Structure–Antibacterial Activity Relationships of Anacardic Acids

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A series of anacardic acids possessing different side-chain lengths were synthesized, and their antimicrobial activity was tested. In the case against *Staphylococcus aureus*, the anacardic acid having the C_{10} alkyl side chain was most active, while against *Propionibacterium acnes*, *Streptococcus mutans*, and *Brevibacterium ammoniagenes*, the anacardic acid possessing the C_{12} alkyl side chain was most effective.

INTRODUCTION

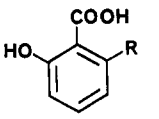
In our continuing search for antimicrobial agents from edible plants, food spices, and beverages (Himejima and Kubo, 1990; Kubo and Himejima, 1991; Kubo *et al.*, 1991, 1992, 1993), we have recently reported the antimicrobial activity against 12 selected microorganisms of 16 phenolic compounds isolated from the cashew *Anacardium occidentale* (Anacardiaceae) nut shell oil (Himejima and Kubo, 1990). Most of them exhibited potent antibacterial activity, especially against Gram-positive bacteria such as *Streptococcus mutans*, *Brevibacterium ammoniagenes*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Propionibacterium acnes*. Among these 16 phenolic compounds, anacardic acids 1–4 were found to exhibit the most effective inhibitory activity against the Gram-positive bacteria tested. Interestingly, the anacardic acids 1–3 were also isolated from the cashew *A. occidentale* apple (Kubo *et al.*, 1986), which has been continuously consumed by many people.

By comparison of the anacardic acids 1–4 with salicylic acid (5), an addition of a C_{15} nonisoprenoid alkyl side chain to 5 resulted in a dramatic change in the antimicrobial activity. Thus, salicylic acid, which has no alkyl side chain, exhibited weak but broad antimicrobial activity against almost all of the microorganisms tested. In other words, its antimicrobial activity is not potent enough to be used exclusively for the control of specific microorganisms (such as those causing acne and tooth decay) but is broad enough to be utilized as a cosmetic preservative. In contrast, anacardic acids exhibited a narrow spectrum of activity mainly against Gram-positive bacteria, but this activity was dramatically increased compared to that of salicylic acid. For example, the activities against *S. mutans* and *S. aureus* of the anacardic acid 6-[8(*Z*),11(*Z*),14-pentadecatrienyl]salicylic acid (1) were 2048 and 64 times more effective than salicylic acid (5), respectively. This suggested that the C_{15} alkyl side chain plays an important role in increasing the antibacterial activity. To understand this role, various derivatives of anacardic acid with different side-chain lengths were synthesized and assayed for comparison.

MATERIALS AND METHODS

General Procedure. All of the procedures were the same as previously described (Nakatsu et al., 1990).

Chemicals. The anacardic acids 1–4 (Figure 1) used for the assay were previously isolated from the cashew *A. occidentale* nut shell oil (Kubo et al., 1986). Their repurification was achieved by recycle HPLC (R-HPLC) (Kubo and Nakatsu, 1991) using an ODS C_{18} column. 6-[8(*Z*)-Heptadecenyl]salicylic acid (18) was a gift from Dr. T. Matsumoto (Matsumoto and Sei, 1987). Salicylic acid (5) and 6-methylsalicylic acid (6) were purchased from Sigma Chemical Co. (St. Louis, MO) and Aldrich Chemical Co. (Milwaukee, WI), respectively. All of the test chemicals were first dissolved in *N,N*-dimethylformamide (DMF) that was purchased from EM Science (Gibbstown, NJ).



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1: $C_{15:3}$, 6-[8(Z),11(Z),14-*n*-Pentadecatrienyl]salicylic acid
2: $C_{15:2}$, 6-[8(Z),11(Z)-*n*-Pentadecadienyl]salicylic acid
3: $C_{15:1}$, 6-[8(Z)-*n*-Pentadecenyl]salicylic acid
4: $C_{15:0}$, 6-*n*-Pentadecylsalicylic acid
5: H, Salicylic acid
6: C_1, 6-Methylsalicylic acid
7: $C_{5:0}$, 6-*n*-Pentylsalicylic acid
8: $C_{10:0}$, 6-*n*-Decylsalicylic acid
9: $C_{20:0}$, 6-*n*-Eicosylsalicylic acid
10: $C_{8:0}$, 6-*n*-Octylsalicylic acid
11: $C_{12:0}$, 6-*n*-Dodecylsalicylic acid
18: $C_{17:1}$, 6-[8(Z)-*n*-Heptadecenyl]salicylic acid

Figure 1. Structures of anacardic acids (1–4) and their derivatives.

Microorganisms and Media. The 12 selected microorganisms (Tables I and II) and the 3 additional fungi used for the assay and their appropriate media were previously described (Himejima *et al.*, 1992; Kubo and Himejima, 1991; Himejima and Kubo, 1991).

Antimicrobial Assay. The bioassay was performed by a broth dilution method as previously reported (Taniguchi and Satomura, 1972). The minimum inhibitory concentration (MIC) was the lowest concentration of the test compound in which no growth was visible. The concentration of DMF in the medium was 1%, which did not affect the growth of any of the microorganisms tested.

Synthesis (Figure 2). Typical Procedure. To a solution of the phosphonate 14 (3.77 g, 11.9 mmol) in 50 mL of dry THF at 0 °C was added a solution of potassium *tert*-butoxide (1.34 g, 11.9 mmol) in 20 mL of THF under an argon atmosphere. The mixture was stirred for 30 min at the same temperature, and a solution of nonanal (1.69 g, 11.9 mmol) in 20 mL of THF was

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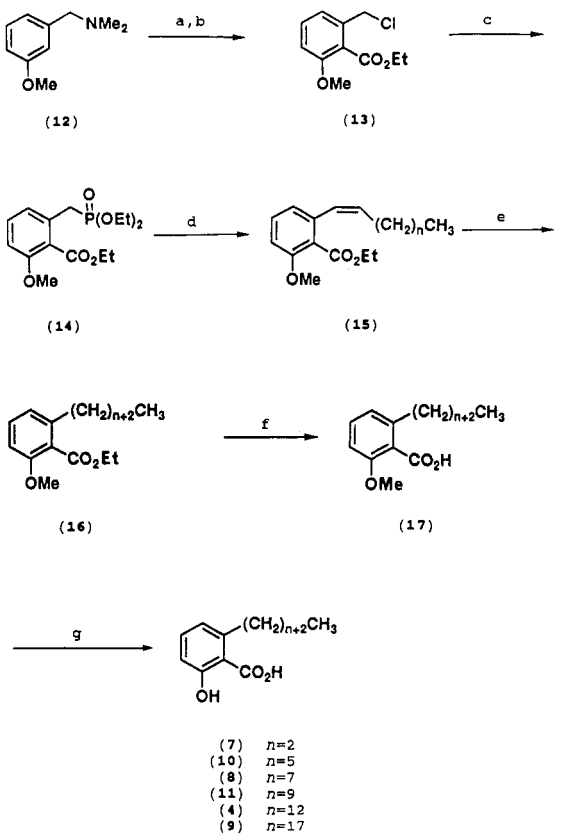

Reagents and conditions:
a) *n*-BuLi, Et_2O, 0°C, $(EtO)_2CO$. b) $ClCO_2Et$, THF, 0°C. c) $(EtO)_3P$, reflux. d) t-BuOK, THF, $CH_3(CH_2)_nCHO$, 0°C-room temperature. e) H_2, 5%Pt-C, AcOEt. f) 20%NaOH-H_2O, DMSO, 120°C. g) BBr_3, CH_2Cl_2, -78°C-room temperature.

Figure 2. Synthetic scheme.

added. After the mixture had been stirred for 5 min at 0 °C, it was allowed to warm to room temperature and was stirred overnight. The mixture, after removal of the solvent *in vacuo*, was quenched with saturated NH_4Cl solution and extracted with ether. The organic layer was washed with water and then brine, dried, and evaporated. The residue was purified by column chromatography (SiO_2, 9:1 *n*-hexane–AcOEt as eleuent) to afford an olefin (**15**, $n = 7$) as a pale yellow oil (2.08 g, 57%): IR (neat, cm^{-1}) 1725, 1645, 1590, 1570, 1462, 1260, 1105, 1060, 965, 730; ^1H NMR (60 MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.25–1.56 (m, 15H), 2.16 (m, 2H), 3.80 (s, 3H), 4.39 (q, $J = 7.2$ Hz, 2H), 6.26 (m, 2H), 6.70–7.41 (m, 3H), 6.76 (dd, $J = 1.8$ and 7.2 Hz, 1H), 7.11–7.41 (m, 2H).

A mixture of the olefin **15** ($n = 7$) (2.08 g, 6.8 mmol) and 5% Pt–C catalyst (0.80 g) in 40 mL of ethyl acetate was shaken for 2 h under hydrogen atmosphere. The catalyst was filtered off, and the filtrate was evaporated. The crude oil was purified by flash chromatography (SiO_2, 9:1 *n*-hexane–ether as eluent) to afford **16** ($n = 7$) (2.05 g, 98%) as a pale yellow oil: IR (neat, cm^{-1}) 1730, 1600, 1590, 1470, 1270, 1105, 1070, 750; ^1H NMR (60 MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.25–1.53 (m, 19H), 2.44–2.68 (m, 2H), 3.81 (s, 3H), 4.39 (q, $J = 7.2$ Hz, 2H), 6.67–7.40 (m, 3H).

A solution of **16** ($n = 7$) (1.94 g, 6.0 mmol) and 10 mL of 20% NaOH solution in 20 mL of DMSO was heated under reflux for 15 h. The mixture was acidified with concentrated HCl (pH 1) and extracted with ether. The organic phase was washed with water, dried, and evaporated to afford **17** ($n = 7$) as colorless needles (1.61 g, 91%): mp 63.2–64.6 °C (from ether); IR (Nujol, cm^{-1}) 2720–2500, 1705, 1650, 1600, 1260, 1075, 805, 730; ^1H NMR (60 MHz, $CDCl_3$) δ 0.86 (t, 3H), 1.25 (m, 16H), 2.57 (m, 2H), 3.89 (s, 3H), 6.74–7.33 (m, 3H).

To a solution of **17** ($n = 7$) (0.257 g, 0.882 mmol) in 7 mL of CH_2Cl_2 was added boron tribromide (1 M solution in CH_2Cl_2, 0.9 mL) dropwise at –60 °C under argon atmosphere. After stirring for 3 h at room temperature, the mixture was poured into ice–water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to afford **8** as colorless needles (0.133 g, 55%): mp 91.2–93.0 °C (from ether); IR (Nujol, cm^{-1}) 2720–2550, 1650, 1600, 1250, 980, 730; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, $J = 6.0$ Hz, 3H), 1.25–1.40 (m, 14H), 1.55–1.65 (m, 2H), 2.95–3.01 (m, 2H), 6.77 (dd, $J = 1.5$ and 7.5 Hz, 1H), 6.87 (dd, $J = 1.5$ and 8.0 Hz, 1H), 7.36 (dd, $J = 7.5$ and 8.0 Hz, 1H), 11.0 (br, 1H). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.27; H, 9.47.

6-n-Pentylsalicylic Acid (**7**): mp 89.5–90.0 °C (from *n*-hexane); IR (Nujol, cm^{-1}) 2700–2580, 1595, 1120, 950, 800, 775, 700; ^1H NMR (60 MHz, $CDCl_3$) δ 0.84 (t, 3H), 1.24–1.33 (m, 6H), 2.86 (m, 2H), 6.79 (m, 2H), 7.39 (m, 1H), 12.10 (br, 1H). MS exact mass calcd for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1107. EI MS *m/z* 208, 198, 162, 149, 134 (base peak), 126, 105.

6-n-Eicosylsalicylic Acid (**9**): mp 91.0–93.5 °C (from ether); IR (Nujol, cm^{-1}) 2720–2580, 1655, 1600, 1380, 1250, 1120, 1095, 810, 720, 710; ^1H NMR (270 MHz, $CDCl_3$ DMSO-d_6) δ 0.88 (t, 3H), 1.28–1.42 (m, 34H), 1.57 (m, 2H), 2.95 (m, 2H), 6.71 (dd, $J = 1.5$ and 7.6 Hz, 1H), 6.79 (dd, $J = 1.5$ and 8.6 Hz, 1H), 7.27 (dd, $J = 7.6$ and 8.6 Hz, 1H), 11.8 (br, 1H). MS exact mass calcd as $C_{27}H_{46}O_3$: 418.3447. Found: 418.3473. EI MS *m/z* 418, 400, 374, 161, 134, 121, 108 (base peak).

6-n-Octylsalicylic Acid (**10**): mp 97.0–97.5 °C (from CH_2Cl_2–*n*-hexane); IR (Nujol, cm^{-1}) 2700–2540, 1655, 1600, 1310, 1250, 900, 815, 735, 705; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, $J = 6.8$ Hz, 3H), 1.26–1.39 (m, 10H), 1.58 (m, 2H), 2.96 (m, 2H), 6.76 (dd, $J = 1.3$ and 7.7 Hz, 1H), 6.86 (dd, $J = 1.3$ and 8.5 Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 10.92 (br, 1H). EI MS *m/z* 250, 232 (base peak), 175, 162, 147, 134, 105.

6-n-Dodecylsalicylic Acid (**11**): mp 97.5–99.0 °C (from CH_2Cl_2–*n*-hexane); IR (Nujol, cm^{-1}) 3050, 2720–2540, 1650, 1605, 1305, 1250, 900, 880, 810, 730, 710; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, $J = 6.8$ Hz, 3H), 1.24–1.37 (m, 18H), 1.58 (m, 2H), 2.96 (m, 2H), 6.76 (dd, $J = 0.9$ and 7.3 Hz, 1H), 6.85 (dd, $J = 0.9$ and 8.1 Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 10.93 (br, 1H). Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.86. Found: C, 74.44; H, 9.93.

Table I. Antimicrobial Activity of Anacardic Acids 1–4 and Salicylic Acid (5)[a]

	MIC, μg/mL				
	1	2	3	4	5
Bs	3.13	6.25	6.25	100	400
Ba	3.13	6.25	6.25	50	400
Sa	6.25	25	100	>800	400
Sm	1.56	3.13	3.13	>800	3200
Pac	0.78	0.78	0.78	0.78	400
Pae	>1600	>800	>800	>800	800
Ea	>1600	>800	>800	>800	800
Ec	>1600	>800	>800	>800	800
Sc	>1600	>800	>800	>800	400
Cu	>1600	>800	>800	>800	400
Po	>1600	>800	>800	>800	>800
Pc	200	>800	>800	>800	200

[a] *Bs*, *Bacillus subtilis* ATCC 9372; *Ba*, *Brevibacterium ammoniagenes* ATCC 6872; *Sa*, *Staphylococcus aureus* ATCC 12598; *Sm*, *Streptococcus mutans* ATCC 25175; *Pac*, *Propionibacterium acnes* ATCC 11827; *Pae*, *Pseudomonas aeruginosa* ATCC 10145; *Ea*, *Enterobacter aerogenes* ATCC 13048; *Ec*, *Escherichia coli* ATCC 9637; *Sc*, *Saccharomyces cerevisiae* ATCC 7754; *Cu*, *Candida utilis* ATCC 9226; *Po*, *Pityrosporum ovale* ATCC 14521; *Pc*, *Penicillium chrysogenum* ATCC 10106.

RESULTS AND DISCUSSION

The antimicrobial activity of anacardic acids 1–4, isolated from the cashew nut shell oil, and salicylic acid (**5**) is listed in Table I. The highest concentration tested was 800 μg/mL, unless otherwise specified, because of limited solubility in the water-based media of some of the samples.

All 16 phenolic compounds isolated from the cashew nut shell oil possess a C_{15} alkyl side chain with zero to three double bonds. A decrease in the number of double bonds in the side chain decreases the antibacterial activity

Table II. Antimicrobial Activity of Analogues of Anacardic Acids

	MIC, μg/mL							
	5 (C_0)	6 (C_1)	7 (C_5)	10 (C_8)	8 (C_{10})	11 (C_{12})	4 (C_{15})	9 (C_{20})
Bs	400	400	50	12.5	3.13	3.13	100	>800
Ba	400	400	200	25	3.13	0.78	50	>800
Sa	400	400	100	12.5	3.13	6.25	>800	>800
Sm	3200	>800	200	50	3.13	1.56	>800	>800
Pac	400	200	100	3.13	1.56	0.39	0.78	>800
Pae	800	>800	>800	>800	>400	>800	>800	>800
Ea	800	>800	>800	>800	>400	>800	>800	>800
Ec	800	800	800	>800	>400	>800	>800	>800
Sc	400	400	200	>800	>400	>800	>800	>800
Cu	400	400	200	>800	>400	>800	>800	>800
Po	>800	>800	100	200	>400	>800	>800	>800
Pc	200	400	100	12.5	>400	>800	>800	>800

against Gram-positive bacteria (Gellerman *et al.*, 1969; Himejima and Kubo, 1991), with the exception of *P. acnes*. Thus, in the case against *P. acnes*, the four natural anacardic acids (1–4) inhibited the growth of this bacterium at the concentration of 0.78 μg/mL. Their antibacterial activity against *P. acnes* was not affected by the degree of unsaturation in the side chain. In addition, the MICs against *S. mutans* differed greatly between $C_{15:1}$ anacardic acid **3** and $C_{15:0}$ anacardic acid **4**. More precisely, **4** did not exhibit any antibacterial activity against this cariogenic bacterium up to 800 μg/mL, while the MIC of **3** was as low as 3.13 μg/mL. Nevertheless, the simplest anacardic acid, 6-pentadecylsalicylic acid (**4**), still exhibited some antibacterial activity. Therefore, **4** was selected as a standard for our further study since this phenolic compound is the most stable and, more importantly, the synthesis of 6-pentadecylsalicylic acid (**4**) and its various congeners can easily be accomplished. The synthesis of 6-pentadecylsalicylic acid (**4**) has previously been described (Yamagiwa *et al.*, 1987). Similarly, five key 6-alkylsalicylic acids (**7**–**11**) were synthesized as outlined below.

Directed metalation of 3-methoxy-*N*,*N*-dimethylbenzylamine (**12**) with *n*-butyllithium, followed by treatment with a large excess of ethyl chloroformate, gave a benzyl chloride (**13**). The phosphonate (**14**) (Yamagiwa *et al.*, 1987), which was obtained from **13** and triethyl phosphite, was treated with potassium *tert*-butoxide and quenched with the corresponding aldehydes to afford a mixture of *cis*- and *trans*-olefins (**15**). Catalytic hydrogenation of **15** using 5% platinum on carbon as a catalyst gave **16**. Alkaline hydrolysis of **16** in refluxing DMSO followed by demethylation with boron tribromide gave the five anacardic acid analogues (**7**–**11**).

Table II shows the antimicrobial activity of a series of synthetic analogues of **4**. As a result, their structure–activity relationships can be summarized as follows. Addition of a C_1 alkyl (methyl) group on salicylic acid (**5**) formed 6-methylsalicylic acid (**6**), which showed a slight decrease in activity against Gram-negative bacteria. Similar to salicylic acid (**5**), it exhibited weak but still broad antimicrobial activity. Then, an addition of a $C_{5:0}$ alkyl (*n*-pentyl) group on salicylic acid (**5**) changed it to 6-pentylsalicylic acid (**7**), which exhibited a slight increase in activity, except against Gram-negative bacteria. In contrast, an addition of a $C_{10:0}$ alkyl (*n*-decyl) group on **5** transformed it to 6-decylsalicylic acid (**8**) and a dramatic change in activity was observed. Thus, it no longer exhibited any activity against all of the Gram-negative bacteria, yeasts, and molds tested up to 400 μg/mL. However, the activity against Gram-positive bacteria was significantly increased, becoming even more potent than the standard 6-pentadecylsalicylic acid (**4**). Interestingly, an addition of a $C_{20:0}$ alkyl (*n*-eicosyl) group on **5** converted it to 6-eicosylsalicylic acid (**9**), and the antimicrobial activity was completely lost up to 800 μg/mL. In addition, 6-[8(*Z*)-heptadecenyl]salicylic acid (**18**) isolated from the leaves of *Ginkgo biloba* (Matsumoto and Sei, 1987) was also tested. This phenolic compound, possessing a $C_{17:1}$ alkyl (heptadecenyl) group, also did not show any antimicrobial activity up to 800 μg/mL. The data so far obtained suggest that the maximum antibacterial activity was found in 6-decylsalicylic acid (**8**). Therefore, the two additional closely related analogues, 6-octylsalicylic acid (**10**) and 6-dodecylsalicylic acid (**11**), possessing a $C_{8:0}$ alkyl (*n*-octyl) and a $C_{12:0}$ alkyl (*n*-dodecyl) side chain, respectively, were also synthesized and tested. Results show that the activity of the synthetic 6-dodecylsalicylic acid (**11**) is comparable with that of 6-[8(*Z*),11(*Z*),14-pentadecatrienyl]salicylic acid (**1**), the most potent antibacterial anacardic acid isolated from the cashew nut shell oil. More specifically, in the case against *S. mutans*, *B. ammoniagenes*, and *P. acnes*, 6-dodecylsalicylic acid (**11**) was most effective, while against *S. aureus*, 6-decylsalicylic acid (**8**) was most potent. Obviously, the activity depends on the bacteria tested in conjunction with the length of the alkyl side chain. This difference may be caused by the differences in the hydrophobic interactions between these antibacterial substances and the membrane lipids of each bacterium (Ingram and Buttke, 1984).

In addition, besides the antibacterial activity, 6-octylsalicylic acid (**10**) also exhibited noticeable antifungal activity against a mold, *Penicillium chrysogenum*, with a MIC of 12.5 μg/mL. Hence, **10** was further tested against three additional fungi, *Mucor mucedo* ATCC 20094, *Rhizopus stolonifer* ATCC 6227b, and *Aspergillus niger* ATCC 16404. Besides *P. chrysogenum*, **10** showed activity against *M. mucedo* with a MIC of 25 μg/mL but did not show any activity against the other fungi up to 800 μg/mL.

In view of the increasing importance of controlling specific bacteria such as *S. aureus*, *P. acnes*, and *S. mutans*, the aforementioned anacardic acids may be considered for practical use, especially for skin and tooth problems caused by these bacteria.

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LITERATURE CITED

Gellerman, J. L.; Walsh, N. J.; Werner, N. K.; Schlenk, H. Antimicrobial effects of anacardic acids. *Can. J. Microbiol.* **1969**, *15*, 1219–1223.

Himejima, M.; Kubo, I. Antimicrobial agents from the cashew *Anacardium occidentale* (Anacardiaceae) nut shell oil. *J. Agric. Food Chem.* **1991**, *39*, 418–421.

Himejima, M.; Hobson, K. R.; Otsuka, T.; Wood, D. L.; Kubo, I. Antimicrobial terpenes from oleoresin of ponderosa pine tree *Pinus ponderosa*: a defense mechanism against microbial invasion. *J. Chem. Ecol.* **1992**, *18*, 1809–1818.

Ingram, L. O.; Buttke, T. M. Effects of alcohols on microorganisms. *Adv. Microb. Physiol.* **1984**, *25*, 253–300.

Kubo, I.; Himejima, M. Anethole, a synergist of polygodial against filamentous microorganisms. *J. Agric. Food Chem.* **1991**, *39*, 2290–2292.

Kubo, I.; Nakatsu, T. Recent examples of preparative-scale recycling high performance liquid chromatography in natural products chemistry. *LC–GC* **1990**, *8*, 933–939.

Kubo, I.; Komatsu, S.; Ochi, M. Molluscicides from the cashew *Anacardium occidentale* (Anacardiaceae) and their large-scale isolation. *J. Agric. Food Chem.* **1986**, *34*, 970–974.

Kubo, I.; Himejima, M.; Muroi, H. Antimicrobial activity of flavor components of cardamom *Elattaria cardamomum* (Zingiberaceae) seed. *J. Agric. Food Chem.* **1991**, *39*, 1984–1986.

Kubo, I.; Muroi, H.; Himejima, M. Antimicrobial activity of green tea flavor components and their combination effects. *J. Agric. Food Chem.* **1992**, *40*, 245–248.

Kubo, I.; Muroi, H.; Himejima, M. Antibacterial activity against *Streptococcus mutans* of mate tea flavor components. *J. Agric. Food Chem.* **1993**, *41*, 107–111.

Matsumoto, T.; Sei, T. Antifeedant activities of *Ginkgo biloba* L. components against the larva of *Pieris rapae crucivora*. *Agric. Biol. Chem.* **1987**, *51*, 249–250.

Nakatsu, T.; Johns, T.; Kubo, I.; Milton, K.; Sakai, M.; Chatani, K.; Saito, K.; Yamagiwa, Y.; Kamikawa, T. Isolation, structure, and synthesis of novel 4-quinolinone alkaloids from *Esenbeckia leiocarpa*. *J. Nat. Prod.* **1990**, *53*, 1508–1513.

Taniguchi, M.; Satomura, Y. Structure and physiological activity of carbostyril compounds. *Agric. Biol. Chem.* **1972**, *36*, 2169–2175.

Yamagiwa, Y.; Ohashi, K.; Sakamoto, Y.; Hirakawa, S.; Kamikawa, T.; Kubo, I. Syntheses of anacardic acids and ginkgoic acid. *Tetrahedron* **1987**, *43*, 3387–3394, and references cited therein.

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