SHORT REPORT

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Investigation of Insect Repellent Activity of Cyclocolorenone Obtained from the Red Alga *Laurencia intricata*

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Abstract: Three known secondary metabolites were isolated from the organic extract of *Laurencia intricata*. Their structures were identified by NMR and MS experiments and comparison with the literature data. An aromadendrane sesquiterpene, (+)-cyclocolorenone showed strong repellent activity against the maize weevil *Sitophilus zeamais* Motschulsky (Coleoptera: Curculionidae) adults. It had the same activity as natural insecticides, pyrethrins, with a ED_{50} value of 2.0 μg/cm^2. This is the first report of insect repellent activity of (+)-cyclocolorenone. The results suggest that the red alga *Laurencia* is a promising source of bioactive compounds which can be used as potential biocontrol agents for stored-product insects.

Keywords: Cyclocolorenone; insect repellent activity; *Sitophilus zeamais*; *Laurencia intricata*.

1. Plant Source

The red alga *Laurencia* (Rhodomelaceae, Ceramiales) is a large genus comprising about 140 species distributed throughout the world's oceans, mainly in temperate areas [1-3]. It is well-known as a rich source of halogenated secondary metabolites and more than 700 compounds with a wide range of biological activities have already been isolated from this genus [3-6]. The red alga *Laurencia intricata* was collected off the coasts of Katsuura, Chiba, Japan on May 24, 2016. A voucher specimen (CMNH-BA-007526) was deposited in the Coastal Branch of Natural History Museum and Institute, Chiba.

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2. Previous Studies

Previous chemical investigations of *L. intricata* have reported the isolation of various types of halogenated secondary metabolites such as neolaurallene and itomanol [7-9]. However, the chemical component of *L. intricata* inhabiting the main island of Japan has not been extensively studied yet. In addition, to the best our knowledge, there are only a few reports to date on the biological activities of secondary metabolites from *L. intricata* [10]. During our screening search for new natural insect repellents from marine bioresources, we found that several organic extracts from *Laurencia* were found to possess repellent activity against the maize weevil *Sitophilus zeamais*. Our previous chemical study on *L. nidifica* led to the isolation of laurinterol with strong repellent activity [11]. Thus, the red alga *Laurencia* can be considered as one of promising natural sources for bioactive metabolites possessing insect repellent activity. In the course of our search for biologically active compounds from this genus, we examined *L. intricata* collected off the coasts of Katsuura, Chiba, Japan. Chemical investigation of the EtOAc fraction with repellent activity resulted in the isolation of three known compounds, including one oxygenated sesquiterpene (**1**), one C_{15}-acetogenin (**2**), and one halogenated triterpene (**3**). This paper describes the isolation, structure elucidation, and insect repellent activities of these isolated compounds.

3. Present Study

The dried alga (26.9 g) of *L. intricata* was extracted twice with MeOH and successively partitioned between EtOAc and H_2O. The EtOAc fraction was subjected to Si-gel column chromatography and preparative TLC to yield three known compounds, (+)-cyclocolorenone (**1**), a C_{15} bromoallene (**2**), which was previously isolated from *L. okamurae* (as *L. okamurai*) collected at Zagashima Island, Ago Bay, Mie prefecture [12], and coined zagashimallene here, and intricatetraol (**3**), which was isolated from *L. intricata* collected at several sites in Hokkaido [8]. The structures of **1**-**3** were elucidated by spectroscopic methods including 1D and 2D NMR, and ESI-MS, together with comparison with those previously reported in the literature. On the other hand, the oxygenated tricyclic sesquiterpene, cyclocolorenone (**1**) has been isolated so far from terrestrial liverworts [13-15], terrestrial plants [16,17], and the soft coral *Nephthea* species [18,19]. This is the first time that the isolation of (+)-cyclocolorenone (**1**) has been reported from marine algae.

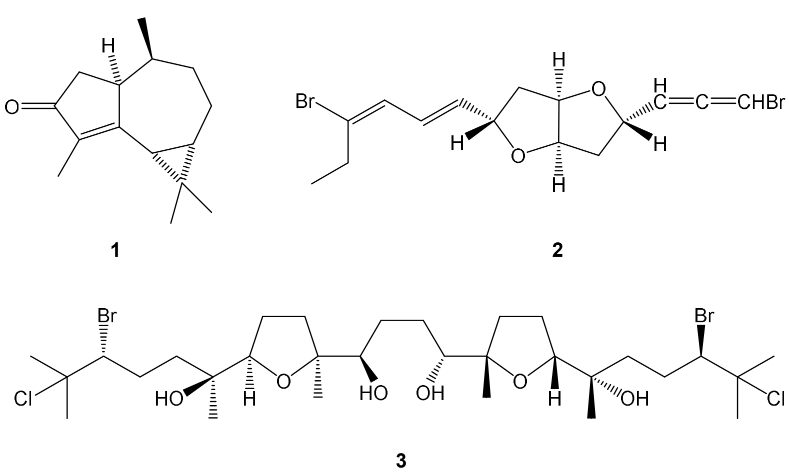

Figure 1. Structures of compounds **1**-**3**.

*(+)-Cyclocolorenone (**1**)*: Colorless oil, $[\alpha]_D^{23}$ +510 (*c* 0.1, $CHCl_3$). $C_{15}H_{22}O$, ESI-MS *m/z* 219 $[M + H]^+$ and 241 $[M + Na]^+$. ^{13}C NMR (100 MHz, $CDCl_3$, *δ*, ppm): 208.2 (C-3), 176.3 (C-5), 140.3 (C-4), 42.5 (C-1), 40.2 (C-2), 32.5 (C-9), 32.3 (C-7), 31.7 (C-10), 29.5 (C-13), 28.5 (C-6), 25.9 (C-11), 21.1 (C-8), 17.4 (C-14), 16.5 (C-12), 8.2 (C-15). The ^{13}C NMR spectra agreed with those reported in the literature [14,19].

*Zagashimallene (**2**)*: Colorless oil, $[\alpha]_D^{23}$ –168 (*c* 0.1, $CHCl_3$). $C_{15}H_{18}Br_2O_2$, ESI-MS *m/z* 389, 391 and 393 $[M + H]^+$. ^{13}C NMR (100 MHz, $CDCl_3$, *δ*, ppm): 201.8 (C-2), 133.1 (C-10), 132.2 (C-13), 130.4 (C-12), 125.9 (C-11), 101.0 (C-3), 84.0 (C-7), 83.7 (C-6), 79.7 (C-9), 76.6 (C-4), 73.8 (C-1), 41.3 (C-8), 40.6 (C-5), 29.7 (C-14), 13.3 (C-15). The ^{13}C NMR spectra agreed with those in the literature [12,20].

*Intricatetraol (**3**)*: Pale yellow oil, $[\alpha]_D^{22}$ +62.3 (*c* 0.1, $CHCl_3$). $C_{30}H_{54}Br_2Cl_2O_6$, ESI-MS *m/z* 739, 741, 743, 745 and 747 $[M + H]^+$. ^{13}C NMR (100 MHz, $CDCl_3$, *δ*, ppm): 86.1 (C-10, 15), 84.2 (C-7, 18), 77.5 (C-11, 14), 73.7 (C-6, 19), 72.0 (C-2, 23), 67.0 (C-3, 22), 37.1 (C-5, 20), 32.9 (C-25, 30), 31.7 (C-9, 16), 29.4 (C-12, 13), 28.9 (C-4, 21), 27.5 (C-1, 24), 26.5 (C-8, 17), 24.2 (C-26, 29), 23.9 (C-27, 28). The ^{13}C NMR spectra agreed with those in the literature [8].

All of the isolated compounds were tested for insect repellent activities against the maize weevil *Sitophilus zeamais*. In our previous study, we found that laurinterol possessed strong activity with ED_{50} value of 12.7 μg/cm^2 [11]. It was noteworthy that cyclocolorenone (**1**) with ED_{50} value of 2.0 μg/cm^2 showed stronger activity than that of laurinterol, and also exhibited the same activity as that of a positive control, pyrethrin standard (ED_{50}: 1.7 μg/cm^2). However, compounds **2** and **3** were inactive. It is highly possible that compound **2**, one of bromoallene readily decomposed during the bioassay since it was unstable at room temperature. In addition, compound **1** was examined for acetylcholinesterase (AChE) inhibitory activity *in vitro*, but showed no activity. Cyclocolorenone (**1**) has been reported to have diverse biological activities such as antifeedant [21], antimicrobial [16], growth-inhibitory [16], and anti-inflammatory [17]. The insect repellent activity of cyclocolorenone (**1**) is reported for the first time here. These results suggest that the red algal genus *Laurencia* may be a potential source of bioactive compounds that could be utilized in the development of natural insect repellents.

Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/RNP

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