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Allelopathic activity of some Sri Lankan seaweed extracts and the isolation of a new brominated nonaromatic isolarene type sesquiterpene from red alga *Laurencia heteroclada harvey*

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ABSTRACT

This study investigated the allelopathic activity of sixteen seaweed extracts using lettuce seed germination bioassay. The results of the preliminary investigation suggested that the methanol extracts of seven seaweeds demonstrated significant properties inhibitory to seed germination. In addition, chemical investigation of an active extract of the allelopathic *Laurencia heteroclada* Harvey led to the isolation of four known compounds as well as a new brominated nonaromatic isolarene type sesquiterpene. The structural elucidation of pure compounds was carried out using spectroscopic methods and by comparison with literature. As seaweeds are highly abundant around Sri Lanka, they could be developed as an ecofriendly natural herbicide in their crude form.

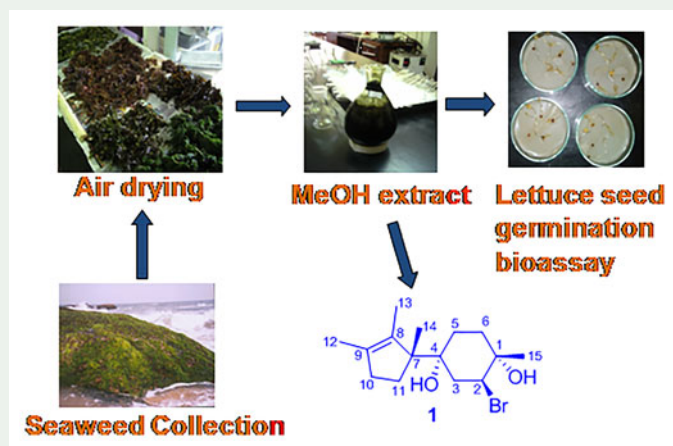
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Seaweeds; brominated nonaromatic isolarene; nonaromatic cuparane; allelopathic activity; lettuce seed germination bioassay



1. Introduction

Plants produce specific compounds which affect the germination of other plant species growing in their surroundings. This phenomenon is called “allelopathy” (Namkeleja, Tarimo, & Ndakidemi, 2014), and it plays an essential role in both natural and cultivated ecosystems. Numerous plants are known to possess allelopathic properties and efforts have been made to utilize them for weed control. Although most common allelopathic plants have potential for weed suppression, their effects are usually short-lived and lack long term impact (Kaur, Aggarwal, Kumar, & Dhiman, 2014). Attempts have been made to isolate and identify allelochemicals in plants, but these allelochemicals were mostly found in low concentrations and were found to be interactive (Soltys, Krasuska, Bogatek, & Gniazdowska, 2013). The use of seaweeds to achieve this purpose is a relatively new and untouched area. “Seaweed” refers to the marine algae that grow almost exclusively in shallow waters at the edge of the world’s oceans (Rinehart et al., 1981).

Red algae of the genus *Laurencia* Harvey (Ceramiales, Rhodomelaceae) encompass a widely distributed variety of morphologically-complex algal species with ambiguous taxonomy (Lyakhova et al., 2006). This genus has yielded diverse bioactive metabolites, that are usually characterized by the presence of halogen atoms (Shklyaev, Yeltsov, Rozhkova, Tolstikov, & Dembitsky, 2004; Vairappan & Tan, 2009; Cabrita, Vale, & Rauter, 2010; Yang et al., 2018) such as sesquiterpenes, diterpenes, triterpenes, and C₁₅- acetogenins. Currently, the genus *Laurencia* is the most studied of all the algal genera; the majority of its constituents are of terpenoidal nature (Cassano, De-Paula, Fujii, Da Gama, & Teixeira, 2008; Tiwari & Troy, 2015). In order to advance our efforts to identify biologically active compounds in Sri Lankan seaweeds (Haroon & Dharmaratne, 2013a; Haroon, Premaratne, Choudhry, & Dharmaratne, 2013b), we investigated the chemical composition of *Laurencia heteroclada* Harvey. This study led to the isolation of a new brominated nonaromatic isolaurene type sesquiterpene (**1**), along with four known compounds: nonaromatic cuparane (**2**), algoane (**3**), caulerpin (**4**), and cholesterol (**5**). Lettuce seed germination bioassay, which is widely used in the detection of allelochemicals, was successfully used to test the allelopathic activity of seaweed extracts (Khanh, Hong, Xuan, & Chung, 2005). The present study reports the isolation and identification of pure compounds together with lettuce seed germination bioassay for screening of seaweed extracts and pure compounds.

2. Results and discussion

Out of sixteen crude MeOH extracts of seaweeds, seven extracts exhibited significant differences in their mean radical length, compared to the control, sterile distilled water (Table S1). However, *Laurencia heteroclada* Harvey and *Caulerpa racemosa* (Forsskål) J. Agardh showed the lowest germination values of 17.5% and 18.0% respectively in the lettuce seed germination while *Caulerpa sertularioides* showed a 25% germination value and appeared to possess the smallest average radical length of 0.63 ± 0.197 . Interestingly, *Caulerpa racemosa* f. *laxa* showed evidence of seed germination stimulation activity. Although other extracts did not inhibit lettuce seed germination at a significant level, reduced root lengths of lettuce seeds might increase the possibility of

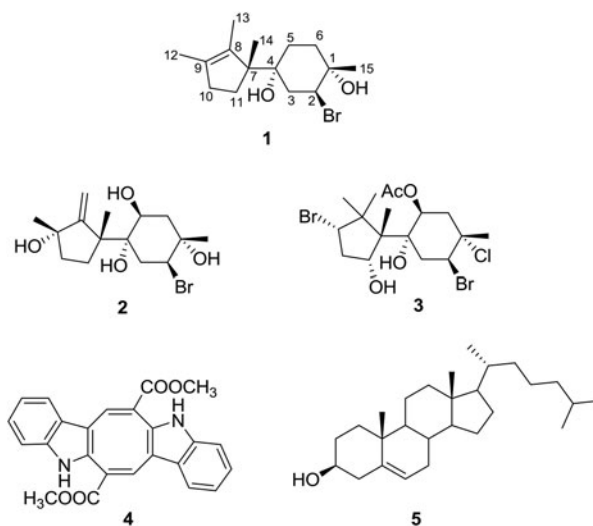


Figure 1. The structures of compounds 1 – 5.

seedling desiccation prior to establishment of roots and may delay growth, since water intake is necessary for seedling growth.

The allelopathic MeOH extract of *L. heteroclada* Harvey was subjected to repeated column chromatography on flash silica gel, yielding five pure compounds. The chemical structures of these pure compounds (Fig. 1) were unambiguously confirmed by extensive spectroscopic analyses (including NMR, IR, and HREI-MS) and by comparison with related studies. Sesquiterpene (**1**) was obtained as white powder. The positive FAB MS of **1** showed the molecular ion peak $[M + H]^+$ at m/z 317 along with isotopic peak at m/z 319 (1:1), indicating the presence of a Br atom in the molecule. HREI-MS displayed the $[M]^+$ at m/z 316.1032, supporting the composition of $C_{15}H_{25}O_2Br$ (Calcd.316.1038) with 3 degrees of unsaturation. Careful comparison of the 1H NMR and ^{13}C NMR data of **1** with those of **3** suggested a similar sesquiterpene skeleton in **1**, with a different substitution pattern and an unsaturation. The IR spectrum of **1** also showed absorption peaks at 1639 and 3467 – 3546 cm^{-1} indicating the presence of olefinic bond and hydroxyl groups.

The ^{13}C -NMR spectrum of compound **1**, in $CDCl_3$ showed 15 carbon signals. DEPT-135 and DEPT-90 spectra showed four methyl, five methylene and one methine carbons, while the rest of the five signals were detected as quaternary carbons. The quaternary olefinic carbons assigned to C-9 and C-8 in **1** were resonated at δ_C 135.2, and 133.6, respectively. Two oxygenated carbons appeared at δ_C 71.5 and 78.5 were assigned to C-1 and C-4 respectively while the bromine-bearing carbon atom resonated at δ_C 61.3 was assigned to C-2. Analysis of DEPT-135 spectra showed five methylene carbons resonated at δ_C 30.3, 33.7, 35.7, 38.0 and 41.8, assigned to C-5, C-11, C-10, C-6 and C-3 respectively.

The 1H NMR ($CDCl_3$, 400 MHz) (Table S2) spectrum of **1** showed signals for four methyl, five methylene, and one methine protons. Methyl protons were resonated at δ_H 1.01 (3 H, s), 1.61 (6 H, s), and 1.64 (3 H, s), assigned to Me-14, Me-12/Me-13 and Me-15, respectively. The characteristic downfield proton at δ_H 4.71 (dd, $J=12.5$, $J=4.6$ Hz) was assigned to H-2, geminal to equatorial bromo substituent. Moreover, a

hydrogen atom resonating at δ_{H} 1.32 as a singlet and another hydrogen atom resonating at δ_{H} 4.89 ($J=2.5$) as a doublet assigned to the OH protons attached to C-4 and C-1 respectively. All of the hydrogen bearing carbons and their protons in **1** were assigned with the aid of HMQC experiments.

The assignments of methylene protons were further supported by the COSY experiments of **1**. The ^1H - ^1H COSY experiments of **1** revealed that the methine H-2 [δ_{H} 4.71 (1 H, dd, $J=12.5$, $J=4.6$ Hz)] was coupled to the methylene H-3 which appeared at δ_{H} 2.18 (1Hb, m) and 1.98 (1Ha, t, $J=13.4$ Hz). The COSY experiments also showed that the H-6 [δ_{H} 2.45 (1Hb, ddd, $J=18.0$, $J=13.2$, 5.2 Hz) and 2.14 (1Ha, m)] were coupled to the methylene H-5 which appeared at δ_{H} 1.57 (1Hb, m) and 1.65 (1Hb, m).

Similarly, in the cyclopentene ring, the methylene H-11 [δ_{H} 1.45 (1Ha, ddd, $J=8.5$, $J=7.0$, $J=2.7$ Hz) and 1.85 (1Hb, sept, $J=13.4$, $J=8.8$, $J=5.0$ Hz)] were coupled to the methylene H-10 which appeared at δ_{H} 2.15 (1Ha, m) and 2.20 (1Hb, m). Furthermore, cross peaks were also observed between Hb-3 (δ_{H} , 2.18) and Ha-3 (δ_{H} , 1.98), between Hb-6 (δ_{H} , 2.45) and Ha-6 (δ_{H} , 2.14), between Ha-11 (δ_{H} , 1.85) and Hb-11 (δ_{H} , 1.45). HMBC correlations of C-14 protons (δ_{H} , 1.01) with C-4 (δ_{C} , 78.5), C-7 (δ_{C} , 58.1), C-11 (δ_{C} , 33.7), and C-8 (δ_{C} , 133.6) were observed along with HMBC correlations of H-5 methylene protons (δ_{H} 1.57/1.65) with C-6 (δ_{C} , 38.0), C-4 (δ_{C} , 78.5) and C-7 (δ_{C} , 58.1). These correlations clearly indicated the connection between the two structural units in the molecule (Fig. S2).

The relative stereochemistry of **1** was deduced by the analysis of the coupling constants and NOESY correlations (Fig. S3). The NOESY interactions between H₃-14 (δ_{H} , 1.01) and Ha-3 (δ_{H} , 1.98) and between Ha-3 (δ_{H} , 1.98) and H₃-15 (δ_{H} , 1.64) showed that CH₃-14 and CH₃-15 are on the same side of the molecule. Additionally, the NOE interactions between H₃-14 (δ_{H} , 1.01) and Ha-11 (δ_{H} , 1.45) and between H₃-14 (δ_{H} , 1.01) and Ha-10 (δ_{H} , 2.15) were observed in the cyclopentene ring. The large coupling constants between H-2 and Ha-3 ($J=12.5$ $J=4.6$ Hz) suggested that H-2 has an *axial* orientation. The orientation of the olefinic double bond in the cyclopentene ring was predicted based on the strong NOESY correlations between H₂-5 (δ_{H} , 1.57-1.65) and CH₃-13 (δ_{H} , 1.61)) and between H₂-10 (δ_{H} , 2.15-2.20) and CH₃-12 (δ_{H} , 1.61). The spectral data of **1** were similar to those of algoane (**3**), a sesquiterpene which has been previously reported in the South African sea hare, *Aplysia dactylomela* (McPhail, Davies-Coleman, Copley, & Eggleston, 1999) which feeds predominantly on the *Laurencia* species. A comparison of overall NMR spectroscopic data (COSY, HMQC and HMBC) and MS data of **1** and **3** revealed that **1** is a new brominated nonaromatic isolaurene type sesquiterpene. Among marine organisms, the red alga *Laurencia* is considered to be the main producer of laurane-type sesquiterpenes (Li, Miao, Li & Ji, 2012; Al-Massarani, 2014).

The absolute configurations at C-1, 2 and 4 were assigned as 1*S*, 2*S*, and 4*R* respectively by the NOESY experiment and by comparing with the structure of the algoane (**3**). This appears to be the first report of isolation of algoane (**3**) from a seaweed. Compound (**2**), the non aromatic cuparane, has been earlier reported by Haroon et al. from the same algal species. Caulerpin (**4**) has been previously reported from the green alga *Caulerpa racemosa* (Anjaneyulu, Prakash & Mallavadhani, 1991) and red alga *Chondria armata* (Govenkar & Wahidulla, 2000), while compound **5** was identified as cholesterol, which has been previously reported from red alga (Nasir,

Saeidnia, Mashinchian-Moradi, & Gohari, 2011). The pure compounds **1**, **2** and **3** were tested against lettuce seed germination assay. The compound **3** showed moderate activity on seed germination inhibition at 1000 ppm while the compounds **1** and **2** were found to be inactive (Table S1). Previous phytochemistry research exhibited that compounds (5Z, 8Z, 11Z, 14Z, 17Z)-eicosapentaenoic acid had been isolated from red alga *Neodilesea yendoana* (Suzuki, Wakana, Denboh, & Tatewaki 1996), and that methyllanosol isolated from *Odonthalia washingtoniensis* (Kubo, 1989) showed allelopathic activity against microalgae and lettuce seed germination bioassay respectively.

3. Experimental

3.1. Algae material

Fresh marine algae, *Ulva fasciata*, *Cladophora* spp, *Halimeda discoidea*, *Caulerpa racemosa* (Forsskål) J. Agardh, *Caulerpa sertularioides*, *Caulerpa racemosa* f. *laxa* (Greville) Weber-van Bosse, *Udotea flabellum*, *Padina pavonica*, *Dictyota kunethi*, *Amphiroa anceps*, *Cheilosporum cultratum*, *Laurencia ceylanica*, *Laurencia heteroclada*, *Gracilaria hikkaduensis*, *Gymnogongrus pygmaeus*, and *Jania* spp. were collected between once a month and once every four months (March, 2006 – March, 2007), depending on availability, from four different locations, including, Arugambay, Hambantota, Krinda and Tangalle. They were identified through direct comparison with algal specimens and confirmed with the help of a taxonomist at the National Herbarium, Royal Botanic Gardens, Peradeniya, Sri Lanka. The voucher specimens were deposited by being fixed in 5% buffered formalin at the Natural Products Laboratory of the Institute of Fundamental Studies in Kandy, Sri Lanka. Algae attached to the rocks and other substrates were collected by hand, while certain algae like *Amphiroa anceps* were found at a depth of 400 m, and collected with the help of local fishermen. The red alga *Laurencia heteroclada* Harvey was collected in Tangalle on the southern coast of Sri Lanka in December 2006.

3.2. General procedure

Melting points were determined on a Büchi 535 melting point apparatus. Optical rotations were measured in MeOH on a Jasco DIP-360 digital polarimeter. IR spectra were recorded on a FT IR-8900 spectrophotometer. UV spectra were obtained on a Hitachi UV 3200 spectrophotometer. 1D and 2D NMR spectra were recorded in CDCl₃ and CD₃OD, Bruker Avance-400 and 500 operating at 400, and 500 MHz, respectively. The ¹³C NMR experiments were conducted on the same instruments at 100 and 125 MHz, respectively. Chemical shifts (δ) were in ppm, relative to the chemical shift of tetramethylsilane (TMS), as internal standard and coupling constants *J* in Hz. The EI MS and CI-MS were measured on a Jeol JMS-600 mass spectrometer. FAB-MS was performed on a Jeol JMS HX 110 mass spectrometer by using glycerol as the matrix. Column chromatography was carried out using silica gel (E-Merck, 230-400 mesh size). TLC separations were performed on precoated plates (Silica gel 60, PF₂₅₄, 0.2 mm, E-Merck), and spots were detected using ceric sulphate as the spray reagent.

3.3. Extraction and isolation

Seaweed samples were carefully washed several times with fresh water to remove salt, sand particles and other debris. They were thoroughly air-dried and pulverized using a grinder. Powdered seaweeds (100 g) were separately extracted three times with methanol (250 ml) under sonication. The MeOH extracts were evaporated in a rotary evaporator to give crude extracts (6–10 g). Then the crude extracts of different seaweed species were tested in the lettuce seed germination bioassay. For the chemical investigation, the dried *L. heteroclada* (350 g) was finely powdered and extracted three times with methanol (750 mL) under sonication. After filtration, the MeOH extract was evaporated to give 15 g of dry extract. The MeOH extract was subjected to column chromatography (CC) on flash silica gel. The above column was eluted with gradient polarities of hexane, ethyl acetate, methanol, and water as eluants yielding seven major fractions: F-1 (300 mg), F-2 (50 mg), F-3 (200 mg), F-4 (30 mg), F-5 (25 mg), F-6 (40 mg), and F-7 (30 mg). Repeated flash silica CC of F-1 (5% EtOAc: *n*-hexane) yielded a pure compound **3** (70 mg, 0.02%). When 50 mg of F-2 (10% EtOAc: *n*-hexane) was subjected to CC, compound **1** (12 mg, 0.0034%) was obtained. Fraction F-3 (18% EtOAc: *n*-hexane), when subjected to CC, yielded two fractions F-31 (100 mg) and F-32 (18 mg). When 100 mg of F-31 (8% CH₂Cl₂: *n*-hexane) were subjected to column chromatography, compound **5** (60 mg, 0.017%) was obtained as a pure compound. Further, fraction F-4 (30% EtOAc: *n*-hexane) on CC afforded **4** (2.5 mg, 0.0007%) as a pure compound, and repeated CC of F-5 (40% EtOAc: *n*-hexane) yielded **2** (14 mg, 0.004%) as a pure compound.

3.4. Lettuce seed germination assay

In this study, seed germination bioassay was employed to determine the allelopathic potential of seaweed extracts and pure isolates (Piyasena and Dharmaratne, 2013).

2-Bromo-3,5,6-trihydro-1,4-dihydroxy isolaurene (**1**)

White powder (12 mg, 0.0034%), mp 70–72 °C, $[\alpha]_D^{25} +93^\circ$ ($c = 0.06$, CHCl₃) UV (MeOH), $\lambda_{\max}$ nm 202; IR (KBr) $\nu_{\max}$ 1639, 1713, 3467, 3546 cm⁻¹; FAB MS (positive mode) m/z 317 [M + H]⁺, 319 [M + 2]⁺; HREI-MS: Calculated for C₁₅H₂₅O₂Br; 316.1038, Observed; 316.1032; ¹H NMR (CDCl₃, 400 MHz): δ 1.01 (3 H, s, H₃-14), 1.22 (1 H, s, OH-4), 1.45 (1 H, ddd, $J = 8.5$ Hz, $J = 7.0$ Hz, $J = 2.7$ Hz, Ha-11), 1.57 (1 H, m, Hb-5), 1.61 (6 H, s, H-12/13), 1.64 (3 H, s, H₃-15), 1.65 (1 H, m, Ha-5), 1.85 (1 H, sept., $J = 13.4$ Hz, $J = 8.8$ Hz, $J = 5.5$ Hz, Hb-11), 1.98 (1 H, t, $J = 13.4$ Hz, Ha-3), 2.14 (1 H, m, Ha-6), 2.15 (1 H, m, Ha-10), 2.18 (1 H, m, Hb-3), 2.20 (1 H, m, Hb-10), 2.45 (1 H, ddd, $J = 18.0$ Hz, $J = 13.2$ Hz, $J = 5.2$ Hz, Hb-6), 4.71 (1 H, dd, $J = 12.5$ Hz, $J = 4.6$ Hz, H-2), 4.89 (1 H, d, $J = 2.5$, OH-1); ¹³C NMR (CDCl₃, 100 MHz): δ 12.7 (C-13), 14.4 (C-12), 20.3 (C-14), 23.3 (C-15), 30.3 (C-5), 33.7 (C-11), 35.7 (C-10), 38.0 (C-6), 41.8 (C-3), 58.1 (C-7), 61.3 (C-2), 71.5 (C-1), 78.5 (C-4), 133.6 (C-8), 135.2 (C-9).

4. Conclusion

In this study, a new brominated compound **1** has been isolated from *Laurencia heteroclada* and identified as 2-bromo-3,5,6-trihydro-1,4-dihydroxy isolaurene by using

different spectroscopic techniques. Compound **3** showed moderate activity against lettuce seed germination bioassay. In addition, some of the seaweeds tested showed significant allelopathic activities and thus could potentially be used as sources of natural herbicides in their crude form.

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