Diterpenoids from the genus *Illicium* and Their Bioactivities

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Abstract Diterpenoids are important chemical constituents isolated from the genus *Illicium*, which possess many pharmacological effects such as anti-inflammatory, antiviral activities, cytotoxicity, and so on. Up to now, 68 diterpenoids have been isolated from the genus *Illicium*, and they are classified as abietane-type, pimarane-type and podocarpane-type. In this paper, the chemical constituents and bioactivities of the diterpenoids from the genus *Illicium* are reviewed.

Keywords *Illicium*, diterpenoids, abietane-type, bioactivities

Introduction

The genus *Illicium* (family Illiciaceae) contains nearly 50 species worldwide, which mainly is distributed in east and southeast Asia. There are 28 species and 2 varieties in the genus that primarily are distributed in southern regions of China. The plants in this genus can be shrub or small tree, and they have the smell of fragrance.^[1] However, many plants of the genus *Illicium* are considered toxic. Its bark and fruit often are used as folk medicine to treat cough, rheumatism, lumbar muscle strain, skin inflammation, and cancer in ancient China.^[2] Previous phytochemical investigations on this genus have resulted in the isolation of some diterpenoids with anti-inflammatory, antiviral activities, cytotoxicity.^[3] Thus, the *Illicium* species have attracted widespread attention in recent years. About 68 diterpenoids have been isolated from the genus *Illicium*. Diterpenoids can be categorized into abietane-type, pimarane-type, and podocarpane-type. Among them, abietane-type diterpenoids are the primary type. Herein, we summarize chemical constituents and pharmacological effects of diterpenoids from the genus *Illicium*.

Different Types of Diterpenoids

Up to date, 68 diterpenoids have been found in many plants of this genus, such as *I. minwanense*, *I. majus*, *I. jiadifengpi*, *I. merrillianum*, and so on. Chemical components of diterpenoids mainly contain abietane-type, pimarane-type, and podocarpane-type.

Abietane-type diterpenoids

Among these diterpenoids, 54 abietane-type diterpenoids have been isolated and identified. Yokoyama *et al.*^[4] obtained a new abietane-type diterpene from a methanol extract of the pericarps of *I. minwanense*, named (+)-8,11,13,15-abietatetraene (**1**). From the twigs and leaves of *I. majus*, Fang *et al.*^[5] found four new diterpenes, named majusanic acid A—D (**2**—**5**), and majusanic acid B exhibited significant anti-inflammatory activity. From the roots of *I. jiadifengpi*, Zhang *et al.*^[6] obtained nine new diterpenes, named jiadifenoic acid A—G (**6**—**12**). Among them, jiadifenoic acid A is a novel dimeric diterpene with

a rare spiro[bicyclo[2.2.2]-oct-5-ene-2,10-cyclopentan]-3-one, and jiadifenoic acid B exhibited significant antiviral activities against Coxsackie virus B. From the fruits of *I. wardii*, Gao *et al.*^[7] purified two novel abietane diterpenes, wardinol A (**13**) and wardinol B (**14**) by intensive spectroscopic analysis. From ethanol extract of branches and leaves of *I. merrillianum*, Tian *et al.*^[8] isolated three new diterpenes, merrilliadione (**15**), 8 β ,14 α -dihydroxy-12,13 α -epoxyabietane (**16**), and 8 α ,14 α -dihydroxy-9,13 β -epoxyabietane (**17**). Compound **15** has a unique isopropyl (13 $\rightarrow$ 11)-abeo-9,11-seco-abietane skeleton, which displayed moderate cytotoxicity against human cancer cells. From the aerial parts of *I. angustisepalum*, Sy *et al.*^[9] obtained twelve novel diterpenes, angustanoic acid A (**18**), angustanal (**19**), angustanoic acid B (**20**), 4-epi-palustric acid-9 α ,13 α -endoperoxide (**21**), angustanoic acid C—F (**22**—**25**), angustanol (**26**), and angustanoic acid G—I (**27**—**29**). Wang *et al.*^[10] isolated compounds, majusanic acid E (**30**), majusanic acid F (**31**), and majusanic acid A—C (**32**—**34**) from the roots of *I. majus*. Zhang *et al.*^[11] found jiadifenoic acid J—L (**35**—**37**) from the stems of *I. jiadifengpi*. Huang *et al.*^[12] isolated and identified 4-epi-dehydroabietic acid (**38**), 4-epi-abietic acid (**39**) and 8,11,13,15-abietatetraen-19-oic acid (**40**) from the bark of *I. jiadifeng*. In addition, lambertic acid (**41**) was afforded from the roots of *I. majus*.^[13] From the twigs and leaves of *I. Majus*, majusanicol (**42**) was obtained.^[14] Besides, twelve known compounds from the genus *Illicium* have been isolated and identified as 7-hydroxy-1,4 α -dimethyl-1,2,3,4,4a,9,10,10a-octahydro-phena-nthrene-1-carboxylic acid (**43**), 7 α -hydroxycalitriscic acid (**44**), 12-hydroxydehydro-abietic acid (**45**), 15-oxo-17-norabiet-8,11,13-trien-18-oic acid (**46**), dehydroabietic acid (**47**), dehydroabietinol (**48**), 8,11,13-abietatrien-15-ol (**49**), aquilarabietic acid J (**50**), epipalustric acid (**51**), 4-epi-7 α ,15-dihydroxydehydroabietic acid (**52**), methyl abiet-8,11,13,15-tetraen-18-oate (**53**), and methy-16-nor-15-oxodehydroabietate (**54**).^[5-9,11,15] Their chemical structures are shown in Figure 1.

Pimarane-type diterpenoids

In addition to abietane-type diterpenoids, pimarane-type diterpenoid was also found in this genus. Six pimarane-type

Figure 1 Chemical structures of abietane-type diterpenoids isolated from the genus *Illicium*.

diterpenoids^[6,9,11,12,15] have been isolated and identified from the genus *Illicium*, named as jiadifenoic acid M (**55**), jiadifenoic acid N (**56**), 4-epi-sandaracopimaric acid (**57**), 4-epi-isopimaric acid (**58**), wulingzhic acid V (**59**), and isopimara-7,15-dien-19-ol (**60**), respectively. Among the compounds mentioned above, jiadifenoic acid M (**55**) exhibited reasonable activity against CVB3 (Coxsackie virus B3). Their chemical structures are shown in Figure 2.

Figure 2 Chemical structures of pimaranane-type diterpenoids isolated from the genus *Illicium*.

Podocarpane-type diterpenoids

Six podocarpane-type diterpenoids^[5,6,11] were found, named jiadifenoic acid H (**61**), jiadifenoic acid I (**62**), jiadifenoic acid O (**63**), jiadifenoic acid P (**64**), (+)-13-methoxypodocarpa-8,11,13-trien-19-oic acid (**65**), and 13-oxopodocarp-8(14)-en-19-oic acid (**66**). Among them, jiadifenoic acid P exhibited reasonable activity against CVB3. Their chemical structures are shown in Figure 3.

Figure 3 Chemical structures of podocarpane-type diterpenoids isolated from the genus *Illicium*.

Diterpene glycosides

From the ethanol extract of *I. brevistylum* (Illiciaceae). Chen *et al.*^[16] identified two new diterpene glycosides, brevistylumside A (**67**) and brevistylumside B (**68**). Their chemical structures are shown in Figure 4.

Figure 4 Chemical structures of diterpenes glycosides isolated from the genus *Illicium*.

Bioactivities of Diterpenoids from the genus *Illicium*

Diterpenoids from the genus *Illicium* have various pharmacological effects such as anti-inflammatory, antiviral activities and cytotoxicity.

Anti-inflammatory activity

Majusanic acid B (**3**) inhibited the β -glucuronidase release in rat PMNs induced by PAF ($IC_{50} = 0.26 \pm 0.03 \mu M$), which is about 10 times higher than that of ginkgolide B^[5] ($IC_{50} = 2.91 \pm 0.47 \mu M$). Compounds 8,11,13,15-abietatetraen-19-oic acid (**40**), methyl-16-nor-15-oxodehydroabietate (**54**), and 12-hydroxydehydroabietic acid (**45**) have strong NF- κ B inhibitory activity, which can reduce LPS-induced 293-NF- κ B-luc fluorescence intensity,^[19] indicating that abietane-type diterpenes are the main anti-inflammatory ingredient from *I. brevistylum*. Compound methylabieta-8,11,13,15-tetraen-18-oate (**53**)^[15] shows good anti-inflammatory activity. Chen^[15] found that the total extracts of *I. brevistylum* and all extracts parts have good NF- κ B inflammation inhibitory effect.

Antiviral activity

In recent years, many diseases were caused by virus infection, which had been a worldwide problem. Thus, it is urgent to find new antiviral drugs. Jiadifenoic acid B (**7**), jiadifenoic acid C (**8**), and 7 α -hydroxycallitrisic acid (**44**) exhibited significant antiviral activities against Coxsackie virus B (RNA virus), which was the first report of diterpenes with anti-Coxsackie virus activity.^[6] It can be clearly seen from the above reports, abietane-type diterpenoids are the main chemical constituents against Coxsackie virus B, providing potential anti-Coxsackie virus drugs in the future. Majusanic acid E (**30**), majusanic acid F (**31**), 4-epi-dehydroabietic acid (**38**), majusanic acid B (**33**), and majusanic acid D (**5**) displayed moderate antiviral activity against the Coxsackie virus B3 with IC_{50} values of 3.3–51.7 μM .^[5,10,12] Jiadifenoic acid M (**55**), jiadifenoic acid N (**56**), jiadifenoic acid P (**64**) and 13-oxopodocarp-8(14)-en-19-oic acid (**66**) exhibited reasonable activity against CVB3 with IC_{50} values of 7.0–22.2 μM and selective index values ($SI = TC_{50}/IC_{50}$) of 49.3, 37.1, 31.3, and 40.9,^[11] respectively.

Cytotoxicity

According to the previous reports, few diterpenoids in this

genus exhibited cytotoxicity. Tian *et al.*^[8] reported that merrilliadione (**15**), 8 β ,14 α -dihydroxy-12,13 α -epoxyabietane (**16**), 8 α ,14 α -dihydroxy-9,13 β -epoxyabietane (**17**), and dehydroabietinol (**47**) displayed moderate cytotoxicity against A549, HCT116, MDA-MB-231, and BEL-7404 cell lines with IC₅₀ values of 9.04–31.81 μ M.

Other bioactivities

Li *et al.*^[17] found that the crude extract of *I. lanceolatum* has antimicrobial activity. De *et al.*^[18] studied the antimicrobial properties of star anise (*I. verum*). The results indicated some compounds isolated from star anise can inhibit the bacterial growth.

Conclusion and Perspective

The plants from the genus *Illicium* have widespread medicinal values. Many chemical constituents have been isolated and identified by spectroscopic analysis and chemical methods. In this paper, we reviewed the main diterpenoids from the genus *Illicium*, including abietane-type, pimarane-type, and podocarpane-type. Some of them possess pharmacological effects such as anti-inflammatory, antiviral activity, and cytotoxicity. At present, researchers have studied many plants from the genus *Illicium*. Some new chemical constituents and bioactivities are being found, which will offer better medicinal values for clinical application in future. However, in-depth investigations on the bioactive mechanism are rarely reported in modern researches, and they should be strengthened on this aspect.

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Conflict of Interest

The authors declare no conflict of interest.

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