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

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Abstract

Aristolochia (馬兜鈴 mǎduōu 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 scented, 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, benzyisoquinolines, amides, flavonoids, lignans, biphenyl ethers, coumarins, tetralones, terpenoids, benzeneoids, 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.

| 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 | talauiminid (3) | Zhai et al, 2004 Zhai et al, 2005 |
| | | veraguensin (4) | |
| | | 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-formyl-nornantenine (12) | |
| | | 7,9-dimethoxytariacuripyrone (13) | |
| | | 9-methoxytariacuripyrone (14) | |
| | | aristolactam 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-oxy]cubebin (25) | |
| | | (−)-cubebin (26) | |
| | | (−)-kaur-15-en-17-ol (27) | |
| | | (−)-pluviatolide (28) | |
| | | (−)-haplomyrfolol (29) | |
| | | (−)-dihydrocubein (30) | |
| | | 9-O-methylcubein (31) | |
| | | (−)-kaur-16-en-19-oic acid (32) | |
| | | (−)-kauran-16α,17-diol (33) | |
| Species  | Part            | Compound                                                                 | Reference                      |
|----------|-----------------|---------------------------------------------------------------------------|--------------------------------|
| A. contorta | fruits        | (−)-kaurene (34)                                                        | Kuo et al, 2012                |
| A. contorta |                | (−)-kauran-16α,17,18-triol (35)                                         |                                |
| A. contorta |                | aristolactam AII; aristolactam AII (36)                                  |                                |
| A. contorta |                | cepharanone B (37)                                                      |                                |
| A. contorta |                | aristelegone A (38)                                                     |                                |
| A. contorta |                | (−)-4,7-dimethyl-6-methoxy-1-tetralone (39)                             |                                |
| A. contorta |                | cadalene (40)                                                           |                                |
| A. contorta |                | β-sitosterol glucoside; β-sitosteryl glucoside (41)                      |                                |
| A. contorta |                | N-trans-feruloyltyramine (42)                                           |                                |
| A. contorta | fruits        | 3’-hydroxyamentoflavone-7-O-methyl ether (43)                            | Chen et al, 2005               |
| A. contorta |                | 3’-hydroxyamentoflavone (44)                                            |                                |
| A. cretica | roots          | aristolochic acid I; aristolochic acid A (1)                            | Georgopoulou et al, 2005       |
| A. cretica |                | aristolochic acid IIIa; aristolochic acid C (45)                        |                                |
| A. cretica |                | 6-O-p-coumaroyl-β-D-fructofuranosyl-(2→1)-α-D-glucopyranoside (46)      |                                |
| A. cretica |                | arillatose B (47)                                                      |                                |
| A. cretica |                | 6-O-p-coumaroyl-α-D-glucopyranose (48)                                   |                                |
| A. cretica |                | 6-O-p-coumaroyl-β-D-glucopyranose (49)                                   |                                |
| A. cretica |                | 7-hydroxyaristolochic acid I (50)                                       |                                |
| A. cretica |                | aristolochic acid II; aristolochic acid B (51)                           |                                |
| A. cymbifera | whole plant    | 2-oxo-populifolic acid (53)                                             | de Barros Machado et al, 2005  |
| A. cymbifera | leaves        | (−)-hinokinin (24)                                                     | Sartorelli et al, 2010         |
| A. cymbifera |                | (−)-kusunokinin (54)                                                   |                                |
| A. cymbifera |                | (−)-copalic acid (55)                                                  |                                |
| A. cymbifera |                | (−)-fargesin (56)                                                      |                                |
| A. cymbifera |                | (+)-sesamin (57)                                                       |                                |
| A. cymbifera |                | epieudesmin (58)                                                       |                                |
| A. elegans | stems and roots| aristolochic acid I; aristolochic acid A (1)                            | Shi et al, 2004                |
| A. elegans |                | β-sitosterol (10)                                                       |                                |
| A. elegans |                | (−)-hinokinin (24)                                                     |                                |
| A. elegans |                | (−)-cubebin (26)                                                        |                                |
| A. elegans |                | (−)-kaur-15-en-17-ol (27)                                               |                                |
| A. elegans |                | aristolactam AII; aristolactam AII (36)                                 |                                |
| A. elegans |                | aristelegone A (38)                                                     |                                |
| A. elegans |                | β-sitosteryl glucoside (41)                                             |                                |
| A. elegans |                | N-trans-feruloyltyramine (42)                                           |                                |
| A. elegans |                | N-trans-cinnamoyltyramine (54)                                          |                                |
| A. elegans |                | aristolactam E (59)                                                    |                                |
| A. elegans |                | aristolactam-AIIIa-6-O-β-D-glucoside (60)                               |                                |
| A. elegans |                | aristoinoline A (61)                                                   |                                |
| A. elegans |                | aristoinoline B (62)                                                   |                                |
| A. elegans |                | aristoinoline C (63)                                                   |                                |
| A. elegans |                | aristogin F (64)                                                       |                                |
| A. elegans |                | 9-methoxyaristolactam I (65)                                            |                                |
| A. elegans |                | isoaristolactam AII (66)                                               |                                |
| A. elegans |                | aristolactam AIIIa (67)                                                |                                |
| A. elegans |                | aristolactam C N-β-D-glucoside (68)                                     |                                |
| A. elegans |                | aristogin A (69)                                                       |                                |
| A. elegans |                | aristogin B (70)                                                       |                                |
| A. elegans |                | aristogin C (71)                                                       |                                |
| A. elegans |                | aristogin D (72)                                                       |                                |
| A. elegans |                | aristogin E (73)                                                       |                                |
| A. elegans |                | 4-methoxy-3,4′-oxydibenzoic acid (74)                                   |                                |
| A. elegans |                | aristolegine B (75)                                                    |                                |
| A. elegans |                | aristolegine C (76)                                                    |                                |
| A. elegans |                | aristolegine D (77)                                                    |                                |
| A. elegans |                | pericampylinone A (78)                                                |                                |
| A. elegans |                | corydaldine (79)                                                       |                                |
| A. elegans |                | thalifoline (80)                                                       |                                |
| Species Part | Compound                                                                 | Reference |
|--------------|--------------------------------------------------------------------------|-----------|
| A. fangchi   | species                                                                 |           |
| 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  | species                                                                 | Holzbach and Lopes, 2010 |
| rhizomes     | β-sitosterol (10)                                                       |           |
|              | 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. laguesiana | roots                                                                  | de Pascoli et al, 2006 |
|              | (−)-(8S,8′R,9S)-cubebin (129)                                           |           |
|              | (−)-(8R,8′R,9R) and (+)-(8R,8′S,9R,9′S)-bicubebin A (131)              |           |
| Species          | Part               | Compound                          | Reference                             |
|------------------|--------------------|-----------------------------------|---------------------------------------|
| A. ligesiana     | leaves             | 
|                  | (6R,6aS,P)-isocorydine (132)   | Ferreira et al, 2010                |
|                  | (6S,6aS,M)-isocorydine (133) |                                   |
|                  | (6aS,M)(+)-norisocorydine (134) |                                   |
|                  | (6S,6aS,M)(+)-corydine-N oxide (135) |                           |
|                  | (6R,6aS,P)(+)-corydine (136)   |                                   |
|                  | (6S,6aS,M)-corydine hydrochloride (137) | and (6R,6aS,M)-corydine hydrochloride (138) |
|                  | lagesianine A (139)   |                                   |
|                  | lagesianine B (140)   |                                   |
|                  | lagesianine C (141)   |                                   |
|                  | lagesianine D (142)   |                                   |
|                  | glycerol (143)        |                                   |
| A. malmeana      | roots              | c–hinokinin (24)                  | Messiano et al, 2008                 |
|                  |                    | c–kusunonin (54)                  |                                       |
|                  |                    | c–(8S,8′R,9S)-cubebin (129)       |                                       |
|                  |                    | c–kolavenic acid (144)            |                                       |
|                  | leaves             | c–hinokinin (24)                  |                                       |
|                  |                    | c–kusunonin (54)                  |                                       |
|                  |                    | c–copalic acid (55)               |                                       |
|                  |                    | c–fargesin (56)                   |                                       |
|                  |                    | c–(8R,8′R,9R) and (c–)(8S,8′R,9S)-cubebins (130) ||
|                  |                    | c–ent-6β-hydroxycopalic acid (145)|                                       |
|                  |                    | c–phillygenin (146)               |                                       |
|                  |                    | c–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)          |                                       |
|                  |                    | aristolamidine (149)              |                                       |
|                  |                    | aristolamidine 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               |
|                  |                    | c–cubebin (26)                    |                                       |
|                  |                    | c–kaur-15-en-17-ol (27)           |                                       |
|                  |                    | c+sesamin (57)                   |                                       |
|                  |                    | c+eudesmin (121)                 |                                       |
|                  | tubercula          | c–(8S,8′R,9S)-cubebin (129)       | de Pascoli et al, 2006               |
|                  |                    | c–(8R,8′R,9R) and (c–)(8S,8′R,9S)-cubebins (130) ||
|                  |                    | (8R,8′R,8′′R,9R,9′′S)-bicubebin A (131) | |
| A. ridicula      | leaves             | ridiculavone A (153)              | Machado and Lopes, 2005              |
|                  |                    | ridiculavone B (154)              |                                       |
|                  |                    | ridiculavoneylehalcone A (155)    |                                       |
|                  |                    | proto-quercitol (156)             | Machado and Lopes, 2008              |
|                  |                    | ridiculavone C (157)              |                                       |
|                  |                    | ridiculavone D (158)              |                                       |
|                  |                    | ridiculavoneylehalcone B (159)    |                                       |
|                  |                    | ridiculavoneylehalcone C (160)    |                                       |
| A. taliscana     | roots              | kaempferol (161)                  | Battu et al, 2011                   |
| A. tagala        | 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; Therapeutic 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).

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 All (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.

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

Figure 2. Aristolactams from the Aristolochia species.
Aporphines

Seventeen aporphine alkaloids have been characterized from *Aristolochia* species (Figure 3). Aporphines with N-formyl substitution, 6α,7-dehydro-N-formylornantenine (11) and N-formylornantenine (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-dioxaaporphine 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.
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 structurally interesting bisbenzyltetrahydroisoquinolines. The isoquinolones, benzylisoquinolines, biphenyl ethers, and N-oxide benzyl benzyltetrahydroisouinoline 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 –CONH2 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 biflavanoids 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, benzoferans, 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 (8R, 8'R, 8''R, 8 '''R, 9R, 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.

**Coumarins**

Although there were only two coumarins, 7,9-dimethoxytariacuripyrone (13) and 9-methoxytariacuripyrone (14), characterized from the roots of *A. brevipes* (Figure 11), these constituents also displayed significant physiological activity (Navarro-Garcia 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. consticta* (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 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-Garcia 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<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-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 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. cymbiorea, 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, talauimidin (3), galgravin (5), aristolignin (6), nectandrin A (7), isonectandrin B (8), and nectandrin B (9) all exhibited neuroprotective bioactivity (Zhai et al, 2008). In addition, (−)-hinokinin (24), (−)-cubebin (26), (−)-pluviatolide (28), and (−)-haplomyrrolol (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

| Source        | Parts                  | Bioactivity            | Reference                  |
|---------------|------------------------|------------------------|----------------------------|
| A. baetica    | stem roots             | insecticidal           | Jbilou et al, 2008         |
| A. bracteolata| whole plant leaves     | antiasplodimal         | Ahmed et al, 2010          |
| A. brevipes   | ground roots           | antimycobacterial      | Navarro-García et al, 2011 |
| A. constricta | stems                  | antispasmodic          | Zhang et al, 2008          |
| A. cymbiorea  | whole plant stems      | antimicrobial          | de Barros Machado et al, 2005 |
| A. elegans    | roots and aerial part  | anti scorpion venom    | Jiménez-Ferrer et al, 2005 |
| A. indica     | roots                  | antibacterial          | Kumar et al, 2006          |
| 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           | 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 smǎ dōu ling) species.

| Compound                  | Source     | Bioactivity                                      | Reference                        |
|--------------------------|------------|--------------------------------------------------|----------------------------------|
| aristolochic acid I (1)  | *A. constricta* | antiinflammatory                                 | Chung et al, 2010a               |
| aristolochic acid A (1)  | *A. fangchi* | antiplatelet                                      | Nascimento et al, 2003           |
| columbin (2)             | *A. albida* | trypanocidal                                      | León-Díaz et al, 2010           |
| talaumidin (3)           | *A. arcuata* | neurotrophic                                      | Zhai et al, 2004                 |
| galgravin (5)            | *A. arcuata* | neuroprotective                                   | Zhai et al, 2004                 |
| aristolignin (6)         | *A. arcuata* | neurotrophic                                      | Zhai et al, 2005                 |
| nectandrin A (7)         | *A. arcuata* | neuroprotective                                   | Zhai et al, 2005                 |
| nectandrin B (8)         | *A. arcuata* | neuroprotective                                   | Zhai et al, 2005                 |
| 7,9-dimethoxytariacuripyrone (13) | *A. brevipes* | antimycobacterial                                | Navarro-García et al, 2011       |
| 9-methoxytariacuripyrone (14) | *A. brevipes* | antimycobacterial                                | Navarro-García et al, 2011       |
| aristolactam I (15)      | *A. constricta* | anti-addictive                                   | Capasso et al, 2006              |
| (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. cymbifera* | antiplatelet                                      | Messiano et al, 2008             |
| (+)-cubebin (26)         | *A. cymbifera* | antiplatelet                                      | de Barros Machado et al, 2005    |
| (+)-kaur-15-en-17-ol (27) | *A. pubescens* | insecticidal                                      | de Barros Machado et al, 2005    |
| (+)-phuviatolide (28)    | *A. constricta* | antiplatelet                                      | Sartorelli et al, 2010           |
| (+)-haplomyrfolol (29)   | *A. constricta* | antiplatelet                                      | Sartorelli et al, 2010           |
| (+)-kaur-16-en-19-oic acid (32) | *A. constricta* | antiplatelet                                      | Sartorelli et al, 2010           |
| (+)-kusunokinin (39)     | *A. malmeana* | insecticidal                                      | Messiano et al, 2008             |
| aristolochic acid II (51)| *A. fangchi* | antiplatelet                                      | Shu 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           |
| (+)-copic 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* | antitrypanosomal                                  | Sartorelli et al, 2010           |
| aristolochic acid IVa (98)| *A. manshuriensis* | antiinflammatory                               | Chung et al, 2011                |
| (+)-sesamin (121)        | *A. pubescens* | insecticidal                                      | Nascimento et al, 2003           |
| aristolactam III (124)   | *A. manshuriensis* | antiinflammatory                               | Chung et al, 2011                |
| aristolamide II (150)    | *A. manshuriensis* | cyclin-dependent kinase inhibiting             | Hegde et al, 2010                |
| kaempferol (161)         | *A. taliscana* | antimicrobial                                     | 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, tetrалones, 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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