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Nematicidal activity of oleanolic acid derivatives on *Meloidogyne incognita*

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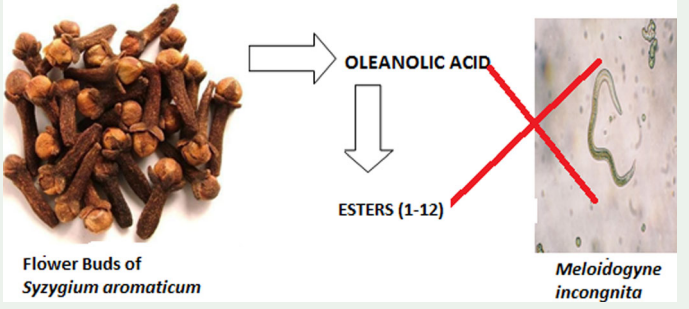
ABSTRACT

In this study, oleanolic acid and its derivatives were studied for their *invivo* nematicidal activity against root-knot nematode (RKN) *Meloidogyne incognita*. A series of C-28-oleanolates including five new **(5, 7–10)** and seven known **(1–4, 6, 11, 12)** compounds were synthesised and their nematicidal activity was determined and compared with the standard nematicide furadan for the first time. The structures of the compounds were elucidated through ^{1}H NMR, ^{13}C NMR and EIMS. Compounds **4, 5, 7, 8** and **10** showed ~ 90% inhibition of RKN at 0.125% concentration after 72 h showing their potential use in nematicidal control.



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KEYWORDS
Oleanolic acid; *Meloidogyne incognita*; nematicidal activity; 28-oleanolates

1. Introduction

Oleanolic acid (OA) is a naturally occurring pentacyclic triterpenoid ($C_{30}H_{48}O_3$) (Xia et al. 2012) which biosynthetically comes from cyclisation of squalene. It is found in stem, leaves and fruits of different edible and medicinal plants (Fai and Tao 2009). *Lantana camara* (Vyas and Argal 2013), *Lisgustrum lucidum* (Xia et al. 2012) and olive oil (Guinda et al. 2010) are rich sources of OA. Apple, grape, sage, elderberry and loquat are also good sources of oleanolic acid (Jäger et al. 2009). In China, it has been used as a drug against hepatitis for several years (Liu et al. 1995). It also has several other biological activities including

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antioxidant (Yin and Chan 2007), antimicrobial (Kim et al. 2015), antinociceptive, anti-inflammatory (Rali et al. 2016), anti-HIV (Zhu et al. 2001), anti-diabetic (Treadway et al. 2001), anti-tumour (Liese et al. 2015) and anticancer (Shanmugam et al. 2014).

Due to its natural abundance and high biological potential, researchers are trying to modify its structure by various chemical changes to increase the stability and water solubility. Chemical structure of OA clearly shows three 'active sites' at C-3, double bond between C-12 and C-13, and C-28 (Pollier and Goossens 2012; Zhang et al. 2012).These sites can be transformed to achieve increased pharmaceutical properties and enhanced bioactivity. C-28 of oleanolic acid can be converted into amides, alcohols, nitriles, triazoles and esters analogues (Gupta et al. 2010). Keeping this view in mind, a series **(1–12)** of 28-esters of oleanolic acid including five new **(5, 7–10)** and seven known derivatives **(1–4, 6, 11, 12)** was prepared, in which carboxlic group of oleanolic acid was converted into ester with a target of enhancing the biological activity.

Root-knot nematodes (RKN; *Meloidogyne* spp.) are pathogenic sedentary endoparasites of the plant root system. They occur worldwide, and their host range includes many important agricultural crops. Hence, a search for the management plant-parasitic nematodes is being undertaken worldwide. Two compounds, acibenzolar-S-methyl, a derivative of salicylic acid and a plant hormone methyl jasmonate which can elicit the plant's defence system against RKN, were recently reported for their direct nematicidal effect on *Meloidogyne incognita* (Schouteden et al. 2017). Considering the background and need for potential nematicides, the nematicidal effect of oleanolic acid and its C-28-oleanolates was studied against root-knot nematode, *Meloidogyne incognita* for the first time in the present work.

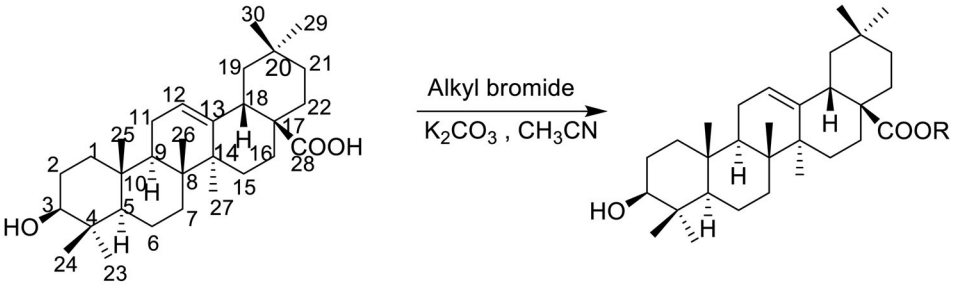
2. Results and discussion

2.1. Chemistry

Oleanolic acid was isolated from the dried flower buds of *Syzygium aromaticum* (clove). In this study, a series of 28-oleanolates **(1–12)** of oleanolic acid was prepared (Figure 1) in quantitative yield. Among them, five compounds **(5, 7–10)** are new, while seven **(1–4, 6, 11, 12)** have been synthesised earlier (Chen et al. 2016). EIMS showed the absence of carboxylic group of oleanolic acid in all ester derivatives **(1–12)** as the characteristic r.D.A fragment *m/z* of 248 was missing and replaced with methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, benzyl and 4-nitro benzyl esters, respectively. In compounds **1–10,** a signal for CH_2 adjacent to oxygen function of ester moiety was observed at δ_H ~3.91 as multiplet. In the benzyl derivatives **(11–12),** the aromatic protons were observed at δ_H 7.31 in benzyl oleanolate and 7.49–8.19 in case of 4-nitro benzyl oleanolate in the ^{1}H NMR. The structures of new compounds **(5, 7–10)** were further confirmed by ^{13}C NMR. Ester carbonyl carbon was appeared at δ_C ~177.8, while oxygenated methylene was observed at δ_C ~64.1 that indicated the conversion of carboxylic group into ester moiety (Experimental section). Their structures are illustrated in Figure 1.

2.2. Nematicidal activity

In the present investigation, nematicidal activity of 28-oleanolates **(1–12)** against root-knot nematode *Meloidogyne incognita* at three different concentrations (1.0%, 0.5%



1. R = CH_3
2. R = CH_2CH_3
3. R = $CH_2CH_2CH_3$
4. R = $CH_2(CH_2)_2CH_3$
5. R = $CH_2(CH_2)_3CH_3$
6. R = $CH_2(CH_2)_4CH_3$
7. R = $CH_2(CH_2)_5CH_3$
8. R = $CH_2(CH_2)_6CH_3$
9. R = $CH_2(CH_2)_7CH_3$
10. R = $CH_2(CH_2)_8CH_3$
11. R = H_2C–C$_6$H$_5$
12. R = H_2C–C$_6$H$_4$–NO_2

Figure 1. Synthetic route of ester formation.

and 0.125%) after 24, 48 and 72 h of exposure were determined (Table S1). The tested alkyl derivatives **(1–10)** showed good toxicity (70 to 90%) against *Meloidogyne incognita* at 0.125% concentration after 72 h. It was observed that mortality increased with increasing concentration and time duration. After 48 h, all these esters displayed moderate-to-good inhibition 60%–80% at 0.125% concentration. Butyl to decyl oleanolates **(4–10)** showed comparable activity as oleanolic acid at 0.125% concentration after 72 h. Among benzyl derivatives **(11–12)**, 4-nitrobenzyl oleanolate was more active (68%) than benzyl oleanolate (58%) at same concentration and same time duration indicating that nitro group enhanced the activity. Nematicidal activity of 28-easters of oleanolic acid was determined for the first time in the present investigation.

3. Experimental

3.1. Chemistry

3.1.1. General

Mass spectrometry was carried out on JEOL JMS600H-1. ^{1}H NMR and ^{13}C NMR spectra were obtained on AVANCE NEO 500 MHz and 125 MHz, respectively. Spectra were taken in deuterated chloroform ($CDCl_3$), and chemical shifts were recorded in δ (ppm).

Residual solvent was used as the internal standard. Reaction was monitored by thin-layer chromatography and visualised by UV lamp (254 nm), iodine spray and 5% H_2SO_4 solution in MeOH. Oleanolic acid was isolated from the flower buds of *Syzygium aromaticum* (clove) according to the method described earlier (Ghulam and Ahmad 2014). Acetone and potassium carbonate were purchased from Sigma-Aldrich (Steinheim, Germany) and Fluka Chemie (Buchs, Switzerland), respectively. All the alkyl halides were purchased from Sigma-Aldrich (Steinheim, Germany). Silica gel (Merck 9385) was used for column chromatography. Thin-layer chromatography was performed on silica gel 60 F_{254} (Merck) (Damstadt, Germany)..

3.1.2. General procedure for the synthesis of 28-Oleanolates and characterisation

To a solution of oleanolic acid (100 mg, 0.23 mmol) in acetonitrile (10 mL), K_2CO_3 (66 mg, 0.46 mmol) was added. After 10 minutes of stirring at room temperature, different alkyl halides were added. The reaction mixture was kept overnight at room temperature, freed of the solvent by keeping in fuming hood overnight. The solid mass left was partitioned between ethyl acetate and water. The organic layer was dried with anhydrous Na_2SO_4, filtered and freed of the solvent through rotary evaporator. The residue thus obtained was purified by silica gel column chromatography using petroleum ether-ethyl acetate (9:1) system to obtain compounds **1–12**.

Methyl oleanolate (1). Yield 71%. White amorphous solid. EIMS *m/z* (rel. int. %): 470 [M^+] (6), 455 (3), 411 (5), 262 (52), 203 (100), 189 (19), 133 (12). ^{1}H NMR ($CDCl_3$) δ: 3.21 (1H, dd, $J = 10.8$, 4.4 Hz, H-3α), 5.29 (1H, t, $J = 3.6$ Hz, H-12), 2.84 (1H, dd, $J = 14.0$, 4.0 Hz, H-18β), 1.13, 0.99, 0.93, 0.91, 0.90, 0.78, 0.73 (each 3H, s, 7XCH_3), 3.63 (3H, s, H-1′).

Ethyl oleanolate (2). Yield 70%. White amorphous solid. EIMS *m/z* (rel. int. %): 484 [M^+] (17), 465 (5), 411 (16), 293 (79), 276 (61), 203 (72), 189 (41), 166 (38), 148 (100). ^{1}H NMR ($CDCl_3$) δ: 3.20 (1H, dd, $J = 10.1$, 3.0 Hz, H-3α), 5.26 (1H, t, $J = 3.6$ Hz, H-12), 2.84 (1H, dd, $J = 13.5$, 3.9 Hz, H-18β), 1.11, 0.97, 0.90, 0.88, 0.87, 0.76, 0.72 (each 3H, s, 7XCH_3), 4.06 (2H, m, H-1′), 1.20 (3H, t, $J = 7.2$ Hz, H-2′).

Propyl oleanolate (3). Yield 65%. White amorphous solid. EIMS *m/z* (rel. int. %): 498 [M^+] (18), 480 (5), 411 (29), 290 (87), 203 (100), 189 (73), 133 (26).^{1}H NMR ($CDCl_3$) δ: 3.19 (1H, dd, $J = 10.8$, 5.4 Hz, H-3α), 5.26 (1H, t, $J = 3.3$ Hz, H-12), 2.85 (1H, dd, $J = 13.5$, 3.6 Hz, H-18β), 1.11, 0.96, 0.90, 0.88, 0.88, 0.76, 0.71 (each 3H, s, 7XCH_3), 3.95 (2H, m, H-1′), 0.92 (3H, t, $J = 7.2$ Hz, H-3′).

Butyl oleanolate (4). Yield 71%. White amorphous solid. EIMS *m/z* (rel. int. %): 512 [M^+] (27), 494 (23), 411 (37), 393 (23), 304 (77), 291 (26), 203 (100), 189 (78). ^{1}H NMR ($CDCl_3$) δ: 3.20 (1H, dd, $J = 10.0$, 3.1 Hz, H-3α), 2.85 (1H, dd, $J = 14.0$, 4.0 Hz, H-18β), 5.26 (1H, t, $J = 3.6$ Hz, H-12), 1.11, 0.97, 0.90, 0.89, 0.88, 0.76, 0.72 (each 3H, s, 7XCH_3), 3.99 (2H, m, H-1′), 0.90 (3H, t, $J = 7.0$ Hz, H-4′).

Pentyl oleanolate (5). Yield 68%. White amorphous solid. EIMS *m/z* (rel. int. %): 526 [M^+] (6), 411 (14), 393 (5), 318 (51), 203 (100), 189 (64). ^{1}H NMR ($CDCl_3$) δ: 3.19 (1H, dd, $J = 9.9$, 3.9 Hz, H-3α), 5.25 (1H, t, $J = 3.0$ Hz, H-12), 2.85 (1H, dd, $J = 14.1$, 3.6 Hz, H-18β), 1.11, 0.97, 0.90, 0.88, 0.87, 0.76, 0.71 (each 3H, s, 7XCH_3), 3.99 (2H, t, $J = 6.6$ Hz, H-1′), 0.88 (3H, t, $J = 7.1$ Hz, H-5′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.4 (C-1), 27.2 (C-2), 79.0 (C-3), 38.4 (C-4), 55.2 (C-5), 17.0 (C-6), 33.0 (C-7), 39.3 (C-8), 47.6 (C-9), 38.4 (C-10), 23.4

(C-11), 122.3 (C-12), 143.9 (C-13), 43.9 (C-14), 29.7 (C-15), 22.2 (C-16), 46.6 (C-17), 41.3 (C-18), 45.9 (C-19), 30.7 (C-20), 33.4 (C-21), 33.8 (C-22), 28.1 (C-23), 15.3 (C-24), 15.6 (C-25), 18.3 (C-26), 23.0 (C-27), 177.8 (C-28), 33.0 (C-29), 23.6 (C-30), 64.3 (C-1′), 28.2* (C-2′), 28.3* (C-3′), 25.9 (C-4′), 14.0 (C-5′). * Values may be interchanged.

Hexyl oleanolate (6). Yield 67%. White amorphous solid. EIMS *m/z* (rel. int. %): 540 [M^+] (5), 411 (8), 332 (15), 293 (34), 203 (30), 189 (10), 167 (20), 149 (100). ^{1}H NMR (CDCl3) δ: 3.19 (1H, dd, $J = 11.0$, 4.0 Hz, H-3α), 5.26 (1H, t, $J = 4.0$ Hz, H-12), 2.85 (1H, dd, $J = 14.0$, 4.5 Hz, H-18β), 1.11, 0.97, 0.90, 0.88, 0.87, 0.76, 0.71 (each 3H, s, 7XCH_3), 3.98 (2H, m, H-1′), 0.88 (3H, t, $J = 6.9$ Hz, H-6′).

Heptyl oleanolate (7). Yield 68%. White amorphous solid. EIMS *m/z* (rel. int. %): 554 (8), 537 (5), 410 (15), 393 (10), 346 (31), 333 (12), 203 (100), 189 (33). ^{1}H NMR ($CDCl_3$) δ: 3.19 (1H, dd, $J = 9.9$, 4.2 Hz, H-3α), 5.25 (1H, t, $J = 3.3$ Hz, H-12), 2.85 (1H, dd, $J = 14.1$, 4.5 Hz, H-18β), 1.11, 0.97, 0.90, 0.88, 0.88, 0.76, 0.71 (each 3H, s, 7XCH_3), 3.98 (2H, m, H-1′), 0.87 (3H, t, $J = 6.8$ Hz, H-7′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.4 (C-1), 27.2 (C-2), 79.0 (C-3), 38.4 (C-4), 55.2 (C-5), 17.0 (C-6), 33.0 (C-7), 39.3 (C-8), 47.6 (C-9), 38.4 (C-10), 23.4 (C-11), 122.6 (C-12), 143.9 (C-13), 43.9 (C-14), 29.7 (C-15), 23.5 (C-16), 46.6 (C-17), 41.3 (C-18), 45.9 (C-19), 30.7 (C-20), 33.4 (C-21), 33.8 (C-22), 28.1 (C-23), 15.3 (C-24), 15.6 (C-25), 18.3 (C-26), 23.0 (C-27), 177.8 (C-28), 33.0 (C-29), 23.6 (C-30), 64.3 (C-1′), 28.8* (C-2′), 26.0 (C-3′), 28.6* (C-4′), 31.8 (C-5′), 25.9 (C-6′), 14.1(C-7′). * Values may be interchanged.

Octyl oleanolate (8). Yield 73%. White amorphous solid. EIMS *m/z* (rel. int. %): 568 [M^+] (10), 550 (5), 410 (29), 393 (8), 360 (81), 347 (17), 203 (100), 189 (60), 133 (20). ^{1}H NMR ($CDCl_3$) δ: 3.19 (1H, dd, $J = 10.2$, 4.5 Hz, H-3α), 5.26 (1H, t, $J = 3.0$ Hz, H-12), 2.83 (1H, dd, $J = 14.1$, 4.2 Hz, H-18β), 1.11, 0.96, 0.90, 0.88, 0.88, 0.76, 0.71 (each 3H, s, 7XCH_3), 3.98 (2H, m, H-1′), 0.86 (3H, t, $J = 7.0$ Hz, H-8′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.4 (C-1), 28.1 (C-2), 79.0 (C-3), 38.7 (C-4), 55.2 (C-5), 17.0 (C-6), 33.1 (C-7), 39.3 (C-8), 47.7 (C-9), 37.0 (C-10), 23.6 (C-11), 122.3 (C-12), 143.9 (C-13), 41.3 (C-14), 29.2 (C-15), 22.7 (C-16), 46.7 (C-17), 41.3 (C-18), 45.6 (C-19), 30.7 (C-20), 33.9 (C-21), 32.8 (C-22), 27.7 (C-23), 15.3 (C-24), 15.6 (C-25), 18.0 (C-26), 23.4 (C-27), 177.8 (C-28), 32.5 (C-29), 23.4 (C-30), 64.2 (C-1′), 28.2 (C-2′), 26.0 (C-3′), 29.2* (C-4′), 29.1* (C-5′), 31.7 (C-6′), 25.9 (C-7′), 14.1 (C-8′). * Values may be interchanged.

Nonayl oleanolate (9). Yield 77%. White amorphous solid. EIMS m/z (rel. int. %): 582 [M+] (25), 408 (49), 393 (11), 374 (81), 361 (28), 203 (100), 189 (78), 173 14), 133 (23). ^{1}H NMR ($CDCl_3$) δ: 3.19 (1H, dd, $J = 10.8$, 4.0 Hz, H-3α), 5.26 (1H, t, $J = 3.2$ Hz, H-12), 2.83 (1H, dd, $J = 14.0$, 4.4 Hz, H-18β), 1.11, 0.97, 0.90, 0.88, 0.88, 0.76, 0.72 (each 3H, s, 7XCH_3), 3.98 (2H, m, H-1′), 0.84 (3H, t, $J = 6.8$ Hz, H-9′). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 38.2 (C-1), 27.7 (C-2), 78.5 (C-3), 38.8 (C-4), 55.7 (C-5), 17.0 (C-6), 33.4 (C-7), 38.9 (C-8), 47.1 (C-9), 36.5 (C-10), 23.1 (C-11), 121.8 (C-12), 142.9 (C-13), 41.2 (C-14), 28.1 (C-15), 22.6 (C-16), 46.1 (C-17), 40.0 (C-18), 45.4 (C-19), 31.3 (C-20), 33.4 (C-21), 32.6 (C-22), 27.2 (C-23), 14.8 (C-24), 15.0 (C-25), 18.3 (C-26), 22.5 (C-27), 177.8 (C-28), 32.2 (C-29), 22.9 (C-30), 63.8 (C-1′), 28.8* (C-2′), 25.6** (C-3′), 28.7* (C-4′), 30.2 (C-5′), 29.0 (C-6′), 31.9 (C-7′), 25.4** (C-8′), 13.6 (C-9′). *, ** Values may be interchanged.

Decyl oleanolate (10). Yield 75%. White amorphous solid. EIMS m/z (rel. int. %): 596 [M+] (8), 578 (5), 410 (15), 388 (34), 203 (100), 188 (26). ^{1}H NMR ($CDCl_3$) δ: 3.20 (1H, dd, $J = 9.3$, 3.3 Hz, H-3α), 5.26 (1H, t, $J = 3.3$ Hz, H-12), 2.84 (1H, dd, $J = 14.4$, 4.5 Hz, H-

18β), 1.11, 0.96, 0.90, 0.88, 0.88, 0.76, 0.71 (each 3H, s, 7XCH_3), 3.98 (2H, m, H-1′), 0.85 (3H, t, $J = 7.2$ Hz, H-10′). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 38.4 (C-1), 27.2 (C-2), 79.0 (C-3), 38.7 (C-4), 55.4 (C-5), 17.0 (C-6), 33.1 (C-7), 39.3 (C-8), 47.7 (C-9), 37.0 (C-10), 23.6 (C-11), 122.3 (C-12), 143.9 (C-13), 41.7 (C-14), 29.2 (C-15), 22.7 (C-16), 46.7 (C-17), 41.3 (C-18), 45.6 (C-19), 30.7 (C-20), 33.9 (C-21), 32.8 (C-22), 27.7 (C-23), 15.3 (C-24), 15.6 (C-25), 18.0 (C-26), 23.0 (C-27), 177.8 (C-28), 32.5 (C-29), 23.4 (C-30), 64.2 (C-1′), 28.1* (C-2′), 26.0* (C-3′), 28.6 (C-4′), 29.5** (C-5′), 29.6** (C-6′), 29.3 (C-7′), 31.9 (C-8′), 25.9 (C-9′), 14.1 (C-10′). *,** Values may be interchanged.

Benzyl oleanolate (11). Yield 65%. White amorphous solid. EIMS m/z (rel. int. %): 546 [M+] (7), 455 (10), 437 (100), 411 (21), 338 (22), 247 (82), 203 (92), 189 (37). ^{1}H NMR ($CDCl_3$) δ: 3.18 (1H, dd, $J = 11.2$, 4.4 Hz, H-3α), 5.27 (1H, t, $J = 3.6$ Hz, H-12), 2.88 (1H, dd, $J = 14.0$, 4.4 Hz, H-18β), 1.10, 0.96, 0.89, 0.87, 0.86, 0.75, 0.59 (each 3H, s, 7XCH_3), 5.07 (1H, d, $J = 12.4$ Hz, OCH_a), 5.02 (1H, d, $J = 12.4$ Hz, OCH_b), 7.31 (5H, s, H-Ar).

4-Nitrobenzyl oleanolate (12). Yield 67%. White amorphous solid. EIMS m/z (rel. int. %): 591 [M+] (5), 558 (6), 453 (7), 437 (10), 410 (15), 383 (45), 248 (20), 203 (100), 189 (25). 1H NMR (CDCl3) δ: 3.18 (1H, dd, $J = 11.0$, 4.3 Hz, H-3α), 5.27 (1H, t, $J = 3.6$ Hz, H-12), 2.88 (1H, dd, $J = 14.0$, 4.4 Hz, H-18β), 1.11, 0.96, 0.90, 0.89, 0.84, 0.75, 0.54 (each 3H, s, 7XCH_3), 5.18 (1H, d, $J = 13.5$ Hz, OCH_a), 5.08 (1H, d, $J = 13.5$ Hz, OCH_b), 7.49 (2H, d, $J = 8.7$ Hz, H-2′, H-6′), 8.19 (2H, d, $J = 8.7$ Hz, H-3′, H-5′).

3.2. Nematicidal activity

Activity was determined under laboratory conditions. *M. incongita* culture was developed according to the method previously described (Ravichandra 2010) and inoculated on locally available brinjal plants and kept under net conditions. 5% aqueous DMSO was used for preparing the stock solutions of compounds using distilled water in order to obtain the required concentration. Commonly used nematicide furadan was used as positive control, while 5% aqueous DMSO as negative control. A total of 100 second-stage juveniles (freshly hatched) were introduced on different compounds for checking the nematicidal effect. Movement of nematodes was checked with the help of needle under different time durations. The larvae were counted with the help of stereoscopic microscopic. Larvae that showed mortality after 72 h was transferred into another cavity containing distilled water, and their mortality was confirmed after 24 h. The experiment was repeated three times. The results are listed in the Table S1.

4. Conclusion

In conclusion, a series of oleanolic esters **(1–12)** was synthesised including five new **(5, 7–10)** and seven known derivatives **(1–4, 6, 11, 12)**. Their nematicidal toxicity was examined against root-knot nematode, Meloidogyne incognita for the first time. Among these compounds, butyl to decyloleanolates **(4–10)** displayed comparable toxicity with that of OA at 0.125% concentration after 72 h. It has been noted that with the increase of carbon chain, activity increases. Hence, oleanolic acid and its ester derivatives can be studied further for their safe and novel nematode control.

Disclosure statement

No potential conflict of interest was reported by the authors.

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