Recent progress in the chemistry and biology of limonoids

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This review covers the isolation and structure determination of limonoids reported during 2014–2016 (with 363 new compounds in 68 papers), together with the relevant biological activities and source organisms. Furthermore, the total synthesis and structural modifications of limonoids and their analogs regarding the bioactivities reported during 2011–2016 have also been summarised.

1. Introduction

Limonoids, a group of highly oxygenated triterpenoids, mainly exist in the Rutaceae and Meliaceae plant families.¹ When they first attracted people’s attention, limonoids were considered a major problem for the citrus juice industry due to the bitter principles through the biochemical transformation of a tasteless limonoid aglycone precursor to a bitter one.² Tetranor-triterpenoids is an alternative name for limonoids because in the process of oxidative changes of triterpenoids, the side chain is eventually oxidized to an α-substituted furyl ring by the loss of four carbon atoms.³ Basic limonoids contain the 4,4,8-trimethyl-17-furyl steroidal signature-skeleton, and all members of the family of limonoid natural products either contain this structure or are derived from such a precursor with different degrees of oxidation and skeletal rearrangement.

Limonoids are classified into different subcategories such as ring-intact limonoids, ring-seco limonoids, degraded limonoids, and highly oxidatively modified limonoids.⁴ Limonoids exhibited a wide spectrum of biological properties including cytotoxic,⁵–⁸ antioxidant,⁹,¹⁰ anti-inflammatory,¹¹,¹² neuroprotective,¹³,¹⁴ antiviral,¹⁵ antimicrobial,¹⁶,¹⁷ antiprotozoal,¹⁸ antimalarial,¹⁹–²¹ insect antifeedant,²²–²⁶ and insecticidal activities.²⁷–²⁹ The present review highlights the advances of limonoids in regard to isolation, total synthesis, and structural modifications with the relevant biological properties.

2. Reviews

Some excellent reviews on various aspects of limonoids studies are listed here. Overview of the distribution and chemistry of limonoids in plants kingdom was collated in 2006.¹ A comprehensive review of ‘Meliaceous limonoids: chemistry and biological activities’ has appeared in 2011.⁴ Topics on the chemistry and pharmacological activities of some limonoids have also been presented.³⁰–³⁵ In 2011, biosynthesis and total...
Fig. 1 Limonoids 1–25 from Trichilia genus.
3. Phytochemistry

To efficiently extract and isolate new limonoid natural products from plants, recently, several techniques have been developed. By combination of preparative high-speed countercurrent chromatography (HSCCC) and off-line LC-ESI-MS/MS analysis, Rodríguez-Rivera et al. reported a new chromatographic technique to detect very low concentrated natural products from Citrus limetta peels; moreover, four detected limonoid glucosides such as nomilinic acid glucoside, limonin glucoside, nomilin glucoside and obacunone glucoside, were easily recovered in the fast eluting. Haldar et al. developed the medium pressure liquid chromatography (MPLC) and LC-ESI-MS/MS-based technique to quickly isolate, identify and obtain some basic limonoids such as azadirone, epoxyazadiradione and azadiradione from neem fruits in preparative scale. The LC-HRMS-guided and preparative high-performance liquid chromatography (prep-HPLC)-based protocol was efficiently performed to isolate twenty-one secondary metabolites (including one limonoid, 1-O-methylclausenolide) from the leaves and stem bark extracts of Clausena anisata. Recently, supercritical CO₂ extraction has been applied to obtain limonoid extracts from the seeds of C. aurantifolia swingle in shorter time when compared with that of the conventional methods. De Paula et al. reported an inexpensive and quick ultrasonassisted extraction (UAE) and HPLC-photodiode array detector (PDA) technique to extract and determine azadirachtin from dried entire fruits of Azadirachta indica A. Juss (Meliaceae). More recently, Rangiah et al. have developed an ultra high performance liquid chromatography/mass spectrometry/selected reaction monitoring (UHPLC/MS/SRM) assay for quantification of five neem metabolites (e.g., azadirachtin A, nimbin, salanin, azadiradione and epoxy or hydroxyazadiradione) from leaf extracts of Meliaceae family plants.

With the development of technology, during 2014–2016, a wide array of new limonoid natural products were isolated from different parts of plants. Recent advances on the isolation and structure determination of limonoids, together with their relevant biological activities are presented according to their source organisms such as Meliaceae, Rutaceae, Euphorbiaceae and Simaroubaceae families.

3.1. Meliaceae

3.1.1. Trichilia. As shown in Fig. 1, 25 new limonoids were isolated from Trichilia genus. For example, trichiconin A–C 1–3, trichilin I 4, 12-deacetoxytrijugin A 5, trichiconlides A 6 and B 7, together with spirotrichilins A 8 and B 9 (ref. 54) were isolated from different parts (e.g., twigs, roots and fruits) of Trichilia connaroides. Hypothetical biosynthetic pathways for 1–3, 6, 8 and 9 were also proposed. Rubescins D 10 and E 11 were
obtained from the roots and stem barks of *T. rubescens*.\textsuperscript{35} Compounds 2 and 3 showed modest anti-HIV activities with EC\textsubscript{50} values of 5.9, and 3.6 μM, respectively; whereas compound 6 showed a moderate inhibitory effect on lipopolysaccharide (LPS) induced nitric oxide (NO) production with an IC\textsubscript{50} value of 40.5 μM. Compound 11 possessed the ability to induce

Fig. 3 Limonoids 34–64 from Cipadessa genus.
apoptosis in hepatoma cells.⁵⁶ Ethanolic extracts of the roots of *T. sinensis* afforded four new limonoids, trichinenlides U–X 12–15, which showed weak acetylcholinesterase (AChE) inhibitory activity at 50 mg mL⁻¹ (their inhibition ratios: 18.8% (12), 21.2% (13), 18.5% (14), and 23.7% (15)).⁵⁷ Ten cedrelone limonoids 16–25 were isolated from the leaves of *T. Americana*. The

![Chemical structures](image)

**Fig. 4** Limonoids 65–86 from *Chukrasia* genus.
structure of 16 was determined by X-ray crystallographic studies. Compounds 20–25 exhibited potent or selective cytotoxic activities with IC_{50} values ranging from 1.0 to 39.6 μM against five human tumor cell lines (e.g., HL-60, SMMC-7721, A-549, MCF-7, and SW480).^{38}

3.1.2. Swietenia. Swieteniaceae L. (Swietenia macrophylla) was obtained from the leaves and twigs of S. mahagoni.^{33} Compound 26 showed potent inhibition against LPS-induced NO generation (IC_{50}: 33.45 μM), and compound 28 exhibited significant antifungal activity (EC_{50}: 7.2 μM).

3.1.3. Cipadessa. As described in Fig. 3, 6 methyl angolensate limonoids, cipaferen E–J 34–39, and 3 mexicanolide-type limonoids, cipaferen K–M 40–42 were isolated from the seeds of Cipadessa baccifera.^{34} 3-De[2-methylbutanoyl]-3-propanoylcipadesin 43,^{43} cineracipadesin G 44,^{44} cipacinoids A–D 45–48,^{45} trijugin-type limonoids ciparasins A–G 49–55,^{46} cipadines-type limonoids ciparasins H–O 56–63,^{47} and prieurianin-type limonoid ciparasins P 64 (ref. 66) were isolated from the fruits, branches and leaves of C. cineas. The absolute configurations of 45 and 47 were unambiguously confirmed by the solid evidence of X-ray crystallography.^{48} Interestingly, compounds 53–55 contained a rare γ-hydroxybutenolide moiety at C-17 position.^{49}

Compound 37 displayed potent cytotoxic activity against B-16 with an IC_{50} value of 8.51 μg mL^{-1}.^{50} Compound 44 showed the potent antifeedant activity against fruit fly (Drosophila melanogaster; antifeedant index (AI) at 1 mM: 32.8%).^{51} Compound 45 (IC_{50}: 16.7 μM) displayed moderate inhibition activity against protein tyrosine phosphatase 1B (PTP1B).^{52} Compounds 50 (EC_{50}: 5.5 μM) and 64 (EC_{50}: 6.1 μM) showed significant anti-HIV activities.^{53}

3.1.4. Chukrasia. As shown in Fig. 4 and 5, 26 new phragmalin-type limonoids (including velutinasins A–H 65–72,^{54} velutinalide C 73,^{55} tabulalin K–M 74–76,^{56} velutabularins K–M 77–79,^{57} chukbularisins A–E 80–84,^{58} tabularisins S 85 and T 86,^{59} chuklarisin A 87 and chuklarisin B 88,^{60} and chukvelutilide Y 89 and Z 90 (ref. 74)) were isolated from the seeds, twigs, stem barks, and leaves of Chukrasia tabularis. The absolute configurations of 65–68 were determined by the CD exciton chirality method. Compounds 65–68,^{54} 89 and 90 (ref. 74) were a rare class of C15-acyl phragmalin-type limonoids, especially compounds 66–68 contained a δ-lactone ring formed between C-16 and C-30 positions.^{60} The steric structure of 77 was further confirmed by single crystal X-ray diffraction.^{61}

Compound 62 exhibited significant inhibition activity against LPS-induced NF-κB production. It suggested that the ortho ester group and/or the 2,7-dioxabicyclo[2.2.1]heptane moiety in these phragmalin limonoids were crucial for the activities.^{62}

Fig. 5 Limonoids 87–92 from Chukrasia genus.
Compounds 81–84, 86, and 88 exhibited significant inhibitory activities against α-glucosidase in vitro with IC₅₀ values of 0.06, 0.04, 0.52, 1.09, 0.15, and 0.96 mM, respectively.  

3.1.5. Walsura. Nine new cedrelone limonoids 93–101 (Fig. 6), including walsuranolide B 93, 11β-hydroxy-23-O-methyl-walsuranolide 94, yunnanolide A 95, yunnanol A 96, 11β-
hydroxyisowalsuranolide, 11β-hydroxy-1,2-dihydroisowalsuranolide, 1α,11β-dihydroxy-1,2-dihydroisowalsuranolide, 11β-hydroxy-12-methoxy-1,2-dihydroisowalsuranolide, and yunnanolide B, were isolated from the leaves and twigs of *Walsura yunnanensis*. As shown in Fig. 6, walsucochinioids C-R were obtained from the twigs and leaves of *W. cochinchinensis*. The steric structures of 102 and 111 were determined by single-crystal X-ray diffraction experiments. The isolation of walsunoids A-I, and walsuronoids D and E (ref. 78) from the leaves of *W. robusta* were reported (Fig. 6). Among them, compound is a novel degradation product of cedrelone-type limonoids, and 126 is a rare cedrelone-type limonoid amide. The structure of 121 was unambiguously measured by X-ray diffraction.

Fig. 7 Limonoids 129–162 from *Toona* genus.
Compounds 95, 97, 127 and 128 exhibited potent cytotoxic activities against five human tumor cell lines (e.g., HL-60, SMMC-7721, A-549, MCF-7, and SW480) with IC\textsubscript{50} values in the range of 2.2–4.5 μM.\textsuperscript{75,78} Compounds 103 and 104 exhibited mild inhibitory activities against mouse and human 11β-HSD1 with IC\textsubscript{50} values of 13.4 and 8.25 μM, respectively.\textsuperscript{76}

Fig. 8 Limonoids 163–187 from Carapa genus.
3.1.6. Toona. As shown in Fig. 7, a 9,11-seco limonoid (toonasecone A 129), seven B-seco-29-nor-limonoids (toonaciniliatones A–D 130–133), and seven B-seco-limonoids (toonaciniliatones E–H 134–137) and ciliatones A–C 137a–137c (ref. 80b) were isolated from the stem barks and the twigs of Toona ciliata. The absolute configurations of C-17 position.

Compound 132 was confirmed by single-crystal X-ray diffraction analysis. In addition, toonasinenines A–J 138–147, toonasinemines A–L 148–159, and toonasins A–C 160–162 (ref. 83) were obtained from the leaves and the root barks of T. sinensis. It is noteworthy that compounds 148–154, and 160–162 contained the rare lactam moiety at C-17 position.

Compound 160 was characterized by X-ray crystallographic analyses. Compound 132 exhibited modest cytotoxicity against HL-60 (IC₅₀: 5.38 μM) and HepG2 cells (IC₅₀: 5.22 μM). Compounds 141, 142 and 144–147 showed potent radical scavenging activities (DPPH IC₅₀: 51.3–104.0 μM; ABTS⁺ IC₅₀: 52.2–167.3 μM); compounds 138–141 exhibited significant anti-inflammatory (selective inhibition of Cox-1 and Cox-2 at 100 μM: >88%), and cytotoxic activities against seven human tumor cell lines (IC₅₀: 2.1–14.7 μM).

Compounds 148 (IC₅₀: 10.21 μM), 149 (IC₅₀: 20.05 μM), 153 (IC₅₀: 12.56 μM), 155 (IC₅₀: 12.56 μM) and 156 (IC₅₀: 20.68 μM) exhibited marked inhibitory effects on NO production in LPS-activated RAW 264.7 macrophages at nontoxic concentration.

![Limonoids 188–204 from Munronia genus.](image-url)
3.1.7. Carapa. As described in Fig. 8, 22 carapanolides C–X 163–184 (ref. 84–87) were isolated from the seeds of Carapa guianensis, a traditional medicine in Brazil and Latin American countries. The structure of 174 was unambiguously confirmed by single crystal X-ray measurements. Andiroloides W–Y 185–187 (ref. 88) were obtained from the flower oil of C. guianensis. Their structures were elucidated on the basis of spectroscopic analyses using 1D/2D NMR spectra and FABMS. Among them, compounds 170 (IC<sub>50</sub>: 37.4 μM), 180 (IC<sub>50</sub>: 22.0 μM), and 181 (IC<sub>50</sub>: 23.3 μM) showed potent NO production inhibitory activities.\textsuperscript{85,87}

3.1.8. Munronia. As shown in Fig. 9, 17 munronins A–Q 188–204 (ref. 89 and 90) were isolated from the whole plants of Munronia henryi. The structure of 195 was confirmed by single-crystal X-ray diffraction analysis.\textsuperscript{89} Interestingly, compound 188 contained a novel 7-oxabicyclo[2.2.1]heptane moiety at the C-11 and C-14 positions. Among them, compounds 189, 195–199, and 202–204 showed significant anti-TMV activity with IC<sub>50</sub>...
values in the range of 14.8–48.3 μg mL⁻¹.⁸⁹,⁹⁰ Compound 188 (IC₅₀ values: 0.44–2.3 μM) exhibited potent cytotoxic activities against five cancer cell lines (e.g., HL-60, SMMC-7721, A-549, MCF-7, and SW480).⁹⁹

3.1.9. Khaya. As shown in Fig. 10, 14,15-didehydroruageanin A 205,⁹¹ 3-O-methylbutyrylseneganolide A 206,⁹¹ and ivorenoids A–F 207–212 (ref. 92) were isolated from the fruits and stems of Khaya ivorensis. Compounds 207 and 208

Fig. 11 Limonoids 231–255 from Xylocarpus genus.
possessed a rare rearranged skeleton and a unique γ-lactone (C-16/C-8). Additionally, khaysenelide A–F 213–218 (ref. 93) with modified furyl ring, and khasenegasins O–Z 219–230 (ref. 94) were obtained from the stem barks and seeds of *K. senegalensis*, respectively. Compounds 213 and 215 were confirmed by single-crystal X-ray crystallography data.

Fig. 12 Limonoids 256–299 from *Aphanamixis* genus.
Compounds 209 (IC$_{50}$: 15.3 μM) and 212 (IC$_{50}$: 17.5 μM) exhibited moderate cytotoxic activity against HL-60 cell line.\textsuperscript{92} Compound 230 displayed the significant neuroprotective activity against glutamate-induced injury in primary rat cerebellar granule neuronal cells with increased viability of 83.3% at 10 μM and 80.3% at 1 μM.\textsuperscript{94}

3.1.10. Xylocarpus. As depicted in Fig. 11, 3 new limonoids, 2,3-dideacetylbilocensis S 231, 30-deacetylbilocensis W 232 and 7-hydroxy-3-oxo-21β-methoxy-24,25,26,27-tetranortirucall-1,14-dien-23(21)-lactone 233, were isolated from the seeds of the Chinese mangrove, Xylocarpus granatum.\textsuperscript{95} With an investigation conducted on the seeds of the Trang mangrove plant X. moluccensis, two phragmalins limonoids 234 and 235,\textsuperscript{96} two mexicanolides limonoids 236 and 237,\textsuperscript{96} twelve thaixylomolins G–R 238–249,\textsuperscript{96,97} and six trangmolins A–F 250–255 (ref. 98) were obtained. The absolute stereostructures of 246, 248 and 250 were unambiguously confirmed by X-ray crystallographic analysis. Compound 249 was the first 7-nor-limonoid with a 6-oxabicyclo[3.2.1]octan-3-one motif. Compound 254 contained the first oxidative cleavage on the C2–C3 bond in limonoids. Moreover, the biosynthetic origins of 250–255 traced back to an andirobin-type limonoid with 1,2-bisketone were also proposed.\textsuperscript{96}

Among them, compound 240 (IC$_{50}$: 77.1 μM) exhibited moderate anti-H1N1 activity;\textsuperscript{96} compound 247 showed moderate cytotoxicities against ovarian A2780 and A2780/T cells with equal IC$_{50}$ values of 37.5 μM for each.\textsuperscript{97}

3.1.11. Aphanamixis. As shown in Fig. 12, 30 new highly oxygenated prieurianin-type limonoids, zaphaprinins A–Y 256–280 (ref. 99) and aphagranols D–H 281–285,\textsuperscript{100} were isolated from the fruits of Aphanamixis grandifolia, which is a wild timber tree distributed mainly in the tropical and subtropical areas of South and Southeast Asia. The absolute configuration of 256 was assigned by single crystal X-ray measurements. On the other hand, 8 aphanamixoid-type aphanamixoids C–J 286–293, and 6 prieurianin-type aphanamixoids K–P 294–299, were obtained from A. polystachya.\textsuperscript{101}

Among them, compounds 264 and 274 showed strong insecticidal activities against Plutella xylostella.\textsuperscript{99} Compounds 286, 289 and 290 exhibited potent antifeedant activities against the generalist Helicoverpa armigera with EC$_{50}$ values of 0.017, 0.008, and 0.012 μmol cm$^{-2}$, respectively. Preliminary structure–activity relationship indicated that Δ (ref. 2 and 30)
configuration and the acetoxy substituent at C-12 position were vital to the antifeedant activity.  

### 3.1.12. Melia

As described in Fig. 13, 8 new limonoids, including 3-deacetyl-28-oxosalannolactone \(300\), 3-deacetyl-28-oxosalanninolide \(301\), 3-deacetyl-17-defurano-17,28-dioxosalanninin \(302\), 3-deacetyl-4\'-demethylsalannin \(303\), 3-deacetyl-28-oxosalannin \(304\), 1-detigloylocholinol \(305\), 3\(\alpha\)-acetoxy-1\(\beta\),7\(\alpha\)-dihydroxy-12\(\alpha\)-methoxynimbolinin \(306\), and 3\(\alpha\)-acetoxy-1\(\alpha\),12\(\alpha\)-dihydroxy-7\(\alpha\)-(2-methylprop-2-enoyl)nimbolinin \(307\), were isolated from the leaves, fruits and stem barks of *Melia azedarach*.  

Recently, an investigation on the fruits of *M. toosendan* resulted in four new limonoids, such as 1\(\alpha\),7\(\alpha\)-dihydroxyl-3\(\alpha\)-ace-toxyl-12\(\alpha\)-ethoxylnimbolinin \(308\), 1\(\alpha\)-tigloyloxy-3\(\alpha\)-acetoxyl-7\(\alpha\)-hydroxyl-12\(\beta\)-ethoxylnimbolinin \(309\), and 12-ethoxynimbolinins \(E\) \(310\) and \(F\) \(311\).  

Among them, compound \(300\) (IC\(50\): 86.0 \(\mu\)M) showed inhibitory effects against LPS-induced NO production in RAW 264.7 cell line; the IC\(50\) values of compounds \(301\) and \(302\) against the Epstein-Barr virus early antigen (EBV-EA) were 299 and 318 molar ratio/32 pmol TPA, respectively.  

### 3.1.13. Chisocheton

A new 30-nor trijugin-type limonoid, chisotrijugin \(312\) (Fig. 14), was isolated from the bark of *Chisocheton cuminganus*. The chemical structure of \(312\) was confirmed by spectroscopic techniques such as UV, IR, MS, 1D and 2D NMR.  

### 3.1.14. Neobeguea

As described in Fig. 15, 11 new limonoids, namely, dodoguin \(313\), dormir A–G \(314–320\), libiguins A \(321\), libiguins B (a) \(322\) and libiguins B (b) \(323\), were isolated from the root barks of *Neobeguea mahafalensis*, a medicinal plant in Madagascar. Interestingly, compounds \(318\), and \(321–323\) contained a C-16/30 \(\delta\)-lactone ring, which was the first time reported in this species. Compounds \(322\) and \(323\) were existing in tautomers. Among them, compound \(313\) displayed sleep-inducing activity in Swiss albino mice;
and compound 322 exhibited a potent sexual enhancing activity.

3.1.15. Entandrophragma. Sixteen entangolensins A–P (324–339) were isolated from the stem barks of *Entandrophragma angolense*, a genus of the Meliaceae family restricted to tropical Africa.\textsuperscript{110a} Their planar structures were comprehensively characterized by HRMS and 1D/2D NMR, and the absolute configurations of most isolates were established by time-dependent density functional theory (TDDFT) calculations of the electronic circular dichroism (ECD) data. Especially compound 324 was the first natural product example of C-9/10-seco mexicanolide. Compounds 329 (IC\(_{50}\): 1.75 μM) and 334 (IC\(_{50}\): 7.94 μM) exhibited significant NO inhibitory activities against LPS-activated RAW 264.7 macrophages. Furthermore, the plausible biosynthetic pathway of these compounds has been described.

Additionally, as shown in Fig. 16, entanutin A (339a) and B (339b) were isolated from the stem barks of *Entandrophragma utile*.\textsuperscript{110b} Their absolute configurations were confirmed by CD exciton chirality method.

3.2. Rutaceae

3.2.1. Hortia. As shown in Fig. 17, 3 new limonoids 340–342 were isolated from the taproots and stem of *Hortia oreadica*.\textsuperscript{111}

![Fig. 16 Limonoids 324–339, 339a, and 339b from Entandrophragma genus.](image-url)
3.2.2. Dictamnus. As described in Fig. 17, kihadanin C 343 with an unusual 3,4-dihydroxy-2,5-dimethoxytetrahydrofuran moiety as E ring, and 23-methoxydasylactone A 344, were isolated from the root barks of Dictamnus dasycarpus. Meanwhile, 9 dictangustones A–I 345–353, were obtained from the root barks of D. angustifolius. Among them, compound 346 displayed significant neuroprotective activity against neuronal death induced by oxidative stress, and compound 352 exhibited potent cytotoxic activities against four cell lines (e.g., Hela, A549, MCF7, and LN229) with IC_{50} values lower than 25 μM.

3.3. Euphorbiaceae

Two highly oxygenated limonoids, such as flexuosoids A 354 and B 355 (Fig. 18), with a C-19/29 lactol bridge and heptaoxygenated substituents at C-1, C-2, C-3, C-7, C-11, C-17, and C-30 positions,
were isolated from the roots of *Phyllanthus flexuosus*. Compounds 354 and 355 showed antifeedant activities against the beet army worm (*Spodoptera exigua*) with EC\textsubscript{50} values of 25.1 and 17.3 \(\mu\text{g cm}^{-2}\), respectively. In addition, compounds 354 (IC\textsubscript{50}: 11.5 \(\mu\text{M}\)) and 355 (IC\textsubscript{50}: 8.5 \(\mu\text{M}\)) displayed moderate cytotoxic activities against the ECA109 human esophagus cancer cell line.

### 3.4. Simaroubaceae

As shown in Fig. 19, two new 16-nor limonoids, harperspinoids A 356 and B 357, with a unique 7/5/6/5 ring system, were obtained from the leaves and branches of *Harrisonia perforata*. Especially the absolute structure of 356 was further confirmed by X-ray crystallographic analysis. Moreover, compound 356 exhibited the notable inhibitory activity against the 11b-HSD1 enzyme with an IC\textsubscript{50} value of 0.60 \(\mu\text{M}\). The biogenetic pathway of these two compounds was also proposed. Perforanoid A 358 (Fig. 19), isolated from the leaves of *H. perforata*, showed cytotoxic activities against HEL, K562, CB3, DP17, and WM9 tumor cell lines (IC\textsubscript{50}: 4.24–25.96 \(\mu\text{M}\)).

### 4. Total synthesis

#### 4.1. Cipadonoid B

In 2011, an efficient strategy for the total synthesis of cipadonoid B 359 was reported (Scheme 1). First, compound 361 was prepared by reaction of silyl enol ether with 360. Then, azedaralide 363 reacted with 361 via the intermediate 362, to give 359 (20% yield) by a ketal-Claisen rearrangement.

#### 4.2. Khayasin, proceranolide, and mexicanolide

Based upon cipadonoid B 359, Faber et al. further reported a concise and enantioselective total synthesis of proceranolide 364, khayasin 365 and mexicanolide 366 (Scheme 2). First, compound 364 was obtained from 370 by epoxidation and cyclization; then, compound 365 was afforded by acylation of 364; finally, conversion of 364 to 366 in the presence of Jones reagent was achieved.

#### 4.3. Limonin

As depicted in Scheme 3, Yamashita et al. described the total synthesis of (±)-limonin 379 in 35 steps. Via an intermediate 372, a tandem radical cyclization of geraniol 371 gave 373 containing a BCD ring system with the C-13\(\alpha\) configuration. Then, the limonoid androstane framework 374 was constructed by a Robinson annulation of 373. Subsequently, compound 376 was produced by epoxidation and nitrile addition, followed by acetonitrile elimination. Through a singlet-oxygen cycloaddition and a Baeyer–Villiger oxidation, compound 378 was obtained via the intermediate 377. Finally, construction of target compound 379 was achieved by a Suarez reaction.

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**Scheme 1** Reagents and conditions: (a) silyl enol ether, TiCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, –78 °C; (b) KH, PhH; (c) MeOTf, CH\textsubscript{2}Cl\textsubscript{2}; (d) azedaralide 363. PTSA, xylene, 180 °C, 4 h.
Scheme 2  Reagents and conditions: (a) KHMDS, THF, −78 °C, then (−)-DIP-Cl, 3-furylaldehyde, 33−44% yield, 80−90% ee; (b) (+)-DIP-Cl, DIPEA, 2-butanone, Et2O, −78 °C, then −105 °C to −30 °C, 16 h, 47% yield, 92.5% ee; (c) TsOH, xylenes, 180 °C, 4 h; (d) 30% H2O2, K2CO3, MeOH, 0 °C to r.t., 12 h, 75%; (e) Al/Hg, EtOH/THF/H2O/NaHCO3, r.t., 1 h, 30%; (f) isobutyric acid, EDCI, DMAP, CH2Cl2, 0 °C to r.t., 4 h, 71%; (g) K2Cr2O7/H2SO4, Me2CO, r.t., 15 min, 68%.

Scheme 3  Reagents and conditions: (a) Mn(OAc)3·2H2O, EtOH, r.t.; (b) Zn, AcOH, r.t.; (c) MVK, t-BuOK, t-BuOH, 35 °C; (d) MeI, t-BuOK, t-BuOH, 40 °C; (e) LiAlH4, THF, 0 °C to reflux; (f) TBSOTf, NaH, THF, 0 °C to r.t.; (g) Ac2O, pyridine, DMAP, CH2Cl2, r.t.; (h) m-CPBA, NaHCO3, CH2Cl2, −20 °C to −5 °C; (i) NaCN, DMSO, 120 °C; (j) Ac2O, pyridine, DMAP, CH2Cl2, r.t.
Scheme 4  Reagents and conditions: (a) 2-methylpropenal (1.0 equiv.), aminonaphthol (15 mol%), 2-butyne (2.0 equiv.), Cy2BH (2.0 equiv.), Me2Zn (2.0 equiv.), toluene, r.t. to −78 °C then −30 °C; (b) 381 or 382, LDA, THF, −78 °C; (c) Burgess reagent.

| Entry | Substrate (0.2 g/L, 8 days in M881) | 17β-Hydroxy (%) | 12β-Hydroxy (%) |
|-------|-----------------------------------|-----------------|-----------------|
| 1     | azadiradione 387                  | 61              | 38              |
| 2     | 1,2-dihydroazadiradione 388       | 59              | 40              |
| 3     | 1,2α-epoxyazadiradione 389        | 57              | 39              |
| 4     | epoxyazadiradione 390             | -               | 99              |
| 5     | 1,2-dihydroepoxyazadiradione 391  | -               | 93              |
| 6     | nimbocinol 392                    | 71              | -               |
| 7     | 7-deacetyloxyazadiradione 393     | -               | 94              |
| 8     | gedunin 394                       | -               | 96              |

Fig. 20  Biotransformation of limonoids.
will lay the foundation for future synthesis of diverse limonoid skeletons.

4.4. Perforanoid A and 10-epi-perforanoid A

More recently, as shown in Scheme 4, Hao et al. developed an efficient way to total synthesis of perforanoid A 358 and 10-epi-perforanoid A 386. The key steps were as follows: allylic alcohol 384 was enantioselectively obtained by alkenylation of 3-formylfuran 383 with 2-methylpropenal; then, Pd-catalyzed coupling of 384 with a vinyl ether gave the γ-lactone ring, with stereoselective construction of the C13 all carbon quaternary center, followed by formation of the cyclopentenone ring by a Rh-catalyzed Pauson-Khand reaction to give 385. Finally, reaction of 385 with 381 or 382 produced 358 (33% yield) and 386 (36% yield), respectively.117 Compound 358 showed potent cytotoxic activities against HEL, K562, and CB3 tumor cell lines with IC_{50} values of 6.17, 4.24, and 3.91 μM, respectively; in contrast, compound 386 did not display any cytotoxic activity.

5. Structural modifications

5.1. Biocatalytic modifications

Biotransformation is a good choice for the production of sufficient amounts of scientifically and commercially valuable...
compounds with the advantages of strict stereo- and region-selectivity, mild reaction conditions and simple operation procedure. As shown in Fig. 20, 8 limonoids including azadiradione 387, 1,2-dihydroazadiradione 388, 1,2α-epoxyazadiradione 389, epoxyazadiradione 390, 1,2-dihydroepoxyazadiradione 391, nimbocinol 392, 7-deacetylpoxyazadiradione 393 and gedunin 394, were converted into their corresponding 12β- and/or 17β-hydroxy derivatives via fungi M881-mediated biocatalysis. Interestingly, when 14β,15β-epoxidation was on the basic limonoid skeleton (e.g., 390, 391, 393, and 394), only 12β-hydroxy derivative was produced as the single metabolite.\footnote{121}

5.2. Chemical modifications

5.2.1. Phragmalin. As depicted in Scheme 5, starting from phragmalin 395 isolated from the seeds of C. tabularis, libiguin A 321 and its analogs 401, 405 and 406 were efficiently obtained by structural modification. This was based on selective amidolysis of the lactone in 395 with MeONHMe, followed by TMSOTf-promoted lactonization of the resulting Weinreb amide with the 30-OH group after protection or oxidation of the 17-OH group.\footnote{122,123}

5.2.2. Toosendanin. Starting from toosendanin 407, we prepared a series of 28-acyloxy derivatives of toosendanin 408–434 (Scheme 6).\footnote{124,125} Among them, compounds 410, 417 and 431 exhibited more potent insecticidal activity than 407 against the pre-third-instar larvae of Mythimna separata Walker in vivo at 1 mg mL\textsuperscript{−1}. Interestingly, it indicated that the proper length of the side chain at the 28-position of 407 was important for the insecticidal activity; however, introduction of the double bond on the side chain decreased the activity.

5.2.3. Limonin. As shown in Scheme 7, a series of limonin derivatives 436–465 were prepared by structural modifications on the A, B or D-ring of limonin 379.\footnote{126,127} It demonstrated that oxygen bridge between C-14 and C-15 positions in limonin derivatives was important for analgesic and anti-inflammatory activities. Compound 443 displayed a promising analgesic and anti-inflammatory activities with high water-solubility (14.5 mg mL\textsuperscript{−1}). Among 446–465, compounds 451 and 459 showed higher antimicrobial activities than 379 against 20 microorganisms.

5.2.4. Obacunone. As depicted in Scheme 8, we semi-synthesized a series of obacunone (466) derivatives, including C7-oxime esters 468–491, C7-oxime sulfonate esters 492–497, and C7-esters 500–532.\footnote{128–132} The structures of 480, 485, 486, 498, 499, and 518 were unambiguously determined by single-crystal X-ray diffraction. Interestingly, when compound 466 was reduced by NaBH\textsubscript{4}, the ratio of reductive products 498 and 499 was related to the reaction mixing solvents. In addition, compounds 472, 485, 486, 490, 495, 501 and 510 (the final mortality rates (FMRs) at 1 mg mL\textsuperscript{−1}: 55.2–72.4%) showed more potent insecticidal activity against M. separata than their precursor 466 (FMR: 41.4%) and toosendanin (FMR: 48.3%). It demonstrated that the configuration of C7-OH of 498 (FMR: 32.1%) and 499 (FMR: 46.4%) was important for the insecticidal activity, and introduction of a chlorine atom on the phenyl ring of the substituents could improve the activity.

5.2.5. Fraxinellone. As shown in Scheme 9, to discover more potent fraxinellone (533)-based insecticidal agents, first, in the presence of selenium dioxide or chromium trioxide, we developed an efficient method for regioselectively allylic oxidation of 533 at its C-4 or C-10 position (A ring) to afford 534 and 579, respectively; then, a series of esters 559–578 and 580–596,\footnote{134} hydrazones 535–544 and 603–615,\footnote{135} and oxime esters 545–558 and 597–602,\footnote{136} were smoothly prepared. On the other hand, when reduction of 533 with Red-Al reagent, we found that the kinds and the amount of the reduction products 617, 628 and 656 at the C-1 or C-8 position (B ring) were related with the molar ratio of Red-Al/533; subsequently, esters 629–655 and 657–665, were synthesized from 628 and 656, respectively.\footnote{137} It was noteworthy that when compound 533 reacted with different chlorination/bromination reagents,
some unexpected furyl-ring (C ring) halogenation products 623–627 were obtained. Moreover, their possible reaction mechanism was also proposed.134 Especially, 20 steric structures of compounds 534, 535, 544, 553, 566, 601, 611, 617, 620–628, 659, 660 and 663, were unambiguously established by X-ray analysis. Among them, compounds 534, 535, 557, 566, 575, 578, 579, 596, 598, 602, 606, 617, 620, 622, 627, 652, 653 and 665 (FMRs: 51.7–73.3%) displayed more promising insecticidal activity than toosendanin (FMR: 48.3%).

The structure–activity relationships demonstrated introduction of the carbonyl or oxime group on the C-4 position of 533 generally resulted in more promising derivatives than those containing a carbonyl or oxime one at the C-10 position; introduction of the heterocyclic fragments at C-4 or C-10 position of 533 was necessary for the insecticidal activity;
the lactone (B ring) of 533 was important for the insecticidal activity; the double bond at the C-2 position of 533 was not necessary for the insecticidal activity; substitution of the oxygen atom on the carbonyl group of 533 by the sulfur one did not improve the insecticidal activity; introduction of the acyl group on the C ring of 533 could lead to more potent compounds than those containing the halogen atom at the same position.130–134

6. Biological activities of the most active limonoids

Due to exhibiting a large number of biological properties, currently, limonoids and their analogs have received much research attention in the medicinal and agricultural fields. Additionally, the most active limonoids and
Scheme 9 Semisynthesis of fraxinellone derivatives. Reagents and conditions: (a) CrO₃, Py, t-BuOOH, MW, 25 W, 25 h, 33°C/C₁₄; (b) HOAc, hydrazides or hydrazines, reflux, 5–48 h; (c) NH₂OH·HCl, EtOH, Py, 80°C; (d) R²CO₂H, DCC, DMAP, CH₂Cl₂, r.t.; (e) NaBH₄, MeOH, 0–5°C, 1.5 h; (f) R²/R³CO₂H, DICC, DMAP, r.t.; (g) SeO₂, MW, 150 W, 2.5 h, 110°C; (h) Lawesson’s reagent, toluene, reflux, 12 h; (i) Red-AL, THF-PhMe, −78–10°C, 24 h; (j) R²COCl, AlCl₃, r.t., 5–12 h; (k) 2.2 equiv. DCDMH, DMF, 0–5°C, 1 h; (l) 2.2 equiv. NBS, DMF, 0–5°C, 2 h; (m) 2.2 equiv. NCS, DMF, 0–5°C, 2.5 h, then 5°C–r.t., 2.5 h.

R³

535, 603: COPh 536, 604: COPhNO₂(p) 537, 605: COPhCl(m) 538, 606: 4-pyridylcarboxyl 539, 607: 3-thiencarboxyl 540, 608: COCH₃CN
541, 609: Ph 542, 610: PhNO₂(p) 543, 611: PhNO₂(o) 544, 612: 2,3,5,6-tetrafluoroanil 613: COPhOMe(p) 614: COPhOme(m) 615: 2,4-dinitrophenyl
Table 1 14 most active limonoids against human cancer cell lines

| Compounds                      | Cells          | IC_{50} (µM) |
|--------------------------------|----------------|-------------|
| 1,2-Dihydrodeacetylhirtin 20   | HL-60          | 4.9         |
| (ref. 58)                      | SMMC-7721      | 3.1         |
|                                | A-549          | 2.9         |
|                                | MCF-7          | 9.8         |
|                                | SW480          | 9.0         |
| 1α-Hydroxy-1,2-dihydrodeacetylhirtin 21 | HL-60          | 3.1         |
| (ref. 58)                      | SMMC-7721      | 1.0         |
|                                | A-549          | 1.1         |
|                                | MCF-7          | 1.0         |
|                                | SW480          | 1.6         |
| 1α-Methoxy-1,2-dihydrodeacetylhirtin 23 | HL-60          | 5.3         |
| (ref. 58)                      | SMMC-7721      | 3.7         |
|                                | A-549          | 5.2         |
|                                | SMMC-7721      | 5.3         |
|                                | A-549          | 6.4         |
| Cipaferen E 37 (ref. 62)       | B-16           | 8.51        |
| Yunanolid A 95 (ref. 75)       | HL-60          | 3.6         |
|                                | SMMC-7721      | 2.4         |
|                                | A-549          | 3.7         |
|                                | MCF-7          | 4.2         |
|                                | SW480          | 3.5         |
|                                | BEAS-2B        | 5.0         |
| Walsuronoids D 127 (ref. 78)   | HL-60          | 2.7         |
|                                | SMMC-7721      | 3.1         |
|                                | A-549          | 4.1         |
|                                | MCF-7          | 3.1         |
|                                | SW480          | 2.8         |
| Walsuronoids E 128 (ref. 78)   | HL-60          | 3.3         |
|                                | SMMC-7721      | 4.1         |
|                                | A-549          | 4.4         |
|                                | MCF-7          | 4.4         |
|                                | SW480          | 4.5         |
| Toonacilatones C 132 (ref. 80) | HL-60          | 5.38        |
|                                | HepG2          | 5.22        |
| Toonasinenines B 139 (ref. 81) | A-549          | 5.7         |
|                                | CHG-5          | 5.0         |
|                                | HCT15          | 5.7         |
|                                | HeLa           | 6.2         |
|                                | HepG2          | 5.5         |
|                                | MDA-MB-231     | 6.0         |
|                                | SGC-7901       | 6.0         |
| Toonasinenines C 140 (ref. 81) | A-549          | 9.7         |
|                                | CHG-5          | 8.3         |
|                                | HepG2          | 9.1         |
|                                | MDA-MB-231     | 9.4         |
|                                | SGC-7901       | 9.4         |
| Toonasinenines D 141 (ref. 81) | A-549          | 2.3         |
|                                | CHG-5          | 2.8         |
|                                | HCT15          | 2.6         |
|                                | HeLa           | 2.9         |
|                                | HepG2          | 3.0         |
|                                | MDA-MB-231     | 2.7         |
|                                | SGC-7901       | 2.1         |
| Munronsins A 188 (ref. 89)     | HL-60          | 0.44        |
|                                | SMMC-7721      | 2.3         |
|                                | A-549          | 1.6         |
|                                | MCF-7          | 1.5         |
|                                | SW480          | 0.86        |

Table 2 33 most active limonoids and their analogs as insecticidal agents

| Compounds                      | Insect pests                  | FMRs (at 1 mg mL^{-1}) |
|--------------------------------|-------------------------------|------------------------|
| Perforanoid A 338 (ref. 117)   | Drosophila melanogaster       | AI^{a} = 32.8% at 1 mM |
| (nicotine: AI = 28.5% at 1 mM) |                               |                        |
| Aphanamixoids C 286 (ref. 101) | Helicoverpa armigera          | EC_{50}^{b} = 9.27 µg cm^{-2} |
| Aphanamixoids F 289 (ref. 101) |                               | EC_{50} = 4.28 µg cm^{-2} |
| Aphanamixoids G 290 (ref. 101) |                               | EC_{50} = 6.82 µg cm^{-2} |
| Flexuosoids A 354 (ref. 115)   | Spodoptera exigua             | ED_{50}^{c} = 25.1 µg cm^{-2} |
| Flexuosoids B 355 (ref. 115)   |                               | ED_{50} = 17.3 µg cm^{-2} |

\[^a\text{Antifeedant index: AI.}\]
\[^b\text{EC}_{50}^{c}\text{value: the effective concentration for 50% feeding reduction.}\]
\[^c\text{ED}_{50}^{c}\text{value: the effective dosage for 50% feeding reduction.}\]
7. Conclusions

However, the availability of limonoids is very limited from natural resources because of intensive collection of plants from the wild and long plant growth period. Although total chemical synthesis of limonoids remains a challenge of significant novelty and interest, it is not a practical option from a commercial point of view. Consequently, sustainable biotechnology and tissue culture techniques may be extensively exploited to enhance production of limonoids to meet the increasing demands. Additionally, to improve the water solubility and bioactivities, structural modifications of limonoids should be further strengthened.

In this review, we summarised 363 new limonoid natural products isolated from plants during 2014–2016, together with their relevant biological activities and source organisms. Moreover, we highlighted recent developments in the total synthesis, structural modifications of limonoids and their analogs regarding their bioactivities during 2011–2016. We hope that this review can provide necessary information for synthetic, medicinal and pesticidal chemistry, and phytochemistry researchers who are interested in the chemistry and biology of limonoids.

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