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学位論文全文に代わる要約
Extended Summary in Lieu of Dissertation

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学位論文題目：
Title of Dissertation

Assessment of Allelopathic Potential and Allelopathic Substances in Myanmar Medicinal Plants for Weed Control
(雑草防除を目的としたミャンマー在来薬用植物のアレロパシーとその原因物質の探索)

学位論文要約：
Dissertation Summary

In agricultural crop production, weeds are a serious restriction. The infestation of weeds reduces agricultural productivity and produce quality by competing with cultivated crops for available resources (Monteiro et al., 2021) and parasitism (Scavo and Mauromicale, 2020), and they also harbor pests and plant pathogens (Qasem and Foy, 2001). Weeds have been controlled either mechanically or by using herbicides (Christensen et al., 2009). Among weed control methods, herbicide application is the most effective. Therefore, agricultural weed control relies heavily on herbicides (Pavlovi´c et al., 2022). However, improper and long-term use of herbicides not only negatively affects human and environmental health but also causes an increase in herbicide-resistant weeds (Kniss et al., 2016; Scavo et al., 2014). For these negative effects, researchers are looking for innovative weed control methods that can ensure biosafety and eco-sustainability (Jabran et al., 2015; Bajwa et al., 2019), and allelopathy appears to be one of the options (Rawat et al., 2017). Allelopathy is an ecological phenomenon in which a plant releases allelopathic compounds or allelochemicals into the surrounding environment, causing either direct or indirect, positive or negative impacts on other plant species (including microbes) (Washington, 1993). Allelopathic plants or organisms produce allelochemicals by leaching, root secretion, or microbial degradation (Fujii and Hiradate, 2007). These allelochemicals (allelopathic compounds) can inhibit the germination, growth, and development of adjacent plants by disrupting physiological mechanisms including photosynthesis, respiration, membrane permeability, cell extension, cell division, and water and nutrient uptake (Soltys et al., 2013; Cheng et al., 2015). In recent years, the possibility of phytochemicals or natural substances being extensively researched as new templates of herbicides for new synthetic herbicide classes (Duke et al., 2000; Macias et al., 2007; Asaduzzaman et al., 2014) has also been considered as a safer alternative to control weeds than conventional herbicides (Bhadoria, 2011; Duke, 2000). Thus, these naturally produced allelochemicals could be manipulated as an environment-friendly herbicide in sustainable agricultural production systems and can also be used as natural biodegradable herbicides (Duke et al., 2000; Vyvyan, 2002). Therefore, searching for allelopathic plants and identifying allelopathic compounds with strong inhibitory activity are receiving the most attention. Among different plant groups, medicinal plants are a rich source of secondary metabolites and possess phytochemical and allelopathic potential (Islam and Kato-Noguchi, 2014; Chevallier, 1996; Wink, 2010). Myanmar also has a diverse source of medicinal plant species (DeFilipps and Krupnick, 2018) with therapeutic properties. However, many medicinal plants in Myanmar still remain to be determined for allelopathic activity and identified as allelopathic substances.

This current research has focused on the investigation of the allelopathic potential and allelopathic-related substances of three medicinal plants from Myanmar, namely, *Marsdenia tenacissima* (Roxb.) Moon and *Croton oblongifolius* Roxb. *Aegle Marmelos* (L.) Correa. These medicinal plants are famous for their medicinal properties and are widely used as a traditional household remedy in Myanmar and other Southeast Asian countries (Kumar et al., 2007; Li et al., 2014; Salatino et al., 2007; Sharma et al., 2007). Based on the report of reviews of the literature, *M. tenacissima* possesses around 196 phytochemicals, including 155 steroids, tri-terpenes, phenolic compounds, and organic acids (Wang et al., 2018); *C. oblongifolius* possesses 399 new compounds, including 339 diterpenoids (Xu et al., 2018); and *A. marmelos* produces more than 100 phytochemical substances, such as tannins, cardiac glycosides, alkaloids, flavonoids, phenol, terpenoids, and steroids (Mujeeb et al., 2014). Although *M. tenacissima*, *C. oblongifolius*, and *A. marmelos* have been reported to possess many phytochemical and pharmacological activities, there is no evidence of allelopathy or its related allelopathic substances. Therefore, this research was conducted with the following three main objectives: (1) to explore the allelopathic potential of *M. tenacissima*, *C. oblongifolius*, and *A. marmelos* on the seedling growth of test plant species; (2) to identify the allelopathic substances in *M. tenacissima*, *C. oblongifolius*, and *A. marmelos*; and (3) to determine the biological activities of characterized compounds against the seedling growth of tested plant species.

Fresh and matured leaves of these three medicinal plants were collected from Khin-U Township, Shwe Bo district, Sagaing Division Region, Myanmar, during July–August 2020. The collected leaves were dehydrated in the shade, chopped into small pieces, and ground to a fine powder. Dry powdered leaves of three medicinal plants were extracted by soaking in 70% (*v/v*) aqueous methanol for 48 h. After filtration, the extract was filtered through a single layer of filter paper. The extract residue was re-extracted by soaking in methanol for 24 hours and filtered. The two filtrates were then mixed and evaporated to obtain crude extracts under reduced pressure at 40°C. The biological activity of crude extracts of three medicinal plants was determined by using six concentrations against the seedling growth of dicot (cress, lettuce, and alfalfa) and monocot plants (barnyard grass, Italian ryegrass, and timothy). The bioassay results showed that the aqueous methanol extracts of *M. tenacissima*, *C. oblongifolius*, and

A. marmelos had significant inhibitory activities on the seedling growth of all test plants. A strong negative correlation was observed between the concentration of three medicinal plant extracts and the shoot and root growth of the test plant species, showing that the inhibitory effect depended on concentration. These results are in accordance with those of other studies: Kyaw and Kato-Noguchi (2020) noted that increasing concentrations of *Acacia pennata* leaf extracts inhibited the seedling growth of six test plants; Laizer et al. (2021) reported that higher concentrations of *Sphaeranthus suaveolens* extracts resulted in greater inhibition of the germination of common bean and rice; and Poonpaiboonpipat et al. (2021) also stated that the highest concentration of *Chromolaena odorata* leaf extract showed the greatest inhibitory effect on amaranthus and barnyard grass. Additionally, the extracts of three medicinal plants that inhibited the 50% growth inhibition of tested plant seedlings (I_{50} values) of the shoot and root growth of all test plants varied, showing that the inhibition of these extracts was species-dependent. The I_{50} values for the shoot and root growth of test plants ranged from 0.80–53.78 for *M. tenacissima*, 3.22–65.75 for *C. oblongifolius*, and 1.61–36.1 mg DW equivalent extract/mL for *A. marmelos*. Based on the I_{50} values of three medicinal plants, all of the extracts inhibited the roots of all test plants more than the shoots. This result may be due to higher root tissue permeability compared with the shoot tissue because the root tissue emerges first during germination and has direct contact with the allelopathic substances (Turk et al., 2005; Ercoli et al., 2007; Gulzar et al., 2016). Root growth depends on cell proliferation, which is greatly affected by allelopathic substances (Frescura et al., 2013). Other studies (Ladhari et al., 2013; Gaaliche et al., 2017) reported that a decrease in mitotic activity in the roots resulted in greater root inhibition by contact with allelochemicals. The growth inhibitory potential of *M. tenacissima, C. oblongifolius, and A. marmelos* has allelopathic potential and may possess allelopathic substances. These three medicinal plants could be used as potent candidates for the isolation and identification of allelopathic compounds for the development of natural herbicides.

For the purification and isolation of bioactive compounds, the extracts of *M. tenacissima*, *C. oblongifolius*, and *A. marmelos* were purified through various chromatography steps: silica gel, Sephadex LH-20, reverse-phase C_{18} cartridges, and HPLC. The chemical structures of the obtained compounds were then characterized by HRESI-MS, ^{1}H-NMR spectra (400, 500 MHz), ^{13}C-NMR spectra (100 MHz), and optical rotation. HRESI-MS was implemented on a Thermo Scientific Orbitrap Exploris 240 Mass Spectrometer and a Bruker AVANCE III 500 MHz NMR spectrometer. Chemical shifts were described according to the residual signal of the solvent (acetone-d_6, CD_3OD, and $CDCl_3$). Cress bioassays were used to evaluate the biological activities of each isolated compound from three medicinal plants.

The extracts of *M. tenacissima* were purified through various chromatography steps, and three allelopathic substances were isolated and determined by spectral data to be steroidal glycoside 1; 3-*O*-[6-deoxy-3-*O*-methyl -*β*-allopyanosyl(1→4)-*β*-oleandropyranosyl]-5,6-dihydrogen-11*α*-*O*-acetyl-12*β*-*O*-tigloyl-17*β*-marsdenin (a novel compound); steroidal glycoside 2; (3-*O*-[6-deoxy-3-*O*-methyl-*β*-allopyanosyl(1→4)-*β*-oleandropyranosyl] -5,6-dihydrogen-11*α*,12*β*-di-*O*-tigloyl-17*β*-marsdenin); and steroidal glycoside 3; (3-*O*-[*β*-cymaropyranosyl(1→4) -*β*-cymaropyranosyl]-8-dehydroxy-11*β*-*O*-acetyl-12*β*-*O*-tigloyl-17*β*-marsdenin) (a novel compound). These three isolated compounds (steroidal glycosides 1, 2, and 3) belong to a group of C_{21} steroidal glycosides (Zhang et al., 2010), and the compounds possess a wide range of pharmacological activities (Wang et al., 2006; Yu and Zhao, 2016; Bailly, 2021; Matsuo et al., 2017; Yuan et al., 2016; Timité et al., 2012). Steroidal glycosides 1, 2, and 3 significantly suppressed the shoot and root growth of cress seedlings with concentration-dependent inhibitory activity. The I_{50} values of the shoot and root growth of cress were 0.46 and 0.03 mM for steroidal glycoside 1, 0.74 and 0.12 mM for steroidal glycoside 2, and 0.25 and 0.03 mM for steroidal glycoside 3, respectively. The I_{50} values also showed that steroidal glycosides 1 and 3 have more growth inhibitory activity than steroidal glycoside 2. The different inhibitory activities of steroidal glycosides might be due to the different molecular structures (Liu et al., 2017) and acyl moieties in the C-11 and C-12 positions (Liu et al., 2021). Panda et al. (2006) reported that pregnane glycosides with acyl moieties such as acetyl, benzoyl, and cinnamoyl, at C-11 or C-12, are more active. Steroidal glycoside 3 and 1 have the same acyl moieties at the C-11 or C-12 position and sugar group, but they differ in the presence of dehydroxy alcohol in steroidal glycoside 3 and a hydroxy group in steroidal glycoside 1 at the C-8 position. Furthermore, the I_{50} values of shoot growth of steroidal glycoside 3 exhibited higher allelopathic potential than steroidal glycoside 1. These two steroidal glycosides (1 and 3), however, showed greater growth inhibitory activities than steroidal glycoside 2, which possesses the Tig group at the C-11 position. Hence, the different inhibitory activities of the identified compounds, steroid glycosides 1, 2, and 3, may be because of the Ac group at the C-11 position, the dehydroxy alcohol, and the hydroxy group at the C-8 position. However, this is the first report of the allelopathic activity of an inhibitory substance (steroidal glycosides 1, 2, and 3) against the seedling growth of cress, and these steroidal glycosides 1, 2, and 3 may contribute to the allelopathic activity of *M. tenacissima*.

Bioassay-guided fractionations of the leaf extracts of *C. oblongifolius* resulted in the isolation of four active compounds as (3*R*,6*R*,7*E*)-3-hydroxy-4-7-megastigmadien-9-one (I), 2-hydroxy alpinolide (a novel compound) (II), alpinolide (III), and epialpinolide (IV). Compound I is a C_{13} *nor*-isopenoid derivative from carotenoids (Sun et al., 2020; D'Abrosca et al., 2004). Many compounds under C_{13} *nor*-isopenoid have many pharmacological (Qi et al., 2016) and allelopathic properties (D'Abrosca et al., 2004; Macías et al., 2008). The allelopathi properties of C_{13} *nor*-isopenoid compounds may be due to the presence of the monoketone group (Chotpatiwetechkul et al., 2022) and -OH group at the C-3 position on the structure (D'Abrosca et al., 2004; Macías et al., 2008). Compounds II, III, and IV are a group of secoguaiane-type sesquiterpenes that are derivatives of the terpenoid and can be found in many plant species of the Zingiberaceae family. Several compounds in the group of sesquiterpenes possess anticancer (Hassan et al., 2018; Rasul et al., 2013; Hsu et al., 2011) and antibacterial properties (Crespo-Ortiz and Wei, 2012). The concentration necessary for 50% growth reduction of the cress seedlings varied from 0.15 to 0.24 mM for (3*R*,6*R*,7*E*)-3-hydroxy-4-7-megastigmadien-9-one, 0.04 to 0.11 mM for 2-hydroxy alpinolide, 0.07 to 0.12 mM for alpinolide, and 0.09 to 0.16 mM for epialpinolide. Among the four compounds, 2-hydroxy alpinolide has a higher allelopathic potential than the other three compounds. The variations in inhibitory activity of these compounds may result from the variations in structure of phytotoxic substances (DellaGreca et al., 2003). In addition, the stronger growth-inhibitory activity of 2-hydroxy alpinolide may be related to a hydroxy group at the C-2 position and the furan ring on the structure. Okada et al. (1990) and Wang et al. (2005) noted that natural furans, with the existence of furan and other aromatic rings, have strong biological activity. These results suggest that four isolated compounds may be responsible for the allelopathic potential of *C. oblongifolius*. This is the first report on the isolation of allelopathic substances from *C. oblongifolius* extracts.

Bioassay-directed chromatographic purification steps of *A. marmelos* extracts resulted in four allelopathic substances identified spectroscopically as umbelliferone (1), (*E*)-4-hydroxycinnamic acid methyl ester (2), cinnamic acid (3) and methyl (*E*)-3′-hydroxyl-4′-methoxycinnamate (4). Umbelliferone, (*E*)-4-hydroxycinnamic acid methyl ester, cinnamic acid, and methyl (*E*)-3′-hydroxyl-4′-methoxycinnamate significantly restricted the hypocotyl and root growth of cress with concentration-dependent inhibitory effects. The I_{50} values of shoots and roots growth of cress were 0.38 and 0.15 mM for umbelliferone, 0.18 and 0.08 mM for (*E*)-4-hydroxycinnamic acid methyl ester, 0.12 and 0.07 mM for cinnamic acid, and 0.26 and 0.18 mM for methyl (*E*)-3′-hydroxyl-4′-methoxycinnamate, respectively. The different inhibitory activities of these compounds may be due to the chemical structure of specific compounds, the presence of ester derivatives, and hydroxyl groups and methoxy substituents in the ortho position (Natella et al., 1999; Cavalier et al., 1992). The allelochemicals such as; phenols, coumarin, terpenoids cause lipid peroxidation (Możdżeń et al., 2021). In addition, phenolic acids, including cinnamic acid, disturb membrane permeability and thus caused the effect on the plant growth processes (Doblinski et al., 2003; Ju et al., 2007; Możdżeń et al., 2021). Xu et al. (2013) confirmed that the allelopathic activity of the phenolic compounds may be due to the hydroxyl groups in most of the methyl positions. The phytotoxicity of *Oxalis pes-caprae* against target species may be associated with the presence of cinnamic ester derivatives (Greca et al., 2007). Pinho et al. (2017) stated that phenolic compounds appear to be less allelopathic to plants when their -OH and -OCH_3 groups are increased. I_{50} values also showed the sensitivity of four compounds was greater against the roots related with the hypocotyls. Comparing the I_{50} values of the compounds, cinnamic acid has more allelopathic potential than the other three compounds. Moreover, based on the I_{50} values, the sensitivity of the four compounds was greater against the roots compared with the hypocotyls. These results might be because the roots are the first tissue to come into contact with phenolic allelochemicals (Jose et al., 2016; Ladhari et al., 2018); it is possible that the inhibitory impact resulted from a decrease in mitotic activity in the roots (Ladhari et al., 2013; Gaaliche et al., 2017). According to the results of this study, *A. marmelos* leaves possess allelopathic activity, which is caused by the compounds umbelliferone, (*E*)-4-hydroxycinnamic acid, methyl ester, cinnamic acid, and methyl (*E*)-3′-hydroxy -l-4′-methoxycinnamate. Although some biological and allelopathic properties of umbelliferone, (*E*)-4-hydroxycinnamic acid methyl ester, cinnamic acid, and methyl (*E*)-3′-hydroxyl-4′-methoxycinnamate have been reported, this is the first report of the allelopathic activity of these four compounds from *A. marmelos* extracts.

In conclusion, the aqueous methanol extracts of *M. tenacissima*, *C. oblongifolius*, and *A. marmelos* exhibited concentration- and species-dependent inhibitory activities on the seedling growth of dicot and monocot plants. These inhibitory activities suggest that these medicinal plants have allelopathic potential and possess allelopathic substances. Accordingly, eleven inhibitory substances (including three novel compounds) were isolated from the leaf extracts of *M. tenacissima*, *C. oblongifolius*, and *A. marmelos*, and these compounds affected the shoot and root growth of cress at different concentration levels. Therefore, the inhibitory activities of these isolated compounds may contribute to the allelopathy of *M. tenacissima*, *C. oblongifolius*, and *A. marmelos*. To the best of our knowledge, this study was the first report of the allelopathic activity of these medicinal plants and their allelopathic compounds. Therefore, our findings suggest that the living and dead plant residues of these medicinal plants and their plant extracts may be used as soil-additive and weed-suppressive resources, and their isolated compounds may be utilized as a potential candidate for developing natural herbicides for sustainable weed management.

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（様式５）(Style5)

(注)　要約は、学位論文全文の約１０分の１としてください。図表や写真を含めても構いません。
(Note)　The Summary should be about 10% of the entire dissertation and may include illustrations