ANTIFEEDING LIMONOIDS FROM *MELIA TOOSENDAN*

Jian-Bo Zhou, Yuji Minami, Fumio Yagi, Kenjiro Tadera, and Munehiro Nakatani*[a]

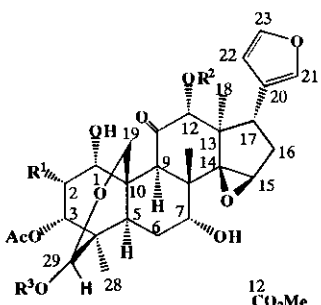
Department of Biochemical Science and Technology, Faculty of Agriculture, Kagoshima University, 1-21-24 Korimoto, Kagoshima 890, Japan
[a]Department of Chemistry and BioScience, Faculty of Science, Kagoshima University, 1-21-35 Korimoto, Kagoshima 890, Japan

Abstract--A new limonoid, azedarachin B, with a C-19/C-29 bridged acyl acetal structure was isolated as an insect antifeedant from the root bark of *Melia toosendan* along with seven known limonoids. The structure of azedarachin B was elucidated by spectroscopic and chemical means and the antifeedant property was also studied.

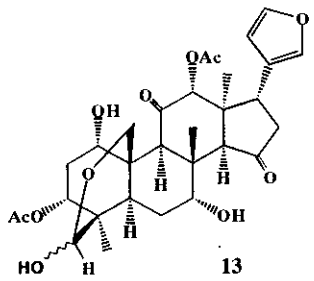
Limonoids from *Melia* species are attracting considerable interest, because of their insect inhibitor properties.[1] *Melia toosendan* closely related to a typical plant *M. azedarach* is native in China and has been used as traditional medicines. We have studied the limonoid constituents to report several types of limonoids as insect antifeedant.[2] In the continuous study, we isolated one new C-19/C-29 bridged acyl acetal, named azedarachin B (1), along with seven known limonoids, trichilin B (2),[3] 12-*O*-acetylazedarachin A (3),[4] 12α-hydroxyamorastatin(4),[5] toosendanin (5),[6] and meliacarpinins A (6),[7] C (7) and D (8).[8]

The isolation of the various congeners monitored by Ehrlich test from the ether extract of the dried root bark was a tedious process requiring careful use of HPLC. An oily mixture, soluble in 50% hexane-ether, was fractionated using silica flash chromatography followed by PTLC. HPLC purification through a reverse column gave 1 along with 2-5, in which two hemiacetals (4 and 5) were, respectively, first isolated as an equilibrium mixture of *exo*- and *endo*- form at C-29 in the ratio about 5:4. The other hand, a precipitate from the above was subjected to DCCC in ascending mode to give meliacarpinins 6-8. This is the first isolation of meliacarpinins from a Meliaceae plant other than *M. azedarach*.

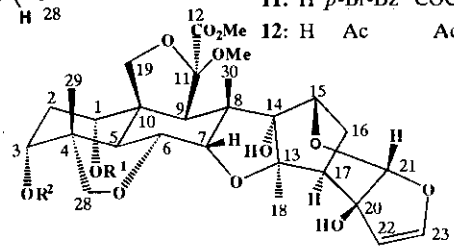
Azedarachin B(1), $C_{32}H_{42}O_{11}$, negative HRFABMS: m/z 601.2649 $[M-H]^-$ (Δ 0.0 mmu), $[\alpha]_D$ -22° (c 0.1, MeOH), exhibited the presence of ester (1730 cm^{-1}), carbonyl (1710 cm^{-1}) and furan (1630 and 1620 cm^{-1}) groups in the IR spectrum. Taking into account the CD ($\Delta\varepsilon_{215}$ +15; $\pi \rightarrow \pi^*$ of furan and $\Delta\varepsilon_{305}$ -20.8; $n \rightarrow \pi^*$ of 11-oxo group) and IR data,



	R^1	R^2	R^3
1:	H	H	$COCHMe_2$
2:	OAc	H	COCHMeEt
3:	H	Ac	COCHMeEt
4:	H	H	H (and 29-epimer)
5:	H	Ac	H (and 29-epimer)
9:	H	H	COCHMeEt
10:	H	Ac	$COCHMe_2$
11:	H	*p*-Br-Bz	$COCHMe_2$
12:	H	Ac	Ac

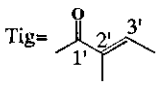


13

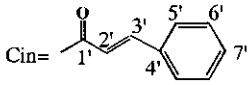


	R^1	R^2
6:	Cin	Ac
7:	Ac	Tig
8:	Tig	Ac

Tig=



Cin=



the ^1H and ^{13}C NMR studies including ^1H-^1H COSY and NOE experiments allowed us to predict **1** to be 12α-hydroxy-29-*exo*-*O*-(2-methylpropanoyl)amorastatin. The ^1H NMR spectrum was very similar to that of azedarachin A (**9**),[4] including the signals due to the 14,15-epoxy[δ 3.77 s (15-H)] and 19/29 acyl acetal bridge [δ 4.27(br d, J=12.8 Hz; 19-Ha) and δ 4.32(d, J=12.8 Hz; 19-Hb)] and one acetyl group, except for the change of 29-*O*-(2-methyl)butanoyl group in **12** to 29-*O*-(2-methyl)propanoyl in **1**.

The fact that 12-OH in **1** is α, was deduced from the chemical shifts of the 1β- and 17-H at δ 4.45 and 3.01. In azedarachins with 12α-OH group, the 1β-H signal is observed at down field from that in 12β-OH derivatives, whereas this relation is reversed for the 17-H signal.[4] The 1β-H signal was shifted upfield to δ 4.27 in the 12-acetate (**10**). The α configuration of the 12-hydroxyl group was unambiguously assigned from the chemical shifts of the furan protons and a CD study of 12-*p*-bromobenzoate (**11**). The furan signals were observed at higher field in the benzoate. Thus the shifts are (for azedarachin B/its 12-benzoate): 21-H 7.21/7.04, 22-H 6.53/6.01 and 23-H 7.32/7.02. The higher chemical shifts in the furan ring can be accounted for by the ring current of the benzoate aromatic ring which is located on the furan ring. On the other hand, the CD spectrum of **13** showed negatively splitted interaction bands between the benzoate and furan chromophores at 250 ($\Delta\varepsilon$ -7.1; $\pi\rightarrow\pi^*$ trandition of the benzoate) and 213 nm ($\Delta\varepsilon$ +9.5; $\pi\rightarrow\pi^*$ trandition of the furan) similar to that observed for the 12-benzoate of trichilin B (12α-OH compound).[9]

The *S* configuration at C-29 was established from the chemical shifts of the 3β- and 6β-H signals at δ 5.31 and 2.01, as well as all of azedarachins and trichilins.[4] Remaining stereochemistry of **1** was confirmed by NOE enhancements of the 7-H and one (δ 4.32) of the 19-H_2 signals by irradiation of the 8-Me peak and the 9-, 21- and 22-H signals by irradiation of the 13-Me signal, and long range couplings between the other peak of 19-H_2 at δ 4.27 and the 5-H signal and the 8-Me peak and the 9-H signal.

Treatment of the hemiacetal(**5**) with TsOH gave the ring D isomer, *iso*-chuanliansu(**13**),[6]

Table 1. ^{13}C and ^{1}H NMR data for azedarachin B (1) (400 MHz, $CDCl_3$)

C		H		C		H	
1	70.2 d	1	4.45 m	17	38.5 d	17	3.01 dd (11.0, 6.2)
2	33.1 t	2α	1.89 br d (15.9)	18(Me)	22.7 q	18(Me)	1.16 s
		2β	2.86 dt (16.3, 4.4)	19	64.6 t	19a	4.27 br d (12.8)
3	73.6 d	3	5.31 br d (4.1)			19b	4.32 d (12.8)
4	39.4 s			20	123.5 s		
5	34.1 d	5	2.72 dd (13.9, 4.0)	21	142.3 d	21	7.32 br s
6	25.3 t	6α	1.72 dt (14.5, 3.9)	22	112.7 d	22	6.53 br s
		6β	2.01 dt (1.8, 14.4)	23	140.6 d	23	7.21 t (1.6)
7	70.1 d	7	3.64 m	28(Me)	19.2 q	28(Me)	0.82 s
8	41.6 s			29	94.2 d	29	5.78 s
9	47.7 d	9	4.51 s	30(Me)	14.4 q	30(Me)	1.13 s
10	42.1 s					OH	1.71, 2.04, 2.12
11	213.4 s			Ac	21.4 q		2.10 s
12	28.8 d	12	4.10 s		169.8 s		
13	46.0 s			1'	175.7 s		
14	72.9 s			2'	28.0 d	2'	2.62 qq (7.3, 7.0
15	59.2 d	15	3.77 s	2'-Me	18.6 q	2'-Me	1.19 d (7.3)
16	35.3 t	16α	2.34 ddd (13.2, 6.2, 0.7)	3'	18.9 q	3'(Me)	1.20 d (7.0)
		16β	1.90 dd (13.5, 11.2)				

as a mixture of 29-epimers, but acetylation of both hemiacetals (4 and 5) afforded only their 29-*exo*-acetates.

The antifeedant activity of the isolated compounds and reaction products was tested against the third-instar larvae of *Spodoptera littoralis* (Boisduval) by a conventional leaf disk method.[10] The most potent is meliacarpinins(6-8), which are active at 50 ppm, corresponding to the concentration of *ca* 1 $\mu g/cm^2$. Then, 12α-hydroxyamorastatin (4) was active at 150 ppm, followed by azedarachin B (1) and trichilin B (2): 200 ppm. Acylation of the 12- or 29-OH group and isomerization of the D-ring epoxide to 15-keto deduced the activity: toosendanin (5): 300 ppm, and 12-*O*-acetylazedarachin A (3), sendanin (12) and *iso*-chuanliansu (13); 400 ppm.

EXPERIMENTAL

^{1}H and ^{13}C NMR were measured in $CDCl_3$ on a JEOL FX-400 spectrometer. IR (KBr) and UV (in MeOH) were recorded on JASCO FT/IR 5300 and Shimadzu UV-210A spectrophotometers. Optical rotation and CD were measured in MeOH using a JASCO J-20A spectrometer.

Plant material. The root bark was collected in December 1992 at Xiangtan, China.

Extraction and isolation. The air-dried root bark (1.5 kg) was defatted with hexane (20 L) and then extracted with ether (20 L) for 2 weeks at 25 ℃ to yied 12.8 g of an extract, which was dissolved in 50 mL of ether and then added to the same volume of hexane to give 9.1 g of a soluble part and 3.1 g of a precipitate. The former was fractionated using silica flash chromatography with 20% hexane-ether, followed by PTLC using 25% MeOH-benzene. HPLC purification of the limonoid fractions using a semiprep. reverse column with 20~35% H_2O-MeOH as solvent gave 1(8.0 mg), 2(2.0 mg), 3(2.8 mg),

4 (4.0 mg) and 5 (16.0 mg). The latter was subjected to DCCC using CH_2Cl_2-MeOH-H_2O (5:5:3 v/v) in ascending mode and the resulting limonoid fractions were flash chromatographed with 50~100% ether/hexane, respectively. HPLC purification using a similar way described above gave 6 (2.1 mg), 7 (1.7 mg) and 8 (6.2 mg).

Azedarachin B (1). An amorphous powder, $C_{32}H_{42}O_{11}$; (-) HRFABMS m/z 601.2649 $[M-H]^-$ (Δ 0.0 mmu); $[\alpha]_D$ -22° (c 0.1, MeOH); UV 213 nm (ε 3800); IR 3500-3200, 1730, 1710, 1630 and 1620cm-1; CD $\Delta\varepsilon_{215}$ +15 and $\Delta\varepsilon_{305}$ -20.8.

***Endo*-isomer of 12-Hydroxyamorostatin (4).** ^{1}H NMR: δ 7.31(1H, br s, 23-H), 7.22(1H, m, 21-H), 6.53(1H, s, 22-H), 5.37(1H, br d, J=4.4 Hz, 3-H), 4.87(1H, d, J=2.1 Hz, 29-H), 4.51(1H, br s, 9-H), 4.50(1H, m, 1-H), 4.29(1H, d, J=12.9 Hz, 19-Hb), 4.23(1H, d, J=12.9 Hz, 19-Ha), 4.10(1H, d, J=6.2 Hz, 12-H), 3.75(1H, s, 15-H), 3.61(1H, m, 7-H), 3.02(1H, m, 17-H), 2.88(1H, dt, J=16.3 and 4.4 Hz, 2α-H), 2.65(1H, dd, J=14.3 and 4.0 Hz, 5-H), 2.56(1H, br t, J=14.9 Hz, 6β-H), 2.09(3H, s, 3-OAc), 1.84(1H, br d, J=16.3 Hz, 2β-H), 1.68(1H, m, 6α-H), 1.15(3H, s, 8-Me), 1.12(3H, s, 13-Me) and 0.89 (3H, s, 4α-Me).

***Endo*-isomer of Toosendanin (5).** ^{1}H NMR: δ 7.31(1H, m, 23-H), 7.10(1H, br s, 21-H), 6.13(1H, br s, 22-H), 5.32(1H, s, 12-H), 4.90(1H, d, J=3.7 Hz, 3-H), 4.79(1H, s, 29-H), 4.59(1H, s, 9-H), 4.50(1H, d, J=12.5 Hz, 19-Hb), 4.34(1H, m, 1-H), 4.20(1H, d, J=12.5 Hz, 19-Ha), 3.75(1H, s, 15-H), 3.61(1H, m, 7-H), 2.98(1H, dd, J=11.0 and 6.2 Hz, 17-H), 2.85(1H, dt, J=16.1 and 4.7 Hz, 2α-H), 2.64(1H, dd, J=13.9 and 4.2 Hz, 5-H), 2.60(1H, dt, J=1.7 and 13.8 Hz, 6β-H), 2.23(1H, dd, J=13.6 and 6.2 Hz, 16α-H), 2.22(1H, m, 2β-H), 2.11(3H, s, 3-OAc), 1.98(3H, s, 12-OAc), 1.90(1H, m, 16β-H), 1.68(1H, m, 6α-H), 1.32(3H, s, 13-Me), 1.19(3H, s, 8-Me) and 0.89(3H, s, 4α-Me).

Meliacarpinin A (6). ^{13}C NMR: δ 170.1(s, C-12), 169.2(s, Me<u>C</u>O), 165.6(s, C-1'), 145.8 (d, C-3'), 145.7(d, C-23), 133.9(s, C-4'), 130.8(d, C-7'), 129.1(d, C-6'/8'), 128.0(d, C-5'/9'), 117.3(d, C-2'), 109.3(d, C-21), 108.0(d, C-22), 106.7(s, C-11), 94.9(s, C-13), 93.1(s, C-14), 86.3(s, C-20), 83.5(d, C-7), 81.2(d, C-15), 76.5(t, C-28), 71.1(d, C-6), 70.9(d, C-3), 70.8(d, C-1), 70.4(t, C-19), 53.3(q, CO<u>2Me</u>), 52.5(q, 11-OMe), 51.5 (s, C-8), 50.8(d, C-17), 49.9(s, C-10), 47.9(d, C-9), 42.4(s, C-4), 35.0(d, C-5), 29.8 (t, C-16), 28.0(t, C-2), 26.4(q, C-18), 21.0(q, <u>Me</u>CO), 18.3(q, C-29) and 17.7(q, C-30).

Acetylation of azedarachin B (1). Azedarachin B (1, 2.0 mg) was acetylated with Ac_2O (0.1 mL) in pyridine (1 mL) at rt for 4 d to give 12-*O*-acetylazedarachin B (10, 1.0 mg). $C_{34}H_{44}O_{12}$; SIMS m/z 645 $[M+1]^+$; $[\alpha]_D$ -55° (c 0.1, MeOH); UV 213 nm (ε 3000); CD $\Delta\varepsilon_{217}$ +25 and $\Delta\varepsilon_{309}$ -10; ^{1}H NMR: δ 7.33(1H, m, 23-H), 7.13(1H, s, 21-H), 6.15(1H, m, 22-H), 5.80(1H, s, 29-H), 5.31(1H, br d, J=4.4 Hz, 3-H), 5.28(1H, s, 12-H), 4.61 (1H, s, 9-H), 4.34(1H, d, J=12.4 Hz, 19-Hb), 4.28(1H, d, J=12.4 Hz, 19-Ha), 4.27(1H, m, 1-H), 3.75(1H, s, 15-H), 3.67(1H, m, 7-H), 2.98(1H, dd, J=11.1 and 6.1 Hz, 17-H), 2.82 (1H, dt, J=16.4 and 4.1 Hz, 2α-H), 2.72(1H, dd, J=13.8 and 4.3 Hz, 5-H), 2.61(1H, hept, J=7.0 Hz, 2'-H), 2.32(1H, d, J=7.7 Hz, 1-OH), 2.25(1H, dd, J=13.2 and 6.3 Hz, 16α-H), 2.11(3H, s, 3-OAc), 2.04(1H, dt, J=2.1 and 14.3 Hz, 6β-H), 1.98(3H, s, 12-OAc), 1.92(1H, dd, J=13.2 and 11.1 Hz, 16β-H), 1.89(1H, br d, J=16.4 Hz, 2β-H), 1.73

(1H, dt, J=14.3 and 3.7 Hz, 6α-H), 1.32(3H, s, 13-Me), 1.20(3H, d, J=7.0 Hz, 2'-Me), 1.19(3H, d, J=7.1 Hz, 2'-Me), 1.17(3H, s, 8-Me) and 0.83(3H, s, 4α-Me).

Acetylatoin of 12α-hydroxyamorastatin (4). 12α-Hydroxyamorastatin (4, 1.7 mg) was acetylated in the above way to give sendanin (12, 0.3 mg) and 1-*O*-acetylsendanin (0.5 mg). 1-*O*-Acetylsendanin, $C_{34}H_{42}O_{13}$, SIMS m/z 659 $[M+1]^+$; UV 209 nm (ε 3500); ^{1}H NMR δ 7.32(1H, m, 23-H), 7.10(1H, s, 21-H), 6.08(1H, m, 22-H), 5.79(1H, s, 29-H), 5.39 (1H, s, 12-H), 5.36(1H, br d, J=4.0 Hz, 3-H), 5.15(1H, d, J=4.0 Hz, 1-H), 4.32(2H, s, 19-H_2), 4.28(1H, s, 9-H), 3.71(1H, s, 15-H), 3.69(1H, m, 7-H), 2.97(1H, dd, J=11.1 and 6.6 Hz, 17-H), 2.87(1H, dd, J=14.6 and 3.7 Hz, 5-H), 2.69(1H, dt, J=16.6 and 4.0 Hz, 2α-H), 2.23(1H, dd, J=12.4 and 6.6 Hz, 16α-H), 2.10(3H, s, Ac), 2.02(3H, s, Ac), 2.02(1H, br d, J=16.6 Hz, 2β-H), 2.01(1H, dt, J=1.6 and 14.5 Hz, 6β-H), 1.97(3H, s, Ac), 1.95(3H, s, Ac), 1.88(1H, dd, J=13.4 and 11.1 Hz, 16β-H), 1.72(1H, dt, J=14.6 and 4.0 Hz, 6α-H), 1.25(3H, s, 13-Me), 1.13(3H, s, 8-Me) and 0.83(3H, s, 4α-Me).

Acetylation of toosendanin (5). Toosendanin (5, 2.0 mg) was acetylated for 1 d in a similar way described above to give 12 (1.2 mg).

Benzoylation of azedarachin B (1). Azedarachin B (1, 2 mg) was treated with *p*-bromobenzoyl chloride (5 mg) and DMAP (10 mg) in pyridine (1.5 mL) at 50 ℃ for 2 d to give the 12-benzoate (11, 0.5 mg). UV 212 nm (ε 5800) and 246 nm (ε 17000); CD Δε$_{305}$ -9.5 (n→π* of 11-oxo group), Δε$_{250}$ -7.1 (π→π* of benzoate) and Δε$_{213}$ +9.5 (π→π* of furan); ^{1}H NMR: δ 7.68(2H, d, J=8.4 Hz, *o*-H), 7.52(2H, d, J=8.4 Hz, *m*-H), 7.04(1H, br s, 21-H), 7.02(1H, t, J=1.6 Hz, 23-H), 6.01(1H, br d, J=1.6 Hz, 22-H), 5.80(1H, s, 29-H), 5.59(1H, s, 12-H), 5.32(1H, br d, J=4.2 Hz, 3-H), 4.34(1H, d, J=13.0 Hz, 19-Hb), 4.30(1H, m, 1-H), 4.28(1H, d, J=13.0 Hz, 19-Ha), 3.80(1H, s, 15-H), 3.70(1H, m, 7-H), 3.06(1H, dd, J=11.0 and 6.2 Hz, 17-H), 2.82(1H, dt, J=16.0 and 4.4 Hz, 2α-H), 2.74(1H, dd, J=13.5 and 3.5 Hz, 5-H), 2.60(1H, quint, J=6.7 Hz, 2'-H), 2.27(1H, dd, J=13.5 and 6.2 Hz, 16α-H), 2.12(3H, s, Ac), 2.06(1H, dt, J=2.1 and 13.5 Hz, 6β-H), 1.95(1H, dd, J=13.5 and 11.0 Hz, 16β-H), 1.77(1H, br d, J=16.0 Hz, 2β-H), 1.75(1H, ddd, J=13.5, 3.5 and 2.1 Hz, 6α-H), 1.44(3H, s, 13-Me), 1.22(3H, s, 8-Me), 1.19(3H, d, J=6.7 Hz, 2'-Me), 1.17(3H, d, J=6.7 Hz, 2'-Me) and 0.83(3H, s, 4α-Me).

Treatment of toosendanin (5) with *p*-toluenesulfonic acid. Toosendanin (5, 5 mg) was treated with a calalytic amount of TsOH in CH_2Cl_2 (1 mL) for 5 h at rt. The reaction gave almost quantitatively a mixture (4.7 mg) of 29- *endo* and *exo* isomers (4 : 5) of *iso*-chuanlinsu (13), $C_{30}H_{38}O_{11}$, SIMS m/z 575 $[M+1]^+$. *Endo*-isomer of 13; ^{1}H NMR: δ 7.36 (1H, t, J=1.5 Hz, 23-H), 7.27(1H, m, 21-H), 6.23(1H, br s, 22-H), 5.03(1H, s, 12-H), 4.81(1H, br d, J=3.5 Hz, 3-H), 4.67(1H, s, 29-H), 4.36(1H, d, J=12.3 Hz, 19-Hb), 4.08 (1H, br d, J=3.9 Hz, 1-H), 3.96(1H, m, 7-H), 3.91(1H, d, J=12.3 Hz, 19-Ha), 3.72(1H, s, 9-H), 3.30(1H, br s, 14-H), 3.27(1H, t, J=9.4 Hz, 17-H), 2.75(1H, dt, J=16.1 and 3.7 Hz, 2α-H), 2.59(1H, dd, J=14.0 and 4.0 Hz, 5-H), 2.55(2H, d, J=9.4 Hz, 16-H_2), 2.02(1H, m, 6β-H), 2.08, 2.07(each 3H, s, Ac), 1.75(1H, br d, J=16.1 Hz, 2β-H), 1.64 (1H, dt, J=14.2 and 4.0 Hz, 6α-H), 1.17(3H, s, 13-Me), 1.00(3H, s, 8-Me) and 0.86(3H, s, 4α-Me). *exo*-isomer of 13; δ 7.36, 7.27 and 6.23(each 1H), 5.30(1H, d, J=3.5 Hz,

3-H), 4.97(1H, s, 12-H), 4.79(1H, s, 29-H), 4.21(1H, d, J=12.3 Hz, 19-Hb), 4.17(1H, d, J=12.3 Hz, 19-Ha), 4.01(1H, d, J=3.9 Hz, 1-H), 3.92(1H, m, 7-H), 3.76(1H, s, 9-H), 3.30(1H, br s, 14-H), 3.27(1H, t, J=9.4 Hz, 17-H), 2.76(1H, dt, J=16.1 and 4.2 Hz, 2α-H), 2.58(1H, dd, J=14.0 and 4.0 Hz, 5-H), 2.55(2H, d, J=9.4 Hz, 16-H_2), 2.02(1H, m, 6β-H), 2.08, 2.07(each 3H, s), 1.75(1H, br d, J=16.1 Hz, 2β-H), 1.64(1H, dt, J=14.2 and 4.0 Hz, 6α-H), 1.12, 1.00 and 0.82(each 3H, s).

Antifeedant activity. The antifeedant potential of the isolated compounds and reaction products was tested by a conventional leaf disk method[10] against the third-instar larvae of *S. littoralis* (Boisduval). Five disks of Chinese cabbage (*Brassica campestris* L. var. *chinensis*) treated with the sample were arranged with another 5 control disks immersed in Me_2CO alone in a Petri dish. 10 larvae were placed in the center, and the score for the treated and untreated leaves eaten by the larvae in 2-24 h was evaluated at appropriate intervals. From these choice test at 50, 100, 150, 200, 300, 400 and 500 ppm concentrations, the minimun inhibitory concentration of each limoniod was determined.

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