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Assessment of the Phytotoxic Potential of *Dregea volubilis* (L.f.) Benth. ex Hook.f. and Identification of Its Phytotoxic Substances for Weed Control

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Abstract: The phytotoxic potential of plants and the effect of their active components on another plant species is being explored as a potential alternative to synthetic herbicides for weed control. In the current study, we investigated the phytotoxic potential of the leaves of *Dregea volubilis* (L.f.) Benth. ex Hook.f. against four test plants [timothy (*Phleum pratense* L.), barnyard grass (*Echinochloa crus-galli* (L.) P. Beauv), lettuce (*Lactuca sativa* L.), and alfalfa (*Medicago sativa* L.)] and observed significant growth inhibition on those plants at concentrations >3 mg D.W. equivalent extract mL^{-1}. A bioassay-governed purification of the *D. volubilis* extracts using different chromatography phases produced two growth inhibitory compounds, 3-hydroxy-α-ionone (compound 1) and 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one (compound 2). The compounds retarded the growth of barnyard grass and cress (*Lepidium sativum* L.) with I_{50} (concentration required for 50% growth suppression) values ranging from 0.098 to 0.450 mM for 3-hydroxy-α-ionone and 0.029 to 0.420 mM for 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one. Thus, the extracts and identified compounds may have the possibility to be utilized as bioagents for weed control.

Keywords: leaf extracts; growth inhibition; 3-hydroxy-α-ionone; 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one

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1. Introduction

Allelopathic plants have been exploited in current agricultural production to ameliorate environmental pollution, soil sickness, human health concerns, unsafe products, and reduction of crop productivity [1]. Allelopathic plants, when utilized as smother crops, cover crops, green manure, mulch, or planted in rotational patterns are helpful in reducing deleterious weeds and enhancing crop yield and soil quality [2]. Weeds are the main constraint of successful crop production, and hand weeding, and weedicide applications have been the common weed control methods. However, increasing the cost and reducing the availability of labor are the main issues in hand weeding. Indiscriminate application of chemical weedicides for weed management has caused harmful effects involving the evolution of weedicide-resistant weeds and serious health risks resulting from dangerous residues in various harvested crops [3]. Thus, the cost and ecological affairs of weed management practices have been considered. Consequently, environmentally friendly methods, such as bioherbicides from natural resources to restrict weed growth have been developed [4].

Natural weedicides including growth inhibitory substances with distinctive modes of action could provide several benefits containing reducing herbicide-resistant weed biotypes and conserving the ecological balance [5–7]. Several growth inhibitory compounds

such as fatty acids (such as decenoic acid and pelargonic acid), sterols and terpenes, and phenolic compounds are examples of natural substances utilized in organic agriculture to control weeds. In addition, sarmentine isolated from *Piper longum* L., and benzoxazoline (BOA) released from different grass species' roots are also examples of natural products [8]. Very recently, Moreno-Robles et al. [9] have also reported the strong phytotoxic effect of 2-benzoxazolinone on the growth of *Cuscuta campestris* Yunck. (a parasitic weed). Weedicides based on natural active substances process few halogen groups and possess comparatively short half-lives, indicating that natural herbicide decay rapidly, and its residuals do not persist in the soil [10].

Studies conducted on allopathy and allopathic substances utilizing the herbal plants have garnered attention in recent years [11–16]. For instance, Kato-Noguchi et al. [11] reported the phytotoxic potential of *Azadirachta indica A. Juss.*, neem and isolated two new compounds, nimbolide B and nimbic acid B. Additionally, five active compounds separated from *Senna garrettiana* (Craib) by Irwin & Barneby showed growth inhibitory effect on seedling growth, seed germination, and plant dry weight of cress [16,17].

Dregea volubilis (L.f.) Benth. ex Hook.f., mainly called green milkweed (a tall stout climber), belongs to the family Apocynaceae, and is native to South Asia, Southeast Asia, and East Asia. It grows up to 11–13 m tall and bears green bisexual sweet-scented flowers in drooping umbels with long glabrous branches. The flowers and leaves of *D. volubilis* are consumed as a seasonal vegetable [18]. Traditionally, *D. volubilis* is used to treat various ailments like asthma, tumours, leucoderma, helminthiasis paralysis, rheumatism, and tonsilitis [19]. Suwitchayanon et al. [20] has documented that certain plant species possessing medicinal properties also have growth inhibitory compounds with allelopathic/phytotoxic potential. Interestingly, a pentacyclic triterpenoid compound with the anti-leishmanial and anti-tumour properties and new polyoxypregnane glycosides have been isolated from the *D. volubilis* [21,22]. Moreover, the antibacterial, antioxidant, anti-inflammatory, and antidiabetic properties of *D. volubilis* extracts have been reported [23–25]. However, very little information is documented about the phytotoxic activity and/or phytotoxic compounds of *D. volubilis.* In our foregoing study, it was found that *D. volubilis* extracts significantly inhibited the growth of cress and Italian ryegrass (*Lolium multiflorum* Lam.) and two phytotoxic compounds are isolated from its extracts. Moreover, the other one fraction of *D. volubilis* have been observed to have strong phototoxic activity, indicating that the other active components can be separated from its extracts [26]. Hence, in the present experiment, we investigated the phytotoxic ability of *D. volubilis* against four test plants and the effect of its isolated other active components on the test plants. In this research, we hypothesized that: (1) *D. volubilis* extracts could have the significant phytotoxic effect on the growth of test plants; (2) the other active compounds could be isolated from its extracts; and (3) these isolated/identified compounds could affect the growth of two test plants.

2. Materials and Methods

2.1. Extraction and Plant Material

Dregea volubilis leaves were gathered in Yezin village, Naypyitaw, Myanmar (19°83′67″ N; 96°27′21″ E) in May 2019 (Figure 1). One hundred grams of leaves (dry) were extracted using 1 L of 70% aqueous MeOH for two days. The extracts were filtered across a filter paper (No. 2; Toyo Ltd., Tokyo, Japan). Then, the residue was reextracted using 1 L of MeOH for one day and filtered. The two obtained filtrates were combined and evaporated until dryness using a rotary evaporator under vacuum at 40 °C to yield the concentrated crude extracts.

Figure 1. *Dregea volubilis*.

2.2. Bioassay

A bioassay was undertaken according to a foregoing method with some changes [26]. Lettuce, alfalfa, timothy, and barnyard grass were chosen as target plants. The concentrated extracts of *D. volubilis* were diluted in 100 mL MeOH. Aliquots of the concentrated extracts (0.6 mL) (1, 3, 10, 30, 100, and 300 mg dry weight (D.W.) equivalent extract mL^{-1}) were put in filter papers in 2.8 cm Petri dishes. The filter papers were moistened with 0.6 mL of 0.05% (*v*/*v*) aqueous solution of Tween 20, polyoxyethylenesorbitan monolaurate (Nacalai Tesque, Inc., Kyoto, Japan). Ten sprouted seedlings of timothy and barnyard grass (monocots) and 10 seeds of alfalfa and lettuce (dicots) were arranged in the Petri dishes. For control treatments, only Tween 20 solutions without methanol extracts were applied. Seedling lengths were assessed after incubation for 48 h in darkness.

2.3. Separation of the Phytotoxic Substances in the D. volubilis Extracts

Plant material (2400 g dry weight) was extracted as mentioned in Section 2.1. The filtrates were condensed at 40 °C using the rotary evaporator to yield a residue. This residue was calibrated to a pH of 7.0 with 1 M NaOH fluid, and this fluid was partitioned 5 times against the same volume of EtOAc (Figure 2). The EtOAc fraction was evaporated after drying over anhydrous Na_2SO_4. The EtOAc fraction exhibited higher growth inhibitory effects compared with the aqueous fraction (data not provided). Thus, the EtOAc fraction was chosen for subsequent bioassay-governed fractionations across different purification phases: silica gel, Sephadex LH-20, C_{18} cartridge, and HPLC analysis. The inhibitory activity for individual chromatographic phase was measured using a cress bioassay, resulting in the separation of two inhibitory substances (Figure 2). These two substances were then purified again by reverse-phase HPLC (3 µm, 4.6 × 250 mm I.D., Inertsil ODS-3; GL Science Inc., Tokyo, Japan) at a flow rate of 0.5 mL min^{-1} with 45% aqueous MeOH (detection: at 40 °C, 220 nm wavelength), and obtained at 95–99 and 102–107 min (retention time). The Lastly, the substances were identified using ESIMS, HRESIMS, and ^{1}H-NMR spectrum (400 MHz, CD_3OD).

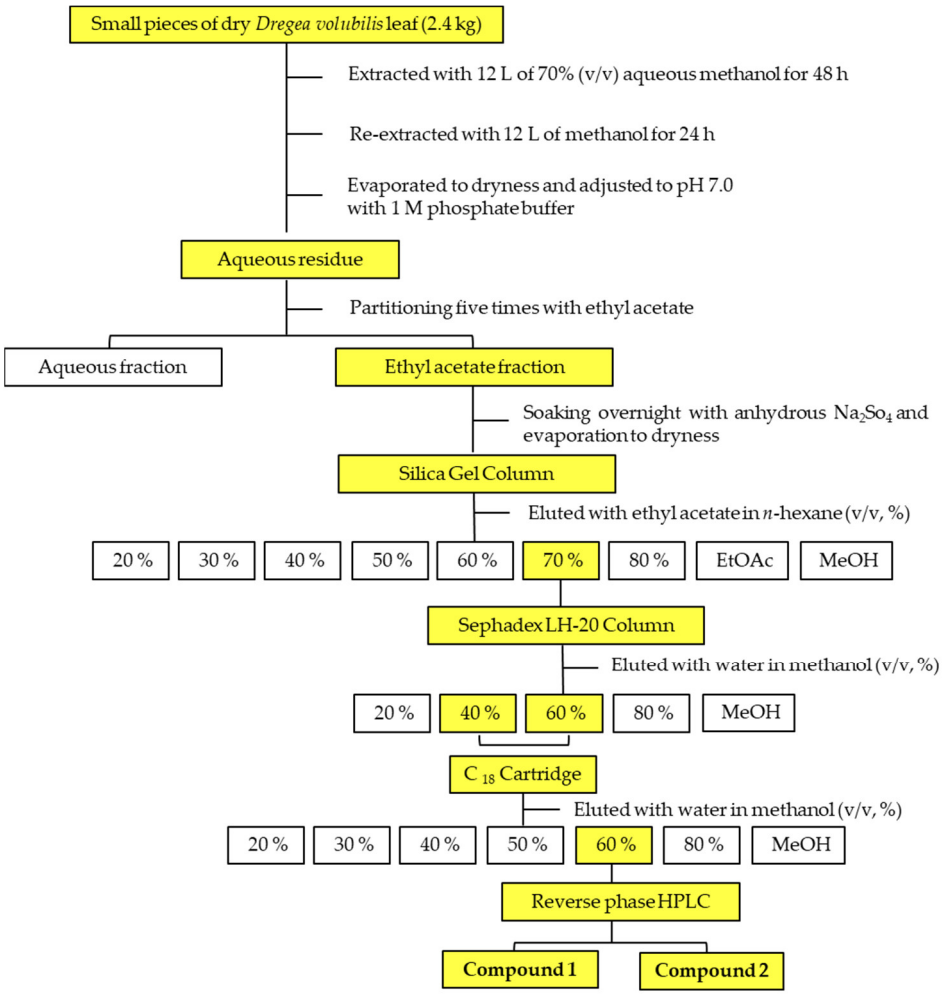


Figure 2. Procedure for extracting and isolating two compounds from *D. volubilis*.

2.4. Bioassay of the Identified Compounds

The identified compounds were diluted in MeOH and added to filter papers (No. 2; Toyo Ltd., Tokyo, Japan) in 2.8 cm Petri dishes. Then, the MeOH was evaporated under the fume hood. The inhibitory effect of the compounds was decided by bioassay with barnyard grass and cress, as described in Section 2.2. Barnyard grass was chosen for its wide distribution, mainly in crop lands while cress was chosen for its known growth features.

2.5. Statistical Analysis

The experiment was replicated six times using a completely randomized manner with ten seedlings for each assessment. ANOVA was carried out using the SPSS statistical package, IBM, Armonk, NY, USA (Version 16). Significant variations between treatment and control, and within the treatments, was tested using Tukey's honestly significant difference (HSD) test at the 0.05 level of significance. I_{50} values were calculated using the regression equation of the concentration-response curves with the GraphPad Prism software package ®Ver. 6.0, San Diego, CA, USA.

3. Results

3.1. Growth Inhibitory Effects of the D. volubilis Extracts

The extracts inhibited the growth of four test plants at all the tested concentrations >3 mg D.W. equivalent extract mL^{-1} (Figure 3A,B). At the concentration of 100 mg D.W. equivalent extract mL^{-1}, the extracts fully retarded the lettuce and timothy seedlings, while the shoots and roots of alfalfa, and barnyard grass were restricted to 4.47, and 25.02 and

0.83, and 0.26% of control, respectively. Moreover, at the tested concentration of 300 mg D.W. equivalent extract mL^{-1}, the *D. volubilis* extracts fully restricted the growth of all the test plants except for the barnyard grass's shoot, its growth was restricted to 6.1% of control. The I_{50} values for the alfalfa, lettuce, barnyard grass, and timothy roots were 1.49, 2.98, 4.97, and 1.8 mg D.W. equivalent extract/mL respectively, which were lower than those for their shoots at 1.64, 4.93, 43.09, and 2.16 mg D.W. equivalent extract/mL, respectively (Table 1). Based on the I_{50} values, barnyard grass and alfalfa exhibited the highest and lowest sensitivity to the extracts, respectively.

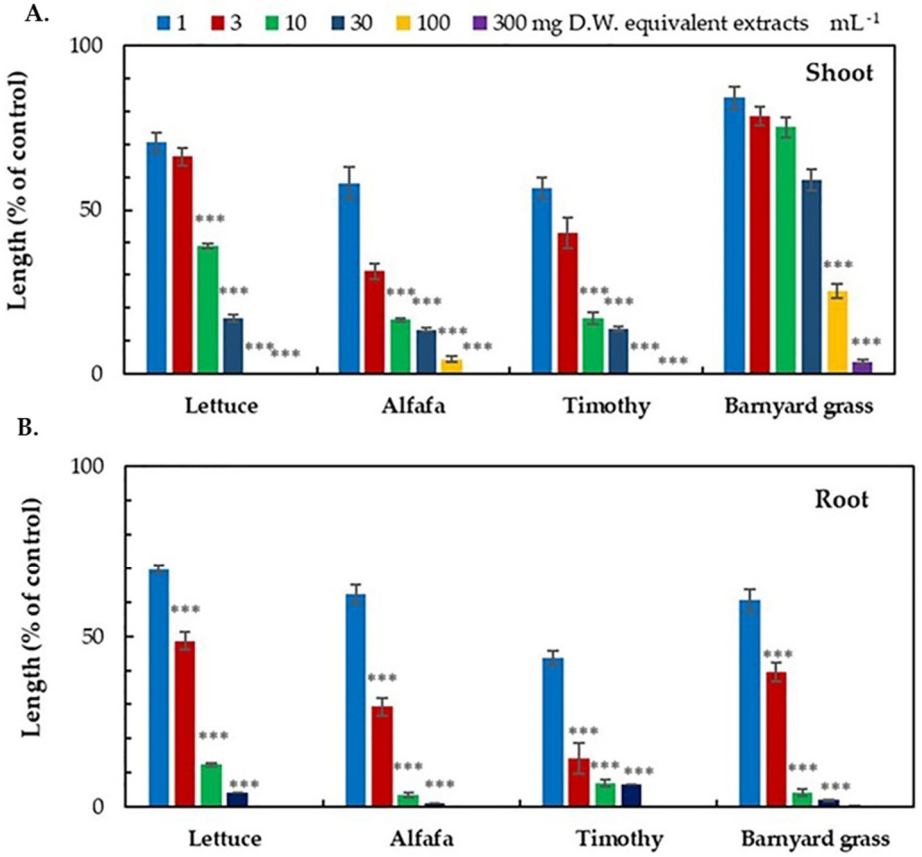


Figure 3. Effect of *D. volubilis* extracts with the concentrations corresponding to the extracts acquired from 1, 3, 10, 30, 100, and 300 mg D.W. equivalent extract mL^{-1} on the (**A**) shoots and (**B**) roots of lettuce (*Lactuca sativa* L.), alfalfa (*Medicago sativa* L.), timothy (*Phleum pratense* L.), and barnyard grass (*Echinochloa crus-galli* (L.) P. Beauv.). Asterisks indicate significant differences between treatment and control: *** $p < 0.001$.

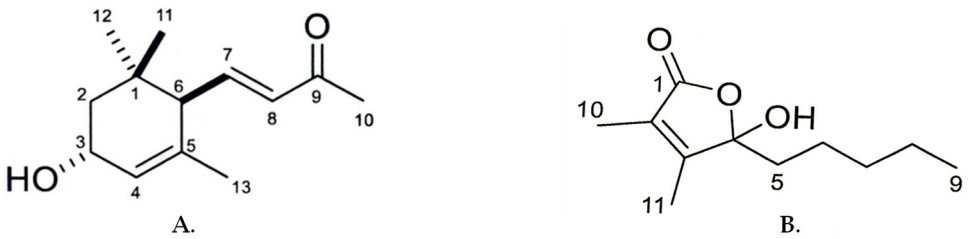
Table 1. I_{50} value of the *D. volubilis* extracts for the shoots and roots of lettuce (*Lactuca sativa* L.), alfalfa (*Medicago sativa* L.), timothy (*Phleum pratense* L.), and barnyard grass (*Echinochloa crus-galli* (L.) P. Beauv.).

Test Plant		I_{50} Values (mg DW Equivalent Extract mL^{-1})	
		Shoot	**Root**
Dicotyledonous	Alfalfa	1.64 d	1.49 d
	Lettuce	4.93 b	2.98 c
Monocotyledonous	Barnyard grass	43.09 a	4.97 b
	Timothy	2.16 c,d	1.80 d

Different letters indicate significant difference ($p < 0.05$) according to Tukey's test.

3.2. Identification of the Growth Inhibitory Substances

The molecular formula of substance 1 was determined as $C_{13}H_{20}O_2$ using HR-ESI-MS at m/z 209.1552 $[M + H]^+$ (calcd for $C_{13}H_{21}O_2$, 209.1542, Δ = +1.0 mmu). The ^1H NMR (400 MHz, $CDCl_3$) spectrum displayed δH 6.53 (dd, J = 15.9, 10.3 Hz, 1H, H-7), 6.10 (d, J = 15.9, 1H, H-8), 5.63 (br s, 1H, H-4), 4.27 (br s, 1H, H-3), 2.50 (d, J = 10.3, 1H, H-6), 2.26 (s, 3H, H-10), 1.84 (dd, J = 13.9, 6.1, 1H, H-2), 1.62 (d, J = 0.7, 3H, H-13), 1.40 (dd, J = 13.9, 6.7, 1H, H-20), 1.03 (s, 3H, H-11), and 0.89 (s, 3H, H-12). By analyzing these data with foregoing reported data [27], the substance was characterized as 3-hydroxy-α-ionone (Figure 4A).



A. 3-hydroxy-α-ionone B. 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one

Figure 4. Structures of (**A**) 3-hydroxy-α-ionone and (**B**) 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one.

The molecular formula of substance 2 was determined as $C_{11}H_{18}O_3$ using ESIMS at m/z 199.1345 $[M + H]^+$ (calcd for $C_{11}H_{19}O_3$, 199.1334). The ^1H NMR (400 MHz, $CDCl_3$) spectrum displayed δ 1.98 (m, 1H, H-5a), 1.94 (q, J = 0.9 Hz, 3H, H-11), 1.82 (q, J = 0.9 Hz, 3H, H-10), 1.75 (m, 1H, H-5b), 1.34 (m, 1H, H-6a), 1.33–1.27 (m, 4H, H-7, 8), 1.16 (m, 1H, H-6b), and 0.87 (t, J = 6.8 Hz, 3H, H-9). Analyzing the obtained data and with the foregoing data [28], the substance was characterized as 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one (Figure 4B).

3.3. Inhibitory Activity of the Isolated Compounds

The growth inhibitory activity of 3-hydroxy-α-ionone (compound 1) and 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one (compound 2) was tested against barnyard grass and cress. Significant inhibitory effects of compound 1 against the growth of two test plants, initiated from 0.03 mM, while that of compound 2 initiated from 0.1 mM (Figure 5A,B and Figure 6A,B). The I_{50} values of compound 1 for barnyard grass shoots and roots were 0.450 and 0.098 mM, respectively, while those for cress shoots and roots were 0.261 and 0.125 mM, respectively (Table 2). The I_{50} values of compound 1 for barnyard grass and cress shoots were 4.59- and 2.08-times higher than those for their roots, respectively. Meanwhile, the I_{50} values of compound 2 for the barnyard grass shoots and roots were 0.19 and 0.03 mM, respectively, while those for the cress shoots and roots were 0.42 and 0.18 mM, respectively. The I_{50} values of compound 2 for the shoots of both test plants were 6.65- and 2.29-times higher than those for their roots, respectively. In addition, it was observed that the I_{50} values of compound 1 for the growth of barnyard grass were more than those of compound 2. In contrast, the I_{50} values of compound 2 for the growth of cress were higher than those of compound 1.

Table 2. I_{50} values of the isolated compounds for the shoots and roots of barnyard grass and cress.

Plant Species	I_{50} Value (mM) Compound 1		I_{50} Value (mM) Compound 2	
	Shoot	**Root**	**Shoot**	**Root**
Cress	0.26 b	0.13 c,d	0.42 a	0.18 c
Barnyard grass	0.45 a	0.10 d	0.19 c	0.03 e

Different letters indicate significant difference ($p < 0.05$) according to Tukey's test.

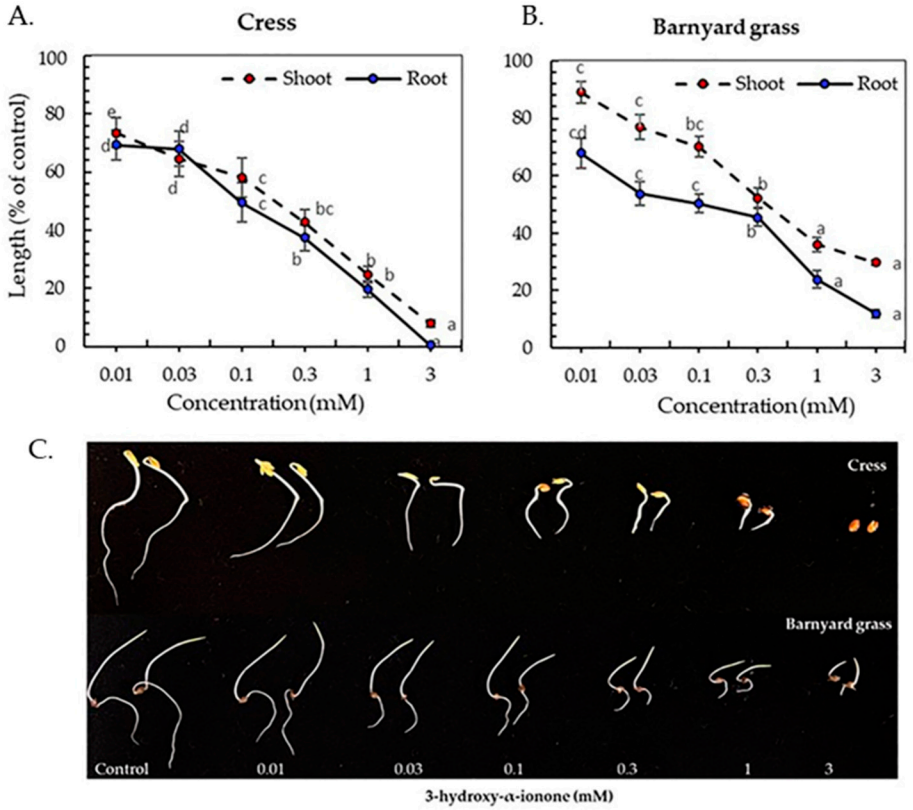


Figure 5. Effects of 3-hydroxy-α-ionone isolated from the *D. volubilis* extracts on the growth of (**A**) cress, (**B**) barnyard grass, and (**C**) both test plants.

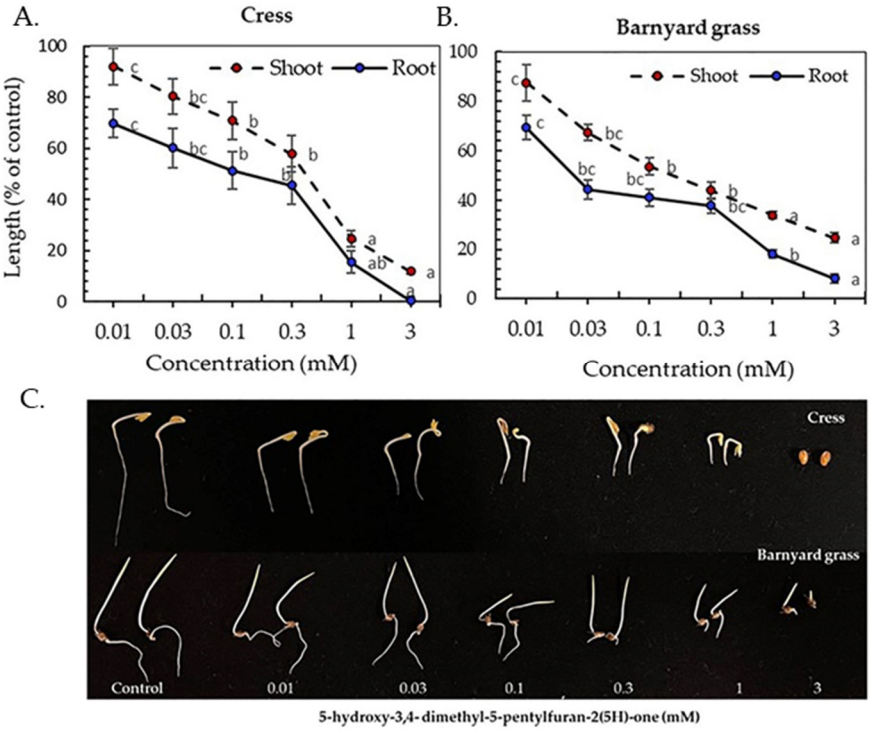


Figure 6. Effects of 5-hydroxy-3,4- dimethyl-5-pentylfuran-2(5H)-one isolated from the *D. volubilis* extracts on the growth of (**A**) cress, (**B**) barnyard grass, and (**C**) both test plants.

4. Discussion

In our previous research, we explored the growth suppressive effect of *D. volubilis* extracts against the growth of cress and Italian ryegrass, and significant growth restriction was observed [26]. To confirm those results, we also assessed the inhibitory effects of this extracts against the growth of other four test plants (alfalfa, lettuce, timothy, and barnyard grass). In the current research, the extracts significantly inhibited the growth of the tested plants, and the extent of inhibition relied on the extract concentrations (Figure 3A,B). The I_{50} values of the compounds for the tested plant species were different, which indicates that the extent of inhibition also relied on the species. The concentration- and species-reliant inhibition against the tested plants was also observed in *Hyptis suaveolens* Poit [29], *Anredera cordifolia* (Tenore) Steenis [30], *Nephrolepis cordifolia* (L.) C. Presl [31], *Senna garrettiana* [17], *Marsdenia tenacissima* (Roxb.) [32], and *Plumbago rosea* [33]. The findings of these studies described that the growth suppressive properties of the extracts of the plants were due to inhibitory/phytotoxic active substances. Moreover, our experimental results showed that the roots of the tested plant species were more sensitive to the extracts than their shoots. A number of studies have also documented that the greater inhibitory effect of various plant species is against the roots of tested plants compared with their shoots [34–37]. These results indicated that the extracts have inhibitory effect and may possess inhibitory substances with allelopathic potential. In our former study, two compounds (loliolide and dehydrovomifoliol) were separated and characterized from *D. volubilis* [26]. In the present study, two other compounds were isolated from its extracts and characterized as 3-hydroxy-α-ionone and 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one using spectroscopy (Figure 4A,B). 3-Hydroxy-α-ionone is derived from the degradation of carotenoids [38] and has been found in *Anredera cordifolia* (Ten.) Steenis leaves [30], raspberry fruits [38], and *Cassia alata* L. [39]. Ionones and their derivatives are elaborated in terpenoid metabolism as essential intermediates, for example, carotenoid biosynthesis [40]. In addition, an analogous active substance, 3-hydroxy-β-ionone, has been extracted from *Rhynchostegium pallidifolium* moss, where the compound restricted the roots and shoots of *L. sativum* [41]. Alternatively, 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one has been separated from the plant species *Viburnum odoratissimum* [42] and *Rosa roxburghii* [43].

In this experiment, we found that 3-hydroxy-α-ionone and 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one separated from the extracts restricted the growth of two test plants (Figures 5A,B and 6A,B). The I_{50} values also revealed that the potency of both identified compounds was greater against the roots than the shoots (Table 2). This finding was in accordance with the results shown in Figure 3, in which the extracts inhibited the roots more than the shoots of test plants. The greater sensitivity of the roots may be because of the complete contact of the roots with allelopathic substances that affect morphological and physiological processes such as membrane permeability and ion uptake [44,45]. Previous studies have documented more sensitivity of roots to allelopathic compounds compared with shoots [46–48]. The I_{50} values of identified compounds were also observed to be different between the two test plants. The different sensitivities of test species to allelopathic compounds greatly depend on the biochemical and physiological attributes of each test plant [49]. The variations in the inhibitory effects of the compounds may result from the differences in their molecular structures, because the phytotoxicity of the compounds is determined by their structural difference. Dayan et al. [50] and Yan et al. [51] also reported that several compounds restrict plant growth to different extents, which may reflect variations in chemical structure. Moreover, the process of inhibition could be caused by changes in the structure of plant cells, cell elongation inhibition, antioxidant system imbalances, the breakdown of activities and functions of various enzymes, and protein synthesis [52]. Therefore, our findings indicated that 3-hydroxy-α-ionone and 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one have inhibitory activity and may provide the phytotoxicity of *D. volubilis.* The observed phytotoxicity may be because of the interactivities between these two compounds or previous identified compounds. The interactions between allelochemicals have also been reported by Pardo-Muras [53] and Chaves [54].

Based on the overall results, it was found that *D. volubilis* extracts and its two identified compounds significantly restricted the growth of test plants, indicating that our obtained results were same as our proposed hypotheses. Hence, the phytotoxic potentials of the *D. volubilis* leaves might be useful for reducing the synthetic herbicides application and also to avoid the hurtful effects of these herbicides on the environment and human health.

5. Conclusions

The extracts of *D. volubilis* leaves had a phytotoxic effect and two active compounds possessing phytotoxic potential were isolated. The chemical structures of compound 1 and 2 characterized them as 3-hydroxy-α-ionone and 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one, respectively. These compounds were active at concentrations 0.03–0.1 mM, suggesting that 3-hydroxy-α-ionone and 5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5H)-one may contribute to the phytotoxicity of *D. volubilis*. Hence, *D. volubilis* leaves could be used as a candidate for soil supplement materials to restrict weed growth in crop fields. Nevertheless, it is necessary to confirm the phytotoxicity of *D. volubilis* in further field research and to determine the biochemical and physiological properties and modes of action of its active compounds.

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