* species and also their divergent bioactivities.

Chemical Constituents

In the period between 2004 and 2011 over eighteen species of *Aristolochia* have been investigated for chemical constituents around the world, and various constituents have been characterized (Table 1). The secondary metabolites from *Aristolochia* species cover 16 major groups classified by their chemical structures, including aristolochic acids and esters, aristolactams, aporphines, protoberberines, isoquinolines, benzylisoquinolines, amides, flavonoids, lignans, biphenyl ethers, coumarins, tetralones, terpenoids, benzenoids, steroids, and others. The aristolochic acids were host of phenanthrene derived metabolites in which the aristolactams also possessed the similar skeleton. The identified terpenoids can further be divided into three subgroups: mono-, sesqui-, and diterpenoids.

Table 1. Chemical constituents from the *Aristolochia* (馬兜鈴 mǎ dōu ling) species.

Species	Part	Compound	Reference
A. species			
		aristolochic acid I; aristolochic acid A (1)	Chen et al, 2010a
A. albida			
	whole plant	columbin (2)	Nok et al, 2005
A. arcuata			
	roots	talaumidin (3)	Zhai et al, 2004 Zhai et al, 2005
		veraguensin (4)	Zhai et al, 2005
		galgravin (5)	
		aristolignin (6)	
		nectandrin A (7)	
		isonectandrin B (8)	
		nectandrin B (9)	
A. brevipes			
	ground roots	β-sitosterol (10)	Navarro-García et al, 2011
		6α-7-dehydro-*N*-formyl-nornantenine (11)	
		E/Z-*N*-formylnornantenine (12)	
		7,9-dimethoxytariacuripyrone (13)	
		9-methoxytariacuripyrone (14)	
		aristololactam I (15)	
		stigmasterol (16)	
		3-hydroxy-α-terpineol (17)	
A. constricta			
	stems	aristolochic acid A (1)	Zhang et al, 2008
		(18)	Capasso et al, 2006
		(19)	
		(20)	
		(21)	
		(22)	
		(23)	
	stems	(−)-hinokinin (24)	Zhang et al, 2008
		9-*O*-[(−)-kaur-15-en-17-oxyl]cubebin (25)	
		(−)-cubebin (26)	
		(−)-kaur-15-en-17-ol (27)	
		(−)-pluviatolide (28)	
		(−)-haplomyrfolol (29)	
		(−)-dihydrocubebin (30)	
		9-*O*-methylcubebin (31)	
		(−)-kaur-16-en-19-oic acid (32)	
		(−)-kauran-16α,17-diol (33)	

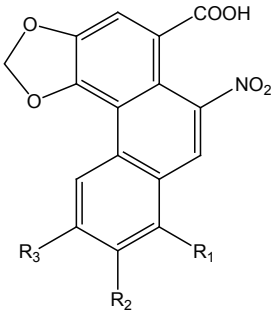
Species	Part	Compound	Reference
		(−)-kaurene (34)	
		(−)-kauran-16α,17,18-triol (35)	
		aristololactam AII; aristolactam AII (36)	
		cepharanone B (37)	
		aristelegone A (38)	
		(+)-4,7-dimethyl-6-methoxy-1-tetralone (39)	
		cadalene (40)	
		β-sitosterol glucoside; β-sitosteryl glucoside (41)	
		N-trans-feruloyltyramine (42)	
A. contorta			
	fruits	3"-hydroxyamentoflavone-7-O-methyl ether (43)	Chen et al, 2005
		3"-hydroxyamentoflavone (44)	
A. cretica			
	roots	aristolochic acid I; aristolochic acid A (1)	Georgopoulou et al, 2005
		aristolochic acid IIIa; aristolochic acid C (45)	
		6-*O*-*p*-coumaroyl-β-D-fructofuranosyl-(2→1)-α-D- glucopyranoside (46)	
		arillatose B (47)	
		6-*O*-*p*-coumaroyl-α-D-glucopyranose (48)	
		6-*O*-*p*-coumaroyl-β-D-glucopyranose (49)	
		7-hydroxyaristolochic acid I (50)	
		aristolochic acid II; aristolochic acid B (51)	
		ariskanin A (52)	
A. cymbifera			
	whole plant	2-oxo-populifolic acid (53)	de Barros Machado et al, 2005
	leaves	(−)-hinokinin (24)	Sartorelli et al, 2010
		(−)-kusunokinin (54)	
		(−)-copalic acid (55)	
		(−)-fargesin (56)	
		(+)-sesamin (57)	
		epieudesmin (58)	
A. elegans			
	stems and roots	aristolochic acid I; aristolochic acid A (1)	Shi et al, 2004
		β-sitosterol (10)	
		(−)-hinokinin (24)	
		(−)-cubebin (26)	
		(−)-kaur-15-en-17-ol (27)	
		aristolactam AII; aristololactam AII (36)	
		aristelegone A (38)	
		β-sitosteryl glucoside (41)	
		N-trans-feruloyltyramine (42)	
		N-trans-cinnamyltyramine(54)	
		aristolactam E (59)	
		aristolactam-AIIIa-6-O-β-D-glucoside (60)	
		aristoquinoline A (61)	
		aristoquinoline B (62)	
		aristoquinoline C (63)	
		aristogin F (64)	
		9-methoxyaristolactam I (65)	
		isoaristolactam AII (66)	
		aristolactam AIIIa (67)	
		aristolactam C N-β-D-glucoside (68)	
		aristogin A (69)	
		aristogin B (70)	
		aristogin C (71)	
		aristogin D (72)	
		aristogin E (73)	
		4-methoxy-3,4'-oxydibenzoic acid (74)	
		aristelegone B (75)	
		aristelegone C (76)	
		aristelegone D (77)	
		pericampylinone A (78)	
		corydaldine (79)	
		thalifoline (80)	

Species	Part	Compound	Reference
		northalifoline (81)	
		N-methylcorydaldine (82)	
		aristelegin A (83)	
		aristelegin B (84)	
		aristelegin C (85)	
		α-methylcubebin (86)	
		β-methylcubebin (87)	
		(−)-5''-methoxyhinokinin (88)	
		(−)-kobusin (89)	
		(+)-medioresinol (90)	
		aristolin (91)	
		ent-kauran-16β,17-diol (92)	
		ent-16β,17-epoxykauran (93)	
		ent-15β,16-epoxykauran-17-ol (94)	
		aristololide (95)	
		N-cis-feruloyltyramine (96)	
		N-p-trans-coumaroyltyramine (97)	
		aristolochic acid IVa; aristolochic acid D (98)	
		aristoloside (99)	
		aristolochic acid IV methyl ester (100)	
		methyl aristolochate; aristolochic acid I methyl ester (101)	
		aristolochic acid D methyl ester (102)	
		aristolochic acid Ia methyl ester (103)	
		magnofoline; magnoflorine (104)	
		oxonuciforine (105)	
		isomoschatoline (106)	
		4,5-dioxodehydroasimilobine (107)	
		methylparaben (108)	
		methyl vanillate (109)	
		p-hydroxybenzaldehyde (110)	
		vanillin (111)	
		methyl 4-hydroxy-3-methoxycinnamate (112)	
		cinnamic acid (113)	
		ω-hydroxypropioguaiacone (114)	
		ficusol (115)	
A. fangchi			
	roots	aristolochic acid A; aristolochic acid I (1)	Cai and Cai, 2010
		aristolochic acid C; aristolochic acid IIIa (45)	
		aristolochic acid B; aristolochic acid II (51)	
		aristolochic acid F (116)	
		aristolochic acid G (117)	
A. gigantea			
	rhizomes	β-sitosterol (10)	Holzbach and Lopes, 2010
		N-trans-feruloyltyramine (42)	
		magnoflorine (104)	
		allantoin (118)	
		E-nerolidol (119)	
		(+)-kobusin (120)	
		(+)-eudesmin (121)	
		aristolactam Ia N-β-D-glucoside (122)	
		aristolactam Ia 8-β-D-glucoside (123)	
		aristolactam IIIa (124)	
		aristolactam 9-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucoside (125)	
	aerial stems	*N-trans*-feruloyltyramine (42)	
		N-p-trans-coumaroyltyramine (97)	
		(+)-kobusin (120)	
		trans-N-feruloyl-3-*O*-methyldopamine (126)	
		N-cis-p-coumaroyl-3-*O*-methyldopamine (127)	
		and *N-trans-p*-coumaroyl-3-*O*-methyldopamine (128)	
A. lagesiana			
	roots	(−)-(8*S*,8'*R*,9*S*)-cubebin (129)	de Pascoli et al, 2006
		(−)-(8*R*,8'*R*,9*R*) and (−)-(8*R*,8'*R*,9*S*)-cubebins (130)	
		(8*R*,8'*R*,8''*R*,8'''*R*,9*R*,9''*S*)-bicubebin A (131)	

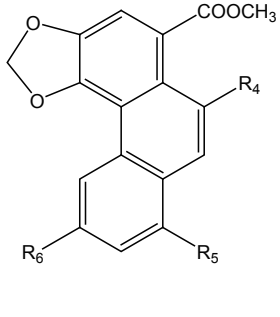
Species	Part	Compound	Reference
A. ligesiana			
	leaves	(6*R*,6a*S*,*P*)-isocorydine (132)	Ferreira et al, 2010
		(6*S*,6a*S*,*M*)-isocorydine (133)	
		(6a*S*,*M*)-(+)-norisocorydine (134)	
		(6*S*,6a*S*,*M*)-(+)-corydine-N?oxide (135)	
		(6*R*,6a*S*,*P*)-(+)-corydine (136)	
		(6*S*,6a*S*,*M*)-corydine hydrochloride (137) and (6*R*,6a*S*,*M*)-corydine hydrochloride (138)	
		lagesianine A (139)	
		lagesianine B (140)	
		lagesianine C (141)	
		lagesianine D (142)	
		glycerol (143)	
A. malmeana			
	roots	(−)-hinokinin (24)	Messiano et al, 2008
		(−)-kusunokinin (54)	
		(−)-(8*S*,8'*R*,9*S*)-cubebin (129)	
		(−)-kolavenic acid (144)	
	leaves	(−)-hinokinin (24)	
		(−)-kusunokinin (54)	
		(−)-copalic acid (55)	
		(−)-fargesin (56)	
		(−)-(8*R*,8'*R*,9*R*) and (−)-(8*R*,8'*R*,9*S*)-cubebins (130)	
		(−)-*ent*-6-*β*-hydroxycopalic acid (145)	
		(−)-phillygenin (146)	
		(−)-2-oxokolavenic acid (147)	
A. manshuriensis			
	stems	aristolochic acid I; aristolochic acid A (1)	Chung et al, 2011
		aristolochic acid IIIa; aristolochic acid C (45)	
		aristolochic acid IVa; aristolochic acid D (98)	
		aristolochic acid-I methyl ester; methyl aristolochate (101)	
		aristolactam IIIa (124)	
		aristopyridinone A (148)	
		aristolamide (149)	
		aristolamide II (150)	
		aristolic acid methyl ester (151)	
		6-methoxyaristolic acid methyl ester (152)	
A. pubescens			
	roots and stems	aristolochic acid A; aristolochic acid I (1)	Nascimento et al, 2003
		(−)-cubebin (26)	
		(−)-kaur-15-en-17-ol (27)	
		(+)-sesamin (57)	
		(+)-eudesmin (121)	
	tubercula	(−)-(8*S*,8'*R*,9*S*)-cubebin (129)	de Pascoli et al, 2006
		(−)-(8*R*,8'*R*,9*R*) and (−)-(8*R*,8'*R*,9*S*)-cubebins (130)	
		(8*R*,8'*R*,8''*R*,8'''*R*,9*R*,9''*S*)-bicubebin A (131)	
A. ridicula			
	leaves	ridiculuflavone A (153)	Machado and Lopes, 2005
		ridiculuflavone B (154)	
		ridiculuflavonylchalcone A (155)	
		proto-quercitol (156)	
		ridiculuflavone C (157)	Machado and Lopes, 2008
		ridiculuflavone D (158)	
		ridiculuflavonylchalcone B (159)	
		ridiculuflavonylchalcone C (160)	
A. tagala			
	roots	kaempferol (161)	Battu et al, 2011
A. taliscana			
	roots	licarin A (162)	León-Díaz et al, 2010
		licarin B (163)	
		eupomatenoid-7 (164)	

Aristolochic acids and esters

The constituents from the *Aristolochia* genus became the interesting topic for the phytochemical and pharmaceutical researchers since the discovery of aristolochic acid derivatives. The naturally occurring aristolochic acids possessed the 3,4-methylenedioxy-10-nitro-phenanthrenic-1-acid skeleton are typical constituents of the *Aristolochia* species and claimed to be responsible for the various biological activity of *Aristolochia* species. Figure 1 lists the eight aristolochic acids that have been characterized from *Aristolochia*. Aristolochic acid I (1) is the most abundant aristolochic acid found in almost all species of *Aristolochia* studied with few exceptions. However, the main concern of recent studies has focused on the negative aspects of aristolochic acids due to the Chinese Herb Nephropathy (Cosyns, 2003). Recently health food supplements containing aristolochic acids have been prohibited for use in weight reduction with complete scientific results supported (The European Agency for the Evaluation of Medicinal Products, 1997; Therapuetic Goods Administration, 2001). In addition, seven methyl esters of aristolochic acid were reported from the *Aristolochia* species and among these only ariskanin A (52) did not possess the 3,4-methylenedioxy substitution pattern. Only few cases of aristolochic acid esters, including aristolic acid methyl ester (151) and 6-methoxyaristolic acid methyl ester (152), do not possess the nitro group at the C-10 position. The majority of these denitroaristolochic acids were reported from the Formosan *A. manshuriensis* (Chung et al, 2011).



	R_1	R_2	R_3
1	OCH_3	H	H
45	H	H	OH
50	OCH_3	OH	H
51	H	H	H
98	OCH_3	H	OH
99	OCH_3	Glc	H
116	H	OH	H
117	OH	H	OH



	R_4	R_5	R_6
100	NO_2	OCH_3	OCH_3
101	NO_2	OCH_3	H
102	NO_2	OCH_3	OH
103	NO_2	OH	H
151	H	OCH_3	OCH_3
152	H	OCH_3	H

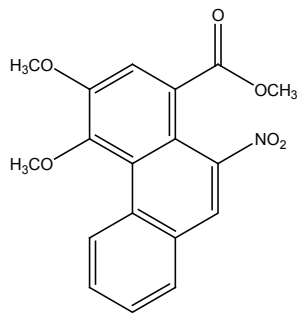


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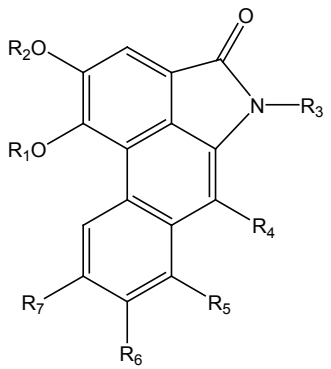
Figure 1. Aristolochic acids and esters from the *Aristolochia* species.

Aristolactams

Aristolactams are regarded as biogenetic intermediates in the biosynthetic pathway of aristolochic acids. They are usually supposed to originate from the cyclization condensation reaction of the reduction products of aristolochic acids. From Figure 2, it is evident that twelve aristolactams have been reported from *Aristolochia* species and among them there were also six compounds having the 3,4-methylenedioxy substitution groups. Aristolactam I (15), aristolactam AII (36), and aristolactam Ia *N*-β-D-glucoside (122) were the frequently encountered aristolactams in the *Aristolochia* species. Aristolactam II (36) found in several species of *Aristolochia* is a simple aristolactam without any substitutions on rings B and C. The 9-oxygenated aristolactams are rare in *Aristolochia* with only compounds 68 and 125 being reported. Compound 125 was one example of 9-oxygenated aristolactam with the substitution of diglucoside.



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
15	CH_2		H	H	OCH_3	H	H
36	CH_3	H	H	H	H	H	H
37	CH_3	CH_3	H	H	H	H	H
59	H	CH_3	H	H	OH	OCH_3	H
60	CH_3	H	H	H	H	H	OGlc
66	H	CH_3	H	H	H	H	H
67	CH_3	H	H	H	H	H	OH
68	CH_2		Glc	OCH_3	OCH_3	H	OH
122	CH_2		Glc	H	OH	H	H
123	CH_2		H	H	Glc	H	H
124	CH_2		H	H	H	H	OH
125	CH_2		H	OGlc-Glc	OCH_3	H	H

Figure 2. Aristolactams from the *Aristolochia* species.

Aporphines

Seventeen aporphine alkaloids have been characterzied from *Aristolochia* species (Figure 3). Aporphines with *N*-formyl substitution, 6α,7-dehydro-*N*-formylnornantenine (11) and *N*-formylnornantenine (12), were reported from *A. brevipes* (Navarro-García et al, 2011). The polar quaternary aporphine magnoflorine (104) was found in *A. elegans* and *A. gigantea*. The 4,5-dioxoaporphine is a small group of aporphine alkaloid found mostly among the *Aristolochia*ceae family and usually considered as possible intermediates of the precursors of aristolactams and aristolochic acids in plants. Only 4,5-dioxodehydro- asimilobine (107) was reported from *A. elegans* (Shi et al, 2004). Most of the aporphines found in *Aristolochia* species possess 4,5-tetrahydro basic skeleton. Lagesianines B-D (140-142) were the dimeric aporphine alkaloids linked through the substituent on nitrogen, oxygenated functions, and substituent on the phenanthrene ring, respectively. These dimeric aporphines were only reported from the leaves of *A. ligesiana* (Ferreira et al, 2010).

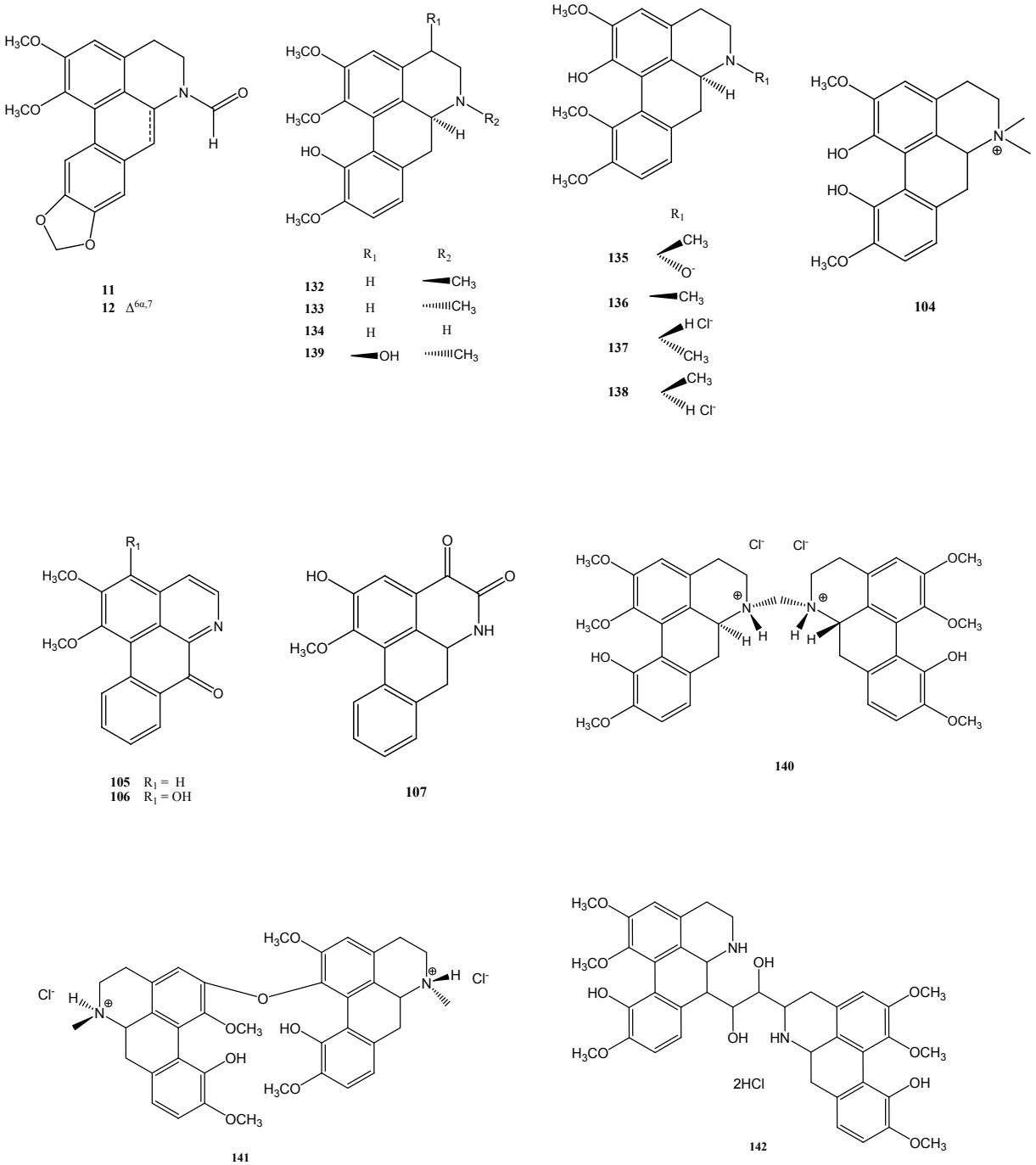


Figure 3. Aporphines from the *Aristolochia* species.

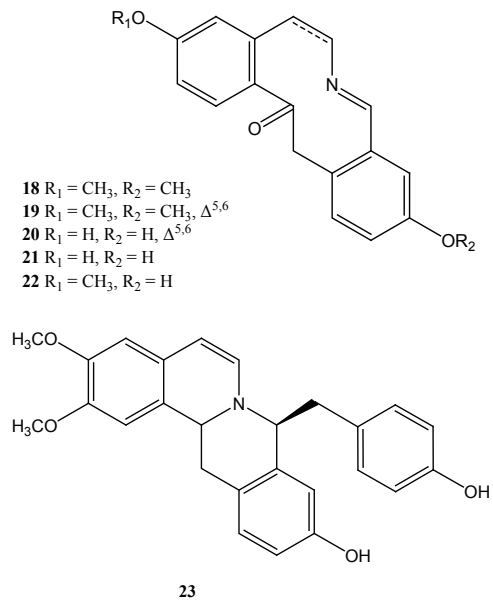


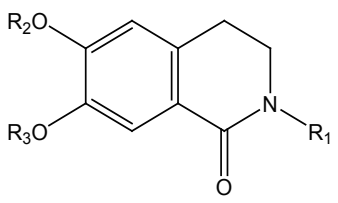
Figure 4. Protoberberines from the *Aristolochia* species.

Protoberberines

Occurrence of protoberberine alkaloids (Figure 4) was rare in *Aristolochia*, and they were only reported from *A. constricta* (Capasso et al, 2006). 8-Benzyltetrahydroprotoberberine type alkaloid, 23, had been obtained by introduction of a benzyl group at C-8 of berberine to result in this unusual carbon skeleton.

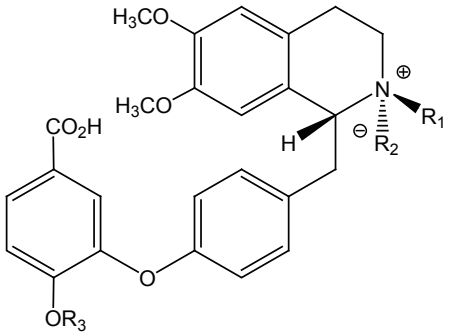
Isoquinolines

The presence of isoquinoline alkaloids 78-82 in the genus *Aristolochia* is limited to *A. elegans*. Purified compounds of this class were listed in the Figure 5. All of these alkaloids reported possessed the tetrahydroisoquinolone basic skeleton. Isoquinoline alkaloids were usually considered as biogenetic intermediates in the catabolic process of bisbenzyl-tetrahydroisoquinoline alkaloids (Shi et al, 2004).



	R_1	R_2	R_3
78	H	H	H
79	H	H	CH_3
80	CH_3	H	CH_3
81	H	CH_3	H
82	CH_3	CH_3	CH_3

Figure 5. Isoquinolines from the *Aristolochia* species.



	R_1	R_2	R_3
61	CH_3	O	CH_3
62	O	CH_3	CH_3
63	O	CH_3	H

Figure 6. Benzylisoquinolines from the *Aristolochia* species.

Benzylisoquinolines

The occurrence of benzylisoquinoline type alkaloids, aristoquinolines A-C (61-63) constitute the first report of *N*-oxide benzoyl benzyltetrahydroisoquinoline ether alkaloids from *Aristolochia* species (Figure 6). These provided the natural evidence for the catabolic process of structurally interesting bisbenzyltetrahydroisoquinol ines. The isoquinolones, benzylisoquinolines, biphenyl ethers, and *N*-oxide benzoyl benzyltetrahydroisoqu inoline ether alkaloids were derived biogenetically from bisbenzylisoquinolines, common metabolites of *Aristolochia* species, in general alkaloid catabolic process (Shi et al, 2004).

Amides

The amides are another type of compounds isolated from several *Aristolochia* plants (Figure 7). One class of the amides from *Aristolochia* species, on structural investigation were found to contain a tyramine unit connected to phenolic acids like *cis*- or *trans*- coumaric and ferulic acids. Aristolamide (149) and aristolamide II (150) isolated from *A. manshuriensis* (Chung et al, 2011) contain $-CONH_2$ group at C-1 which possessed the phenanthrene basic skeleton was another class of amide reported from *Aristolochia* species.

Flavonoids

Flavonoids continue to attract the researchers' interests due to their structural diversity, biological and ecological significance. They affect plant interactions with microsymbionts (Romeo et al, 1998), insect predators and pollinators (Harborne, 1986; Stafford, 1997), and also function in pigmentation and act as protectants against UV irradiation (Brouillard, 1988; Ylstra et al, 1992; Harborne, 1994). Virtually almost all higher plants produce flavonoids, however, some

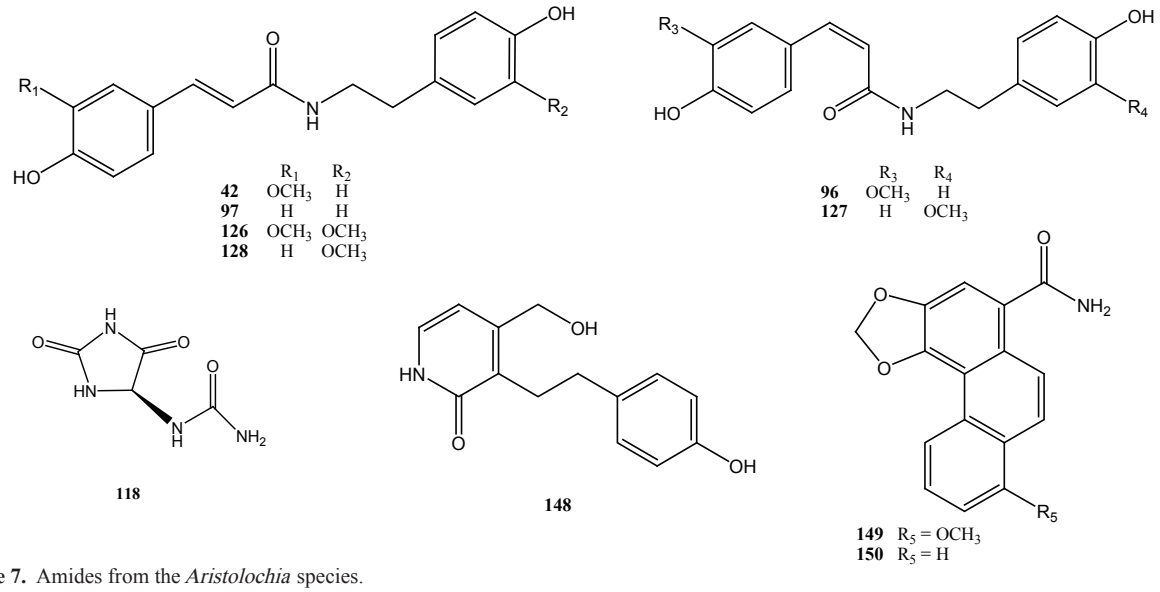


Figure 7. Amides from the *Aristolochia* species.

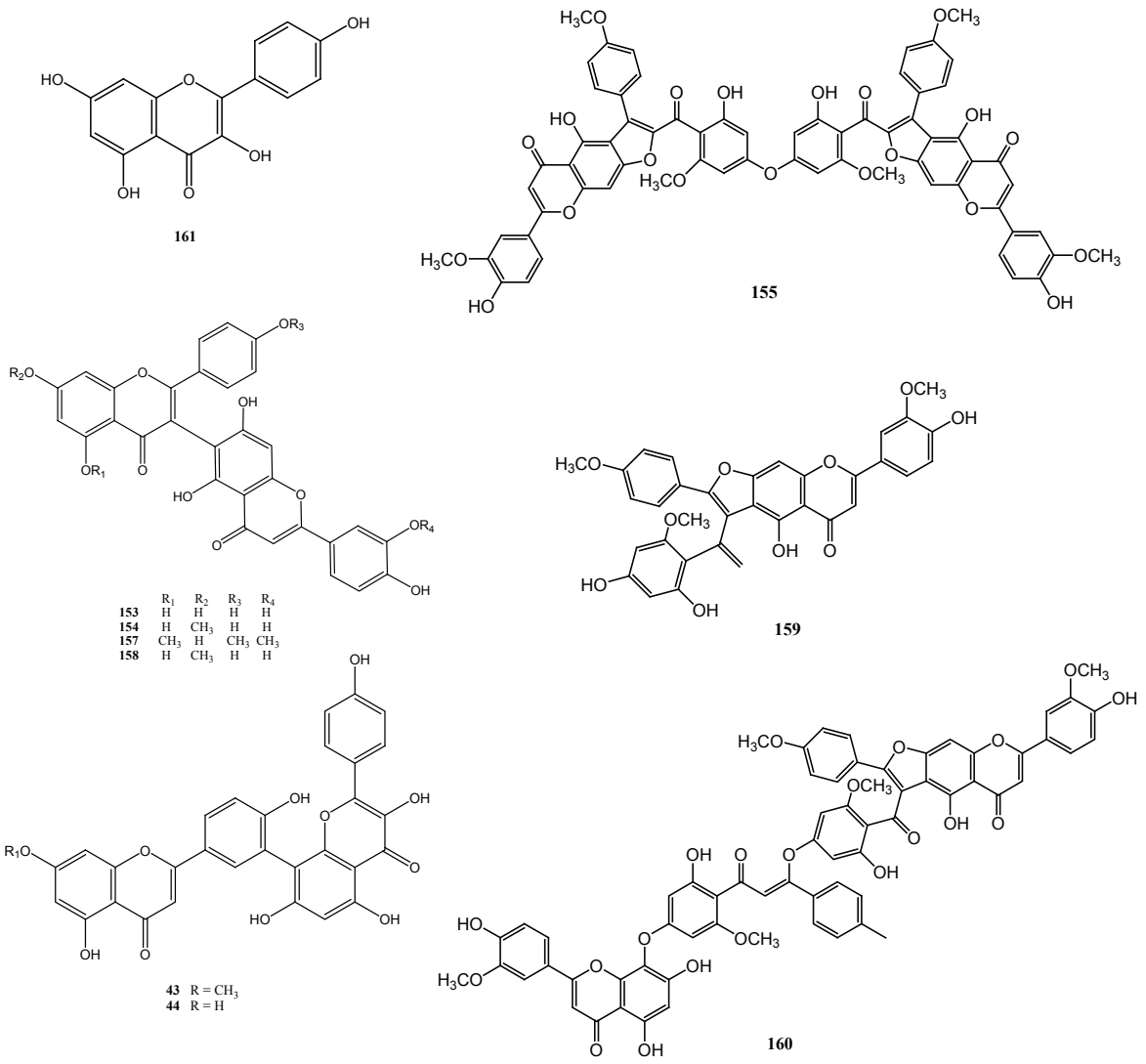


Figure 8. Flavonoids from the *Aristolochia* species.

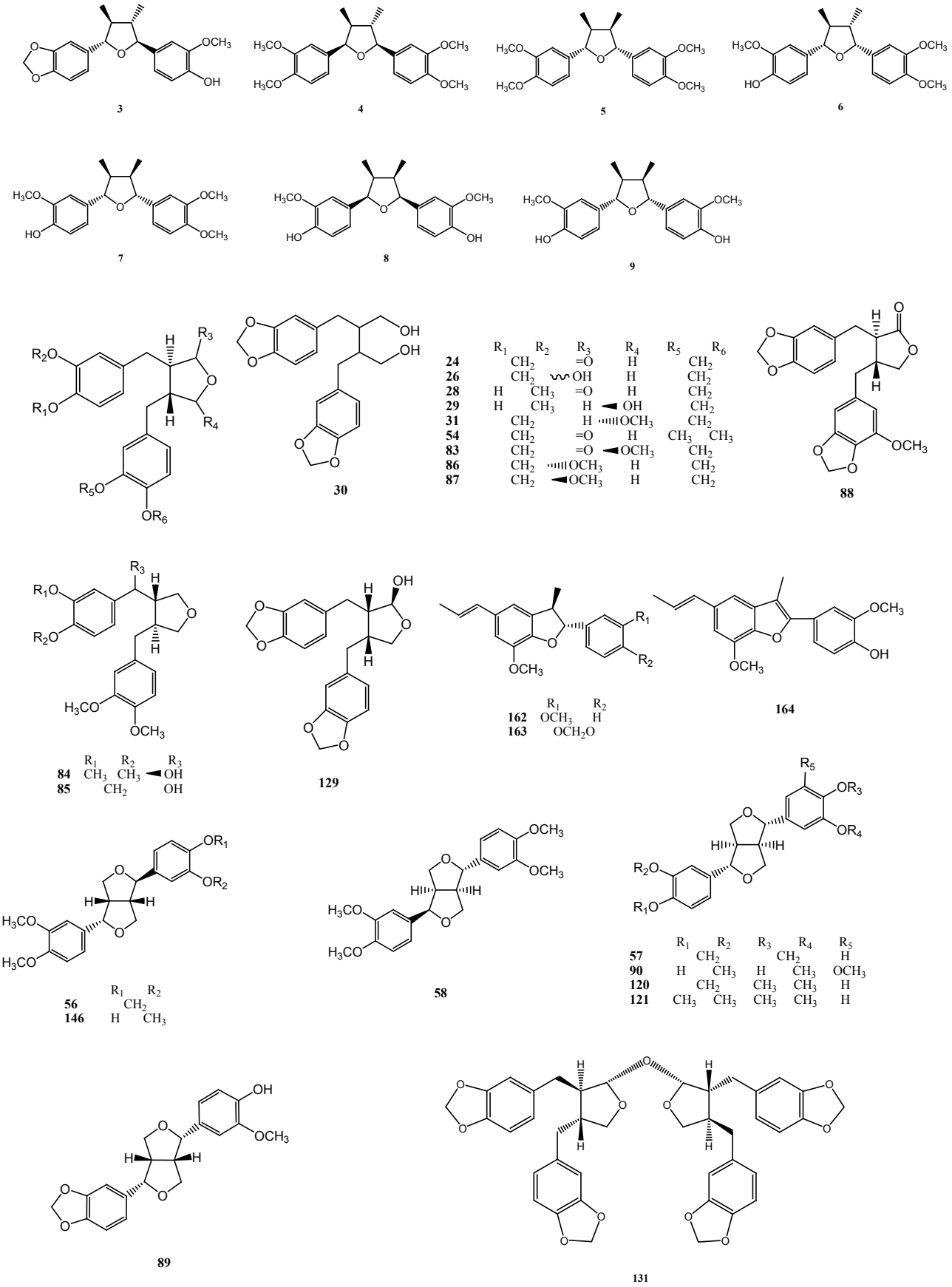


Figure 9. Lignans from the *Aristolochia* species.

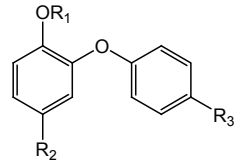
of them are fairly unique, in which many specific compounds are accumulated during plant growth and development. Six bisflavones, one unusual chalcone-flavone dimer and two tetramers were characterzied from *A. ridicula* (Machado and Lopes, 2005; 2008) (Figure 8). These reports constitute the presence of bi- and tetraflavonoids in the family *Aristolochia*ceae. In addition, there was also simple flavone reported from *Aristolochia* species, like kaempferol (161) from *A. tagala* (Battu et al, 2011).

Lignans

Lignans were another important type of metabolites found in several species of *Aristolochia*. There are five basic skeletons of neolignans and lignans with structural diversity reported from *Aristolochia* genus (Figure 9), including diaryldimethyltetrahydrofuranoids, dibenzylbutanoids, benzofurans, and bisepoxylignans. The 2,5-diaryl-3,4-dimethyl- tetrahydrofuranoids 3-9 were all characterized from the roots of *A. arcuata* (Zhai et al, 2004; 2005). Occurrence of the dibenzylbutane type lignans is the most common in *Aristolochia* genus. These lignans could be further divided into dibenzyltetrahydrofurans, dibenzylbutyrolactones, and dibenzylbutane diol depending on their oxidation states. Licarin A (162), licarin B (163), and eupomatenoid-7 (164) were benzofuran type lignans only reported from A. taliscana (León-Díaz et al, 2010). The other type of lignans frequently encountered in *Aristolochia* species were the bisepoxylignans which were exemplified in Figure 9, reported from *A. cymbifera*, *A. elegans*, *A. gigantea*, and *A. malmeana*, respectively. In addition, there was also one dimeric lignan (8*R*, 8′*R*, 8"R, 8‴*R*, 9*R*, 9″*S*)-bicubebin A (131) linked through the oxygen atom (de Pascoli et al, 2006).

Biphenyl ethers

Seven biphenyl ethers had been reported, including aristogins A-E (69-73), F (64), and 4-methoxy-3,4-oxydibenzoic acid (74) (Figure 10). All these compounds have only been reported from *A. elegans* (Shi et al, 2004) and they are usually considered as one of the end products in the catabolic process of bisbenzylisoquinoline alkaloids.



	R_1	R_2	R_3
64	CH_3	CO_2H	CH_2OH
69	CH_3	CHO	CO_2CH_3
70	CH_3	CO_2CH_3	CHO
71	CH_3	CO_2CH_3	CO_2CH_3
72	H	CO_2CH_3	CO_2CH_3
73	CH_3	CO_2CH_3	CH_2OH

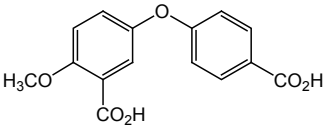


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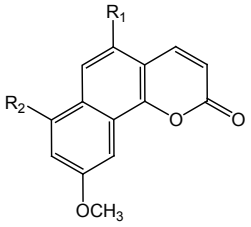
Figure 10. Biphenyl ethers from the *Aristolochia* species.

Coumarins

Although there were only two coumarins, 7,9-dimeth oxytariacuripyrone (13) and 9-methoxytariacuripyrone (14), characterized from the roots of *A. brevipes* (Figure 11), these constituents also displayed significant physiological activity (Navarro-García et al, 2011).

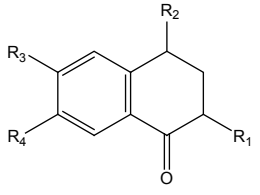
Tetralones

Among five tetralones reported from *Aristolochia* species so far (Figure 12), four tetralones, aristelegones A-D (38, 75-77) have been characterized in the stems and roots of *A. elegans* collected in Taiwan (Shi et al, 2004). Aristelegone A (38) and (+)-4,7-dimethyl-6-methoxy-1- tetralone (39) were reported from the stems of *A. constricta* (Zhang et al, 2008). Most of these identified tetralones possessed a keto substituent at C-1 except that aristelegone D (77) had 1,2-diol functionalities.



13 $R_1 = OCH_3$, $R_2 = OCH_3$
14 $R_1 = NO_2$, $R_2 = H$

Figure 11. Coumarins from the *Aristolochia* species.



	R_1	R_2	R_3	R_4
38	H	CH_3	OH	CH_3
39	H	CH_3	OCH_3	CH_3
75	OH	CH_3	OCH_3	CH_3
76	H	CH_3	OH	CH_2OH

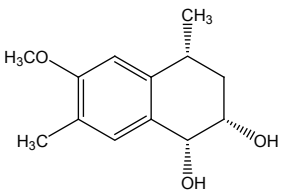


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Figure 12. Tetralones from the *Aristolochia* species.

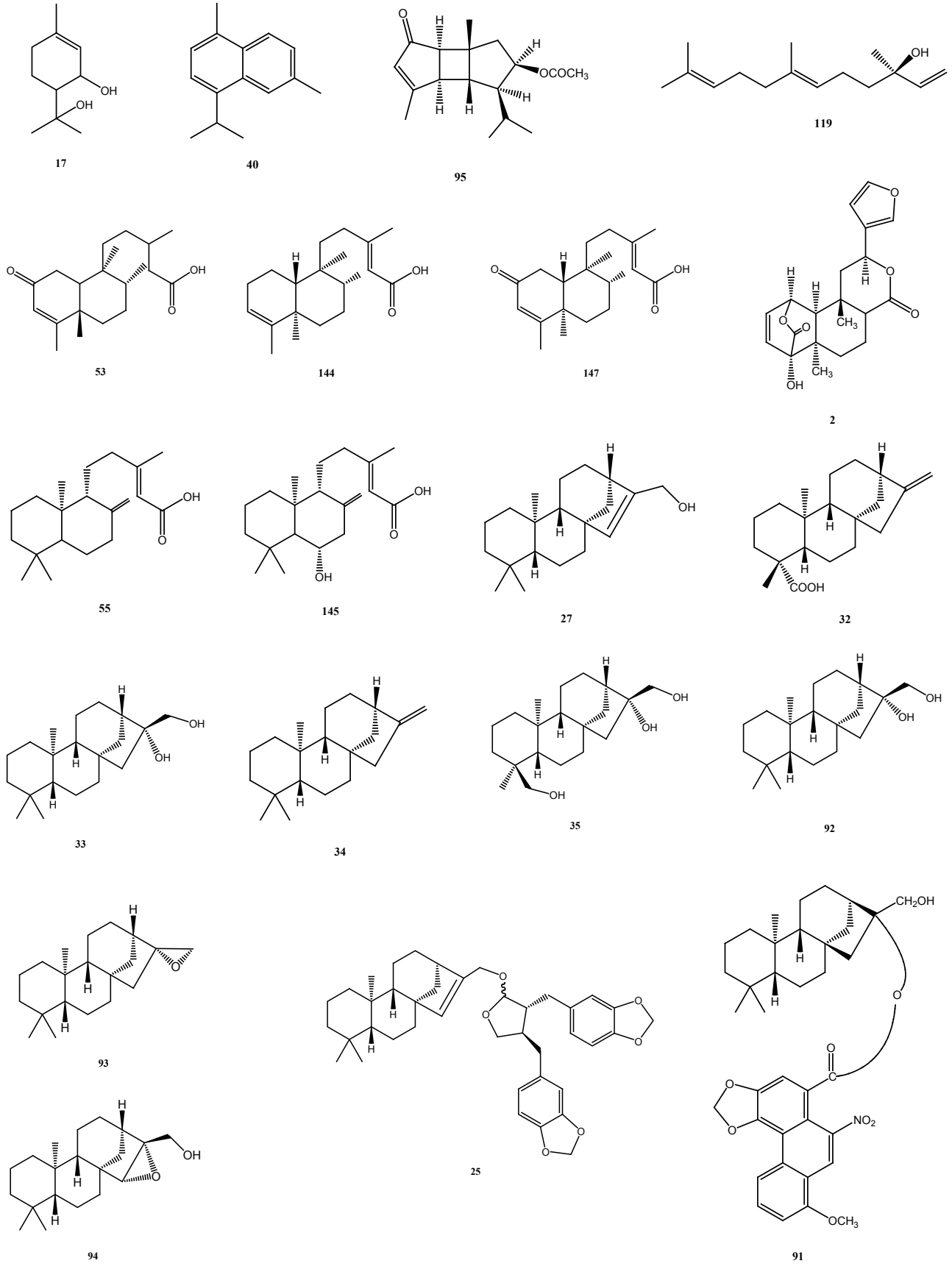

Figure 13. Terpenoids from the *Aristolochia* species.

Terpenoids

Although there were so many terpenoids characterized from *Aristolochia* species in our previous review (Wu et al, 2005), the number of terpenoids reported in the period between 2004 and 2011 was comparatively limited (Figure 13). Only one monoterpene, 3-hydroxy-α-terpineol (17), was identified from the roots of *A. brevipes* (Navarro-García et al, 2011). Three sesquiterpenoids, cadalene (40) (Zhang et al, 2008), aristololide (95) (Shi et al, 2004), and E-nerolidol (119) (Holzbach and Lopes, 2010), belonged to the cadinane, bourbonanes, and farnesane basic skeleton, respectively, were also characterized from the *Aristolochia* species. The diterpenoids with three types of C_{20} carbon skeletons constitute the largest group of terpenoid metabolites in *Aristolochia*. First type of diterpenoid is the clerodane basic skeleton. 2-Oxo-populifolic acid (53) was reported from *A. cymbifera* and (−)-kolavenic acid (144) and (−)-2-oxokolavenic acid (147) were purified from *A. malmeana*, respectively. A furanolactone diterpene belonged to the clerodane type was isolated from the rhizomes of *A. albida* (Nok et al, 2005) and identified as columbin (2). Second type is labdanes in which only (−)-copalic acid (55) and (−)-*ent*-6-*β*-hydroxycopalic acid (145) possessed this basic skeleton that were only a little different from the clerodane type diterpenoids. From the reports up to date, it revealed that *Aristolochia* species were rich sources of *ent*-kaurane diterpenoids. In our reviewing period, totally eight ent-kaurane diterpenoids were reported from *A. constricta*, *A. elegans*, and *A. pubescens*. In addition, one *ent*-kaurane lignan 9-*O*-[(−)-kaur-15-en-17-oxyl]cubebin (25), and one *ent*-kaurane diterpenoid ester of aristolochic acid aristolin (91) were also characterized from *A. constricta* and *A. elegans*, respectively. Aristolin (91) is the first example of an ester composed of aristolochic acid and a diterpenoid, in which C-16 hydroxy group of ent-kauran-16-β, 17-diol involves in the ester linkage with C-11 carboxylic acid group of aristolochic acid (Shi et al, 2004).

Benzenoids

A number of benzenoid derivatives were isolated from different *Aristolochia* species, which include phenylmethanoids and phenylpropanoids (Figure 14). Four simple benzenoid derivatives 108-111 were isolated from the stems and roots of *A. elegans* (Shi et al, 2004). Eight phenylpropanoids, including aglycones 112-115 from *A. elegans* and glycosides 46-49 from *A. cretica*, respectively, were reported and most of them

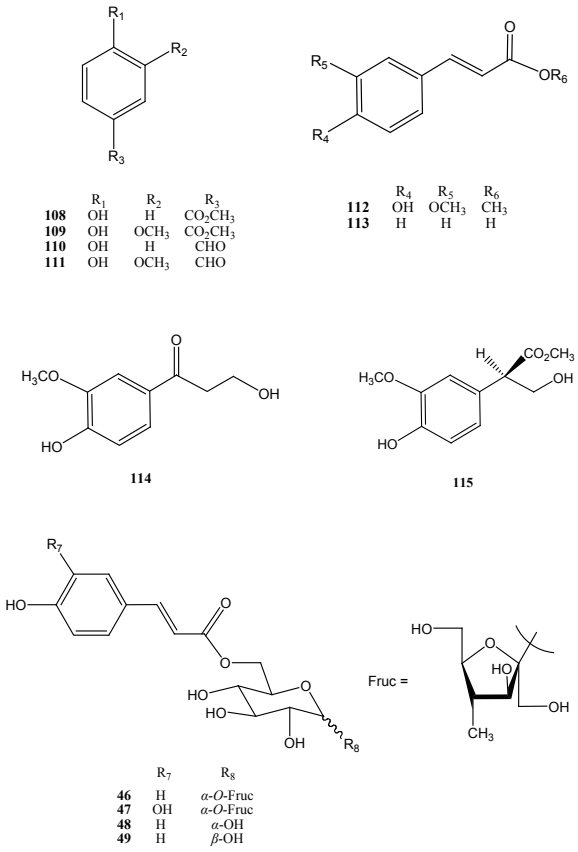

Figure 14. Benzenoids from the *Aristolochia* species.

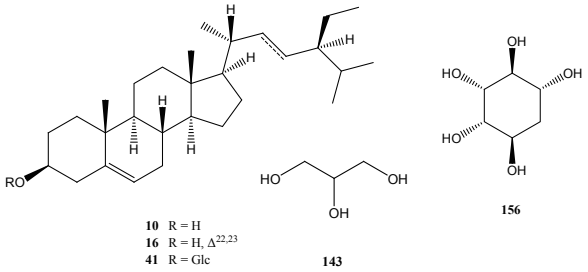

Figure 15. Steroids and others from the *Aristolochia* species.

are ferulic, cinnamic, p-coumaric, and caffeic acids derivatives.

Steroids and others

Steroids are usually encountered in natural sources, and those presented in *Aristolochia* species are mostly derivatives of β-sitosterol and stigmasterol. Among these steroids, β-sitosterol (10) and β-sitosteryl glucoside (41) were frequently found in several *Aristolochia* species (Figure 15). In addition, some miscellaneous compounds including glycerol (143) and proto-quercitol (156) were also reported from *Aristolochia* species.

Pharmacology

There were a lot of worthy achievements related to the pharmacology of *Aristolochia* to be published to evidence the extensive use of *Aristolochia* species in folk/traditional medicines. The aristolochic acids have been considered to be the most potent fraction of the *Aristolochia* constituents. Aristolochic acid I, the most active constituent of *Aristolochia* has been used for medicinal purposes since the Graeco-Roman period. However, following the observations that the compound was mutagenic and carcinogenic, it was removed from pharmaceutical products since a decade (Pharmacopoeia of the People's Republic of China, 1977). Various bioactivity studies have been reported to assess the traditional uses of *Aristolochia* species and these results were summarized in Table 2. Some of the *Aristolochia* species, including *A. baetica*, *A. bracteolata*, *A. indica*, *A. malmeana*, and *A. pubescens*, have been reported to exhibit insecticidal and repellent activities. The crude extracts of *A. brevipes*, *A. cymbifrea*, *A. indica*, *A. mollissima*, and *A. taliscana* also display significant antimicrobial activities. The phytochemical compositions and pharmacology of *Aristolochia* genus have evoked a great deal of interest due to their multiple traditional uses and various bioactivity reports on their crude extracts. Therefore, *Aristolochia* become one of the intensely investigated genera and a large number of papers have been published on the production of physiologically important metabolites by *Aristolochia*.

The divergent bioactivities reports of the compounds identified from the *Aristolochia* species was listed in Table 3. It was famous that in the previous studies aristolochic acid I (1) exhibited significant cytotoxicity thus aristolochic acid I (1) (Chen et al, 2010a), aristolochic acid-IVa (98), aristolactam IIIa (124), and aristolamide II (150) (Chung et al, 2011) were examined for their anti-inflammatory potentials and displayed significant effects. The lignans purified from *A. arcuata*, talaumidin (3), galgravin (5), aristolignin (6), nectandrin A (7), isonectandrin B (8), and nectandrin B (9) all exhibited neuroprotective bioactivity (Zhai et al, 2005). In addition, (−)-hinokinin (24), (−)-cubebin (26), (−)-pluviatolide (28), and (−)-haplomyrfolol (29) from *A. constricta* also displayed antispasmodic activity. There was also one diterpenoid, (−)-kaur-16-en-19-oic acid (32) to show the antispasmodic effect (Zhang et al, 2008). *A. constricta* is a medicinal plant found in Ecuador and widely distributed in South America. The protoberberines 18-21 from *A. constricta* exhibited the anti-addictive effects and these results indicated that the alkaloids were able to produce significant influence on the opiate withdrawal *in vitro* and these compounds were able to exert their effects both at μ and κ opioid agonists (Capasso et al, 2006).

Licarin A (162), licarin B (163), and eupomatenoid-7 (164) reported from *A. taliscana* (León-Díaz et al, 2010); and 7,9-dimethoxytariacuripyrone (13), 9-methoxytariacuripyrone (14), and aristololactam I (15) from *A. brevipes* (Navarro-García et al, 2011) were examined for their antimycobacterial effects and the results confirmed their potentials indicated in the crude

Table 2. Bioactivity of the crude extracts of the *Aristolochia* (馬兜鈴 mǎ dōu ling) species.

Source	Parts	Bioactivity	Reference
A. baetica	stem	insecticidal	Jbilou et al, 2008
	roots	antiproliferative	Chaouki et al, 2010
A. bracteolata	whole plant	antiplasmodial antiallergic	Ahmed et al, 2010 Chitme et al, 2010
	leaves	antifeedant	Elango et al, 2011
A. brevipes	ground roots	antimycobacterial	Navarro-García et al, 2011
A. constricta	stems	antispasmodic	Zhang et al, 2008
A. cymbifrea	whole plant	antimicrobial	de Barros Machado et al, 2005
	stems	antibacterial	Alviano et al, 2008
A. elegans	roots and aerial part	anti scorpion venom	Izquierdo et al, 2010
	roots	anti scorpion venom	Jiménez-Ferrer et al, 2005
A. indica	roots	antibacterial	Kumar et al, 2006
		antifungal	Kumar et al, 2006
	leaves	anti snake venom	Samy et al, 2008
	leaves	mosquito-adulticidal	Kamaraj et al, 2010
		mosquito-repellent	Kamaraj et al, 2010
		mosquito-larvicidal	Kamaraj et al, 2010
A. malmeana	roots	insecticidal	Messiano et al, 2008
A. mollissima	rhizome and aerial part	antimicrobial	Yu et al, 2007
A. pubescens	roots and stems	insecticidal	Nascimento et al, 2003
A. tagala (syn: A. acuminata)	roots	antiinflammatory	Battu et al, 2011
A. taliscana	roots	antimycobacterial	León-Díaz et al, 2010

extracts. *Mycobacterium tuberculosis* (MTB) is one of the species of the so-called tuberculosis complex and is the causative agent of tuberculosis (TB). The increase in the number of cases of TB has been associated with the infection of humans with HIV, in addition to the appearance and development of TB-resistant drugs, both multidrug-resistant (MDR), as well as extremely drug-resistant (XDR). These studies demonstrated that the dichloromethane extracts of rhizomes of *A. brevipes* and hexane extracts of *A. taliscana* possesses strong in vitro antimycobacterial activity against *Mycobacterium tuberculosis* strains. Among the tested compounds, licarin A (162) was the most active compound, with minimum inhibitory concentrations (MICs) of 3.12-12.5 μg/mL against the following *M. tuberculosis* strains: H37Rv, four mono-resistant H37Rv variants and 12 clinical MDR isolates, as well as against five non-tuberculous mycobacteria (NTM) strains.

Table 3. Bioactivity of the compounds identified from the *Aristolochia* (馬兜鈴 smă dōu ling) species.

Compound	Source	Bioactivity	Reference
aristolochic acid I (1)		antiinflammatory	Chen et al, 2010a
	A. constricta	antispasmodic	Zhang et al, 2008
	A. pubescens	insecticidal	Nascimento et al, 2003
	A. fangchi	antiplatelet	Shen et al, 2008
aristolochic acid A (1)	*A. fangchi*	cytotoxic	Cai and Cai, 2010
columbin (2)	*A. albida*	trypanocidal	Nok et al, 2005
		antitrypanosomal	
talaumidin (3)	*A. arcuata*	neurotrophic	Zhai et al, 2004
			Zhai et al, 2005
		neuroprotective	Zhai et al, 2005
galgravin (5)	*A. arcuata*	neurotrophic	Zhai et al, 2005
aristolignin (6)	*A. arcuata*	neurotrophic	Zhai et al, 2005
nectandrin A (7)	*A. arcuata*	neurotrophic	Zhai et al, 2005
		neuroprotective	
isonectandrin B (8)	*A. arcuata*	neurotrophic	Zhai et al, 2005
		neuroprotective	
nectandrin B (9)	*A. arcuata*	neurotrophic	Zhai et al, 2005
		neuroprotective	
7,9-dimethoxytariacuripyrone (13)	*A. brevipes*	antimycobacterial	Navarro-García et al, 2011
9-methoyitariacuripyrone (14)	*A. brevipes*	antimycobacterial	Navarro-García et al, 2011
aristololactam I (15)	*A. brevipes*	antimycobacterial	Navarro-García et al, 2011
(18)	*A. constricta*	anti-addictive	Capasso et al, 2006
(19)	*A. constricta*	anti-addictive	Capasso et al, 2006
(20)	*A. constricta*	anti-addictive	Capasso et al, 2006
(21)	*A. constricta*	anti-addictive	Capasso et al, 2006
(−)-hinokinin (24)	*A. constricta*	antispasmodic	Zhang et al, 2008
	A. cymbifera	antitrypanosomal	Sartorelli et al, 2010
(−)-cubebin (26)	*A. constricta*	antispasmodic	Zhang et al, 2008
(−)-kaur-15-en-17-ol (27)	*A. pubescens*	insecticidal	Nascimento et al, 2003
(−)-pluviatolide (28)	*A. constricta*	antispasmodic	Zhang et al, 2008
(−)-haplomyrfolol (29)	*A. constricta*	antispasmodic	Zhang et al, 2008
(−)-kaur-16-en-19-oic acid (32)	*A. constricta*	antispasmodic	Zhang et al, 2008
(−)-kusunokinin (39)	*A. malmeana*	insecticidal	Messiano et al, 2008
aristolochic acid II (51)	*A. fangchi*	antiplatelet	Shen et al, 2008
2-oxo-populifolic acid (53)	*A. cymbifera*	antimicrobial	de Barros Machado et al, 2005
(−)-kusunokinin (54)	*A. cymbifera*	antitrypanosomal	Sartorelli et al, 2010
(−)-copalic acid (55)	*A. cymbifera*	antitrypanosomal	Sartorelli et al, 2010
(−)-fargesin (56)	*A. cymbifera*	antitrypanosomal	Sartorelli et al, 2010
(+)-sesamin (57)	*A. cymbifera*	antitrypanosomal	Sartorelli et al, 2010
epieudesmin (58)	*A. cymbifera*	antitrypanosomal	Sartorelli et al, 2010
(+)-eudesmin (82)	*A. pubescens*	insecticidal	Nascimento et al, 2003
aristolochic acid IVa (98)	*A. manshuriensis*	antiinflammatory	Chung et al, 2011
(+)-sesamin (121)	*A. pubescens*	insecticidal	Nascimento et al, 2003
aristolactam IIIa (124)	*A. manshuriensis*	antiinflammatory	Chung et al, 2011
		cyclin-dependent kinase inhibiting	Hegde et al, 2010
aristolamide II (150)	*A. manshuriensis*	antiinflammatory	Chung et al, 2011
kaempferol (161)	*A. tagala*	antiinflammatory	Battu et al, 2011
licarin A (162)	*A. taliscana*	antimycobacterial	León-Díaz et al, 2010
licarin B (163)	*A. taliscana*	antimycobacterial	León-Díaz et al, 2010
eupomatenoid-7 (164)	*A. taliscana*	antimycobacterial	León-Díaz et al, 2010

Chagas disease is a chronic illness caused by the flagellate protozoan *Trypanosoma cruzi*, and it is the major cause of morbidity and mortality in many regions of South America. *A. cymbifera* has been used in traditional medicine as an abortifacient and an emmenagogue as well as in the treatment of fever, diarrhea, and eczema. The experimental results of purification of *A. cymbifera* and bioactivity study demonstrated that (−)-kusunokinin (54) and (−)-copalic acid (55) were the most active compounds against trypomastigotes of *T. cruzi*. Additionally, (−)-copalic acid (55) demonstrated the highest parasite selectivity as a result of low toxicity to mammalian cells, despite a considerable hemolytic activity at higher concentrations. Among the isolated compounds, (−)-kusunokinin (54) could be considered the most promising candidate, as it displayed significant activity against intracellular amastigotes and trypomastigotes without hemolytic activity (Sartorelli et al, 2010).

Nephrotoxicity

Chinese herbs nephropathy (CHN) is a rapidly progressive interstitial nephropathy reported after the introduction of Chinese herbs in a slimming regimen followed by young Belgian women (Vanherweghem et al, 1993; Nortier et al, 2000). Because of manufacturing error, there were several reports on the adverse effects of this slimming regimen. Firstly, in 1992, some cases of women presenting with a rapidly progressive renal failure after having followed a slimming regimen including powdered extracts of Chinese herbs, one of them being *Stephania tetrandra* were recorded. This outbreak of renal failure eventually resulted in about 100 cases in 1998, 70 % of them being in end-stage renal disease (ESRD) (Vanherweghem, 2002). Chinese herbs nephropathy is characterized by early, severe anemia, mild tubular proteinuria and initially normal arterial blood pressure in half of the patients (Cosyns, 2003). The recent studies have confirmed that the main culprit leading to renal injury is aristolochic acid found in many Chinese herbal preparations (Balachandran et al, 2005; Nedelko et al, 2009; Chen et al, 2010b; Zhu et al, 2010; Chen et al, 2012). Aristolochic acid, a potent human carcinogen produced by *Aristolochia* plants, is associated with urothelial carcinoma of the upper urinary tract (UUC). Following metabolic activation, aristolochic acid reacts with DNA to form aristolactam (AL)-DNA adducts. These lesions concentrate in the renal cortex, where they serve as a sensitive and specific biomarker of exposure, and are found also in the urothelium, where they give rise to a unique mutational signature in the TP53 tumor-suppressor gene. From the research results, it could be concluded that exposure to aristolochic acid contributed significantly to the incidence of UUC, a finding with significant implications for global public health (Chen et al, 2012).

Conclusion

This review of literature including phytochemical and pharmacological investigations on *Aristolochia* species have covered 164 compounds belonged to the classes of aristolochic acids and esters, aristolactams, aporphines, protoberberines, isoquinolines, benzylisoquinolines, amides, flavonoids, lignans, biphenyl ethers, coumarins, tetralones, terpenoids, benzenoids, steroids, and others with extensive physiological activities. Recently, the focus of the pharmacology of the *Aristolochia* species was mainly on the nephrotoxic aristolochic acids responsible for a tragic disease of Chinese herb nephropathy recognized in 1992. It may thus be of more than academic interest to examine the remaining *Aristolochia* plants for their aristolochic acid presence to prevent the issues like Chinese herb nephropathy and Balkan endemic nephropathy. This review will help researchers and scientists in locating the detailed information on *Aristolochia* species and address the continuous development in the phytochemistry and the therapeutic application of the *Aristolochia* species in the period between 2004 and 2011.

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References

Ahmed, E.H.M., Nour, B.Y.M., Mohammed, Y.G., Khalid, H.S., 2010. Antiplasmodial activity of some medicinal plants used in Sudanese folk-medicine. Environmental Health Insights 4, 1–6.

Alviano, W.S., Alviano, D.S., Diniz, C.G., Antoniolli, A.R., Alviano, C.S., Farias, L.M., Carvalho. M.A.R., Souza, M.M.G., Bolognese, A.M., 2008. In vitro antioxidant potential of medicinal plant extracts and their activities against oral bacteria based on Brazilian folk medicine. Archives of Oral Biology 53, 545–552.

Andrei, Ed. 1977. Farmacopeia homeopatica Brasileira, Sao Paulo.

Balachandran, P., Wei, F., Lin, R.C., Khan, I.A., Pasco, D.S., 2005. Structure activity relationships of aristolochic acid analogues: toxicity in cultured renal epithelial cells. Kidney International 67, 1797–1805.

Balbach, A. 1979. Flora nacional na medicina domestica, 11th Ed., Edel, Sao Paulo, pp. 45, 458, 573, 739, 840.

Battu, G.R., Parimi, R., Shekar, K.B.C., 2011. *In vivo* and *in vitro*

pharmacological activity of *Aristolochia tagala* (syn: *Aristolochia acuminate*) root extracts. Pharmaceutical Biology 49, 1210–1214.

Bensky, D., Gamble, A., Kaptchuk, T., and Bensky, L.L. 1993. Chinese herbal medicine: materia medica, revised Ed., Eastland Press, Seattle, p. 136.

Brouillard, R. 1988. The flavonoids – advances in research since 1980, Chapman and Hall, New York, p. 525.

Cai, Y., Cai, T.G., 2010. Two new aristolochic acid derivatives from the roots of *Aristolochia fangchi* and their cytotoxicities. Chemical and Pharmaceutical Bulletin 58, 1093–1095.

Capasso, A., Piacente, S., Tommasi, N.D., Rastrelli, L., Pizza, C., 2006. The effect of isoquinoline alkaloids on opiate withdrawal. Current Medicinal Chemistry 13, 807–812.

Chaouki, W., Leger, D.Y., Eljastimi, J., Beneytout, J.L., Hmamouchi, M., 2010. Antiproliferative effect of extracts from *Aristolochia baetica* and *Origanum compactum* on human breast cancer cell line MCF–7. Pharmaceutical Biology 48, 269–274.

Chen, Y.G., Yu, L.L., Huang, R., Liu, J.C., Lv, Y.P., Zhao, Y., 2005. 3"-Hydoxyamentoflavone and its 7-*O*-methyl ether, tow new biflavonoids from *Aristolochia contorta*. Archives of Pharmacal Research 28, 1233–1235.

Chen, Y.Y., Chiang, S.Y., Wu, H.C., Kao, S.T., Hsiang, C.Y., Ho, T.Y., Lin, J.G., 2010a. Microarray analysis reveals the inhibition of nuclear factor-kappa B signaling by aristolochic acid in normal human kidney (HK-2) cells. Acta Pharmacologica Sinica 31, 227–236.

Chen, Y.Y., Chung, J.G., Wu, H.C., Bau, D.T., Wu, K.Y., Kao, S.T., Hsiang, C.Y., Ho, T.Y., Chiang, S.Y., 2010b. Aristolochic acid suppresses DNA repair and triggers oxidative DNA damage in human kidney proximal tubular cells. Oncology Reports 24, 141–153.

Chen, C.H., Dickman, K.G., Moriya, M., Zavadil, J., Sidorenko, V.S., Edwards, K.L., Gnatenko, D.V., Wu, L., Turesky, R.J., Wu, X.R., Pu, Y.S., Grollman, A.P., 2012. Aristolochic acid-associated urothelial cancer in Taiwan. Proceedings of the National Academy of Sciences of the United States of America 109, 8241–8246.

Chitme, H.R., Malipatil, M., Chandrashekhar, V.M., Prashant, P.M., 2010. Antiallergic activity of *Aristolochia* bracteolate Lank in animal model. Indian Journal of Experimental Biology 48, 46–52.

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., Wu, Y.C., 2011. A novel alkaloid, aristopyridinone A and anti-inflammatory phenanthrenes isolated from *Aristolochia manshuriensis*. Bioorganic & Medicinal Chemistry Letters 21, 1792–1794.

Correa, M.P. 1978. Dicionario das plantas uteis do Brasil e das exoticas cultivadas, Vols. 1-2, Imprensa Nacional, Rio de Janeiro, pp. 1926–1978.

Cosyns, J.P., 2003. Aristolochic acid and 'Chinese herbs nephropathy': a review of the evidence to date. Drug Safety 26, 33–48.

de Barros Machado, T., Leal, I.C.R., Kuster, R.M., Amaral, A.C.F., Kokis, V., de Silva, M.G., dos Santos, K.R.N., 2005. Brazilian phytopharmaceuticals – evaluation against hospital bacteria. Phytotherapy Research 19, 519–525.

de Pascoli, I.C., Nascimento, I.R., Lopes, L.M.X., 2006. Configurational analysis of cubebins and bicubebin from *Aristolochia lagesiana* and *Aristolochia pubescens*. Phytochemistry 67, 735–742.

Duke, J.A. 1985. CRC handbook of medicinal herbs, CRC Press, Boca Raton, FL, p. 63.

Duke, J.A, and Ayensu, E.S. 1985. Medicinal plants of China, Vol. 1, Reference Publications Inc., Algonac, MI, p. 131.

Elango, G., Rahuman, A.A., Kamaraj, C., Bagavan, A., Zahir, A.A., 2011. Screening for feeding deterrent activity of herbal extracts against the larvae of malaria vector *Anopheles subpictus* Grassi. Parasitology Research 109, 715–726.

Ferreira, M.L.R., de Pascoli, I.C., Nascimento, I.R., Zukerman-Schpector, J., Lopes, L.M.X., 2010. Aporphine and bisaporphine alkaloids from *Aristolochia lagesiana* var. *intermedia*. Phytochemistry 71, 469–478.

Georgopoulou, C., Aligiannis, N., Fokialakis, N., Mitaku, S., 2005. Acretoside, a new sucrose ester from *Aristolochia cretica*. Journal of Asian Natural Products Research 7, 799–803.

Gonzalez, F. 1999. A phylogenetic analysis of the Aristolochioideae (*Aristolochia*ceae), Ph. D thesis, The City University of New York.

Harborne, J.B. 1986. Plant flavonoids in biology and medicine: biochemical, pharmacological, and structure-activity relationships, in Cody, V., Middleton, E. Jr., Harborne, J.B. eds, Progress in clinical and biological research, Alan R. Liss, New York, p. 15.

Harborne, J.B. 1994. The flavonoids – advances in research since 1986, Chapman and Hall, London.

Hegde, V.R., Borges, S., Patel, M., Das, P.R., Wu, B., Gullo, V.P., Chan, T.M., 2010. New potential antitumor compounds from the plant *Aristolochia manshuriensis* as inhibitors of the CDK2 enzyme. Bioorganic & Medicinal Chemistry Letters 20, 1344–1346.

Holzbach, J.C., Lopes, L.M.X., 2010. Aristolactams and alkamides of *Aristolochia gigantea*. Molecules 15, 9462–9472.

Hou, D. 1996. Flora of Taiwan, 2nd Ed., Vol. 2, Editorial Committee of the Flora of Taiwan, Taipei, pp. 636–642.

How, F.C. 1985. A dictionary of the families and genera of Chinese seed plants, 2nd Ed., Science Press, Beijing, p. 43.

Hutchinson, J. 1973. The families of flowering plants, 3rd Ed., Clarendon Press, Oxford, p. 510.

Izquierdo, A.M., Zapata, E.V., Jiménez-Ferrer, J.E., Muñoz, C.B., Aparicio, A.J., Torres, K.B., Torres, L.O., 2010. Scorpion antivenom effect of micropropagated *Aristolochia elegans*. Pharmaceutical Biology 48, 891–896.

Jbilou, R., Amri, H., Bouayad, N., Ghailani, N., Ennabili, A., Sayah, F., 2008. Insecticidal effects of extracts of seven plant species on larval development, α-amylase activity and offspring production of *Tribolium castaneum* (Herbst) (Insecta: Coleoptera: Tenebrionidae). Bioresource Technology 99, 959–964.

Jiangsu New Medicine College. 1977. Encyclopedia of Chinese materia medica, Vol. 1, Shanghai Science and Technology Press, Shanghai, p. 294.

Jiménez-Ferrer, J.E., Pérez-Terán, Y.Y., Román-Ramos, R., Tortoriello, J., 2005. Antitoxin activity of plants used in Mexican traditional medicine against scorpion poisoning. Phytomedicine 12, 116–122.

Kamaraj, C., Rahuman, A.A., Mahapatra, A., Bagavan, A., Elango, G., 2010. Insecticidal and larvicidal activities of medicinal plant extracts against mosquitoes. Parasitology Research 107, 1337–1349.

Kumar, V.P., Chauhan, N.S., Padh, H., Rajani, M., 2006. Search for antibacterial and antifungal agents from selected Indian medicinal plants. Journal of Ethnopharmacology 107, 182–188.

León-Díaz, R., Meckes, M., Said-Fernández, S., Molina-Salinas, G.M., Vargas-Villarreal, J., Torres, J., Luna-Herrera, J., Jiménez-Arellanes, A., 2010. Antimycobacterial neolignans isolated from *Aristolochia taliscana*. Memórias do Instituto Oswaldo Cruz, Rio de Janeiro 105, 45–51.

Li, S.Z. 1977. Ban Tso Gan Mo, Peoples Health Press, Beijing, p. 1595.

Liu, T.S., and Lai, M.J. 1976. Flora of Taiwan, Vol. 2, Epoch, Taipei, p. 572.

Lopes, L.M.X., Nascimento, I.R., and Da Silva, T. 2001. Phytochemistry of the *Aristolochia*ceae family, in: Mohan, R.M.M. ed., Research advances in phytochemistry, Vol. 2, Global Research Network, Kerala, pp. 19–108.

Machado, M.B., Lopes, L.M.X., 2005. Chalcone-flavone tetramer and biflavones from *Aristolochia ridicula*. Phytochemistry 66, 669–674.

Machado, M.B., Lopes, L.M.X., 2008. Tetraflavonoid and biflavonoids from *Aristolochia ridicula*. Phytochemistry 69, 3095–3102.

Messiano, G.B., Vieira, L., Machado, M.B., Lopes, L.M.X., de Bortoli, S.A., Zukerman-Schpector, J., 2008. Evaluation of insecticidal activity of diterpenes and lignans from *Aristolochia malmeana* against *Anticarsia gemmatalis*. Journal of Agricultural and Food Chemistry 56, 2655–2659.

Nascimento, I.R., Murata, A.T., Bortoli, S.A., Lopes, L.M.X., 2003. Insecticidal activity of chemical constituents from *Aristolochia pubescens* against *Anticarsia gemmatalis* larvae. Pest Management

Science 60, 413–416.
Navarro-García, V.M., Luna-Herrera, J., Rojas-Bribiesca, M.G., Álvarez-Fitz, P., Ríos, M.Y., 2011. Antibacterial activity of *Aristolochia brevipes* against multidrug-resistant *Mycobacterium tuberculosis*. Molecules 16, 7357–7364.
Nedelko, T., Arlt, V.M., Phillips, D.H., Hollstein, M., 2009. TP53 mutation signature supports involvement of aristolochic acid in the aetiology of endemic nephropathy-associated tumours. International Journal of Cancer 124, 987–990.
Nok, A.J., Sallau, B.A., Onyike, E., Useh, N.M., 2005. Columbin inhibits cholesterol uptake in bloodstream forms of *Trypanosoma brucei* − A possible trypanocidal mechanism. Journal of Enzyme Inhibition and Medicinal Chemistry 20, 365–368.
Nortier, J.L., Martinez, M.C.M., Schmeiser, H.H., Arlt, V.M., Bieler, C.A., Petein, M., Depierreux, M.F., Pauw, L.D., Abramowicz, D., Vereerstraeten, P., Vanherweghem, J.L., 2000. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). The New England Journal of Medicine 342, 1686–1692.
Perry, L.M. 1980. Medicinal plants of the East and Southeast Asia, MIT press, Cambridge.
Pharmacopoeia of the People's Republic of China, 1977. English Edition, The Pharmacopeia Commission of PROC, Beijing.
Pharmacopeia of China, Vol. 1, 1985. Peoples Press, Beijing, pp. 36–38.
Romeo, J., Downum, K., and Verpoorte, R. 1998. Recent advances in phytochemistry, Plenum Publication, New York.
Samy, R.P., Thwin, M.M., Gopalakrishnakone, P., Ignacimuthu, S., 2008. Ethnobotanical survey of folk plants for the treatment of snakebites in Southern part of Tamilnadu, India. Journal of Ethnopharmacology 115, 302–312.
Sartorelli, P., Carvalho, C.S., Reimão, J.Q., Lorenzi, H., Tempone, A.G., 2010. Antitrypanosomal activity of diterpene and lignans isolated from *Aristolochia cymbifera*. Planta Medica 76, 1454–1456.
Shen, M.Y., Liu, C.L., Hsiao, G., Liu, C.Y., Lin, K.H., Chou, D.S., Sheu, J.R., 2008. Involvement of p38 MAPK phosphorylation and nitrate formation in aristolochic acid-mediated antiplatelet activity. Planta Medica 74, 1240–1245.
Shi, L.S., Kuo, P.C., Tsai, Y.L., Damu, A.G., Wu, T.S., 2004. The alkaloids and other constituents from the root and stem of *Aristolochia elegans*. Bioorganic & Medicinal Chemistry 12, 439–446.
Simoes, C.M.O., Mentz, L.A., Schenkel, E.P., Iragang, B.E., and Stehmann, J.R. 1986. Plants da Medicina Popular no Rio Grande do Sul, UFRGS Ed, Porto Alegre, p. 50.
Stafford, H.A., 1997. Roles of flavonoids in symbiotic and defense functions in legume roots. The Botanical Review 63, 27–39.
Tang, W., and Eisenbrand, G. 1992. Chinese drug of plant origin chemistry, pharmacology and use in traditional and modern medicine, Springer-Verlag, Berlin, p. 145.
The European Agency for the Evaluation of Medicinal Products, 1997, Veterinary Medicines Evaluation unit, London.
Therapuetic Goods Administration, 2001. Practitioner alert, Commonwealth department of Health and Aged care, Australia.
Vanherweghem, J.L., Depierreux, M., Tielemans, C., Abramowicz, D., Dratwa, M., Jadoul, M., Richard, C., Vandervelde, D., Verbeelen, D., Vanhaelen-Faster, R., Vanhealen, M., 1993. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. Lancet 431, 387–391.
Vanherweghem, J.L., 2002. Chinese herbs (*Aristolochia*) nephropathy. Nieren-und Hochdruckkrankheiten 31, 344–349.
Watson, L., and Dallwitz, M.J. 1992. The families of flowering plants, CSIRO Publicatoins, Melbourne.
Wu, T.S., Damu, A.G., Su, C.R., and Kuo, P.C. 2005. Chemical constituents and pharmacology of *Aristolochia* Species, in: Atta-ur-Rahman, ed., Studies in natural product chemistry (bioactive natural proudcts), Vol. 32, Elsevier, Amsterdam, pp. 855–1018.
Ylstra, B., Touraev, A., Moreno, R.M.B., Stöger, E., van Tunen, A.J., Vicente, O., Mol, J.N.M., Heberle-Bors, E., 1992. Flavonols stimulate development, germination, and tube growth of tobacco pollen. Plant Physiology 100, 902–907.
Yu, J.Q., Liao, Z.X., Cai, X.Q., Lei, J.C., Zou, G.L., 2007. Composition, antimicrobial activity and cytotoxicity of essential oils from *Aristolochia mollissima*. Environmental Toxicology and Pharmacology 23, 162–167.
Zhai, H., Nakatsukasa, M., Mitsumoto, Y., Fukuyama, Y., 2004. Neurotrophic effects of talaumidin, a neolignan from *Aristolochia arcuata*, in primary cultured rat cortical neurons. Planta Medica 70, 598–602.
Zhai, H., Inoue, T., Moriyama, M., Esumi, T., Mitsumoto, Y., Fukuyama, Y., 2005. Neuroprotective effects of 2,5-diaryl-3,4-dimethyltetrahydrofuran neolignans. Biological and Pharmaceutical Bulletin 28, 289–293.
Zhang, G., Shimokawa, S., Mochizuki, M., Kumamoto, T., Nakanishi, W., Watanabe, T., Ishikawa, T., Matsumoto, K., Tashima, K., Horie, S., Higuchi, Y., Dominguez, O.P., 2008. Chemical constituents of *Aristolochia constricta*: antispasmodic effects of its constituents in guinea-pig ileum and isolation of a diterpeno−lignan hybrid. Journal of Natural Products 71, 1167–1172.
Zhu, S., Sunnassee, A., Yuan, R., Ren, L., Chen, X., Liu, L., 2010. Fatal renal failure due to the Chinese herb ''GuanMuTong'' (*Aristolochia manshuriensis*): Autopsy findings and review of literature. Forensic Science International 199, e5–e7.