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Arylnaphthalene lactones: structures and pharmacological potentials

Soyoung Park · Seungsu Kim · Dongyun Shin

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Abstract Natural arylnaphthalene lactones are representative lignans that are found in various dietary and medicinal plants. Their unique structural features and significant pharmacological activity have attracted considerable attention from both synthetic and medicinal chemists. Owing to their unique structural features such as relative rigid tetracyclic skeleton, structural diversity of more than five substituents, and no chiral center, arylnaphthalene lactones are recognized as a valuable scaffold for drug discovery, in addition to their significant pharmacological activities. This review covers the structures and isolation of all naturally occurring arylnaphthalene lactone congeners reported. Based on the aryl substituents, they were categorized as Type I and Type II and further classified according to the oxidation state of the ring and glycosylation level. Special attention has been paid to natural arylnaphthalene lactones owing to their broad spectrum of biological activities such as cytotoxic, antiplatelet, antiviral, anti-HIV, antifungal, neuroprotective, and anti-inflammatory properties. All the products were reorganized based on their biological activities, and selected data are presented.

Keywords Arylnaphthalene lactones · Lignan · Medicinal · Natural · Activity

Introduction

Arylnaphthalene lignan lactones are naturally occurring fused tricyclic naphthalene lactones with aryl substituents. Structurally, arylnaphthalene lignan lactones consist of two arylpropanoid units and are classified as Type I and Type II (Fig. 1) based on the relative position of lactone and the aryl substituents (Teponno et al. 2016). Approximately 59 natural arylnaphthalene lignan lactones and their glycosylated congeners have been isolated from various dietary and medicinal plants and structurally elucidated. The broad spectrum of their pharmacological benefits has also been reported such as antiproliferative, antiplatelet aggregation, antiviral, antifungal, neuroprotective, and anti-inflammatory activities.

The unique structural features as well as promising bioactivities of arylnaphthalene lactones have drawn considerable attention from synthetic chemists. Since the first synthesis of an arylnaphthalene lignan lactone skeleton in 1895 by the Bucher group (Michael and Bucher 1895) via the condensation of arylpropiolic

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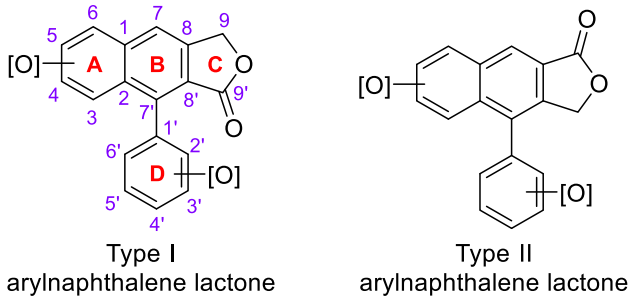


Fig. 1 Structure of arylnaphthalene lactones

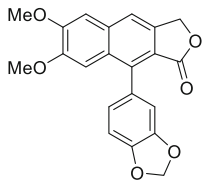
acids, various synthetic approaches for arylnaphthalene lignan lactones have been designed and applied successfully. Major synthetic approaches include the intramolecular Diels–Alder reaction for the construction of an arylnaphthalene lactone from arylpropiolic anhydride (Brown and Stevenson 1964, 1965; Maclean and Stevenson 1966; Block and Stevenson 1971; Holmes and Stevenson 1970, 1971; Stevenson and Holmes 1971; Stevenson and Block 1971; Block and Stevenson 1973; Stevenson and Weber 1989, 1991; Anastas and Stevenson 1991; Park et al. 2014). Intermolecular Diels–Alder approaches were also investigated using isobenzofurans and acetylenedicarboxylate (de Silva et al. 1980; Plaumann et al. 1980). Other valuable synthetic methodologies utilizing key reactions such as the Blaise reaction-intramolecular [4 + 2] reaction (He et al. 2012), Garratt–Braverman cyclization (Block and Stevenson, 1971, 1973; Arnold et al. 1973; Yamamoto et al. 2015), benzoin condensation-thermal cyclization (Hayat et al. 2015a, b), and transition-metal catalyzed synthesis (Park et al. 2020) have been reported.

Although the isolation and chemistry of natural lignan products has been broadly reviewed (Teponno et al. 2016; Li et al. 2020), a focused and comprehensive review on the structures and beneficial biological activities of natural arylnaphthalene lignan lactones has not been published. The purpose of this review is to provide a compilation of naturally occurring arylnaphthalene lignan lactones in terms of structure, isolation, and pharmacological activity.

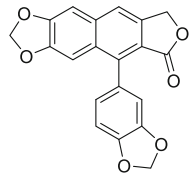
Structures and isolation

Arylnaphthalene lignan lactones are found in a variety of dietary and medicinal herbs including *Phyllanthus, Justicia, Haplophyllum*, and *Cleistanthus*. Arylnaphthalene lignan lactones are classified into two types based on their structures, 1-phenyl-2-hydroxymethylnaphthalene-2-carboxylic acid lactone (Type I) and 1-phenyl-3-hydroxymethylnaphthalene-3-carboxylic acid lactone (Type II). To provide a visual reference guide for each compound and to present an overview of the biological activities of arylnaphthalene lactones, all naturally occurring derivatives are classified by their types in Figs. 2 and 3. In Fig. 2, Type I compounds are presented, and they can be divided into three groups as 7-unsubstituted, 7-oxygenated-, and 7-*O*-glycosylated arylnaphthalene lactones. The first subclass of arylnaphthalene lactones includes four oxygenated congeners: justicidin B (**1**) (Gözler et al. 1984; Luo et al. 2014; Rao et al. 2006; Batsuren et al. 1981; Batirov et al. 1981; Lin et al. 1995; Gertsch et al. 2003; Hesse et al. 1992; Hemmati et al. 2016; Mohagheghzadeh et al. 2002) taiwanin C (**2**) (Yang et al. 2006; Anjaneyulu et al. 1981; Ban et al. 2002; Sastry and Rao 1983), daurinol (**4**) (Batsuren et al. 1981; Hesse et al. 1992), isodaurinol (**5**) (Hesse et al. 1992), and chinensin (**7**) (Ghosal et al. 1974; Cow et al. 2000), which are basic forms of natural arylnaphthalene lactones and only differ in the substituents on the alcohols. Several compounds that are further oxygenated at ring A or ring D such as deoxydehydropodophyllotoxin (**8**) (Novelo et al. 1993), dehydro-β-peltatin methyl ether (**11**) (Novelo et al. 1993), phyllamyricin C (**12**) (Rao et al. 2006; Lin et al. 1995), koelreuterin-1 (**6**) (Song et al. 1994), and justicidin H (**3**) (Yang et al. 2006) have been identified. Justicidinoside C (**9**) (Asano et al. 1996), which is the mono-glycosylated product of justicidin C, has also been isolated. 9-Hydroxy or 9-methoxy naphthalene lactones such as piscatorin (**10**) (Windayani et al. 2014; Gertsch et al. 2003), phyllamyricin

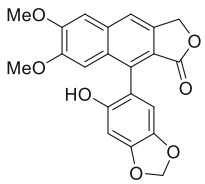
A. Type I arylnaphthalene lactones



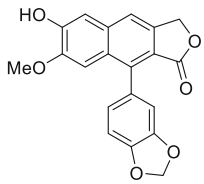
1. Justicidin B
Gozler, Gozler et al. 1984
H. buxbaumii
Luo, Hu et al. 2014
J. procumbens
Rao, Fang et al. 2006
P. polyphyllus
Batsuren, Batirov et al. 1981
H. dauricum
Lin, Lee et al. 1995
P. myrtifolius
Gertsch, Tobler et al. 2003
P. piscatorum
Hesse, Gozler et al. 1992
H. cappadocicum



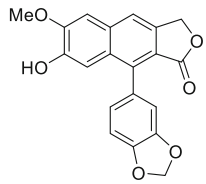
2. Taiwanin C
Yang, Wu et al. 2006
J. procumbens
Anjaneyulu, Ramaiah et al. 1981
C. collinus
Ban, Lee et al. 2002
A. chiisanensis
Sastry and Rao 1983
C. patulus



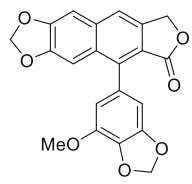
3. Justicidin H
(6'-Hydroxy Justicidin B)
Yang, Wu et al. 2006
J. procumbens



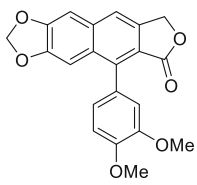
4. Daurinol
(5'-Demethyljusticidin B)
Batsuren, Batirov et al. 1981
H. dauricum
Hesse, Gozler et al. 1992
H. cappadocicum



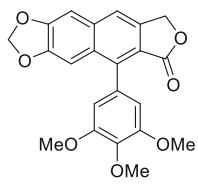
5. Isodaurinol
Hesse, Gozler et al. 1992
H. cappadocium



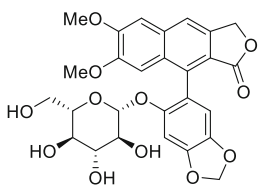
6. Koelreuterin-1
Song, Zhang et al. 1994
K. henryi



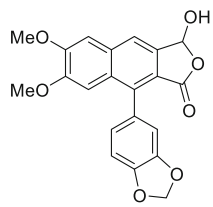
7. Chinensin
Ghosal, Chauhan et al. 1974
P. chinensis



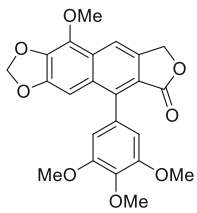
8. Deoxydehydropodophyllotoxin
Novelo, Cruz et al. 1993
H. verticillata



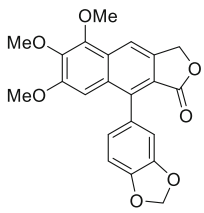
9. Justicidinoside C
Asano, Chiba et al. 1996
J. procumbens



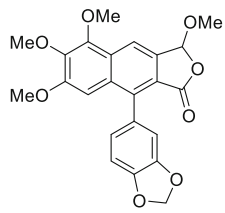
10. Piscatorin
Windayani 2014
P. myrtifolius
Gertsch, Tobler et al. 2003
P. piscatorum



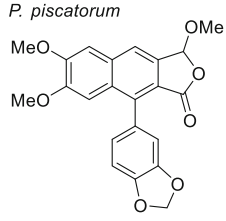
11. Dehydro-β -peltatin methyl ether
Novelo, Cruz et al. 1993
H. verticillata



12. Phyllamyricin C
Rao, Fang et al. 2006
P. polyphyllus
Lin, Lee et al. 1995
P. myrtifolius

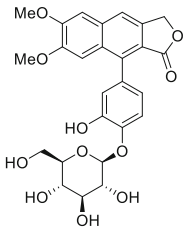


13. Phyllamyricin D
Lin, Lee et al. 1995
P. myrtifolius

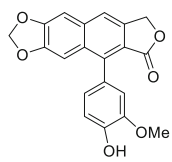


14. Phyllamyricin E
Lin, Lee et al. 1995
P. myrtifolius

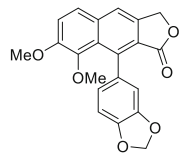
Fig. 2 Structure and isolation of Type I arylnaphthalene lactones



15. Procumbenoside L
Jin et al. 2017
J. procumbens

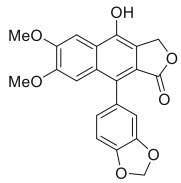


16. 5-(4-Hydroxy-3-methoxyphenyl)furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(8H)-one
Liu et al 2008
B. marginatum

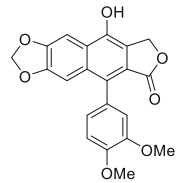


17. 3,4-Dimethoxy-3',4'-methylenedioxy-2,7'-cycloligna-7,7'-dieno-9,9'-lactone
Mohagheghsadeh et al. 2002
L. austriacum

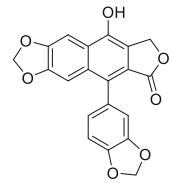
B. 7-Oxygenated Type I arylnaphthalene lactones



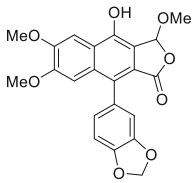
18. Diphyllin
Burden, Crombie et al. 1969
H. tuberculatum
Chen, Hsin et al. 1996
J. procumbens
Rao, Fang et al. 2006
P. polyphyllus
Gozler, Gozler et al. 1984
H. Vulcanicum
Anjaneyulu, Ramaiah et al. 1981
C. collinus
Hesse, Gozler et al. 1992
H. cappadocicum
Susplugas, Hung et al. 2005
J. patentiflora
Sastry and Rao 1983
C. patulus



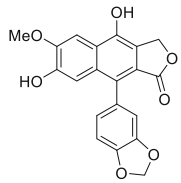
19. Chinensinaphthol (Isodiphyllin)
Chen, Hsin et al. 1996
J. procumbens
Day, Chiu et al. 1999
J. ciliata
Ghosal, Chauhan et al. 1974
P. chinensis



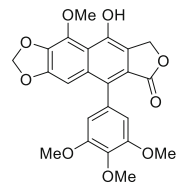
20. Taiwanin E
Chen, Hsin et al. 1996
J. procumbens
Anjaneyulu, Ramaiah et al. 1981
C. collinus
Wang, Tseng et al. 2014
E. trifoliatus
Susplugas, Hung et al. 2005
J. patentiflora



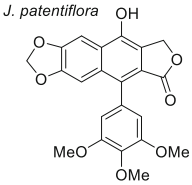
21. Cleistanone
Ramesh, Ravindranath et al. 2003
C. collinus



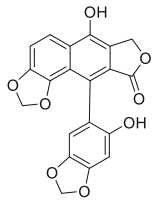
22. Haplomyrtin
Wu and Wu 2006
P. oligospermus
Evcim, Gozler et al. 1986
H. myrtifolium



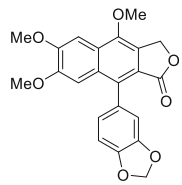
23. 5-Methoxy-dehydropodophyllotoxin
Novelo, Cruz et al. 1993
H. verticillata



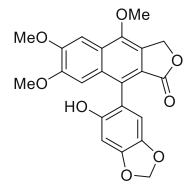
24. Dehydropodophyllotoxin
Novelo, Cruz et al. 1993
H. verticillata



25. 2'-Hydroxy-justirumalin
Rezanka et al. 2009
A. mollis

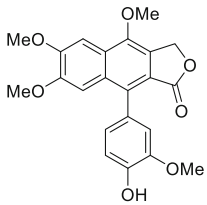


26. Justicidin A
Burden, Crombie et al. 1969
H. tuberculatum
Day, Lin et al. 2002
J. procumbens
Wu and Wu 2006
P. oligospermus
Lin, Lee et al. 1995
P. myrtifolius
Hesse, Gozler et al. 1992
H. cappadocicum
Day, Chiu et al. 1999
J. ciliata
Susplugas, Hung et al. 2005
J. patentiflora

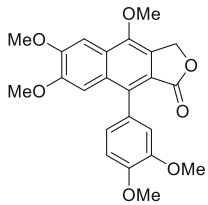


27. 6'-Hydroxy Justicidin A
Yang, Wu et al. 2006
J. procumbens

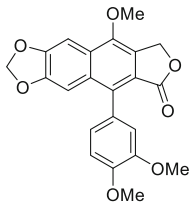
Fig. 2 continued



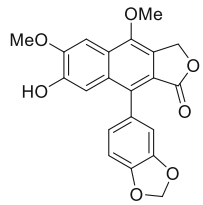
28. Cilinaphthalide A
Day, Chiu et al. 1999
J. ciliata



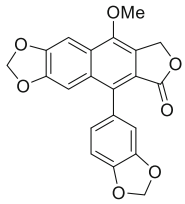
29. Cilinaphthalide B
Weng, Ko et al. 2004
J. procumbens
Day, Chiu et al. 1999
J. ciliata



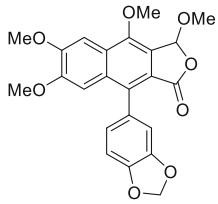
30. Chinensinaphthol-methyl ether
Luo, Hu et al. 2014
J.procumbens



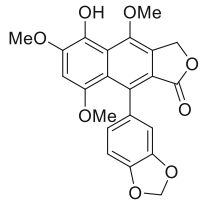
31. Phyllanthusmin A
Wu and Wu 2006
P. oligospermus
Ren et al., 2014
P.poilanei



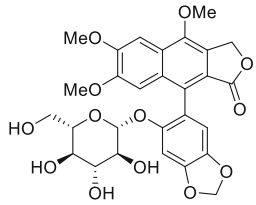
32. Justicidin F
(Taiwanin E methyl ether)
Chen, Hsin et al. 1996
J. procumbens
Day, Chiu et al. 1999
J. ciliata



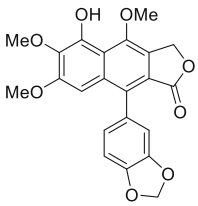
33. Justicidin P
Wang and Ripka 1983
J. extensa



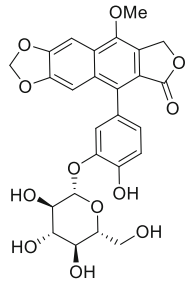
34. Justicinol
Susplugas, Hung et al. 2005
J.patentiflora



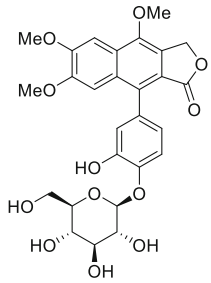
35. Justicidinoside B
Asano, Chiba et al. 1996
J. procumbens



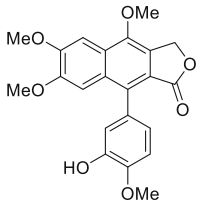
36. 5-Hydroxyjusticidin A
Tian, Hao et al. 2006
M. patentiflora



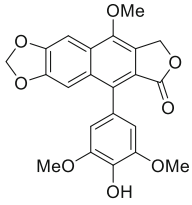
37. Justalakonin
Kavitha et al. 2003
J. purpurea



38. Procumbenoside K
Jin et al. 2017
J. procumbens



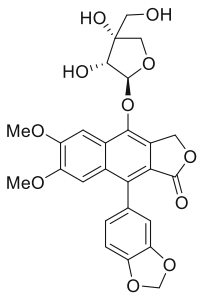
39. Pronaphthalide A
Jin et al. 2014
J. procumbens



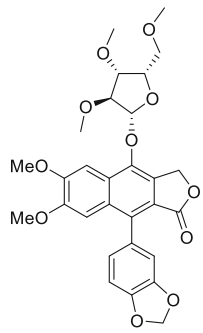
40. 4'-O-demethyl-7-O-methyldehydropodophyllotoxin
Wei et al. 2018
H. nymphaeifolia

Fig. 2 continued

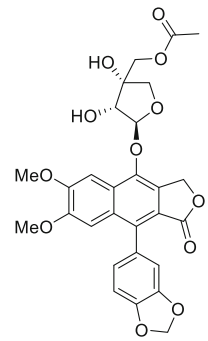
C. 7-O-glycosylated Type I arylnaphthalene lactones



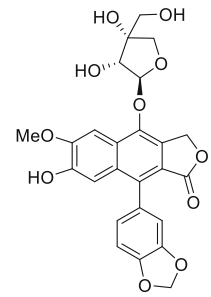
41. Tuberculatin
(diphyllin aposide)
Susplugas, Hung et al. 2005
J. patentiflora
Innocenti, Puricelli et al. 2002
H. patavinum



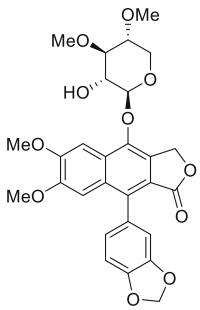
42. Cleistanthin D
Anjaneyulu, Ramaiah et al. 1981
C. collinus



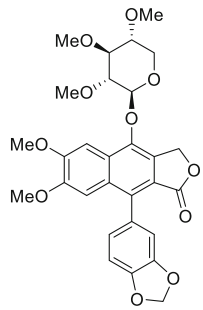
43. Diphyllin acetylapioside
(mono-O-acetyl diphyllin) apioside
Nukul, Abu Zarga et al. 1987
H. buxbaumii
Prieto, Giner et al. 2002
H. hispanicum



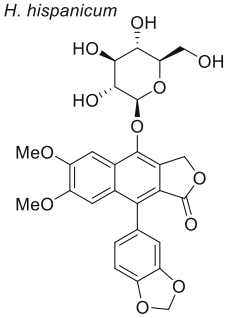
44. Haplomyrtoside
Gozler, Gozler et al. 1996
H. Cappadocium



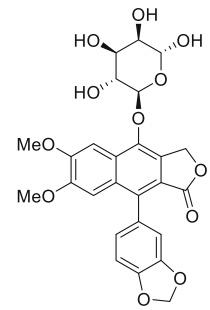
45. Cleistanthin A
Anjaneyulu, Ramaiah et al. 1981
C. collinus
Sastry and Rao 1983
C. patulus
Tuchinda et al., 2006
P. taxodiifolius



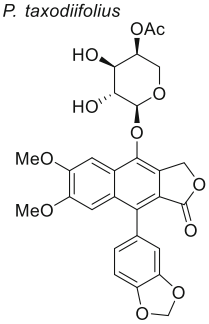
46. Cleistanthin A methyl ether
Tuchinda et al., 2006
P. taxodiifolius



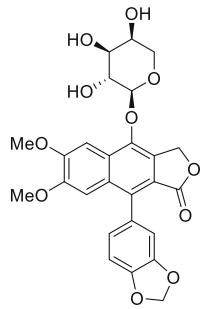
47. Cleistanthin B
(Diphyllin O-glycoside)
Anjaneyulu, Ramaiah et al. 1981
C. collinus
Al-Abed, Sabri et al. 1990
H. buxbaumii
Ren, Lantvit et al. 2014
P. poilanei



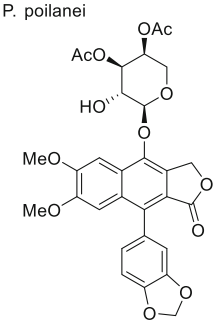
48. Mananthoside A
Chen, Liu et al. 2002
M. patentiflora



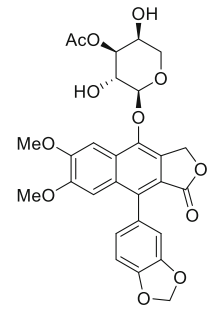
49. Phyllanthusmin B
Lin, Lee et al. 1995
P. myrtifolius
Ren, Lantvit et al. 2014
P. poilanei



50. Phyllanthusmin C
Lin, Lee et al.1995
P. myrtifolius
Ren, Lantvit et al. 2014
P. poilanei

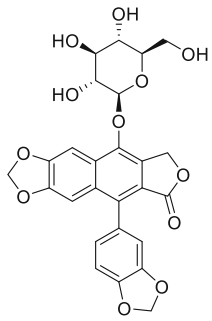


51. Phyllanthusmin D
Ren, Lantvit et al. 2014
P. poilanei

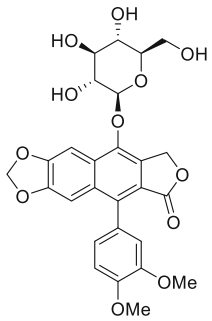


52. Phyllanthusmin E
Ren, Lantvit et al. 2014
P. poilanei

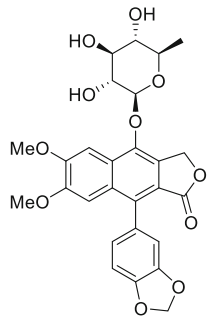
Fig. 2 continued



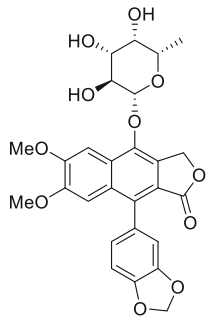
53. Procumbenoside C
Liu et al. 2008
J. procumbens



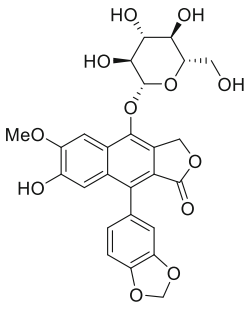
54. Procumbenoside D
Liu et al. 2008
J. procumbens



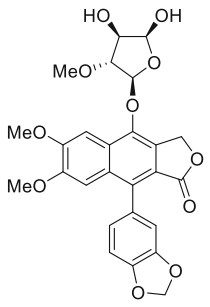
55. Patentiflorin A
Susplugas, Hung et al. 2005
J. patentiflora



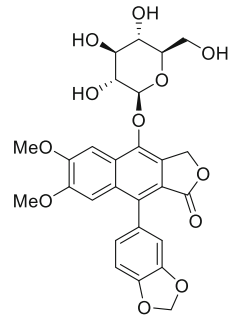
56. Patentiflorin B
Susplugas, Hung et al. 2005
J. patentiflora



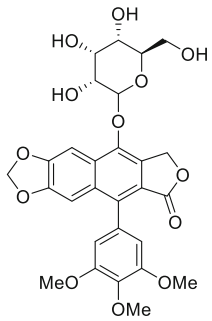
57. Procumbenoside I
Jin et al. 2017
J. procumbens



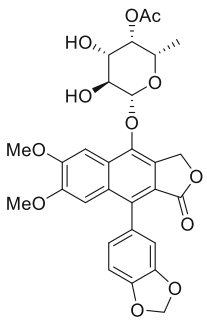
58. Acutissimalignan A
Tuchinda et al. 2008
P. acutissima



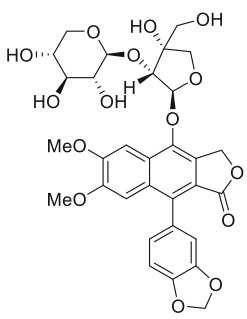
59. 7-O-β-D-glucopyranosyl - justicidin B
Borges et al. 2018
P. brasiliensis



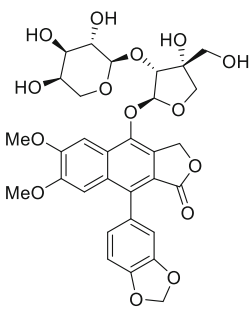
60. 7-O-(β-D-glucopyranosyl) - dehydropodophyllotoxin
Liu et al. 2015
C. boivinianus



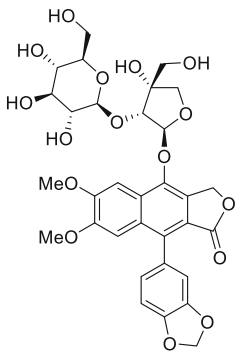
61. 4"-O-acetylpatentiflorin B
Susplugas, Hung et al. 2005
J. patentiflora



62. Majidine
Al-Abed, Sabri et al. 1990
H. buxbaumii
Innocenti, Puricelli et al. 2002
H. patavinum



63. Procumbenoside A
Day, Lin et al. 2002
J. procumbens

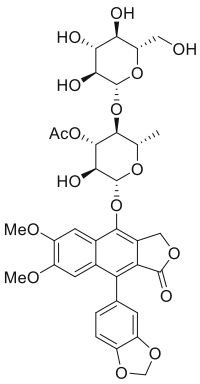


64. Procumbenoside B
Weng, Ko et al. 2004
J. procumbens

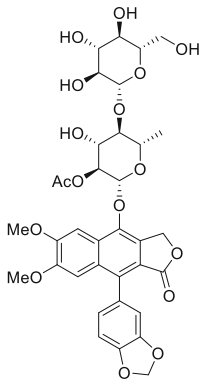
Fig. 2 continued

D (**13**) (Lin et al. 1995), and phyllamyricin E (**14**) (Lin et al. 1995) have been reported.

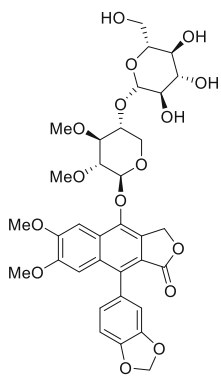
The second structural subclass includes C7-oxygenated Type I arylnaphthalene lactones. To date, 23 congeners have been isolated, in which the C7 of arylnaphthalene lactone is substituted with either the hydroxyl or methoxy group. Diphyllin (**18**) (Burden et al. 1969; Chen et al. 1996; Rao et al. 2006; Gözler et al. 1984; Anjaneyulu et al. 1981; Hesse et al. 1992; Susplugas et al. 2005; Sastry and Rao 1983),



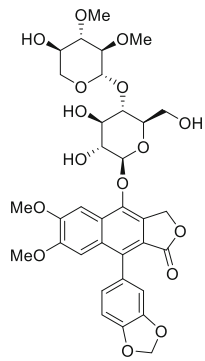
65. Justiprocumin A
Zhang, Rumschlag-Booms et al. 2017
J. gendarussa



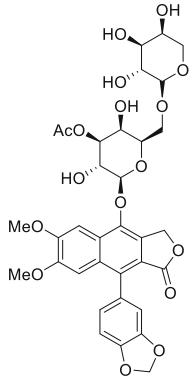
66. Justiprocumin B
Zhang, Rumschlag-Booms et al. 2017
J. gendarussa



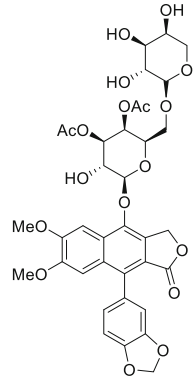
67. Ramontoside
Satyanarayana, Krupadanam et al. 1991
F. ramontchi



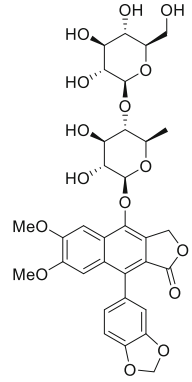
68. Cleistanthin C
Anjaneyulu, Ramaiah et al. 1981
C. collinus



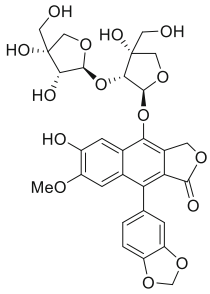
69. Mananthoside B
Chen, Liu et al. 2002
M. patentiflora



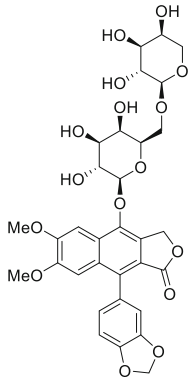
70. 4"-O-acetylmananthoside B
Susplugas, Hung et al. 2005
J. patentiflora



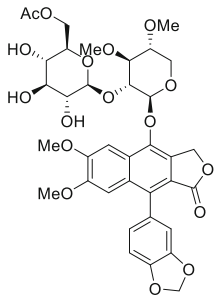
71. Mananthoside C
Tian, Hao et al. 2006
M. patentiflora



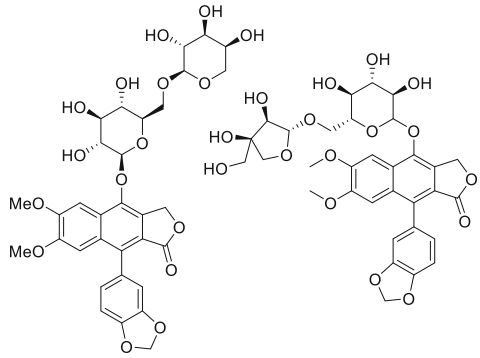
72. Mananthoside F
Tian, Hao et al. 2006
M. patentiflora



73. Mananthoside I
Tian, He et al. 2008
M. patentiflora



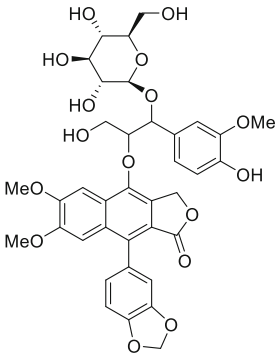
74. Taxodiifoloside
Tuchinda et al., 2006
P. taxodiifolius



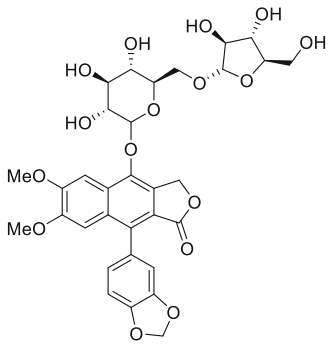
75. Arabelline
Al-Abed, Sabri et al. 1990
H. buxbaumii
Innocenti, Puricelli et al. 2002
H. patavinum

76. 7-O-β-D-apiofuranosyl-(1'''→ 6")-β-D-glucopyranosyldiphyllin
Pandey et al. 2011
J. prostrata

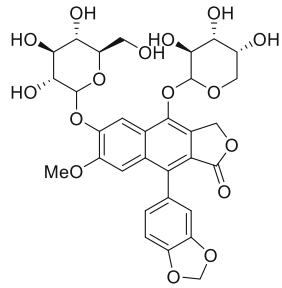
Fig. 2 continued



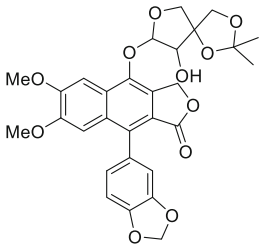
77. Procumbenoside M
Jin et al. 2017
J. procumbens



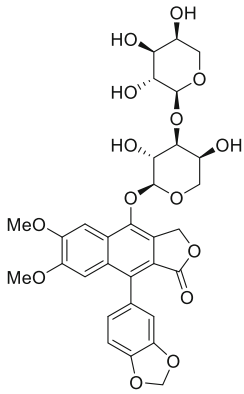
78. Reticulatuside A
Ma et al. 2012
P. reticulatus



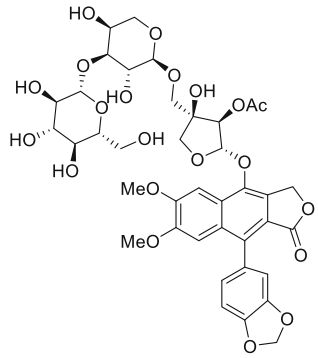
79. Reticulatuside B
Ma et al. 2012
P. reticulatus



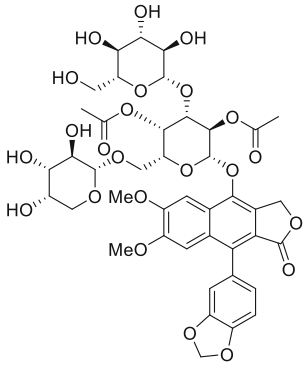
80. Pronaphthalide J
Jin et al. 2014
J. procumbens



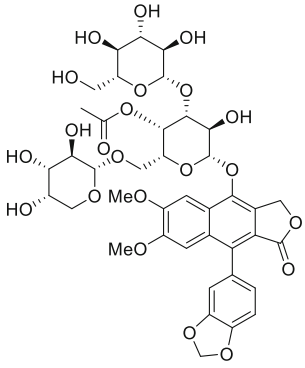
81. Diphyllin 7-O-α-L-arabino-pyranosyl-(1'''→3'')-α-L-arabinopyranoside
Yu et al. 2016
P. glaucus



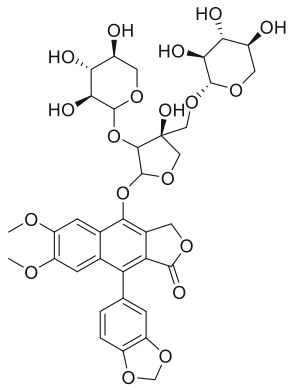
82. Qudsine
Al-Abed, Sabri et al. 1990
H. buxbaumii



83. Mananthoside D
Tian et al. 2006
M. patentiflora

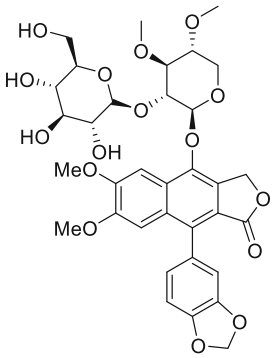


84. Mananthoside E
Tian et al. 2006
M. patentiflora

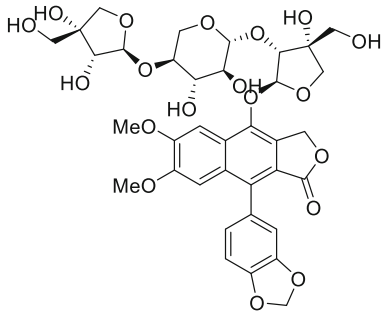


85. Procumbenoside E
Wu et al. 2012
J. procumbens

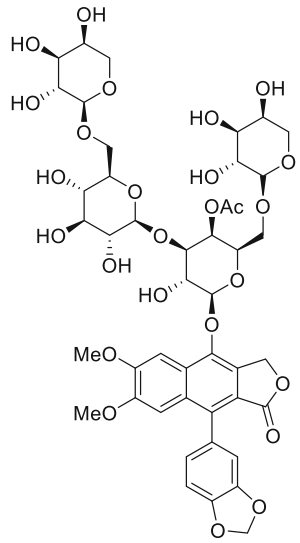
Fig. 2 continued



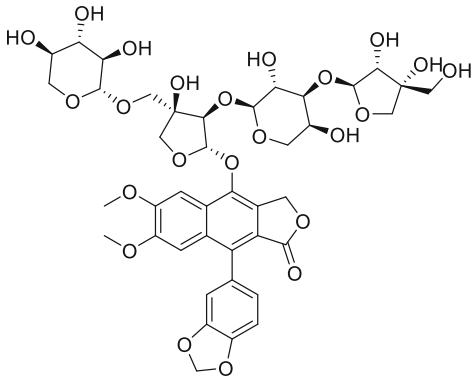
86. Cleistanthoside A
Zhang, Ma et al. 2014



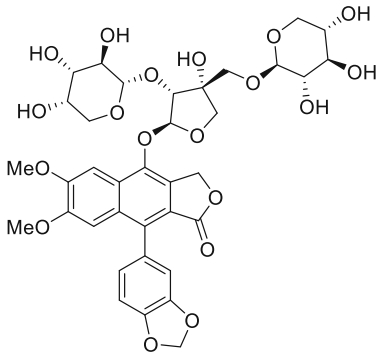
87. Patavine
Innocenti, Puricelli et al. 2002
H. patavinum



88. Mananthoside J
Tian, He et al. 2008
M. patentiflora



89. Ciliatoside B
Day et al. 2000
J. ciliata



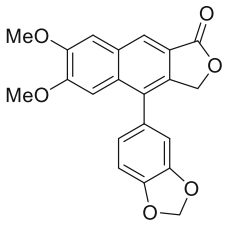
90. Ciliatoside A
Burden, Crombie et al. 1969
J. ciliata

Fig. 2 continued

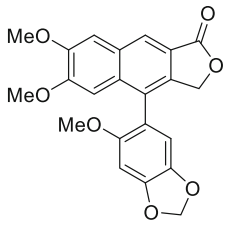
chinensinaphthol (**19**) (Chen et al. 1996; Day et al. 1999Ghosal et al. 1974), taiwanin E (**20**) (Chen et al. 1996; Anjaneyulu et al. 1981; Wang et al. 2014), cleistanone (**21**) (Ramesh et al. 2003), 6′-hydroxyjusticidin A (**27**) (Yang et al. 2006), 5-hydroxyjusticidin A (**36**) (Tian et al. 2006a, b), dehydropodophyllotoxin (**24**) (Novelo et al. 1993), 2'-hydroxyjustirumalin (**25**) (Rezanka et al. 2009), justicidin A (**26**) (Burden et al. 1969; Day et al. 2002; Wu and Wu 2006; Lin et al. 1995; Hesse et al. 1992; Day et al. 1999; Susplugas et al. 2005), Khalid et al. 1981, haplomyrtin (**22**) (Wu and Wu 2006; Evcim et al. 1986), 5-methoxydehydropodophyllotoxin (**23**) (Novelo et al. 1993), cilinaphthalide A (**28**) (Day et al. 1999), cilinaphthalide B (**29**) (Weng et al. 2004; Day et al. 1999), chinensinaphthol methyl ether (**30**) (Luo et al. 2014), phyllanthusmin A (**31**) (Wu and Wu 2006; Ren et al. 2014), justicidin F (**32**) (Chen et al. 1996; Day et al. 1999), justicidin P (**33**) (Wang and Ripka 1983), justicinol (**34**) (Susplugas et al. 2005), and justicidinoside (**35**)

Type 2

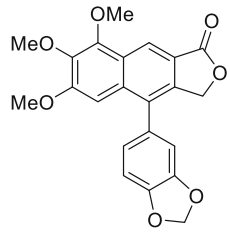
A. Type II arylnaphthalene lactones



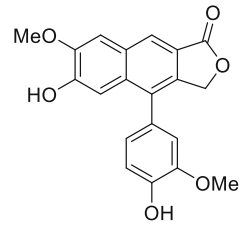
91. Retrojusticidin B
Lin, Lee et al.1995
P. myrtifolius



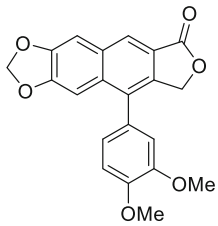
92. Procumphthalide A
Weng, Ko et al. 2004
J. procumbens



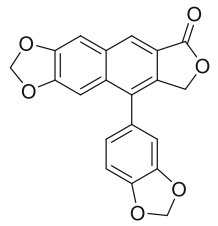
93. Phyllamyricin A
Windayani 2014
P. myrtifolius



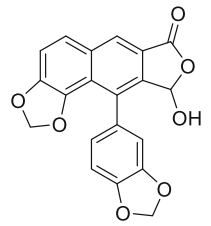
94. Detetrahydroconidendrin
Kuo et al. 1990
J. formosana



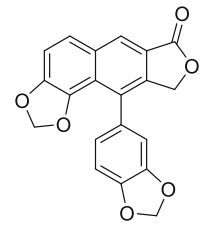
95. Retrochinensin
Ghosal and Banerjee 1979
J. prostata



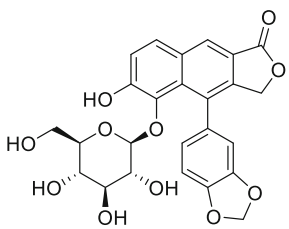
96. Justicidin E
Wada and Munakata 1970
J. procumbens



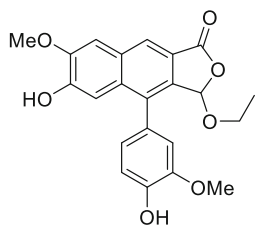
97. Jusmicranthin
Rajasekhar and Subbaraju 2000
J. neesii



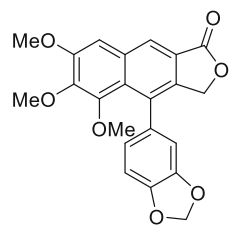
98. Helioxanthin
Ban, Lee et al. 2002
A. chiisanensis
Ghosal, Chauhan et al. 1974
P. chinensis
Burden, Crombie et al. 1969
H. scabra



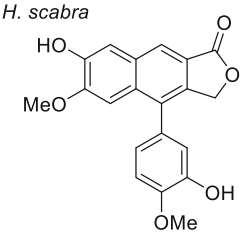
99. Elenoside
Navarro, Alonso et al. 2001
J. hyssopifolia



100. Vitexdoin I
Zheng et al. 2014
V. negundo



101. Chaihunaphthone
Liu et al 2008
B. marginatum



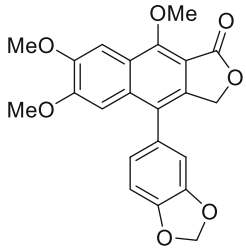
102. 5,3'-dihydroxy-4,4'-dimethoxy-2,7'-cycloligna-7,7'-diene-9,9'-lactone
Zhang et al. 2010
L. elegans

Fig. 3 Structure and isolations of Type II arylnaphthalene lactones

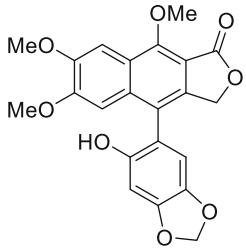
(Asano et al. 1996), justalakonin (**37**) (Kavitha et al. 2003), procumbenoside K (**38**) (Jin et al. 2017), pronapthalide A (**39**) (Jin et al. 2014) and 4'-O-demthyl-7-O-methyldehydropodophylotoxin (**40**) (Wei at al. 2018) have been reported. Among these, justicidin P is a 7-oxygenated derivative of justicidin A and justicidinoside B is the glycosylated product of 6′-hydroxyjusticidin A.

The third subclass of Type I arylnaphthalene lactones are 7-*O*-glycosyl congeners. A variety of saccharides are conjugated at the 7-hydroxy group of diphyllin, haplomyrtin, taiwanin E, and 4-hydroxy-daurinol. The 7-*O*-glycosylated Type I naphthalene lactones presented in Fig. 1 summarize the naturally occurring glycosylated congeners. Monosaccharide-conjugated derivatives include tuberculatin (**41**)

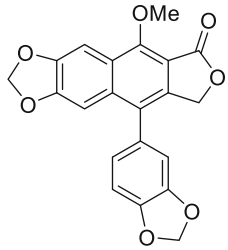
B. 7- Oxygenated Type II arylnaphthalene lactones



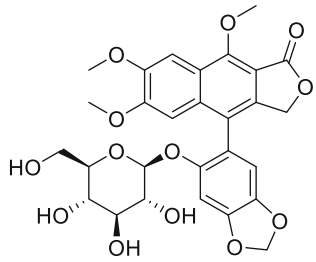
103. Justicidin C
(Neojusticidin B)
Day, Chiu et al. 1999
J. ciliata
Ohta and Munakata 1970
J. procumbens



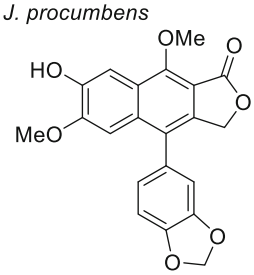
104. 6'-Hydroxyjusticidin C
Yang, Wu et al. 2006
J. procumbens



105. Justicidin D
(Neojusticidin A)
Ohta and Munakata 1970
J. procumbens



106. Justicidinoside A
Asano, Chiba et al. 1996
J. procumbens



107. Neojusticin C
Yang, Wu et al. 2006
J. procumbens

Fig. 3 continued

(diphyllin apioside) (Susplugas et al. 2005; Innocenti et al. 2002), cleistanthin D (**42**) (Anjaneyulu et al. 1981), diphyllin acetylapioside (**43**) (Nukul et al. 1987; Prieto et al. 2002), haplomyrtoside (**44**) (Gözler et al. 1996), cleistanthin A (**45**) (Anjaneyulu et al. 1981; Sastry and Rao 1983; Tuchinda et al. 2006), cleistanthin A methyl ether (**46**) (Tuchinda et al. 2006), cleistanthin B (**47**) (diphyllin O-glycoside) (Anjaneyulu et al. 1981; Al-Abed et al. 1990; Ren et al. 2014), mananthoside A (**48**) (Chen et al. 2002), phyllanthusmin B (**49**) (Lin et al. 1995; Ren et al. 2014), phyllanthusmin C (**50**) (Lin et al. 1995; Ren et al. 2014), phyllanthusmin D (**51**) (Ren et al. 2014), phyllanthusmin E (**52**) (Ren et al. 2014), procumbenoside C (**53**) (Liu et al. 2008a), procumbenoside D (**54**), Liu et al. (2008b), patentiflorin A (**55**) (Susplugas et al. 2005), patentiflorin B (**56**) (Susplugas et al. 2005), procumbenoside I (**57**) (Jin et al. 2017) acutissimalignan A (**58**) (Tuchinda et al. 2008) 7-O-β-D-glucopyranosyljusticidin B (**59**) (Borges et al. 2018), 7-O-(β-D-glucopyranosyl)-dehydropodophyllotoxin (**60**) (Liu et al. 2015) and 4″-*O*-acetylpatentiflorin B (**61**) (Susplugas et al. 2005). Disaccharide-conjugated congeners include majidine (**62**) (Al-Abed et al. 1990; Innocenti et al. 2002), procumbenoside A (**63**) (Day et al. 2002), procumbenoside B (**64**) (Weng et al. 2004), justiprocumin A (**65**) (Zhang et al. 2017), justiprocumin B (**66**) (Zhang et al. 2017), ramontoside (**67**) (Satyanarayana et al. 1991), cleistanthin C (**68**) (Anjaneyulu et al. 1981), mananthoside B (**69**) (Chen et al. 2002), 4″-*O*-acetylmananthoside B (**70**) (Susplugas et al. 2005), mananthoside C (**71**) (Tian et al. 2006a, b), mananthoside F (**72**) (Tian et al. 2006a, 2006b), mananthoside I (**73**) (Tian et al. 2008), taxodiifoloside (**74**) (Tuchinda et al. 2006), arabelline (**75**) (Al-Abed et al. 1990; Innocenti et al.

2002), and 7-O-β-D-apiofuranosyl-(1"'→6")-β-D-glucopyranosyldiphyllin (**76**) (Pandey et al. 2011), procumbenoside M (**77**) (Jin et al 2017), reticulatuside A (**78**) (Ma et al. 2012), reticulatuside B (**79**) (Ma et al. 2012), pronapthalide J (**80**) (Jin et al. 2014), Diphyllin 7-O-α-L-arabinopyranosyl-(1"'→3")-α-L-arabinopyranoside (**81**) (Yu et al. 2016) and cleistanthoside A (**86**) (Zhang et al. 2014). Eight trisaccharide-conjugated diphyllins, namely mananthoside D (**83**) (Tian et al. 2006a, b), mananthoside E (**84**) (Tian et al. 2006a, b), procumbenoside E (**85**) (Wu et al. 2012), mananthoside J (**88**) (Tian et al. 2006a, b), patavine (**87**) (Innocenti et al. 2002), ciliatoside B (**89**) (Day et al. 2000), ciliatoside A (**90**) (Burden et al. 1969), and qudsine (**82**) (Al-Abed et al. 1990), have been reported.

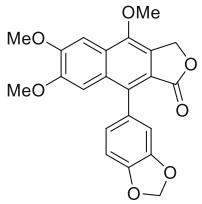
Type II arylnaphthalene lactones are characterized by the trans relationship of lactone carbonyl and the aryl group. Twelve Type II congeners were isolated and structurally elucidated, including retrojusticidin B (**91**) (Lin et al. 1995), procumphthalide A (**92**) (Weng et al. 2004), phyllamyricin A (**93**) (Windayani et al. 2014), detetrahydroconidendrin (**94**) (Kuo et al. 1990), retrochinensin (**95**) (Ghosal and Banerjee 1979), justicidin E (**96**) (Wada and Munakata 1970), jusmicranthin (**97**) (Rajasekhar and Subbaraju 2000), helioxanthin (**98**) (Ban et al. 2002; Ghosal et al. 1974; Burden et al. 1969), and elenoside (**99**) (Navarro et al. 2001), vitexdoin I (**101**) (Zheng et al. 2014), Chaihunaphthone (**102**) (Liu et al. 2008a, b) and 5,3'-dihydroxy-4,4'-dimethoxy-2,7'-cycloligna-7,7'-diene-9,9'-lactone (**103**) (Zhang et al, 2010)

Pharmacological activities

Cytotoxic activities

The reported antiproliferative activities of natural arylnaphthalene lactones are presented in Fig. 4. Significant cytotoxic activity was observed with justicidin A (**26**) and tuberculatin (**41**) against human hepatoma cellular carcinoma (Hep3B and HepG2), human breast cancer (MCF-7 and MCF-7-ras), human cervical carcinoma (SiHa), and other cancer cell lines. In addition, these two compounds strongly enhanced tumor-necrosis factor α (TNF-α) generation in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells (Day et al. 2002). Later, 6′-hydroxyjusticidin A (**27**), which was isolated from *Justicia procumbens*, was evaluated for its cytotoxicity against human cancer cell lines. It showed remarkable inhibitory activity in human bladder cancer cells (EJ) with 50% inhibitory concentration (IC_{50}) values of 57.1 μM and enhanced the generation of reactive oxygen species and induced apoptosis through the caspase pathway (He et al. 2012). Similar results of the mechanism of action were reported by Luo and Hu et al. in 2014. They isolated five lignans, 6′-hydroxyjusticidin A (**27**), justicidin H (**3**), justicidin B (**1**), chinensinaphthol methyl ether (**30**), and taiwanin E methyl ether (**32**) from *J. procumbens* and tested their cytotoxic activities. Justicidin H (**3**) exhibited the best inhibitory activity against human promyelocytic leukemia (HL-60) and mouse lymphocytic leukemia (L1210 and P3881D1) cells with an IC_{50} ranging from 3.9 to 26.2 μM (Luo et al. 2014). To investigate the mechanism of action of justicidin H (**3**), these authors also evaluated its effects on human leukemia K562 cells. The IC_{50} of justicidin H (**3**) was 15.07 μM for K562 cells and reduced mitochondria membrane potential (deltapsi(m)). It also increased the expression of TRPC6 related to regulating calcium homeostasis in cell signaling and induced apoptosis through the caspase pathway (Luo et al. 2018).

Diphyllin (**18**) was tested to investigate whether it could act as a vacuolar-ATPase (V-ATPase) inhibitor against human gastric cancer cells (SGC7901) and esophageal cancer cells (TE-1 and ECA-109). The IC_{50} for SGC7901 was demonstrated to be 7.8 μM. Diphyllin (**18**) also inhibited the expression of V-ATPases in a dose-dependent manner. In addition, the transmembrane pH gradient was reversed, thereby causing tumor microenvironment acidification (Shen et al. 2011). It also showed significant inhibition against TE-1 and ECA-109 cells with IC_{50} values of 0.3 and 0.2 μM, respectively, with S-phase arrest and reduced V-ATPase activity. Reportedly, diphyllin inhibited mammalian target of rapamycin complex 1 (mTORC1), hypoxia-inducible factor-1α (HIF-1α), and vascular endothelial growth factor (VEGF) mRNA expression (Chen et al. 2018). Three diphyllin glycosides cleistanthin A (**45**), cleistanthoside A (**86**), and cleistanthoside A tetraacetate were also evaluated for their effect as V-ATPases and their cytotoxicity against human cell lines. Apart from cleistanthoside A (**86**), cleistanthin A (**45**) and cleistanthoside A tetraacetate were more potent than paclitaxel against

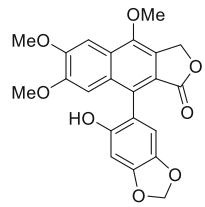


26 Justicidin A

ED_{50} [μg/ml]

0.029	Hep3B	0.003	CaSki
0.02	HepG2	0.0074	SiHa
0.39	MCF-7	0.0018	HT-3
0.074	MCF-7 ras	0.0022	PLC/PRF/5
0.002	T-24		

(Day, Lin et al. 2002, Dan et al. 2010, Weng, Ko et al. 2004)

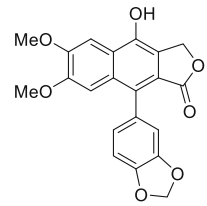


27 6'-Hydroxyjusticidin A

IC_{50} [μg/ml]

1.81	HCT-8	0.49	BCG-823
3.61	BEL-7402	0.37	KB
2.22	KETR3	3.49	MCF-7
0.16	HELA		

(Wang, Tong et al. 2014)

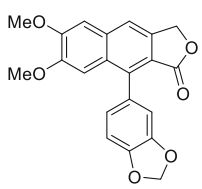


18 Diphyllin

ED_{50} [μg/ml]

3.6	Hep3B	2.97	SGC7901
0.4	HepG2	0.106	ECA-109
2.7	212	0.078	TE-1

(Day, Lin et al. 2002, Shen, Zou et al. 2011, Chen, Liu et al. 2011)

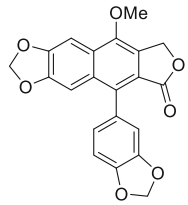


1 Justicidin B

IC_{50} [μg/ml]

0.2	KB
3.3	PBM
3.2	Jurkat T

(Burden, Crombie et al. 1969, Gertsch, Tobler et al. 2003)

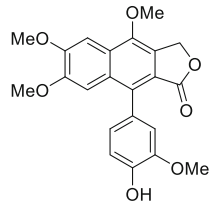


32 Justicidin F (Taiwanin E methyl ether)

ED_{50} [μg/ml]

2.6 HT-3

(Day, Chiu et al. 1999)

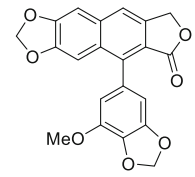


28 Cilinaphthalide A

ED_{50} [μg/ml]

1.3	T-24
3	CaSki
0.3	HT-3

(Day, Chiu et al. 1999)

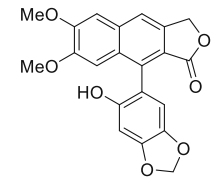


6 Koelreuterin-1

ED_{50} [μg/ml]

0.0035	SK-MEL-5
0.0067	SK-OV-3

(Song, Zhang et al. 1994)

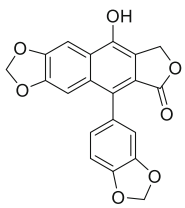


3 Justicidin H (6'-Hydroxyjusticidin B)

IC_{50} [μg/ml]

7.61 K562

(Burden, Crombie et al. 1969)

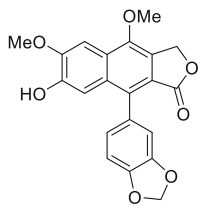


20 Taiwanin E

IC_{50} [μg/ml]

0.54 MCF-7

(Wang, Tseng et al. 2014)

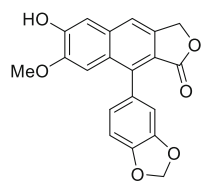


31 Phyllanthusmin A

IC_{50} [μg/ml]

2.24 KB

(Wu and Wu 2006)

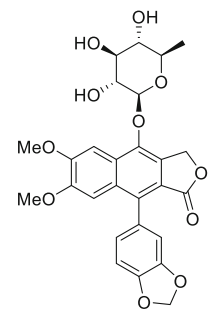


4 Daurinol

IC_{50} [μg/ml]

0.71 HCT116

(Kang, Oh et al. 2011)

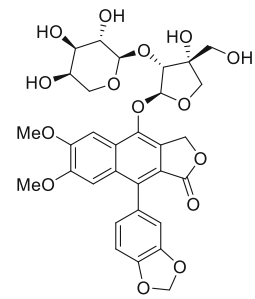


55 Patentiflorin A

IC_{50} [μg/ml]

0.002	KB
0.0015	MCF-7

(Susplugas, Hung et al. 2005)



63 Procumbenoside A

ED50 [μg/ml]

3.1	Hep3B
3.9	HepG2
3.1	212

(Day, Lin et al. 2002)

Fig. 4 Arylnaphthalene lactones with cytotoxic activity against different cell lines. Hep3B, human cervical carcinoma; HepG2, human hepatoma cell; MCF-7, human breast cancer cell; MCF-7 ras, Ha-ras oncogene transformed from MCF-7; EJ, human bladder cell; K562, human leukemia cell; SGC7901, human gastric cancer cell; TE-1 and ECA-109, human esophageal cancer cells; SK-OV-3, human ovarian carcinoma; SK-MEL-5, melanoma**; PLC/PRF/5, human** hepatoma; HT-3, SiHa, and CaSki, human cervical carcinoma

HepG2 cells with the IC_{50} values of 36 and 39 nM, respectively. They also inhibited V-ATPase activity, which is critical to tumor invasion and metastasis development. At nanomolar concentrations, they neutralize the pH of lysosomes (Zhang et al. 2014).

A bioassay-guided fractionation of the stems and roots of *Phyllanthus oligospermus* resulted in the

isolation of three arylnaphthalene lignan lactones, phyllanthusmin A-C (**31**, **49**, **50**). The most active compound was phyllanthusmin A (**31**) showing a marked cytotoxic effect against mouse leukemia (P-388) and human epidermoid carcinoma (KB) cells with IC_{50} values of 0.13 and 2.24 μg/mL, respectively (Wu and Wu 2006). Phyllanthusmin A-E (**31**, **49**–**52**), diphyllin (**18**), and cleistanthin B (**47**) were also evaluated for cytotoxicity against colon cancer cells (HT-29). Phyllanthusmin D (**51**) was the most potent with IC_{50} values at 170 nM; however, cleistanthin B (**47**) and phyllanthusmin A (**31**) were inactive. These results suggest that the presence of more lipophilic acetyl groups results in higher cytotoxicity. In this connection, mechanistic studies of phyllanthusmin D (**51**) were also evaluated. It was found that unlike etoposide, phyllanthusmin D (**51**) did not mediate its cytotoxic effects by inhibiting DNA topoisomerase IIα but did so by inducing HT-29 apoptosis through caspase-3 activation (Ren et al. 2014). However, daurinol (**4**) acts as a catalytic human topoisomerase IIα inhibitor and demonstrated significant cytotoxic activity against human colorectal cancer cells (HCT116) with an IC_{50} of 2.03 μM. It induced S-phase arrest through the increased expression of cyclin E and A (Kang et al. 2011). In a further investigation, Woo et al. (2017) evaluated daurinol (**4**) for anti-metastatic activity against human breast cancer cells (MDA-MB-231) and human lung cancer cells (A549). Daurinol (**3**) decreased the expression of focal adhesion kinase, which is hyper-activated and overexpressed in most solid tumors, but did not block the AKT pathway in both cell lines. Using a trans-well assay, daurinol (**3**) was found to inhibit migration and invasion (Woo et al. 2017).

Among the eight compounds, cilinaphthalide A (**28**), cilinaphthalide B (**29**), chinensinaphthol methyl ether (**30**), justicidin A (**26**), neojusticin B (**103**), taiwanin E methyl ether (**32**), chinensinaphthol (**19**), and diphyllin (**18**) were isolated from the whole plant of *Justicia ciliate*. The potent cytotoxic effects of justicidin A (**26**) were reported against human cervical carcinoma (CaSki, SiHa, and HT-3) and human hepatoma (PLC/PRF/5 and T-24) cells with IC_{50} values at 3.0×10^{-3}, 7.4×10^{-3}, 1.8×10^{-3}, 2.2×10^{-3}, and 2.0×10^{-3} μg/mL, respectively (Day et al. 1999). Significant cytotoxicity was observed for most of the compounds, justicinol (**34**), patentiflorin A-B (**55**, **56**), 4″-*O*-acetylpatentiflorin B (**61**), and 4″-*O*-acetylmananthoside B (**70**), isolated from the leaves and stems of *Justicia patentiflora* with nanomolar values of IC_{50}. The most active compound was patentiflorin A (**55**) with the nanomolar range of IC_{50} 0.004 and 0.003 against mouth epidermoid carcinoma (KB) and breast cancer (MCF-7) cells, respectively (Susplugas et al. 2005).

Antiplatelet aggregation activities

In 1996, Chen et al. determined the 50% inhibitory activity to the arachidonic acid (AA)-induced aggregation of rabbit platelets at 20 μg/mL from the EtOH extract of the whole plant of *J. procumbens*. They isolated nine arylnaphthalide lignans, neojusticin A (**105**), justicidin B (**1**), justicidin A (**26**), taiwanin E methyl ether (**32**), neojusticin B (**103**), chinensinaphthol methyl ether (**30**), taiwanin E (**20**), chinensinaphthol (**19**), and diphyllin (**18**), from *J. procumbens* and evaluated these for their antiplatelet activity. All compounds were less effective than indomethacin; however, neojusticin A (**105**), taiwanin E methyl ether (**32**), justicidin B (**1**), and taiwanin E (**20**) were more active than aspirin with IC_{50} values at 1.1, 1.7, 8.0, and 8.0 μM, respectively (C.-C. Chen et al. 1996). In a further study, Weng et al. isolated two additional new arylnaphthalide lignans, procumbenoside B (**64**) and cilinaphthalide B (**29**) from *J. procumbens* and tested the antiplatelet effects induced by adrenaline in human platelet-rich plasma. Cilinaphthalide B (**29**), justicidin A (**26**), and taiwanin E methyl ether (**32**) exhibited a moderate antiplatelet activity in a concentration-dependent manner. Among these, at high concentrations, taiwanin E methyl ether (**32**) completely abolished the aggregation with an IC_{50} value of 27.7 μM and inhibited the secondary phase aggregation at low concentrations. These results indicate that justicidin A (**26**) and taiwanin E methyl ether (**32**) likely suppress cyclooxygenase activity and reduce thromboxane formation (Weng et al. 2004) (Fig. 5).

Antiviral activities

A series of lignans isolated from *J. procumbens* were tested for activities against the vesicular stomatitis virus. Justicidin A-B (**26, 1**), diphyllin (**18**), diphyllin apioside (**41**), and diphyllin apioside-5-acetate exhibited strong antiviral activities. Their minimum inhibitory concentration (MIC) values were less than

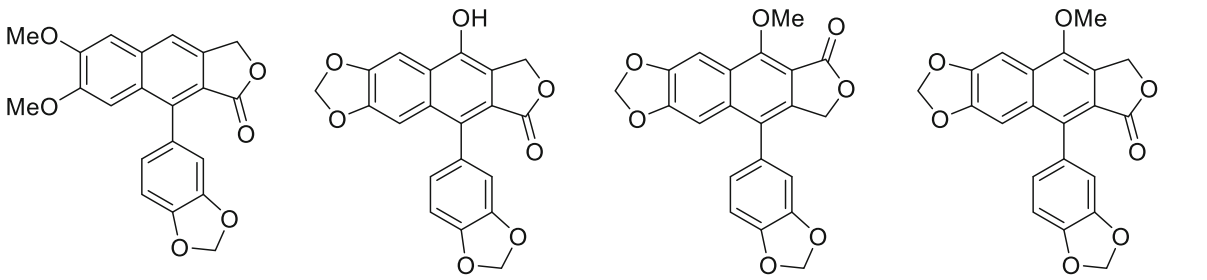


Fig. 5 Arylnaphthalene lactones with antiplatelet activity. Inhibitory concentrations (IC) were determined in arachidonic acid (AA)-induced aggregation of rabbit platelets (C.-C. Chen et al. 1996), a. Platelet aggregation induced by adrenaline in human platelet-rich plasma (Weng et al. 2004)

0.25 μg/mL whereas 6′-glucosides justicidinoside A-C (**106**, **35**, **9**) and Type II justicidin C and D (**103, 105**) exhibited lower antiviral activity (the MICs ranged from 16 to 125 μg/mL). It is tempting to suggest that the weak activity of justicidinoside A-C (**106**, **35**, **9**) is because of the steric bulk of their sugar moiety and that Type I arylnaphthalene lactones were more effective than Type II (Luo et al. 2018). Using the standard plaque reduction assay against human cytomegalovirus, only taiwanin C (**2**) and retrojusticidin B (**91**) showed clear antiviral activity with half maximal effective concentration (EC_{50}) values at 1.2 and 7.2 μM, respectively (Chen et al. 1996). Similar antiviral activities were reported for helioxanthin (**98**) in HepG2.2.15 cells using Southern blot hybridization with the EC_{50} value at 1 μM. Helioxanthin (**98**) reduced 3.5 kb of hepatitis B virus mRNA in a dose-dependent manner with EC_{50} values at 0.09 μM (Li et al. 2005). In addition, helioxanthin (**98**) also exhibited strong antiviral activities against hepatitis C virus and herpes simplex virus type 1 with EC_{50} values at 3 and 2 μM, respectively, but showed weak activity against herpes simplex virus type 2 and Epstein–Barr virus with EC_{50} values at 35 and above 20 μM, respectively (Yeo et al. 2005) (Table1).

Anti-HIV activities

Anti-HIV bioassays with six lignans, phyllamyricin A (**93**), phyllamyricin B, phyllamyricin C (**12**), retrojusticidin B (**91**), justicidin A (**26**), and justicidin B (**1**) isolated from *Phyllanthus myrtifolius* were first

Table 1 Arylnaphthalene lactones with antiviral activities

Compound	Virus	MIC (μg/mL)
Justicidin A (**26**)	Vesicular stomatitis virus	0.13
Justicidin B (**1**)	Vesicular stomatitis virus	≥ 0.06
Diphyllin (**18**)	Vesicular stomatitis virus	0.25
Tuberculatin (**41**)	Vesicular stomatitis virus	0.25
		EC_{50} [μM]
Taiwanin C (**2**)	Cytomegalovirus	1.2
Retrojusticidin B (**91**)	Cytomegalovirus	7.2
Helioxanthin (**98**)	Cytomegalovirus	7.3
	Hepatitis B virus	1
	Hepatitis C virus	3
	Herpes simplex virus type 1	2

MIC, minimum inhibitory concentration; EC_{50}, half maximal effective concentration

Table 2 Anti-HIV activities of arylnaphthalene lignan lactones

Compound	IC_{50}
Retrojusticidin B (**91**)[a]	
HIV-RT	5.5 μM
Justiprocumin B (**66**)[b]	
BAL	15 nM
SF162	15 nM
LAV0.04	14 nM
89.6	21 nM

BAL, SF162, LAV0.04, and 89.6 are HIV-1 clinical isolates

[a]Using reverse transcriptase assay

[b]Using standardized human peripheral blood mononuclear cell culture assay (PBMC assay)

conducted by Chang et al. (1995) using human immunodeficiency virus-1 reverse transcriptase assay (HIV-RT). Among these, phyllamyricin B and retrojusticidin B (**91**) were shown to contribute to the selective inhibitory effect against HIV-RT with IC_{50} values at 3.5 and 5.5 μM, respectively, whereas they exhibited much lower activity against human DNA polymerase-α (hDNAP-α) with IC_{50} values at 289 and 989 μM (Chang et al. 1995) (Table 2). In a subsequent study in 1996, Lee et al. identified additional lignans from *P. myrtifolius* and evaluated their anti-HIV activities. Phyllamyricin B and C were inactive and phyllamyricin E (**14**) exhibited very low anti-HIV-RT activity; however, phyllamyricin A (**93**) showed an increase in HIV-RT activity by 65% at 1.89 μM (Lee et al. 1996). From the stems and barks of *Justicia gendarussa* justiprocumin A and B (**65**, **66**) were isolated and justiprocumin B (**66**) was assayed for its anti-HIV activity against four HIV-1 isolates using a standardized human peripheral blood mononuclear cell culture assay. The HIV-1 isolates BAL, SF162, LAV0.04, and 89.6 were used. Justiprocumin B exhibited IC_{50} values at 15, 15, 14, and 21 nM, respectively, whereas the clinically used drug for HIV-1 zidovudine (AZT) showed less activity with the IC_{50} value ranging from 77 to 95 nM (Zhang et al. 2017).

Antifungal activities

Antifungal activities of arylnaphthalene lactones are summarized in Table 3. In 2003, the Gertsch group validated antifungal properties of water, dichloromethane, and MeOH extracts of *Phyllanthus piscatorum*. While the extracts did not exhibit an inhibitory effect against gram-positive bacterial strains of *Pseudomonas aeruginosa, Bacillus cereus*, *Staphylococcus aureus*, and *Staphylococcus epidermis*, they showed significant activity against *Aspergillus fumigatus, Aspergillus flavus*, and *Candida albicans* (Gertsch et al. 2004). In a subsequent study, the dichloromethane extract of *P. piscatorum* resulted in the activity of arylnaphthalene lactone justicidin B (**1**) and piscatorin (**10**) when tested against *A. flavus, A. fumigatus*, and *C. albicans*. The most active compound was justicidin B (**1**) with MIC values ranging from 1 to 16 μg/mL; however, showing a higher concentration of 128 μg/mL against *Blastoschizomyces capitatus* and *Cryptococcus neoformans neoformans* (Gertsch et al. 2003). Bioassay-guided fractionation of the leaf extract of *P. myrtifolius* led to the isolation of seven lignans, namely, phyllamyricin C (**12**), retrojusticidin B (**91**), phyllamyricin A (**93**), phyllamyricin F, justicidin B (**1**),

Table 3 Antifungal activities of arylnaphthalene lignan lactones

Compound	MIC [μg/mL]			
	Fusarium oxysporum	*Aspergillus fumigatus*	*Candida albicans*	*Aspergillus flavus*
Retrojusticidin B (**91**)	16	–	–	–
Phyllamyricin A (**93**)	32	–	–	–
Phyllamyricin C (**12**)	4	–	–	–
Phyllamyricin E (**14**)	16	–	–	–
Piscatorin (**10**)	16	≥3	≥8	≥25
Justicidin B (**1**)	8	≥1	≥4	≥16

MIC, minimum inhibitory concentration

phyllamyricin E (**14**), and piscatorin (**10**). Their activities were validated using the susceptibility test and conidial germination inhibition assay. Phyllamyricin A (**93**), phyllamyricin E (**14**), justicidin B (**1**), and phyllamyricin F exhibited strong inhibition against *Fusarium oxysporum* ATCC 44,187 with an average inhibition zone of 62–68% (1000 μg/mL). In addition, phyllamyricin C (**12**) showed the most significant antifungal activity with MIC and minimum fungicidal concentration values of 4.0 and 62.5 μg/mL, respectively, and the seven lignans inhibited conidia germination of *F. oxysporum* in a concentration-dependent manner (Windayani et al. 2014).

Neuroprotective activities

Justicidin A (**26**) was investigated for neuroprotective activities in a cellular model of Alzheimer's disease induced by amyloid beta $(A\beta)_{25\text{-}35}$ in SH-SY5Y cells. $A\beta_{25\text{-}35}$-induced hyperphosphorylation of tau and okadaic acid-induced hyperphosphorylation were significantly inhibited by pre-treatment with justicidin A at 62.5, 125, and 250 nM in a dose-dependent manner. At the same concentration, justicidin A produced a significant level of decrease in the phosphorylation of glycogen synthase kinase-3beta (GSK-3β) and stimulated the phosphorylation of AMP-activated protein kinase (AMPK). In addition, treatment with justicidin A, resulted in an increase in the level of the LC3 II/I ratio. These results show that justicidin A induced autophagy and inhibited neuronal cell death through reducing hyperphosphorylation of tau (Gu et al. 2016).

Anti-inflammatory activities

Prieto et al. (1996) reported for the first time the anti-inflammatory activity of an MeOH extract of *Haplophyllum hispanicum*. The edema of carrageenan-induced paw and TPA-induced ear in mice showed 50% and 37% inhibition at 0.5 mg/ear. Following the guided bioassay, the active compound diphyllin acetylapioside (**43**) was isolated and showed a significant inhibitory effect against TPA-induced inflammation in mice with a 50% inhibitory dose (ID_{50}) value at 0.27 μMol/ear (Prieto et al. 1996). In a further investigation, the same authors validated the anti-inflammatory effects on eicosanoid metabolism using an HPLC–DAD-based method. Diphyllin acetylapioside showed complete inhibition of 5-lipoxygenase activity at 50 μM and exhibited strong inhibitory effects against LTB_4 and 5-hydroxy-6,8,11,14-eicosateraenoic acid with IC_{50} values of 0.6 and 0.7 μM, respectively; however, diphyllin apioside (**41**) did not exhibit any effect on 5-lipoxygenase (Prieto et al. 2002). Five lignans isolated from the root of *Acanthopanax chiisanenesis* were examined for their effect on the production of TPA-induced PGE_2 in rat peritoneal macrophages to elucidate their mechanism of action. Taiwanin C (**2**) exhibited the most significant inhibitory effect with an IC_{50} value at 0.12 μM but showed no effect on the expression of TPA-induced COX-2 protein. However, with IC_{50} values at 1.06 and 9.3 1 μM, taiwanin C inhibited the activities of separated COX-1 and COX-2. These results suggest that taiwanin C (**2**) inhibits PGE_2 production by directly inhibiting COX enzymatic activity (Ban et al. 2002). Three arylnaphthalide lignans from *Phyllanthus polyphyllus* displayed anti-inflammatory effects as measured by NO, TNF-α, and interleukin (IL-12). Justicidin B (**1**) exhibited the highest IC_{50} values of NO production from LPS/IFN-γ-stimulated peritoneal macrophages at 12.5 μM followed by phyllamyricin C (**12**) at 25 μM, and dipyllin (**18**) at 50 μM and 100 μM showing inhibition percentages of 99%, 99%, and 64%, respectively. In addition, they showed significant inhibition of IL-12 and TNF-α production with IC_{50} values ranging from 12.5 to 100 μM (Rao et al. 2006).

Conclusion

Natural arylnaphthalene lactones have a 7′-phenyl naphthalene lactone skeleton in which the phenyl ring and naphthalene ring are polyhydroxylated, which are further transformed to methyl ethers or dioxolane. The hydroxy group, especially that at the C7 position is commonly conjugated with a variety of sugars to present mono-, di-, and triglycoside metabolites. Structurally, they can be classified into Type I and Type II arylnaphthalene lactones by the *cis* and *trans* relationship of lactone carbonyl and the aryl substituents. More than a hundred natural arylnaphthalene lactones have been reported from a wide range of natural sources such as Acanthaceae, Phyllanthaceae, and Schisandraceae.

Arylnaphthalene lactones exhibit various significant biological activities, which have been

summarized here based on their pharmacological activity. Although all the natural compounds were not fully evaluated, some results such as antiproliferative and antiviral activity could give insights for drug discovery. In fact, several arylnaphthalene lactones such as diphyllin and daurinol have been investigated as anticancer drug candidates with impressive in vitro and in vivo antiproliferative activity. More recently, daurinol was investigated extensively as an anti-autoimmune arthritis drug candidate. In the realm of medicinal chemistry, identifying new and valuable scaffolds is always of great interest. Thus, arylnaphthalene lactones attract considerable attention owing to their unique structural features, which include a relative rigid structure, no stereogenic center, and more than nine potential derivatizable sites. The unique structural features and promising pharmacological activities of arylnaphthalene lactones provide great prospects for future drug discovery.

Author contributions DS planned this manuscript. SP and SK searched the reported publications related to this review article. DS and SP wrote the draft of the manuscript, and SP prepared all figures. All authors approved the manuscript in its final form for publication.

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Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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