



## Chemical Constituents and Pharmacology of the *Aristolochia* (馬兜鈴 mǎ dōu líng) species

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### Abstract

*Aristolochia* (馬兜鈴 mǎ dōu líng) 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, benzyloquinolines, 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 líng*) species.

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

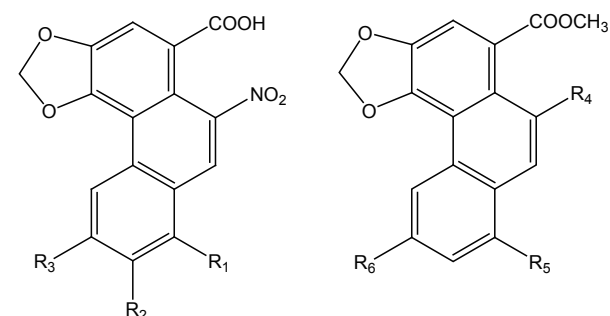
Species	Part	Compound	Reference
		(-)-kaurene (34) (-)-kauran-16 $\alpha$ ,17,18-triol (35) aristolactam AII; aristolactam AII (36) cepharanone B (37) aristelegone A (38) (+)-4,7-dimethyl-6-methoxy-1-tetralone (39) cadalene (40) $\beta$ -sitosterol glucoside; $\beta$ -sitosteryl glucoside (41) <i>N</i> -trans-feruloyltyramine (42)	
<i>A. contorta</i>			
	fruits	3"-hydroxyamentoflavone-7-O-methyl ether (43) 3"-hydroxyamentoflavone (44)	Chen et al, 2005
<i>A. cretica</i>			
	roots	aristolochic acid I; aristolochic acid A (1) aristolochic acid IIIa; aristolochic acid C (45) 6- <i>O</i> - <i>p</i> -coumaroyl- $\beta$ -D-fructofuranosyl-(2 $\rightarrow$ 1)- $\alpha$ -D- glucopyranoside (46) arillatose B (47) 6- <i>O</i> - <i>p</i> -coumaroyl- $\alpha$ -D-glucopyranose (48) 6- <i>O</i> - <i>p</i> -coumaroyl- $\beta$ -D-glucopyranose (49) 7-hydroxyaristolochic acid I (50) aristolochic acid II; aristolochic acid B (51) ariskanin A (52)	Georgopoulou et al, 2005
<i>A. cymbifera</i>			
	whole plant	2-oxo-populifolic acid (53)	de Barros Machado et al, 2005
	leaves	(-)-hinokinin (24) (-)-kusunokinin (54) (-)-copalic acid (55) (-)-fargesin (56) (+)-sesamin (57) epieudesmin (58)	Sartorelli et al, 2010
<i>A. elegans</i>			
	stems and roots	aristolochic acid I; aristolochic acid A (1) $\beta$ -sitosterol (10) (-)-hinokinin (24) (-)-cubebin (26) (-)-kaur-15-en-17-ol (27) aristolactam AII; aristolactam AII (36) aristelegone A (38) $\beta$ -sitosteryl glucoside (41) <i>N</i> -trans-feruloyltyramine (42) <i>N</i> -trans-cinnamyltyramine(54) aristolactam E (59) aristolactam-AIIIa-6-O- $\beta$ -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- $\beta$ -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)	Shi et al, 2004

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

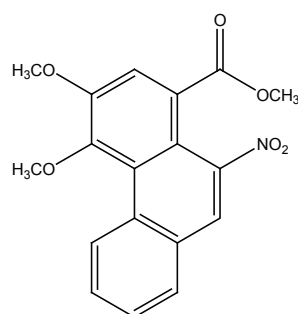
Species	Part	Compound	Reference
<i>A. ligesiana</i>			
	leaves	(6 <i>R</i> ,6 <i>aS</i> , <i>P</i> )-isocorydine (132) (6 <i>S</i> ,6 <i>aS</i> , <i>M</i> )-isocorydine (133) (6 <i>aS</i> , <i>M</i> )-(+)-norisocorydine (134) (6 <i>S</i> ,6 <i>aS</i> , <i>M</i> )-(+)-corydine-N <sup>?</sup> oxide (135)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

### 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; Therapeutic Goods Administration, 2001). In addition, seven methyl esters



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>		R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>
1	OCH <sub>3</sub>	H	H	100	NO <sub>2</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>
45	H	H	OH	101	NO <sub>2</sub>	OCH <sub>3</sub>	H
50	OCH <sub>3</sub>	OH	H	102	NO <sub>2</sub>	OCH <sub>3</sub>	OH
51	H	H	H	103	NO <sub>2</sub>	OH	H
98	OCH <sub>3</sub>	H	OH	151	H	OCH <sub>3</sub>	OCH <sub>3</sub>
99	OCH <sub>3</sub>	Glc	H	152	H	OCH <sub>3</sub>	H
116	H	OH	H				
117	OH	H	OH				



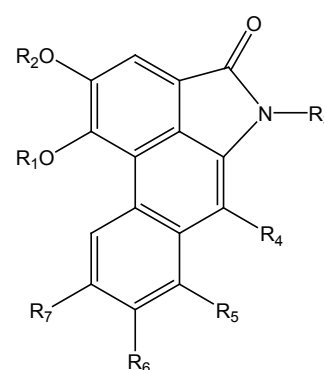
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Figure 1. Aristolochic acids and esters from the *Aristolochia* species.

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 aristolochic acid methyl ester (151) and 6-methoxyaristolochic 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).

### 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*- $\beta$ -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.



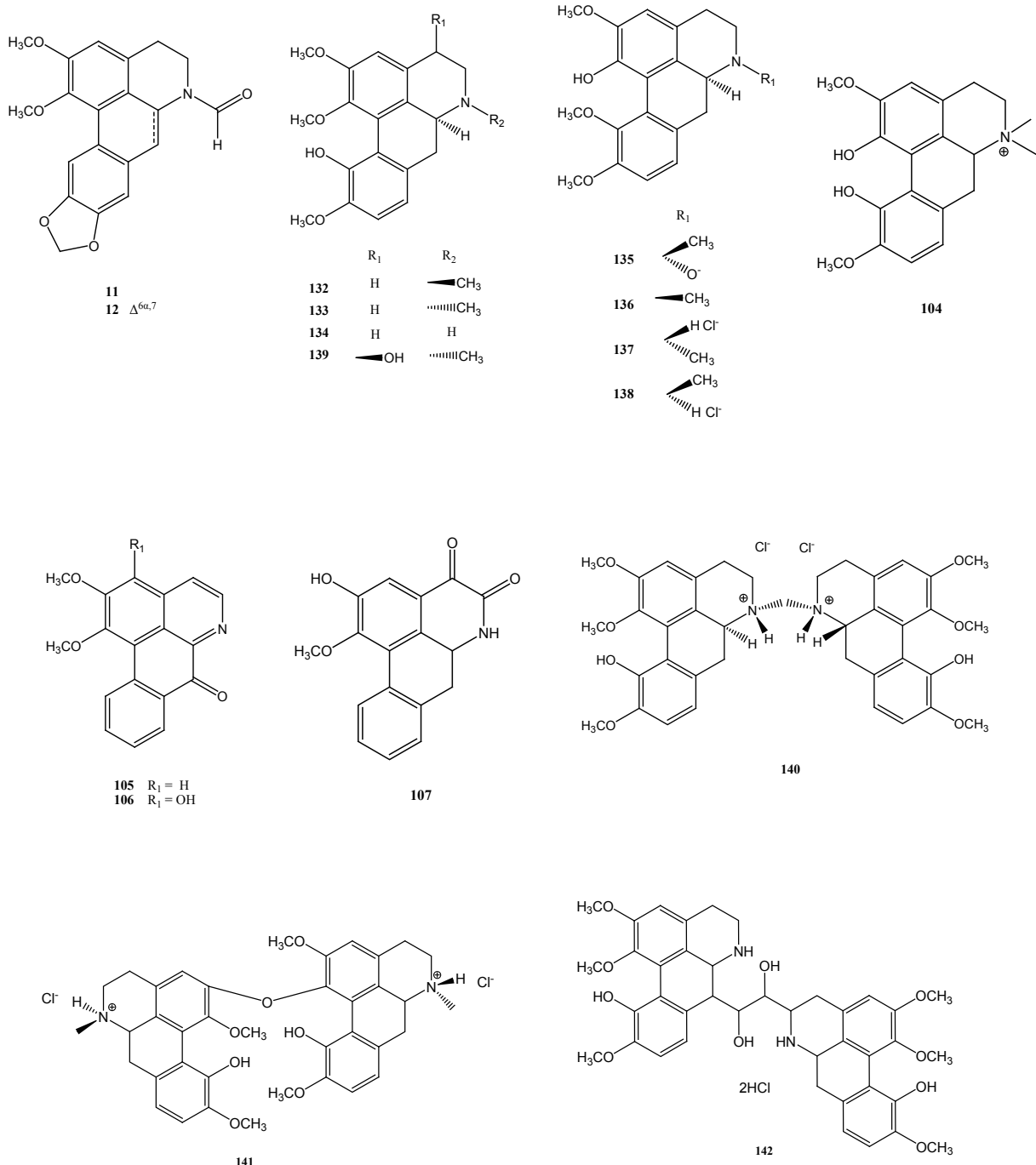
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>
15	CH <sub>2</sub>	H	H	H	OCH <sub>3</sub>	H	H
36	CH <sub>3</sub>	H	H	H	H	H	H
37	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	H	H
59	H	CH <sub>3</sub>	H	H	OH	OCH <sub>3</sub>	H
60	CH <sub>3</sub>	H	H	H	H	H	OGlc
66	H	CH <sub>3</sub>	H	H	H	H	H
67	CH <sub>3</sub>	H	H	H	H	H	OH
68	CH <sub>2</sub>	H	Glc	OCH <sub>3</sub>	OCH <sub>3</sub>	H	OH
122	CH <sub>2</sub>	H	Glc	H	OH	H	H
123	CH <sub>2</sub>	H	H	H	Glc	H	H
124	CH <sub>2</sub>	H	H	H	H	H	OH
125	CH <sub>2</sub>	H	H	OGlc-Glc	OCH <sub>3</sub>	H	H

Figure 2. Aristolactams from the *Aristolochia* species.

**Aporphines**

Seventeen aporphine alkaloids have been characterized from *Aristolochia* species (Figure 3). Aporphines with *N*-formyl substitution, 6 $\alpha$ ,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 *Aristolochiaceae* 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.

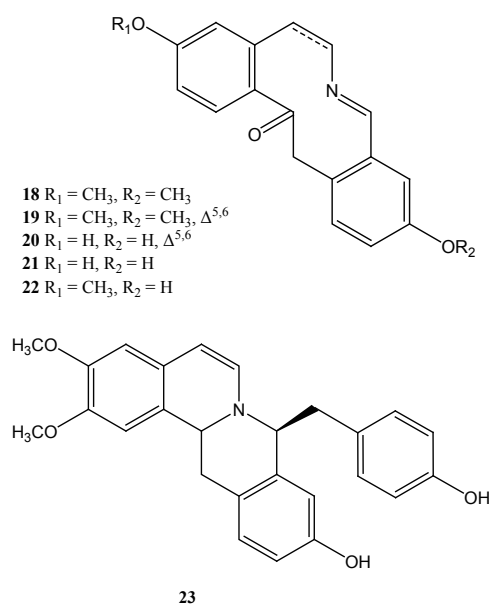


Figure 4. Protoberberines from the *Aristolochia* species.

### 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 bisbenzyltetrahydroisoquinoline alkaloids (Shi et al, 2004).

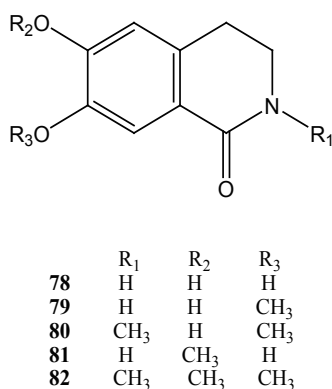


Figure 5. Isoquinolines from the *Aristolochia* species.

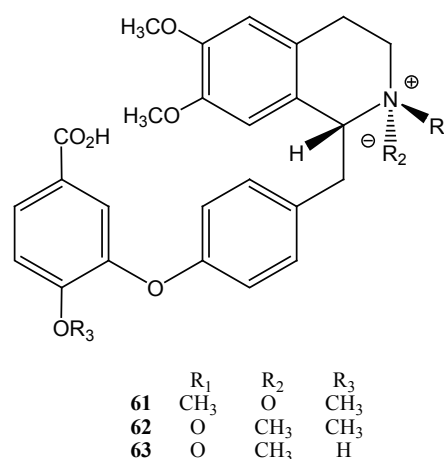


Figure 6. Benzyloquinolines from the *Aristolochia* species.

### Benzyloquinolines

The occurrence of benzyloquinoline 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 bisbenzyltetrahydroisoquinolines. The isoquinolones, benzyloquinolines, biphenyl ethers, and *N*-oxide benzoyl benzyltetrahydroisoquinoline 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  $-\text{CONH}_2$  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



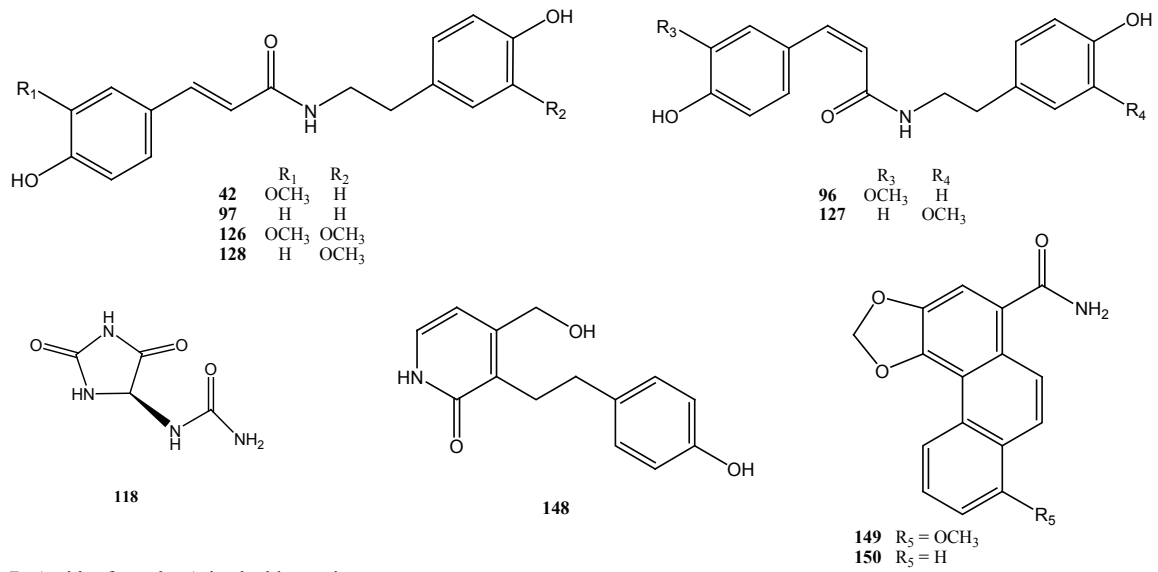


Figure 7. Amides from the *Aristolochia* species.

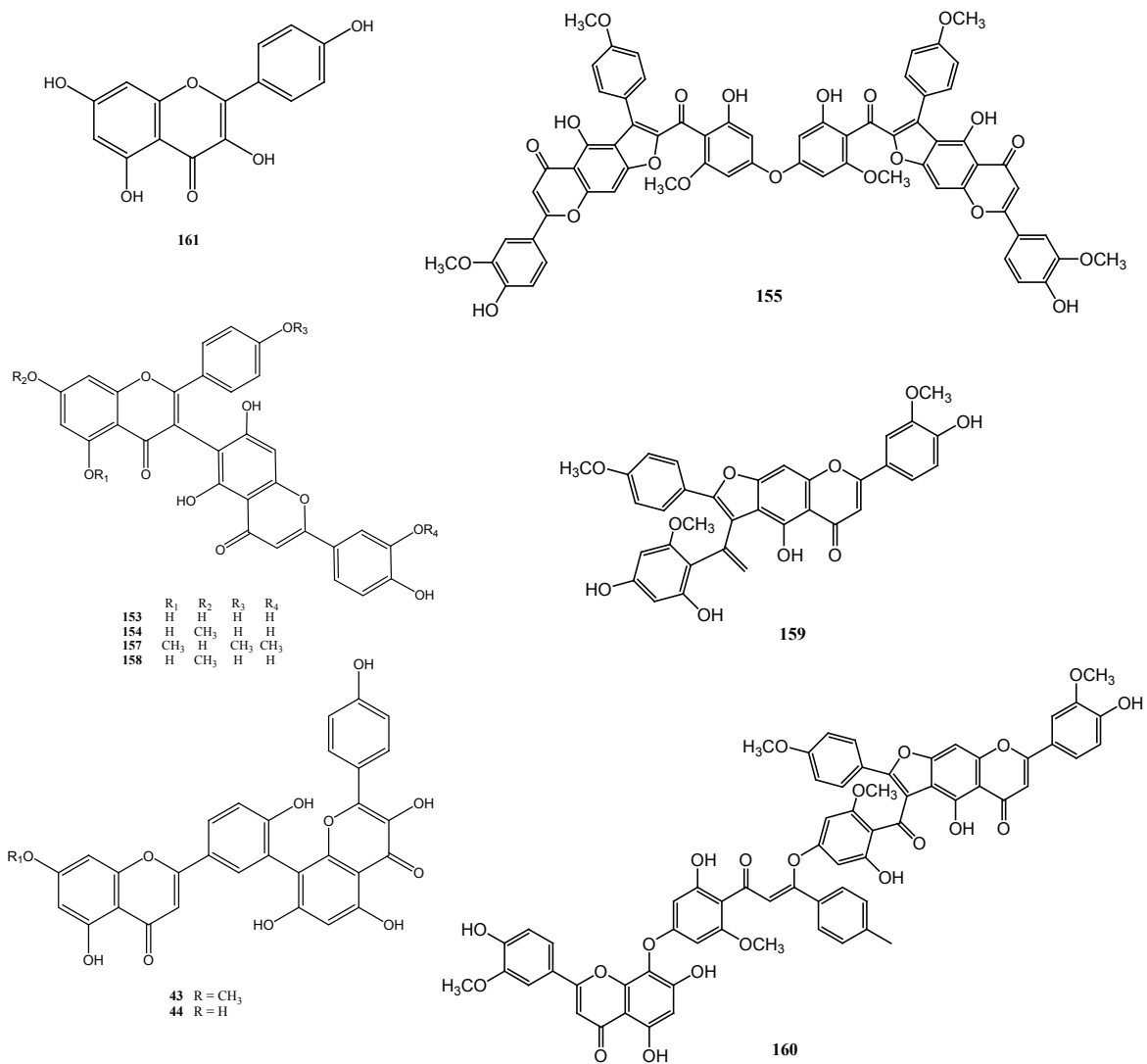


Figure 8. Flavonoids from the *Aristolochia* species.

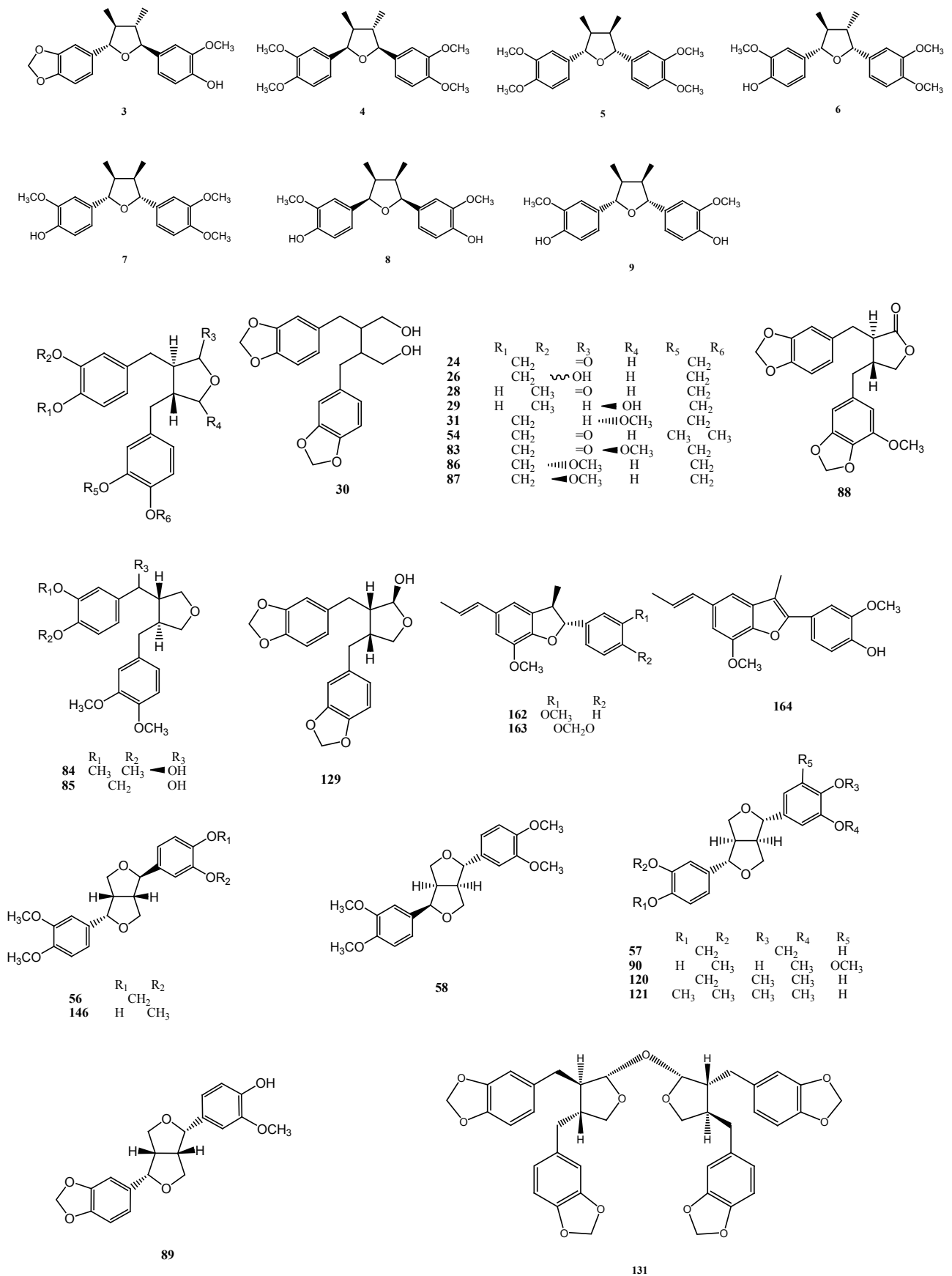


Figure 9. Lignans from the *Aristolochia* species.

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 characterized from *A. ridicula* (Machado and Lopes, 2005; 2008) (Figure 8). These reports constitute the presence of bi- and tetraflavonoids in the family *Aristolochiaceae*. 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 bisepoxy lignans. 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 bisepoxy lignans 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.

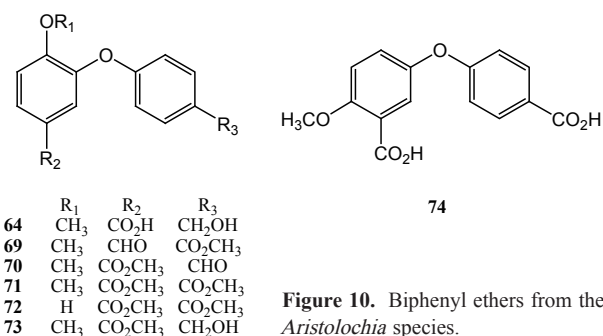


Figure 10. Biphenyl ethers from the *Aristolochia* species.

### Coumarins

Although there were only two coumarins, 7,9-dimethoxytariacuripyronone (13) and 9-methoxytariacuripyronone (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.

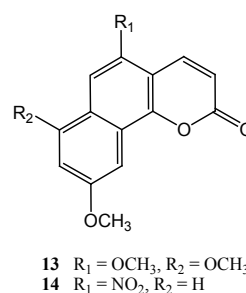


Figure 11. Coumarins from the *Aristolochia* species.

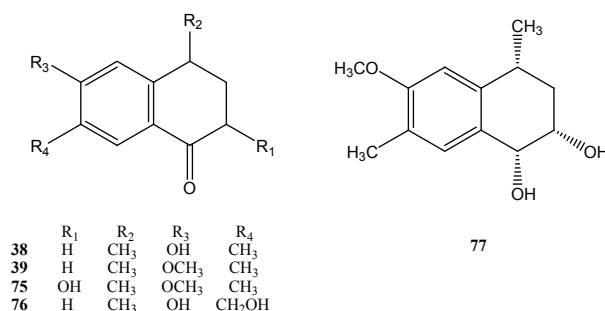


Figure 12. Tetralones from the *Aristolochia* species.

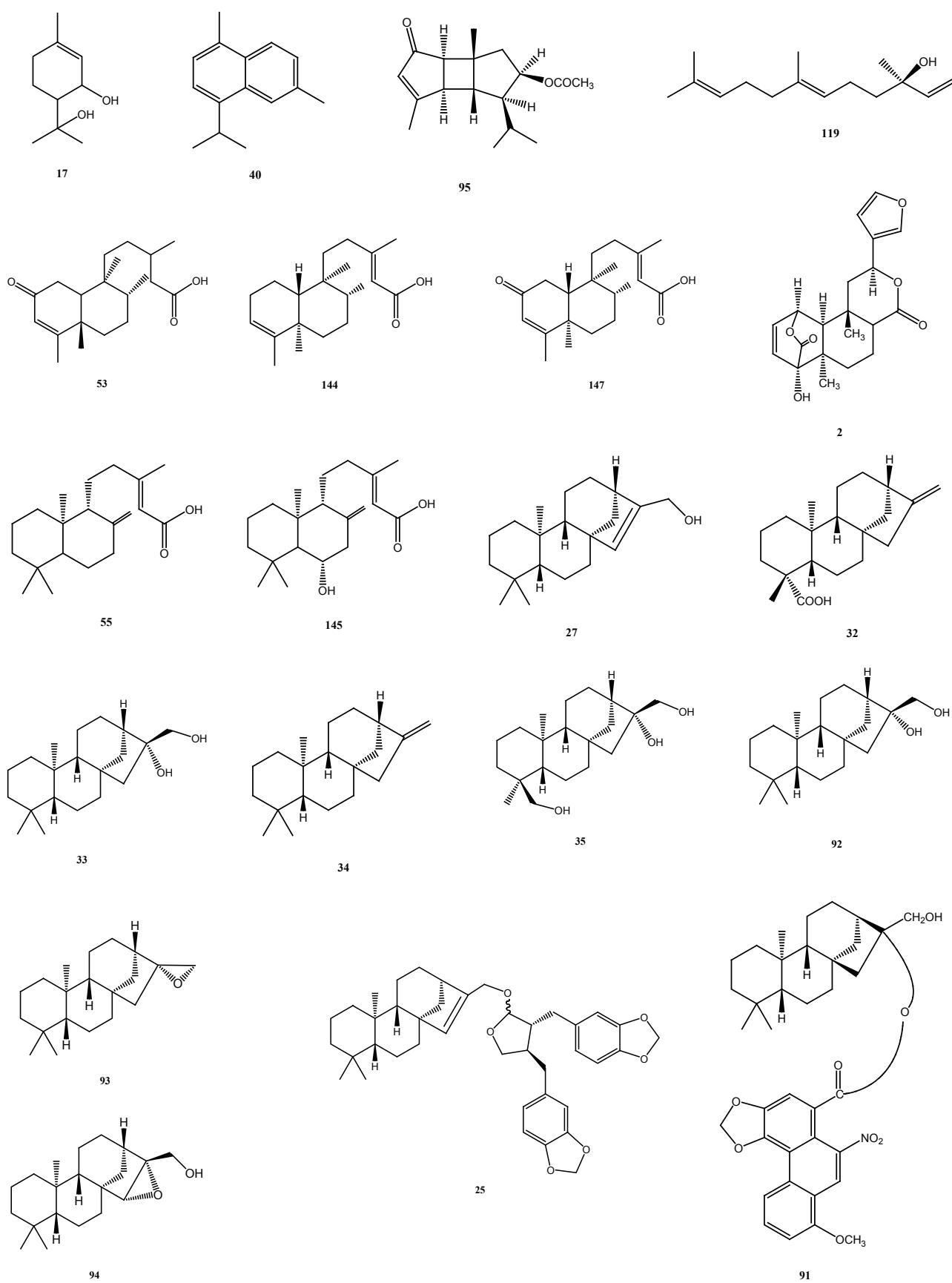


Figure 13. Terpenoids from the *Aristolochia* species.

## 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- $\alpha$ -terpineol (17), was identified from the roots of *A. brevipes* (Navarro-García et al, 2011). Three sesquiterpenoids, cadalene (40) (Zhang et al, 2008), aristolide (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<sub>20</sub> 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- $\beta$ -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- $\beta$ , 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

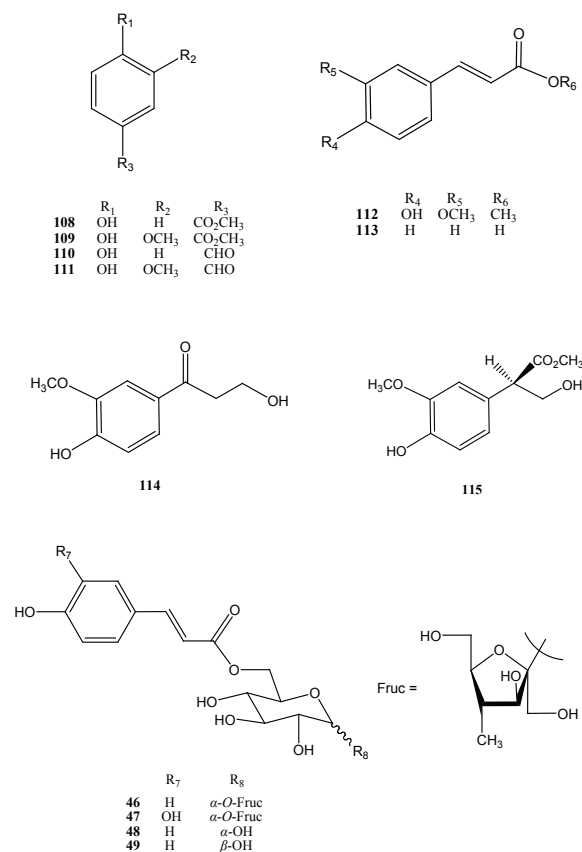


Figure 14. Benzenoids from the *Aristolochia* species.

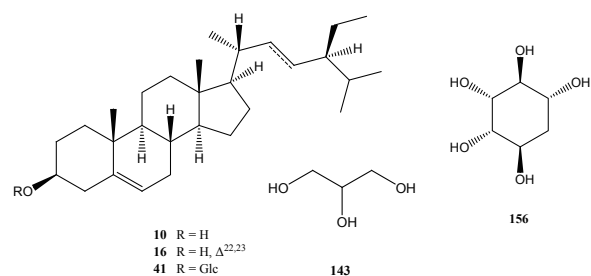


Figure 15. Steroids and others from the *Aristolochia* species.

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  $\beta$ -sitosterol and stigmasterol. Among these steroids,  $\beta$ -sitosterol (10) and  $\beta$ -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

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

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

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  $\mu$  and  $\kappa$  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-dimethoxytariacuripyron (13), 9-methoxytariacuripyron (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

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 *smā dōu ling*) species.

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