Review:
Phytochemistry and Pharmacology of Munronia Genus (Meliaceae)

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Abstract: Munronia is a genus in the Meliaceae family, which consists of over 17 species that are distributed in the subtropical and tropical area of Asia, including southern China, Vietnam, Myanmar, Sri Lanka, India, Indonesia, and the Philippines. It is known that these plants contain valuable bioactive compounds. Since the first isolation of new stigmastane steroid was reported in 2003, researchers have been able to study the chemical composition of these plants, especially the largest secondary metabolite obtained, limonoid. About 97 compounds were isolated successfully and characterized. The reported compounds showed various biological activities, such as antifeedant, antimicrobial, antiangiogenic, cytotoxic against several cancer cell lines, inducing apoptosis, and anti-tobacco mosaic virus activities. Therefore, the results suggest that the use of this plant as a source of bioactive compounds is promising for the medicinal chemistry field.

Keywords: biological activity; limonoid; Meliaceae; Munronia; phytochemistry

INTRODUCTION

Meliaceae is a family of woody plant which is grown in tropical and subtropical regions. This family consists of approximately 50 genera covering 1,400 species [1]. Meliaceae is well known as a source of diverse natural compounds with interesting biological activity. Some compounds including sesquiterpenoids [2-7], triterpenoids [8-18], diterpenoids [19-21], steroids [22-25], limonoids [26-27], alkaloids [28-29], lignan [30-32], flavaglines [33-35], and flavonoids [36-37] have been successively extracted from this family. Those isolated compounds showed interesting biological activities including cytotoxic [38-41], insecticidal [42-43], antimycobacterial [6], antifungal [44-45], antiinflammatory [9,46-47], and antiviral [48]. The high diversity of compounds together with its interesting bioactivity showed that Meliaceae family is a promising source for bioactive compounds for drug development in future.

Munronia is a genus that belongs to the family of Meliaceae, which consists of over 17 species [49] that are distributed in southern China, Vietnam, Myanmar, Sri Lanka, India, Indonesia, and the Philippines [50-51]. Some species of this genus are considered to be endemic. M. yinggelinensis is discovered in Hainan province, China [49] while M. delavayi is a vulnerable perennial species that is endemic in the dry-hot valley of the middle/lower Jinsha River [52]. Other rare species of this genus including M. pinnata, are a valuable medicinal plant in Sri Lanka [53]. This species is one of the most expensive plant material (US$ 50–110/kg) used in traditional medicine [54]. Plants of this genus have been known in folk medicine since historical times. In Sri Lanka, the powders of this plant are used to treat malaria, dysentery, fever, skin diseases, and blood cleansing from poisonous snake bites, as well as to prevent hiccups, vomiting, and sore throats [55-56].

To rationalize the link between the valuable

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medicinal uses of this plant and its chemical compositions, researchers are putting effort to explore these plants. The first chemical composition of this plant described is the isolation of a new sterol containing an octadecenoyl, including other compounds such as glycosides and sesquiterpenoids, from *M. henryi* [57]. After that, dozens of new compounds, including limonoids, tirucallane-type triterpenoids, phytosterols, diterpenoids, and glycosides have been successfully isolated mostly from the whole plant and aerial parts of this plant. Furthermore, these isolated metabolites showed extensive biological activity such as insect antifeedant, antifungal, antiangiogenic, anti-tobacco mosaic virus, and anticancer activity. Although research on the exploration of new metabolites from genus *Munronia* is still going on, to the best of our knowledge, there is no reported review discussed on the phytochemical and biological activity of this genus. This review is expected to provide guidance on the major chemical constituent and biological activity of genus *Munronia*.

**BOTANY**

*Munronia* is a genus of the Meliaceae family that consists of over 17 species that are mainly distributed in the tropics and subtropics of Asia [50]. The plants from this genus have unbranched shrubs or sparsely branched with 10–50 cm in length. Simple odd-pinnate leaves, crenate to serrate, with petiole 1.5–4.0 cm. The stems are usually not braced, glabrous or apical, and covered with appressed puberulence. In general, it has white hermaphrodite flowers. The fruit contains 5 valved loculicidal capsule, each locule contains 1 or 2 seeds with yellowish gray color [58].

**PHYTOCHEMISTRY**

**Overview on Isolated Compounds from *Munronia* Genus**

The first report that the *Munronia* compound was isolated began in 2003 with the isolation of a new steroid stigmastane with an octadecenoyl substituent. Then, about 97 compounds have been identified from this genus, which includes steroid, terpenoid, limonoid, and other metabolites. Out of all the isolated compounds, limonoid compounds were the largest isolated metabolites from this genus.

**Steroid**

There were two classes of steroid compounds isolated from whole plant parts of certain species of the genus *Munronia*, such as pregnane and stigmastane-type steroid. Qi et al. [57] reported a new compound, sitosterol-3-O-12’,13’-epoxy-9’-oxo-(10’E)-octadecenoate (1) with the pregnane-type steroid 2β,3β,4β-trihydroxypregnan-16-one (2) from *M. henryi*. From *M. delavayi*, Cai et al. [59] isolated one pregnane-type steroid, 2α,3α,15β-trihydroxy-20(S)-tigloyl-pregnane (3) and five stigmastane steroids, i.e. β-daucosterol (4), 6-hydroxystigmast-4-en-3-one (5), sitoindoside I (6), sitoindoside II (7), β-sitosterol (8), which come from the same sitosterol core with C-3 modified substituent were obtained. Furthermore, Yan et al. [50] reported pregnane-type steroid, such as munronin S (9) bearing tygloyl oxy unit at C-12 [50]. The chemical structures and source of isolated steroids of the genus *Munronia* are shown in Fig. 1 and Table 1, respectively.

**Terpenoid**

A total of 10 terpenoid compounds, divided into sesquiterpenoid, diterpenoid, and triterpenoids were identified and characterized in genus *Munronia*. Qi et al. [51] obtained 4α,7α-aromadendranediol (10), an aromadendrene-type sesquiterpenoid from *M. henryi*. Meanwhile, *M. delavayi* gave a simple diterpenoid compound, geranylgeraniol (11) isolated by Cai et al. [60] from the whole plant of this species. Furthermore, Yan et al. [61] reported the isolation and structural determination of a new diterpenoid, munronin R (12) from *M. henryi*. Another type of terpenoid compounds reported in genus *Munronia* was triterpenoid compounds. All triterpenoid compounds isolated from this genus possessed a tirucallane-type triterpenoid. From ethanolic extract of whole plants *M. delavayi*, Cai et al. [60] reported seven tirucallane-type triterpenoids, i.e. sapelin A (13), munronosides I-IV (14-17), melianodiol (18), and (3β)-22,23-epoxytirucall-7-ene-3,24,25-triol (19). In the
Table 1. Compounds isolated from genus *Munronia*

<table>
<thead>
<tr>
<th>Type</th>
<th>Species</th>
<th>Compounds</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td><em>M. henryi</em></td>
<td>sitosterol-3-0(12',13'-epoxy-9'-oxo-(10'E)-octadecenoate (1)</td>
<td>[57]</td>
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<td></td>
<td></td>
<td>2β,3β,4β-trihydroxypregnan-16-one (2)</td>
<td>[57]</td>
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<td></td>
<td><em>M. delavayi</em></td>
<td>2α,3α,15β-trihydroxy-20(S)-tigloylpregnane (3)</td>
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<tr>
<td></td>
<td></td>
<td>β-daucosterol (4)</td>
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<td></td>
<td></td>
<td>6-hydroxystigmast-4-en-3-one (5)</td>
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<td></td>
<td></td>
<td>sitoindoside I (6)</td>
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<td>sitoindoside II (7)</td>
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<td></td>
<td>β-sitosterol (8)</td>
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<td></td>
<td></td>
<td>munronin S (9)</td>
<td>[59]</td>
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<tr>
<td>Terpenoid</td>
<td><em>M. henryi</em></td>
<td>4α,7α-aromadendranediol (10)</td>
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<td></td>
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<td>munronin R (12)</td>
<td>[61]</td>
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<td></td>
<td><em>M. delavayi</em></td>
<td>geranylgeraniol (11)</td>
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<td></td>
<td></td>
<td>sapelin A (13)</td>
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<td>munronosides I-IV (14-17)</td>
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<td>melianadiol (18)</td>
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<td>(3β)-22,23 epoxytrirucall-7-ene-3,24,25-triol (19)</td>
<td>[60]</td>
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<td>Limonoid</td>
<td><em>M. henryi</em></td>
<td>munroniamide (20)</td>
<td>[51]</td>
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<td></td>
<td></td>
<td>munronins A-F (21-26)</td>
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<td>munronolide (27)</td>
<td>[65]</td>
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<td></td>
<td></td>
<td>munronolide 21-O-β-D-glucopyranoside (28)</td>
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<td>munronins A-N (54-67)</td>
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<td>munronins O-Q (68-70)</td>
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<td>chisonimbolin F (71)</td>
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<td></td>
<td>12-O-methylvolkensin (72)</td>
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<td>C-seco nibimolin (73)</td>
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<td>prieurianin (74)</td>
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<td>aphanamixoid F (75)</td>
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<td><em>M. delavayi</em></td>
<td>6α-hydroxy-14,15-deoxyhavanensin triacetate (76)</td>
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<td>Glycosides</td>
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<td>munroninamide (20)</td>
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<td>munronins A-F (21-26)</td>
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<td>munronolide (27)</td>
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<td></td>
<td><em>M. delavayi</em></td>
<td>munronin G (29)</td>
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<td></td>
<td>mulavanins A-E (30-34)</td>
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<td></td>
<td></td>
<td>mombasol (35)</td>
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<td></td>
<td></td>
<td>14,15β-epoxy prieurianin (36)</td>
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<td></td>
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<td>nymania 3 (37)</td>
<td>[66]</td>
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<td></td>
<td><em>M. sinica</em></td>
<td>6,7-bis(acetylxylo)-4,4,8-trimethyl-3-oxo-(5α,6α,7α,13α,17α,20γ)-carda-1,14-</td>
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<td></td>
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<td>dienolide (38)</td>
<td>[67]</td>
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<td></td>
<td><em>M. unifoliata</em></td>
<td>munronoids A-J (39-48)</td>
<td>[68]</td>
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<td></td>
<td>munronoids K-O (49-53)</td>
<td>[69]</td>
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<tr>
<td>Ceramides</td>
<td><em>M. henryi</em></td>
<td>1-O-β-D-glucopyranosyl-(2S,3S,4R,8Z)-2-N-(2’-hydroxytetracosanoyl)-</td>
<td>[57]</td>
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<td></td>
<td></td>
<td>heptadecasphinga-8-ene (95)</td>
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<td>(2S,3S,4R,8E)-2-N-(2’-hydroxytetracosanoyl)-heptadecasphinga-8-ene (96)</td>
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<td>(2S,3R,4E)-2-N-(2’-hydroxytetracosanoyl)heptadecasphinga-4-ene (97)</td>
<td>[57]</td>
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</table>
position of C-29, 14-17 attached to a trisaccharide moiety, which was, O-β-D-glucopyranosyl-(1→3)-O-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranosyl. The chemical structures and source of terpenoid compounds reported in genus *Munronia* are shown in Fig. 2 and Table 1, respectively.
Limonoid

Structurally, limonoids are defined as degraded triterpenoids with about four loose carbon atoms in the side chain position, and it is therefore called the tetranortriterpenoid [62]. These compounds are highly oxygenated and rearranged than triterpenoids, having such a broad structural diversity including additional hydroxyl, ketone, ester, ring-opening, and formation of furan or lactone groups in the side chain [63]. The Meliaceae family is known to be the source of a large number of limonoids including genus Munronia [64].

The first limonoid isolation, i.e. munroniamide (20) from M. henryi was reported by Qi and coworkers [51]. Compound 20 has an open ring at A and B, carrying α,β-unsaturated lactone moiety in the A ring and lactam unit in side chain. The further chemical investigation on this species gave six new limonoid compounds, i.e. munronins A-F (21-26). In compounds 23-26, the side chains were relatively rare in limonoid compounds, which is α,β-unsaturated lactone, α,β-unsaturated lactam, and alkyne groups, respectively [57]. From the same species, Zhang et al. [65] obtained limonoid compound, munronolide (27) and munronolide 21-O-β-D-glucopyranoside (28). Surprisingly, 28 were the first record compound with the glucose moiety attached to C-21 position. From M. delavayi, munronin G (29) has been obtained by Cai and Luo [60]. Munronin G (29) showed same skeleton with munronolide (27), with the major difference was the presence of a furan ring in the side chain. The chemical structures and source of 20-29 are shown in Fig. 3 and Table 1, respectively.

The extensive isolation and identification of compounds from M. delavayi, Lin et al. [66] reported new limonoid compounds, mulavanins A-E (30-34) together with three known limonoids, i.e. mombasol (35), 14,15β-epoxyprieurianin (36) and nymania 3 (37). It was reported that tigloyl unit appears to be attached on C-12 of 30-34. From M. sinica, Li et al. [67] obtained limonoid compound, 6,7-bis(acetyloxy)-4,4,8-trimethyl-3-oxo-(5α,6α,7α,13α,17α,20ξ)-carda-1,14-dienolide (38). Species of M. unifoliata also produced many new limonoids with interesting diversity. Fifteen new limonoids were successfully isolated and characterized by Ge et al. [68-69] named, munronoids A-J (39-48) and...

Fig 3. The chemical structure of 20-29
munronoids K-O (49-53). These limonoids possessed skeleton of peierianin, evodulone, euphane, and havanensin-types of limonoids. The structures and source of limonoid 30-53 is shown in Fig. 4 and Table 1, respectively.

Other limonoid compounds also isolated from this species, namely chisonimbolinin F (71), 12-O-
methylvolkensin (72), C-seco nimbolinin (73), prieurianin (74), aphanamixoid F (75), and 6α-hydroxy-
14,15-deoxyhavanensis triacetate (76). Compound 54 represents the first limonoid reported with a novel 7-
oxabicyclo[2.2.1]-heptane moiety produced by incorporating C-11 and C-14 via an oxygen atom [70].

The latest phytochemistry investigation from M. pinnata,
showed the presence of limonoids, munropins A-F (77-82). Munropins A (77) and B (78) were classified as a prieurianin skeleton with α,β-unsaturated γ-lactam moieties at C-17. Munropins C (79), D (80), and E (81)
including prieurian-type limonoids with an α,β-unsaturated γ-lactone moiety, an acetyl group, and an acetoxyacetyl group at C-17, respectively. Munropin F (82) was assigned as a nimbidin-type limonoid with a γ-hydroxy-α,β-unsaturated γ-lactone moiety [71]. The chemical structures and source of limonoids 54-82 are shown in Fig. 5 and Table 1, respectively.

**Other compounds**

Glycosides, ceramides, and flavonoids were also found in several species of *Munronia*. *M. henryi* produced glycosides, α-D-glucopyranosyl-6'-O-hexadecanoate (83), 4-O-α-D-psicofuranos-α-D-glucopyranose (84), and glyceryl-1-tetracosanoicate (85) [57]. Meanwhile, *M. sinica* contained other glycosides such as musinins A and B (86 and 87), glucosyacetosyringone (88), cannabide D (89), corchoionoside C (90), and (+)-3-oxo-α-ionyl glucoside (91) [67]. Flavonoid compounds were obtained from *M. delavayi*, such as kaempferol (92), quercetin (93), and rutin (94) [59]. Qi et al. [57] showed the presence of three ceramides, 1-O-β-D-glucopyranosyl-(2S,3S,4R,8Z)-2-N-(2'-hydroxytetracosanoyl)-hepta-decapinga-8-ene (95), (2S,3S,4R,8E)-2-N-(2'-hydroxytetracosanoyl)-hepta decapinca-8-ene (96), and (2S,3R,4E)-2-N-(2'-hydroxy tetracosan-oyl)heptadecapinca-4-ene (97). The chemical structures and source of 83-97 are shown in Fig. 6 and Table 1, respectively.

### BIOLOGICAL ACTIVITIES

Plants of the genus *Munronia* have long been used in traditional medicine in various countries such as China, India, and Sri Lanka for treatment of dysentery, fever, malaria, skin disease, and purification of blood due to venomous snake bite [55] and to prevent hiccups, vomiting and sore throats [56]. Four species have been reported from this genus, and compounds have shown interesting biological activities such as insect antifeedant [51,57], antimicrobial [66], anti-tobacco mosaic virus [61,68-69], antiangiogenic [67], and cytotoxic activity [61].

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Fig 6. The chemical structure of 83-97
Insect Antifeedant Activity

The first reported antifeedant activity of compounds isolated from the genus Munronia was reported from M. henryi. Qi et al. [72] reported that munroniamide (2) exhibited moderate activity, while ceramide 95 showed significant antifeedant activity. Meanwhile, ceramides 96 and 97 showed negative activity against Pieris brassicae L. For azadirachtin, munroniamide (2) showed only 10% mortality while 95 showed 50% mortality (azadirachtin was 100% mortality). Furthermore, Qi et al. [51] also reported antifeedant activity of limonoids and munronins A-E (21–25) showed moderate activity with a mortality rate of about 10–20%, meanwhile munronin F (26) showed negative. Azadirachtin was used as a positive control in all the experiment. From species M. unifoliata, Ge et al. [68] reported that munronoid A (39) and munronoid D (42) showed moderate insecticidal activities, with lethal concentration 50 (LC₅₀) values at a concentration of 200 μg/mL and 23.3% (39), 53.3% (42) against Brassica oleracea var. capitata.

Antimicrobial Activity

Li et al. [66] reported the isolation of limonoids and other constituents from M. delavayi for antimicrobial activity. The results showed that mulavanin D (33) and 2α,3α,15β-trihydroxy-20(S)-tigloyl-pregnane (3) showed modest activity against Microsporum gypseum and Trichophyton rubrum with minimum inhibitory concentration (MIC) values at 25 and 50 μg/mL, respectively. In this test, amphotericin B was used as a positive control with a MIC of 1.56 μg/mL against both fungi.

Antiangiogenic, Cytotoxic and Inducing Apoptosis Activity

A limonoid compound reported in M. sinica, 38, has an inhibition ratio of about 58.7% at a concentration of 40 μg/mL. The results show that the intersegmental vessels of embryos treated with 38 were significantly less than that of the control PTK787. The cytotoxic activity of compounds isolated from M. sinica, limonoid 38 and glycosides 86-91, by Li et al. [67] also tested against A549 lung cancer cells using MTT assay. The results clearly showed that compounds 38, 86, 87, and 91 exhibited a certain antiproliferative activity. Based on the acridine orange staining, compound 38 showed an obvious effect of inducing apoptosis of A549 lung cancer cells [67]. The in vitro cytotoxicity against human cancer HL-60, SMMC-7721, A-549, MCF-7, and SW-480 cell lines were investigated for limonoids, 54-76. The result showed that compounds 54 and 74 exhibited cytotoxic effects for all five cancer cell lines, with half-maximal inhibitory concentration (IC₅₀) values in the range of 0.4–4.8 μM [61].

Anti-tobacco Mosaic Virus Activity (Anti-TMV Activity)

The limonoids isolated by Ge et al. [68] from M. unifoliata were tested for anti-TMV activity. Munronoid A (39) was screened according to the conventional half-leaf and leaf-disk method along with Western blot analysis, and showed strong anti-TMV activity, with an inhibition value at a concentration of 1 μg/mL was 50%. Munronoid C (41), munronoid D (42), and munronoid F (44) were screened by the conventional halfleaf method along with Western blot analysis, and showed moderate antiviral activities, with inhibition values at a concentration of 500 μg/mL were 25.4% (41), 29.3% (42), and 37.2% (44), respectively. Further investigations on anti-TMV activity on limonoids obtained from M. unifoliata, munronoid K-O (49-53) were evaluated using half-leaf, enzyme-linked immunosorbent assay, and Western blot methods. Limonoids 49 and 53 showed stronger anti-TMV treatment activities than the positive control ningnanmycin. All compounds (49-55) showed inhibitory activities against TMV [69]. According to M. henryi, Yan et al. [61] evaluated the anti-TMV activity of limonoids, i.e. munronins A-N (54-67). Among these evaluated compounds, compounds 55, 61, 62, 63, 64, 65, and 74 showed significant anti-TMV activity, with IC₅₀ values in the range 19.6–44.4 μg/mL. The preliminary structure-activity relationships of these limonoids indicated that the presence of an α,β-unsaturated lactone and an acetyl group located at C-7 are important for increasing the activity. Furthermore, munronins O-Q (68-70) which was also isolated from M. henryi, was tested for anti
TMV activity. Among these, 70 exhibited the best activity, with an IC_{50} value of 14.8 μg/mL, which was two-fold stronger than that of control ningnamycin (44.6 μg/mL).

■ CONCLUSION

For 17 years, researchers have been interested in investigating the chemical composition of genus *Munronia*, a valuable medicinal plant in many countries, such as China, India, and Sri Lanka. About five species out of over 17 plants from genus *Munronia* has been extensively investigated. 97 compounds isolated from genus *Munronia* distributed into steroids, terpenoids, limonoids, and other metabolites. Various biological activities have been reported from these metabolites, including insect antifeedant, antimicrobial, antiangiogenic, cytotoxic, and inducing apoptosis, and anti-tobacco mosaic virus activity.

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