

Chapter

Cytotoxic Activity of Secondary Metabolite Compounds from Myanmar Medicinal Plants

*Khun Nay Win Tun, Nanik Siti Aminah,
Alfinda Novi Kristanti, Hnin Thanda Aung
and Yoshiaki Takaya*

Abstract

Plants are the storage place for many active ingredients that are currently used in pharmaceuticals. Proofs have been expanded for ages to indicate the profitable capacity of medicinal plants used in various infections, especially for cancer treatment. The plants, *Chromolaena odorata* (Family Asteraceae), *Croton oblongifolius* Roxb. (Family Euphorbiaceae), *Tinospora cordifolia* (Family Menispermaceae), *Melastoma malabathricum* L. (Family Melastomaceae), and *Dioscorea bulbifera* (Family Dioscoreaceae) have been used for a long time in Myanmar's traditional medicine. This study aimed to review systematically the cytotoxic activity of the whole plants and their extracts, fractions, and isolated compounds from these selected medicinal plants. This chapter also be substantiated for additional analysis on phytochemical constituents and pharmacological action of therapeutic plants species in Myanmar.

Keywords: cytotoxic activity, Myanmar, medicinal plants, isolated compounds, secondary metabolite

1. Introduction

Cancer is defined as the abnormal proliferation of cells in our bodies, which can result in death. As a result, there is currently no effective cancer therapy available, and the disease has the potential to spread globally. Plants are a rich source of novel bioactive compounds. This is because of their innate biological capabilities, which have the potential to be used in medicine and other disciplines of human health promotion. There is a significant need for new anticancer medications that are more effective and less damaging to healthy cells, such as plant-derived substances. The preliminary strategy for identifying active chemicals in plants is cytotoxic screening [1–3].

Chromolaena odorata is a tropical and subtropical flowering shrub widely distributed in various parts of the world. Fresh leaves or a decoction of *C. odorata* have been used for folk medicine in Vietnam. In other traditional medicine, it is useful for burn wounds, leech bites, skin infections, soft tissue wounds, and dento-alveolitis.

In Myanmar, local people are used for stomachache, cancer, and urinary tract infection. Chemical components of this plant have been discovered as chalcones, flavonoids, glycosides, anthraquinones, triterpenoids, fatty acids, coumarino lignoids, and phenolic compounds [4–12].

Croton oblongifolius is a medium-size tree and is widely distributed throughout Asia and Myanmar. In folk medicine, this plant is useful for dysmenorrhea, purgative, dyspepsia, and dysentery. In Myanmar, it is used to treat diarrhea (seeds) and liver disorders (barks). Phytochemical studies of *C. oblongifolius* have been reported in several different types of research and many clerodane diterpenes, cembranoid diterpenes, halimane-type diterpenoids, labdane diterpenoids, furanocembranoids, and megastigmane glycosides have been isolated from the stem barks, leaves, and roots [5–21].

Tinospora cordifolia is a huge evergreen and annual climbing plant distributed throughout the world. The plant is used to treat skin diseases, allergic conditions, jaundice, urinary disorders, anaemia, rheumatism, inflammation, and diabetes in both traditional and homeopathic medicine. In Myanmar, this plant is used for diabetes and hypertension. An important phytoconstituents reported from this plant were clerodane furano diterpene glucosides, phenylpropene disaccharides, phenylpropanoids, clerodane diterpenoid, steroids, terpenoids, and alkaloids [22–31].

Melastoma malabathricum is an evergreen shrub that belongs to the family Melastomataceae. In Malaysia, India, and Indonesia, this plant has traditionally been used to treat a variety of symptoms and disorders. In Myanmar, this plant is used to treat various kinds of cancer, toothache, diabetes, asthma, and lung disorders. Chemical constituents reported from *M. malabathricum* were flavonoids, triterpenes, alkaloids, steroids, lipids, phenolic compounds, and tannins [32–37].

Dioscorea bulbifera is a perennial vine widely distributed throughout tropical and temperate areas. It is commonly known as air potato. This herb is used in the treatment of leprosy and cancer by triple people in Bangladesh. In China, this herb is utilized for cancer and thyroid diseases. In Myanmar, this plant is used for various cancer diseases such as breast cancer, cervix cancer, etc. Phytochemical studies revealed the presence of alkaloids, anthraquinones, norclerodane diterpenoids, clerodane diterpenoids, flavonoids, phenolic compounds, steroidal saponins, steroidal sapogenins, and glycosides [38–49].

Our main focus for this chapter is secondary metabolites derived from the plant's kingdom, i.e., *C. odorata*, *C. oblongifolius*, *Tinospora cordifolia*, *M. malabathricum*, and *D. bulbifera*, and cytotoxic compounds obtained from them (**Table 1**).

Plants name	Family	Local name	Traditional/local uses
<i>Chromolaena odorata</i>	Asteraceae	Bhi-sub	stomachache, cancer, and urinary tract infection
<i>Croton oblongifolius</i>	Euphorbiaceae	Thet-yin-gyi	diarrhea and liver disorders
<i>Tinospora cordifolia</i>	Menispermaceae	Sin-don-ma-nwe	diabetes and hypertension
<i>Melastoma malabathricum</i>	Melastomaceae	Say-aoe-bote	various kinds of cancer, toothache, diabetes, asthma, and lung disorders
<i>Dioscorea bulbifera</i>	Dioscoreaceae	Myauk-U	breast cancer and cervix cancer

Table 1.
Myanmar medicinal plants and their traditional (or) local uses.

2. Secondary metabolites

Secondary metabolites can be found in abundance in plants. They are the focus of several research since they have a wide range of biological actions. Scientific reports have demonstrated the medicinal value of various parts of plant species (*C. odorata*, *C. oblongifolius*, *T. cordifolia*, *M. malabathricum*, and *D. bulbifera*) against a wide range of human ailments. Only the cytotoxicity of various secondary metabolites from different plant species will be discussed in this study.

3. Cytotoxic activity of asteraceae

In 2013, Kouamé and his coworkers isolated 5-hydroxy-7,4'-dimethoxyflavanone, 2'-hydroxy-4,4',5',6'-tetramethoxychalcone, and cadalene from the hexane soluble

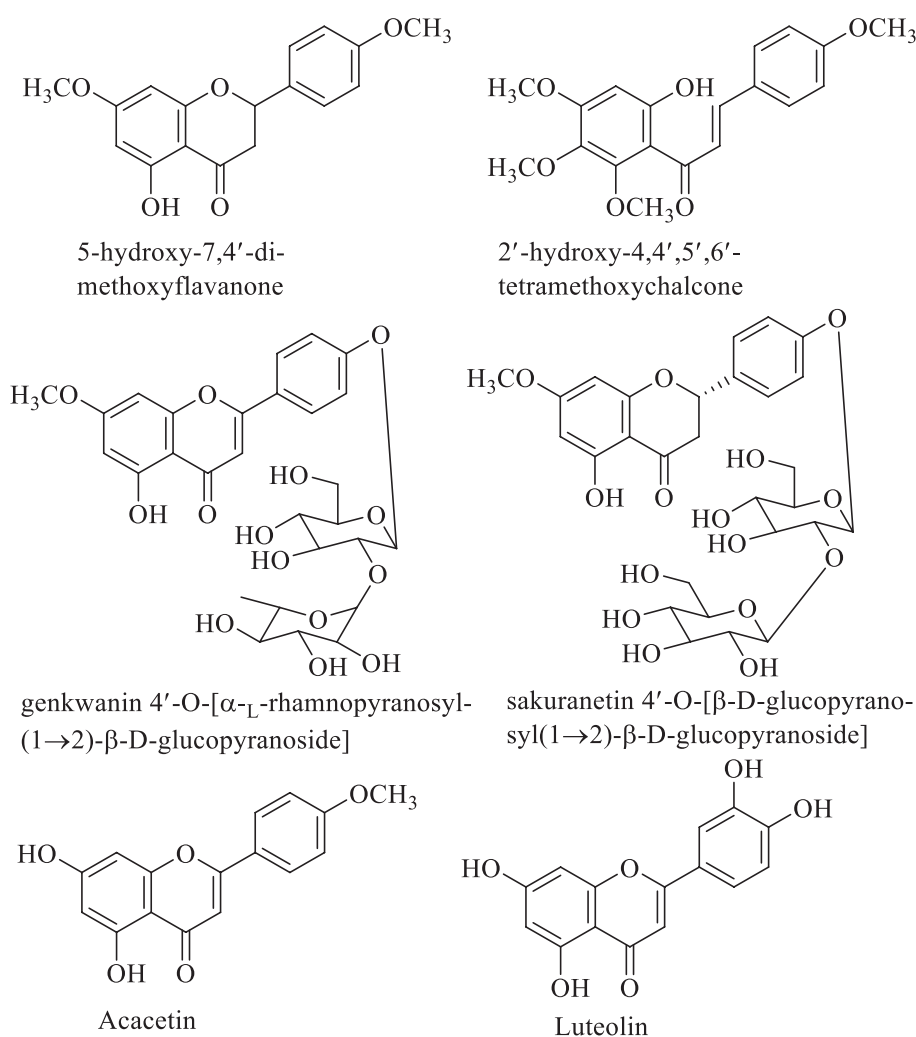


Figure 1.
Cytotoxic compounds from *Chromolaena odorata*.

fraction of *C. odorata*. These were screened for their cytotoxicity and anticancer properties. A chalcone, 2'-hydroxy-4,4',5',6'-tetramethoxychalcone has both cytotoxic and antitumorigenic actions against a wide range of cell lines (Cal51, MCF7, and MDAMB-468). Also, it enhances apoptosis in Cal51 breast cancer cells when combined with the Bcl2 inhibitor ABT737 [50]. Another research group reported that genkwanin 4'-O-[α -L-rhamnopyranosyl(1 $\rightarrow$ 2)- β -D-glucopyranoside] has cytotoxic effects on LLC (IC₅₀: 28.2 μ M) and HL-60 (IC₅₀: 11.6 μ M) cancer cell line. Similarly, sakuranetin 4'-O-[β -D-glucopyranosyl(1 $\rightarrow$ 2)- β -D-glucopyranoside] displayed potential cytotoxic activity in HL-60 (IC₅₀: 10.8 μ M) cancer cell line [11]. Likewise, Suksamrarn and colleagues document that acacetin (IC₅₀: 24.6 μ M) and luteolin (IC₅₀: 19.2 μ M) possessed moderate cytotoxic activity in human small cell lung cancer cells (NCI-H187). Luteolin (IC₅₀: 38.4 μ M) showed weak activity on human breast cancer cells (BC) [51]. A recent study proved that the EtOH leaves extract from *C. odorata* has anticancer and antiproliferative activity [52]. Another finding reported that EtOAc soluble fraction from EtOH leaves extract from *C. odorata* had cytotoxic and antiproliferative actions on HeLa cells [53]. In other reports, both the aqueous and EtOH extract of *C. odorata* demonstrated cytotoxic effects, with LC₅₀ values of 324 and 392 μ g/mL, respectively [54]. The chemical structures of some cytotoxic compounds are shown in **Figure 1**.

4. Cytotoxic activity of euphorbiaceae

Numerous investigations indicated that the *C. oblongifolius* shows cytotoxic properties. Neocrotocembranol obtained from the stem bark of *C. oblongifolius* displayed cytotoxic activity toward P-388 cells with an IC₅₀ value of 6.48 μ g/mL [13]. *C. oblongifolius* contain methyl 15,16-epoxy-3,13(16),14-ent-clerodatrien-18,19-olide-17-carboxylate, dimethyl 15,16-epoxy-12-oxo-3,13(16),14-ent-clerodatrien-17,18-dicarboxylate, nasimaluns A and B, levatin, (–)-hardwickiic acid, 15-hydroxy-cis-ent-cleroda-3,13(E)-diene, and patchoulone. These diterpenoids exhibited mild cytotoxic activity against HUCCA-1 (human cholangiocarcinoma cancer cells), KB (human epidermoid carcinoma of the mouth), HeLa (cervical adenocarcinoma cells), MDA-MB231 (human breast cells), and T47D (human mammary adenocarcinoma cells) cell lines with the IC₅₀ values ranging from 10 to 50 μ g/mL [14]. Additionally, the in vitro cytotoxic activity of 2,3-dihydroxy-labda-8(17),12(E),14-triene has been demonstrated non-specific moderate activities in KATO-3 (IC₅₀ value 2.2 μ g/mL), SW620 (IC₅₀ value 2.7 μ g/mL), BT474 (IC₅₀ value 4.6 μ g/mL), HEP-G2 (IC₅₀ value 3.7 μ g/mL), and CHAGO (IC₅₀ value 3.3 μ g/mL) [15]. Moreover, crotohalimaneic acid, crotohalimonetic acid, and 12-benzouloxy crotohalimaneic acid from *C. oblongifolius* were examined for their cytotoxic activity against human breast ductal carcinoma (BT474), lung carcinoma (CHAGO), human liver hepatoblastoma (HEP-G2), human gastric carcinoma (KATO-3), and human colon adenocarcinoma (SW620). The latter compound was inactive and the remaining two compounds displayed non-specific strong cytotoxic activity, and the IC₅₀ values for crotohalimaneic acid were 7.5, 0.1, 0.2, 0.4, 0.2, and for crotohalimonetic acid were 0.1, 0.1, 5.2, 8.2, 0.1 μ g/mL, respectively [17]. In another study, novel furanocembranoids, found from the stem bark of *C. oblongifolius*, have been shown broad cytotoxic effects on BT474, CHAGO, Hep-G2, KATO-3, and SW-620 [18]. Besides, croblongifolin obtained from *C. oblongifolius* was reported to have high cytotoxic activities against human hepatocarcinoma (HEP-G2) (IC₅₀ 0.35 μ M), breast carcinoma (BT474) (IC₅₀ 0.12 μ M), colon carcinoma (SW620) (IC₅₀ 0.47 μ M), lung carcinoma (CHAGO) (IC₅₀ 0.24 μ M), and gastric carcinoma (KATO 3)

(IC₅₀ 0.35 μ M) [19]. In a cytotoxic study by Sommit et al., natural labdanes (labda-7,12(E),14-triene-17-al and 17-hydroxylabda-7,12(E)14-triene) and their modified derivatives (15-hydroxylabda-7,13(E)diene-17,12-olide, labda-7,13(E)-diene-17,12-olide, 12,17-dihydroxylabda-7,13(E)-diene) were found to have non-specific moderate cytotoxicity against BT474, CHAGO, HEP-G2, KATO-3, and SW620 [20]. The ethyl acetate extract of *C. oblongifolius* was found to be cytotoxic toward the A549 lung cancer cell line [55]. In 2020, Poofery et al. studied the cytotoxic activity of ethyl acetate extract from *Bridelia ovata* and *Croton oblongifolius*. They reported that both extracts possessed anticancer properties in breast cancer cells and induce apoptosis in these cells

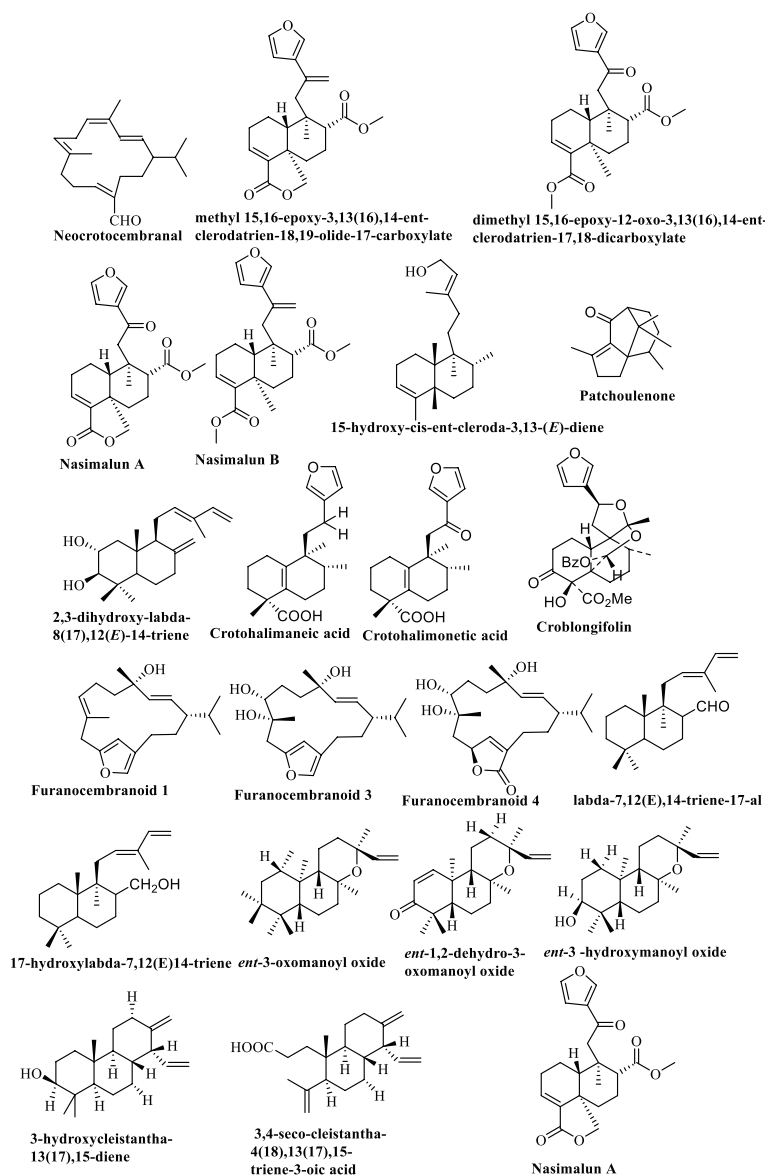


Figure 2.
Cytotoxic compounds from *Croton oblongifolius*.

via a mitochondrial pathway and oxidative stress [56]. In addition, Chaichantipyuth and coworkers isolated eight new labdane-type diterpenoids and a clerodane from the stem bark of *C. oblongifolius*. They examined the cytotoxic capability of specific compounds and semisynthesis products against human tumor cell lines (KATO-3, BT474, CHAGO, HEPG-2, and SW620) in vitro MTT assay. Among which isolates, ent-3-oxomanoyl oxide, ent-1,2-dehydro-3-oxomanoyl oxide, ent-3 α -hydroxymanoyl oxide, nidorellol, and ent-6 α ,7 β ,8 α , -trihydroxylabda-13(16),14-diene showed strong cytotoxic activity (<1 $\mu\text{g/mL}$) against KATO-3, moderated activity against BT474, and undifferentiated against CHAGO, HEPG-2, and SW620. Similarly, hardwickiic acid had a substantial effect (<1 $\mu\text{g/mL}$) on BT474, while semisynthesis products (ent-3 β -hydroxymanoyl oxide and ent-3 β -hydroxy-1,2-dehydromanoyl oxide) had a modest effect in all cell lines. The remaining isolates were inert [57]. The authors found, two new cleistanthane-type diterpenoids, 3-hydroxycleistantha-13(17),15-diene and 3,4-seco-cleistantha-4(18),13(17),15-triene-3-oic acid, have cytotoxic activity against various human tumor cell lines. Both were isolated from the stem bark of *C. oblongifolius*. 3-hydroxycleistantha-13(17),15-diene showed nonspecific strong cytotoxic activity (KATO-3; IC₅₀ value 6.0 $\mu\text{g/mL}$, BT474; IC₅₀ value 6.1 $\mu\text{g/mL}$, HEP-G2; IC₅₀ value 0.5 $\mu\text{g/mL}$, CHAGO; IC₅₀ value 5.5 $\mu\text{g/mL}$) and 3,4-seco-cleistantha-4(18),13(17),15-triene-3-oic acid showed weak activity (KATO-3; IC₅₀ value 9.6 $\mu\text{g/mL}$, BT474; IC₅₀ value 10 $\mu\text{g/mL}$, HEP-G2; IC₅₀ value 8.6 $\mu\text{g/mL}$) [58]. In another study, Nasimalun A has a cytotoxic effect on the MOLT-3 cell line with an IC₅₀ value of 26.44 $\mu\text{g/mL}$ [59]. The chemical structures of some cytotoxic compounds are shown in **Figure 2**.

5. Cytotoxic activity of menispermaceae

In 2010, Uddin and his coworkers tested the cytotoxicity of various fractions (pet ether, CCl₄, CHCl₃, and aqueous soluble fraction) of *T. cordifolia* methanolic crude extract by brine shrimp lethality bioassay. They recorded that CCl₄ and CHCl₃ soluble fractions showed highly cytotoxic in *Artemia salina* with LC₅₀ values of 0.402 and 0.691 $\mu\text{g/mL}$ [60]. Likewise, in 2021, Modi and coworkers documented that ethanol stem and leaves extract of *T. cordifolia* had a cytotoxic effect in *A. salina* with LC₅₀ values of 462.38 and 676.08 $\mu\text{g/mL}$ [61]. Furthermore, Jagetia and Rao studied the cytotoxic effects of DCM extract of *T. cordifolia* on cultured HeLa cells. They suggested that the cytotoxic effect on DCM extract of *T. cordifolia* may be due to lipid peroxidation and release of lactate dehydrogenase (LDH) and decline in glutathione-S-transferase (GST) [62]. In another study, the cytotoxic activity of aqueous and hexane extract of *T. cordifolia* was evaluated against six cancer lines, including prostate (PC-3), colon (Colo-205), HCT-116), lung (A-549, NCI-H322), and breast cancer (T47D). Results showed that aqueous extract has potent cytotoxic activity (67–99%) in prostate, lung, and colon cancer lines [63]. Also, the in vitro cytotoxic activity of methanolic stem extract from *T. cordifolia* against human breast cancer cell line MDA-MB-231 and normal Vero epithelial cell line. It was revealed that methanolic stem extract displayed cytotoxic activity toward human breast cancer cells with an IC₅₀ value of $59 \pm 4.05 \mu\text{g/mL}$ [64]. In addition to the anti-proliferative activity, various fractions (ethanol, pet ether, DCM, butanol, and aqueous) from *T. cordifolia* were evaluated against cervical carcinoma (HeLa) cell lines by MTT and SRB methods. It was noted that both DCM (MTT; IC₅₀: $54.23 \pm 0.94 \mu\text{g/mL}$, and SRB; $48.91 \pm 0.33 \mu\text{g/mL}$) and ethanol extract (MTT; IC₅₀: $101.26 \pm 1.42 \mu\text{g/mL}$, and SRB; $87.93 \pm 0.85 \mu\text{g/mL}$) displayed significant cytotoxic effect in HeLa cell with their respective assay [65]. Moreover, Bala and his coworkers

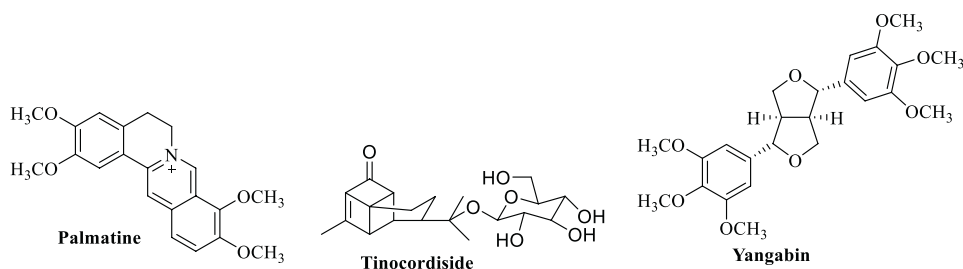


Figure 3.
 Cytotoxic compounds from *Tinospora cordifolia*.

also reported the anti-cancer and immunomodulatory activities of different extracts, fractions, and isolated compounds from the stem of *T. cordifolia*. They were screened against four different human cancer cell lines, KB (human oral squamous carcinoma), CHOK-1 (hamster ovary), HT-29 (human colon cancer), SiHa (human cervical cancer), and murine primary cells. All extracts and fractions showed promising activity against KB and CHOK-1 cells while the isolated palmatine (KB; IC₅₀: 46.1 µM, HT-29; IC₅₀: 49.1 µM), tinocordiside (KB; IC₅₀: 45.5 µM, CHOK-1; IC₅₀: 44.9 µM), and yangambin (KB; IC₅₀: 43.8 µM) also showed promising activity with their respective cell lines [25]. The chemical structures of some cytotoxic compounds are shown in **Figure 3**.

6. Cytotoxic activity of Melastomaceae

The cytotoxic effect of the ethyl acetate fraction from *Melastoma malabathricum* in human breast and lung cancer cell lines (MCF-7 and A549) was studied by using an MTT assay. Results showed that MCF-7 and A549 cells undergo secondary necrosis 24 hours post-treatment with *M. malabathricum* extract [66]. Another observation showed that after 72 h of treatment, the *M. malabathricum* leaves extract exhibited important anticancer activity in the MCF-7 (IC₅₀: 7.14 µg/mL) cell line, although the methanol and chloroform extract from the flowers had modest activities in MCF-7 (IC₅₀: 33.63 µg/mL and 45.76 µg/mL) cell line [67]. In addition, Zakaria et al. studied the in vitro antiproliferative activity of various extracts (aqueous, chloroform, and methanol extracts) from *M. malabathricum*. The aqueous extract was found to be potent inhibitor of Caov-3 (IC₅₀: 58 µg/mL), HL-60 (IC₅₀: 58 µg/mL) cell lines, whereas CHCl₃ extract showed antiproliferative activity toward Caov-3 (IC₅₀: 34 µg/mL), HL-60 (IC₅₀: 96 µg/mL), and CEM-SS (IC₅₀: 22 µg/mL) cell lines. The methanol extract established antiproliferative activity in more cell lines, such as MCF-7 (IC₅₀: 87 µg/mL), HeLa (IC₅₀: 88 µg/mL), Caov-3 (IC₅₀: 41 µg/mL), HL-60 (IC₅₀: 13 µg/mL), CEM-SS (IC₅₀: 30 µg/mL), and MDA-MB-231 (IC₅₀: 59 µg/mL) cancer cell lines [68]. In 2019, Isnaini et al. studied the quercetin and kaempferol level in *M. malabathricum* ethanolic fruit extract. The analysis was done by HPLC MS/MS. In comparison to kaempferol (43.52 µg/g), quercetin (67.78 µg/g) had a greater concentration in the test sample. They also compared the extract to quercetin in terms of antioxidant and cytotoxic properties. The authors concluded that the extract exhibits antioxidant (IC₅₀: 16.82 ± 0.24 ppm) and cytotoxic properties (LC₅₀: 313.44 ppm) which may be attributed to the presence of quercetin [69]. The compounds such as flavonoids, naringenin, and kaempferol-3-O-(2'',6''-di-O-*p*-trans-coumaroyl)glucoside, isolated from the flower of *M. malabathricum*, have been proved to be the potent inhibitor of MCF7 with IC₅₀ values of 0.28 µM and 1.3 µM [70].

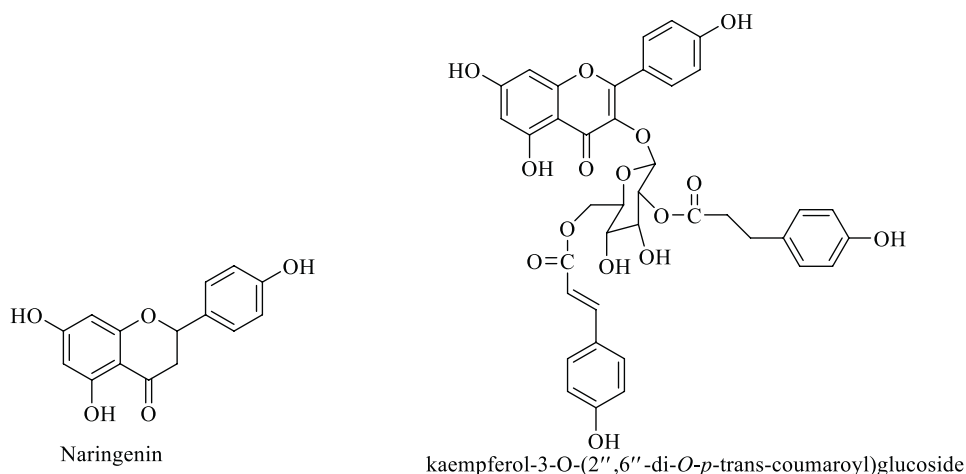


Figure 4.
Cytotoxic compounds from *Melastoma malabathricum*.

In another cytotoxic study by Hamid et al., the *M. malabathricum* leaves extract showed inhibitory effects on the MDA-MB-231 cell line after 48 and 72 h treatments [71]. The chemical structures of some cytotoxic compounds are shown in **Figure 4**.

7. Cytotoxic activity of dioscoreaceae

Several studies have been performed to examine the cytotoxic activity of constituents in *Dioscorea bulbifera*. Many studies have observed cytotoxic compounds, largely found as steroidal saponins. Isolated pennogenin-3-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 3)-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]- β -D-glucopyranoside and penogenin-3-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]- β -D-glucopyranoside demonstrated cytotoxic activity in two human hepatocellular carcinoma cell lines (Bel-7402; 99.1% and 92.6% inhibition, SMMC7721; IC₅₀ value 4.54 μ M and 4.85 μ M) [47]. Diosgenin-3-O-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 3)]- β -D-glucopyranoside and diosgenin-3-O-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)]- β -D-glucopyranoside were obtained from the rhizomes of *D. bulbifera* and displayed moderate cytotoxic activities against two human hepatocellular carcinoma cell lines (Bel-7402; IC₅₀ values 10.87 and 19.10 μ M, and SMMC7721; IC₅₀ values 3.89 and 7.47 μ M) [48]. In another study, spiroconazole A, penogenin-3-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]- β -D-glucopyranoside, and 26-O- β -D-glucopyranosyl-(25R)-5-en-furost-3 β ,17 α ,22 α ,26-tetraol-3-O- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)- α -L-rhamnopyranosyl-(1 $\rightarrow$ 4)-[α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)]- β -D-glucopyranoside were reported to have moderate activity against human urinary bladder carcinoma cell (ECV-304) [72]. In 2018, Wang and colleagues evaluated the cytotoxic activity of three new norclerodane diterpenoids (diosbulbin E acetate, diosbulbin R, and diosbulbin S) in the SMMC-7721 cancer cell line. These compounds were isolated from the ethanol extract of *D. bulbifera*. Interestingly, the isolates showed no inhibitory effects on SMMC-7721 (IC₅₀ > 40 μ M) [73]. Chloroform and methanol soluble fractions from *D. bulbifera* were

tested for their cytotoxic activity in T47D breast cancer cells by Rinto Muhammad Nur and Laurentius Hartanto Nugroho. The results revealed that the chloroform fraction displayed the highest activity with an IC_{50} value of $115.63 \pm 86.01 \mu\text{g/mL}$. They also screened the combined leaf chloroform fractions and the data showed that fractions F-5 (IC_{50} : $14.55 \pm 8.62 \mu\text{g/mL}$) and F-6 (IC_{50} : $14.55 \pm 8.62 \mu\text{g/mL}$) were found to be the most toxic fractions. Nevertheless, both fractions (F-5 and F-6) were very weak when compared with the cancer drug, Doxorubicin (IC_{50} : $0.04 \pm 0.02 \mu\text{g/mL}$) [74]. Mainasara et al. reported that *D. bulbifera* has cytotoxic effects on MAD-MB-231 and MCF-7 breast cancer cell lines. The IC_{50} values for MAD-MB-231 were found to be 41.17, 15.71, and 11.53 $\mu\text{g/mL}$, at 24, 48, and 72 h of

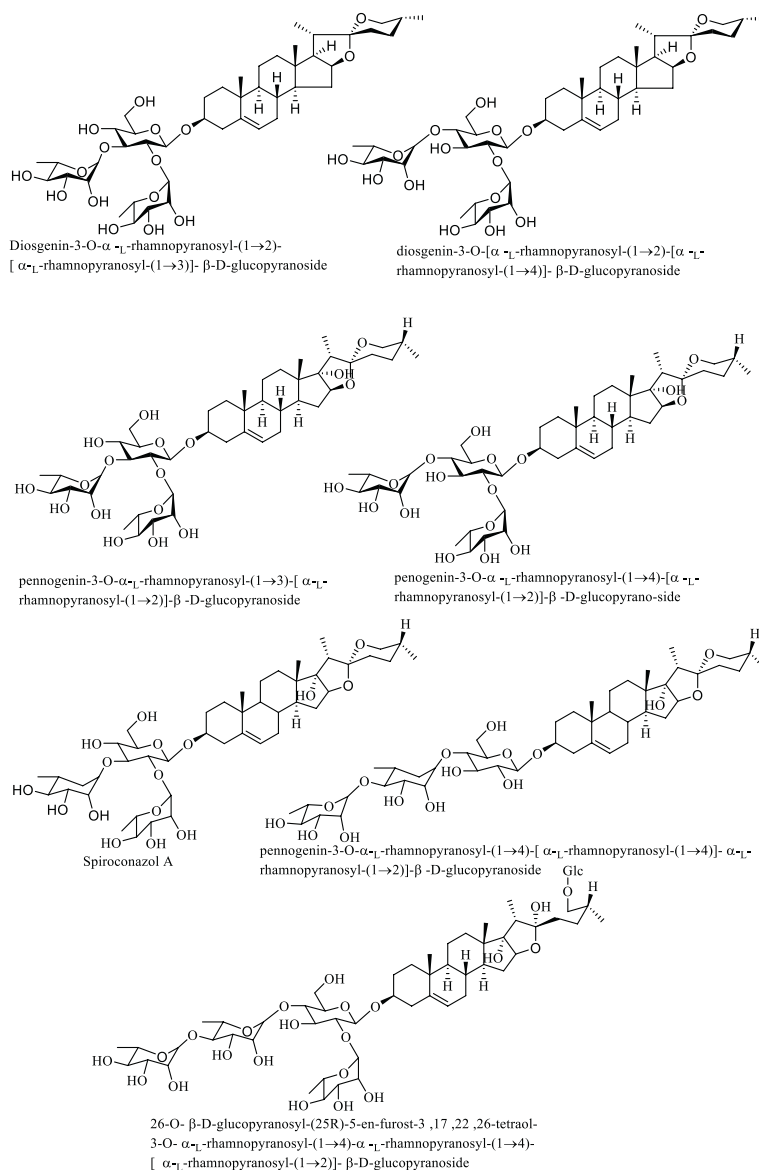


Figure 5.
Cytotoxic compounds from *Dioscorea bulbifera*.

incubation time. For MCF-7 cell lines, the IC_{50} values were 4.29, 1.86, and 1.23 $\mu\text{g/mL}$, respectively, after 24, 48, and 72 h of incubation time. They also studied cycle analysis and apoptosis by using flow cytometry analysis. It was found that *D. bulbifera* induced apoptosis at various phases, with a considerable drop in viable cells after 24 h and significant improvements after 48 and 72 h of treatment [75]. Wang et al. observed the antitumor activity of various extracts and compound diosbulbin B from *D. bulbifera* in mice model [76]. In another study, two new phenolic derivatives (diosbulbiol A and diosbulbiol B) from the tubers of *D. bulbifera* were tested for their cytotoxic activity against SMMC7721, MCF-7, K562 and A549 cancer cell lines. Interestingly, these two compounds showed no inhibitory effect on all selected cell lines ($IC_{50} > 40 \mu\text{M}$) [77]. The chemical structures of some cytotoxic compounds are shown in Figure 5.

8. Conclusions

Several investigations have been conducted on the bioactivities of Myanmar medicinal herbs. Novel anticancer medicines and lead compounds are still abundant in higher plants. The key benefits of anticancer natural compounds are their low toxicity, low cost, and wide range of modes of action. In this chapter, we examined and studied the potential of Myanmar medicinal plants as a source of cytotoxic compounds. Although several of these plants' metabolites exhibited potential bioactivities, some of them were determined to be inert or to have weak activities in present investigations. This chapter will surely assist academics and practitioners working with these specific plant species in determining the best application for them. Because the majority of cytotoxic effects are evaluated in vitro, their therapeutic advantages may not be adequately demonstrated. Animal models and human trials should be used in a future study to assess how effective they are at providing a platform for enhancing anticancer therapeutic approaches.

Acknowledgements

The authors are grateful to: (1) Daw Ni Ni Aung at the Department of Botany, Lashio University for her valuable support, and (2) Universitas Airlangga for the funding support.

Conflict of interest

The authors declare no conflict of interest.

Author details

Khun Nay Win Tun^{1,2}, Nanik Siti Aminah^{1,3*}, Alfinda Novi Kristanti^{1,3},
Hnin Thanda Aung⁴ and Yoshiaki Takaya⁵

1 Faculty of Science and Technology, Department of Chemistry, Universitas Airlangga, Komplek Kampus C UNAIR, Jl. Mulyorejo, Surabaya, Indonesia

2 Department of Chemistry, Patheingyi University, Patheingyi, Myanmar

3 Biotechnology of Tropical Medicinal Plants Research Group, Universitas Airlangga, Indonesia

4 Department of Chemistry, Mandalay University, Mandalay, Myanmar

5 Faculty of Pharmacy, Meijo University, Nagoya, Japan

*Address all correspondence to: nanik-s-a@fst.unair.ac.id

IntechOpen

© 2022 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Khazir J, Riley DL, Pilcher LA, De-Maayer P, Mir BA. Anticancer agents from diverse natural sources. *Natural Product Communications*. 2014;**9**(11):1655-1669
- [2] Wang H, Khor TO, Shu L, Su ZY, Fuentes F, Lee JH, et al. Plants vs. cancer: A review on natural phytochemicals in preventing and treating cancers and their druggability. *Anti-Cancer Agents in Medicinal Chemistry*. 2012;**12**(10):1281-1305. DOI: 10.2174/187152012803833026
- [3] Lee JJ, Saiful Yazan L, Kassim NK, Che Abdullah CA, Esa N, Lim PC, et al. Cytotoxic activity of *Christia vespertilionis* root and leaf extracts and fractions against breast cancer cell lines. *Molecules*. 2020;**25**(11):2610. DOI: 10.3390/molecules25112610
- [4] Vijayaraghavan K, Rajkumar J, Bukhari SN, Al-Sayed B, Seyed MA. *Chromolaena odorata*: A neglected weed with a wide spectrum of pharmacological activities (Review). *Molecular Medicine Reports*. 2017;**15**(3):1007-1016. DOI: 10.3892/mmr.2017.6133
- [5] Pel P, Chae HS, Nhoek P, Kim YM, Khiev P, Kim GJ, et al. A stilbene dimer and flavonoids from the aerial parts of *Chromolaena odorata* with proprotein convertase subtilisin/kexin type 9 expression inhibitory activity. *Bioorganic Chemistry*. 2020;**99**:103869. DOI: 10.1016/j.bioorg.2020.103869
- [6] Omokhua-Uyi AG, Abdalla MA, Leonard CM, Aro A, Uyi OO, Van Staden J, et al. Flavonoids isolated from the South African weed *Chromolaena odorata* (Asteraceae) have pharmacological activity against uropathogens. *BMC Complementary Medicine and Therapies*. 2020;**20**(1):233. DOI: 10.1186/s12906-020-03024-0
- [7] Zhang ML, Irwin D, Li XN, Sauriol F, Shi XW, Wang YF, et al. PPAR γ agonist from *Chromolaena odorata*. *Journal of Natural Products*. 2012;**75**(12):2076-2081. DOI: 10.1021/np300386d
- [8] Putri DA, Fatmawati S. A New Flavanone as a Potent Antioxidant Isolated from *Chromolaena odorata* L. Leaves. *Evidence-Based Complementary and Alternative Medicine*. 2019;**2019**:1453612. DOI: 10.1155/2019/1453612
- [9] Pisutthanan N, Liawruangrath B, Liawruangrath S, Bremner JB. A new flavonoid from *Chromolaena odorata*. *Natural Product Research*. 2006;**20**(13):1192-1198. DOI: 10.1080/14786410600899050
- [10] Emani L, Ravada S, Meka B, Garaga M, Golakoti T. A New Flavanone from the Leaves of *Chromolaena odorata*. *Natural Product Communications*. 2015;**10**(9):1555-1559
- [11] Hung TM, Cuong TD, Dang NH, Zhu S, Long PQ, Komatsu K, et al. Flavonoid glycosides from *Chromolaena odorata* leaves and their in vitro cytotoxic activity. *Chem Pharm Bull (Tokyo)*. 2011;**59**(1):129-131. DOI: 10.1248/cpb.59.129
- [12] Dhar R, Kimseng R, Chokchaisiri R, Hiransai P, Utaipan T, Suksamrarn A, et al. 2',4-Dihydroxy-3',4',6'-trimethoxychalcone from *Chromolaena odorata* possesses anti-inflammatory effects via inhibition of NF- κ B and p38 MAPK in lipopolysaccharide-activated RAW 264.7 macrophages. *Immunopharmacology*

and Immunotoxicology. 2018;**40**(1):43-51. DOI: 10.1080/08923973.2017.1405437

[13] Roengsumran S, Singtothong P, Pudhom K, Ngamrochanavanich N, Petsom A, Chaichantipyuth C. Neocrotocembranols from *Croton oblongifolius*. Journal of Natural Products. 1999;**62**(8):1163-1164. DOI: 10.1021/np9900268

[14] Youngsa-ad W, Ngamrojanavanich N, Mahidol C, Ruchirawat S, Prawat H, Kittakoop P. Diterpenoids from the roots of *Croton oblongifolius*. Planta Medica. 2007;**73**(14):1491-1494. DOI: 10.1055/s-2007-990247

[15] Roengsumran S, Petsom A, Kuptiyanuwat N, Vilaivan T, Ngamrojanavanich N, Chaichantipyuth C, et al. Cytotoxic labdane diterpenoids from *Croton oblongifolius*. Phytochemistry. 2001;**56**(1):103-107. DOI: 10.1016/s0031-9422(00)00358-7

[16] Takeshige Y, Kawakami S, Matsunami K, Otsuka H, Lhieochaiphant D, Lhieochaiphant S. Oblongionosides A-F, megastigmane glycosides from the leaves of *Croton oblongifolius* Roxburgh. Phytochemistry. 2012;**80**:132-136. DOI: 10.1016/j.phytochem.2012.05.011

[17] Roengsumran S, Pornpakakul S, Muangsins N, Sangvanich P, Nhujak T, Singtothong P, et al. New halimane diterpenoids from *Croton oblongifolius*. Planta Medica. 2004;**70**(1):87-89. DOI: 10.1055/s-2004-815466

[18] Pudhom K, Vilaivan T, Ngamrojanavanich N, Dechangvipart S, Sommit D, Petsom A, et al. Furanocembranols from the stem bark of *Croton oblongifolius*. Journal of Natural Products. 2007;**70**(4):659-661. DOI: 10.1021/np060520t

[19] Roengsumran S, Musikul K, Petsom A, Vilaivan T, Sangvanich P, Pornpakakul S, et al. Croblongifolin, a new anticancer clerodane from *Croton oblongifolius*. Planta Medica. 2002;**68**(3):274-277. DOI: 10.1055/s-2002-23138

[20] Sommit D, Petsom A, Ishikawa T, Roengsumran S. Cytotoxic activity of natural labdanes and their semi-synthetic modified derivatives from *Croton oblongifolius*. Planta Medica. 2003;**69**(2):167-170. DOI: 10.1055/s-2003-37708

[21] Roengsumran S, Achayindee S, Petsom A, Pudhom K, Singtothong P, Surachetapan C, et al. Two new cembranoids from *Croton oblongifolius*. Journal of Natural Products. 1998;**61**(5):652-654. DOI: 10.1021/np9704765

[22] Singh D, Chaudhuri PK. Chemistry and Pharmacology of *Tinospora cordifolia*. Natural Product Communications. 2017;**12**(2):299-308

[23] Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S. Immunomodulatory active compounds from *Tinospora cordifolia*. Journal of Ethnopharmacology. 2012;**141**(3):918-926. DOI: 10.1016/j.jep.2012.03.027

[24] Singh B, Sharma P, Kumar A, Chadha P, Kaur R, Kaur A. Antioxidant and in vivo genoprotective effects of phenolic compounds identified from an endophytic *Cladosporium velox* and their relationship with its host plant *Tinospora cordifolia*. Journal of Ethnopharmacology. 2016;**194**:450-456. DOI: 10.1016/j.jep.2016.10.018

[25] Bala M, Pratap K, Verma PK, Singh B, Padwad Y. Validation of ethnomedicinal potential of *Tinospora cordifolia* for anticancer and immunomodulatory

- activities and quantification of bioactive molecules by HPTLC. *Journal of Ethnopharmacology*. 2015;**175**:131-137. DOI: 10.1016/j.jep.2015.08.001
- [26] Sivasubramanian A, Gadepalli Narasimha KK, Rathnasamy R, Campos AM. A new antifeedant clerodane diterpenoid from *Tinospora cordifolia*. *Natural Product Research*. 2013;**27**(16):1431-1436. DOI: 10.1080/14786419.2012.722088
- [27] Pan L, Terrazas C, Lezama-Davila CM, Rege N, Gallucci JC, Satoskar AR, et al. Cordifolide A, a sulfur-containing clerodane diterpene glycoside from *Tinospora cordifolia*. *Organic Letters*. 2012;**14**(8):2118-2121. DOI: 10.1021/ol300657h
- [28] Maurya R, Manhas LR, Gupta P, Mishra PK, Singh G, Yadav PP. Amritosides A, B, C and D: clerodane furano diterpene glucosides from *Tinospora cordifolia*. *Phytochemistry*. 2004;**65**(14):2051-2055. DOI: 10.1016/j.phytochem.2004.05.017
- [29] Phan VK, Chau VM, Nguyen TD, La VK, Dan TH, Nguyen HN, et al. Aporphine alkaloids, clerodane diterpenes, and other constituents from *Tinospora cordifolia*. *Fitoterapia*. 2010;**81**(6):485-489. DOI: 10.1016/j.fitote.2010.01.005
- [30] Ahmad F, Ali M, Alam P. New phytoconstituents from the stem bark of *Tinospora cordifolia* Miers. *Natural Product Research*. 2010;**24**(10):926-934. DOI: 10.1080/14786410802435679
- [31] Patel MB, Mishra S. Isoquinoline alkaloids from *Tinospora cordifolia* inhibit rat lens aldose reductase. *Phytotherapy Research*. 2012;**26**(9):1342-1347. DOI: 10.1002/ptr.3721
- [32] Sirat HM, Susanti D, Ahmad F, Takayama H, Kitajima M. Amides, triterpene and flavonoids from the leaves of *Melastoma malabathricum* L. *Journal of Natural Medicines*. 2010;**64**(4):492-495. DOI: 10.1007/s11418-010-0431-8
- [33] Mazura MP, Susanti D, Rasadah MA. Anti-inflammatory action components from *Melastoma malabathricum*. *Pharmaceutical Biology*. 2007;**45**(5):372-375
- [34] Wong KC, Hag Ali DM, Boey PL. Chemical constituents and antibacterial activity of *Melastoma malabathricum* L. *Natural Product Research*. 2012;**26**(7):609-618. DOI: 10.1080/14786419.2010.538395
- [35] Yoshida TNF, Hosotani KNA, Okudat T. Dimeric hydrolysable tannins from *melastoma Malabathricum*. *Phytochemistry*. 1992;**31**(8):2829-2833. DOI: 10.1016/0031-9422(92)83641-b
- [36] Yoshida T, Nakata F, Hosotani K, Nitta A, Okuda T. Tannins and Related Polyphenols of *Melastomataceous* Plants. V. Three New Complex Tannins from *Melastoma malabathricum* L. *Chemical & Pharmaceutical Bulletin*. 1992;**40**(7):1727-1732. DOI: 10.1248/cpb.40.1727
- [37] Mayasari D, Murti YB, Pratiwi SUT, Sudarsono S, Hanna G, Hamann MT. TLC-Based Fingerprinting Analysis of the Geographical Variation of *Melastoma malabathricum* in Inland and Archipelago Regions: A Rapid and Easy-to-Use Tool for Field Metabolomics Studies. *Journal of Natural Products*. 2022;**85**(1):292-300. DOI: 10.1021/acs.jnatprod.1c00622
- [38] Li H, Peng Y, Zheng J. *Dioscorea bulbifera* L.-induced hepatotoxicity and involvement of metabolic activation of furanoterpenoids. *Drug Metabolism Reviews*. 2020;**52**(4):568-584. DOI: 10.1080/03602532.2020.1800724

- [39] Ngan NTT, Hoang NH, Truong VV, Hien NT, Lan NN, Tung NV, et al. Anti-inflammatory norclerodane diterpenoids and tetrahydrophenanthrene from the leaves and stems of *Dioscorea bulbifera*. *Fitoterapia*. 2021;**153**:104965. DOI: 10.1016/j.fitote.2021.104965
- [40] Chaniad P, Tewtrakul S, Sudsai T, Langyanai S, Kaewdana K. Anti-inflammatory, wound healing and antioxidant potential of compounds from *Dioscorea bulbifera* L. *bulbils*. *PLoS One*. 2020;**15**(12):e0243632. DOI: 10.1371/journal.pone.0243632
- [41] Liu JS, Gao WN, Zheng J, Wang GK, Yang QS. Chemical constituents from fresh tubers of *Dioscorea bulbifera*. *Zhongguo Zhong Yao Za Zhi*. 2017;**42**(3):510-516. DOI: 10D540/j.cnki.cjcmm.2017.0009
- [42] Komori T. Glycosides from *Dioscorea bulbifera*. *Toxicon*. 1997;**35**(10):1531-1536. DOI: 10.1016/s0041-0101(97)00032-9
- [43] Chaniad P, Wattanapiromsakul C, Pianwanit S, Tewtrakul S. Anti-HIV-1 integrase compounds from *Dioscorea bulbifera* and molecular docking study. *Pharmaceutical Biology*. 2016;**54**(6):1077-1085. DOI: 10.3109/13880209.2015.1103272
- [44] Liu H, Tsim KW, Chou GX, Wang JM, Ji LL, Wang ZT. Phenolic compounds from the rhizomes of *Dioscorea bulbifera*. *Chemistry & Biodiversity*. 2011;**8**(11):2110-2116. DOI: 10.1002/cbdv.201000279
- [45] Kuete V, Betrandteponno R, Mbaveng AT, Tapondjou LA, Meyer JJ, Barboni L, et al. Antibacterial activities of the extracts, fractions and compounds from *Dioscorea bulbifera*. *BMC Complementary and Alternative Medicine*. 2012;**12**:228. DOI: 10.1186/1472-6882-12-228
- [46] Tang Y, Xue YB, Zhou L, Zhang JW, Yao GM, Luo ZW, et al. New norclerodane diterpenoids from the tubers of *Dioscorea bulbifera*. *Chem Pharm Bull (Tokyo)*. 2014;**62**(7):719-724. DOI: 10.1248/cpb.c14-00057
- [47] Liu H, Chou GX, Wu T, Guo YL, Wang SC, Wang CH, et al. Steroidal sapogenins and glycosides from the rhizomes of *Dioscorea bulbifera*. *Journal of Natural Products*. 2009;**72**(11):1964-1968. DOI: 10.1021/np900255h
- [48] Liu H, Chou GX, Wang JM, Ji LL, Wang ZT. Steroidal saponins from the rhizomes of *Dioscorea bulbifera* and their cytotoxic activity. *Planta Medica*. 2011;**77**(8):845-848. DOI: 10.1055/s-0030-1250633
- [49] Li SS, Iliya IA, Deng JZ, Zhao SX. Flavonoids and anthraquinone from *Dioscorea bulbifera* L. *Zhongguo Zhong Yao Za Zhi*. 2000;**25**(3):159-160
- [50] Kouamé PB, Jacques C, Bedi G, Silvestre V, Loquet D, Barillé-Nion S, et al. Phytochemicals isolated from leaves of *Chromolaena odorata*: impact on viability and clonogenicity of cancer cell lines. *Phytotherapy Research*. 2013;**27**(6):835-840. DOI: 10.1002/ptr.4787
- [51] Suksamrarn A, Chotipong A, Suavansri T, Boongird S, Timsuksai P, Vimuttipong S, et al. Antimycobacterial activity and cytotoxicity of flavonoids from the flowers of *Chromolaena odorata*. *Archives of Pharmacal Research*. 2004;**27**(5):507-511. DOI: 10.1007/BF02980123
- [52] Yusuf H, Kamarlis RK, Yusni Y, Fahrani M. The anticancer activity of ethanol extract of *Chromolaena odorata* leaves in 7,12-Dimethylbenz[a]anthracene in (DMBA) induced breast cancer Wistar rats (*Rattus norvegicus*).

Pharmacia. 2021;**68**(2):493-499.
DOI: 10.3897/pharmacia.68.e63956

[53] Yusuf H, Fahriani M, Murzalina C. Anti-Proliferative and apoptotic effect of soluble ethyl acetate partition from ethanol extract of *Chromolaena odorata* Linn leaves against Hela cervical cancer cell line. Asian Pacific Journal of Cancer Prevention. 2022;**23**(1):183-189.
DOI: 10.31557/APJCP.2022.23.1.183

[54] Asomugha RN, Ezejiofor AN, Okafor PN, Ijeh II. Acute and Cytotoxicity Studies of Aqueous and Ethanolic Leaf Extracts of *Chromolaena odorata*. Pakistan Journal of Biological Sciences. 2015;**18**(1):46-49.
DOI: 10.3923/pjbs.2015.46.49

[55] Poofery J, Khaw-On P, Subhawa S, Sripanidkulchai B, Tantraworasin A, Saeteng S, et al. Potential of Thai Herbal Extracts on Lung Cancer Treatment by Inducing Apoptosis and Synergizing Chemotherapy. Molecules. 2020;**25**(1):231. DOI: 10.3390/molecules25010231

[56] Poofery J, Sripanidkulchai B, Banjerdpongchai R. Extracts of *Bridelia ovata* and *Croton oblongifolius* induce apoptosis in human MDA-MB-231 breast cancer cells via oxidative stress and mitochondrial pathways. International Journal of Oncology. 2020;**56**(4):969-985. DOI: 10.3892/ijo.2020.4973

[57] Chaichantipyuth C, Petson A, Taweechoitipatr P, Muangsins N, Chaichit N, Puthong S, et al. New labdane-type diterpenoids from *Croton oblongifolius* and their cytotoxic activity. Heterocycles. 2005;**65**(4):809.
DOI: 10.3987/com-0510327

[58] Roengsumran S, Pata P, Ruengraweeewat N, Tummatorn J, Pornpakakul S, Sangvanich P, et al. New

cleistanthane diterpenoids and 3,4-seco-cleistanthane diterpenoids from *Croton oblongifolius*. Chemistry of Natural Compounds. 2009;**45**:641.
DOI: 10.1007/s10600-009-9442-7

[59] Wijesekera K. A bioactive diterpene; Nasimalum A from *Croton oblongifolius* Roxb. Prayog. Ras. 2017;**1**:41-44

[60] Uddin MH, Hossain MA, Kawsar MH. Antimicrobial and cytotoxic activities of *Tinospora cordifolia* (fam: menispermaceae). International Journal of Pharmaceutical Sciences and Research. 2011;**2**(3):656-658. DOI: 10.13040/IJPSR.0975-8232.2(3).656-58

[61] Modi B, Koirala N, Aryal SP, Shrestha J, Koirala S, Upadhyaya J, et al. *Tinospora cordifolia* (Willd.) Miers: phytochemical composition, cytotoxicity, proximate analysis and their biological activities. Molecular and Cellular Biology. 2021;**67**(1):50-57. DOI: 10.14715/cmb/2021.67.1.8

[62] Jagetia GC, Rao SK. Evaluation of cytotoxic effects of dichloromethane extract of guduchi (*Tinospora cordifolia* Miers ex Hook F & THOMS) on cultured HeLa cells. Evidence-based Complementary and Alternative Medicine. 2006;**3**(2):267-272.
DOI: 10.1093/ecam/nel011

[63] Sharma AK, Kumar S, Pandey AK. Ferric reducing, anti-radical and cytotoxic activities of *Tinospora cordifolia* stem extracts. (2014). Biochemistry & Analytical Biochemistry. 2014;**3**(2):1-5. DOI: 10.4172/2161-1009.1000153

[64] Ahmad R, Srivastava AN, Khan MA. Evaluation of in vitro anticancer activity of stem of *Tinospora cordifolia* against human breast cancer and Vero cell

lines. *Journal of Medical Plants Studies*. 2015;**3**(4):33-37

[65] Polu PR, Nayanbhirama U, Khan S, Maheswari R. Assessment of free radical scavenging and anti-proliferative activities of *Tinospora cordifolia* Miers (Willd). *BMC Complementary and Alternative Medicine*. 2017;**17**:457. DOI: 10.1186/s12906-017-1953-3

[66] Idris A, Zulkipli IN, Zulhilmi NR, Lee HF, Rajabalaya R, Chee LY, et al. *Melastoma malabathricum* ethyl acetate fraction induces secondary necrosis in human breast and lung cancer cell lines. *Pharmacognosy Magazine*. 2017;**13**(Suppl 3):S688-S692. DOI: 10.4103/pm.pm_465_15

[67] Roslen NA, Alewi NA, Ahamada H, Rasad MS. Cytotoxicity screening of *Melastoma malabathricum* extracts on human breast cancer cell lines in vitro. *Asian Pacific Journal of Tropical Biomedicine*. 2014;**4**(7):545-548. DOI: 10.12980/APJTB.4.2014C658

[68] Zakaria ZA, Rofiee MS, Mohamed AM, Teh LK, Salleh MZ. In vitro antiproliferative and antioxidant activities and total phenolic contents of the extracts of *Melastoma malabathricum* leaves. *Journal of Acupuncture and Meridian Studies*. 2011;**4**(4):248-256. DOI: 10.1016/j.jams.2011.09.016

[69] Isnaini I, Yasmina A, Nur'amin HW. Antioxidant and Cytotoxicity Activities of Karamunting (*Melastoma malabathricum* L.) Fruit Ethanolic Extract and Quercetin. *Asian Pacific Journal of Cancer Prevention*. 2019;**20**(2):639-643. DOI: 10.31557/APJCP.2019.20.2.639

[70] Susanti D, Sirat HM, Ahmad F, Ali RM, Aimi N, Kitajima M. Antioxidant

and cytotoxic flavonoids from the flowers of *Melastoma malabathricum* L. *Food Chemistry*. 2007;**103**(3):710-716. DOI: 10.1016/j.foodchem.2006.09.011

[71] Hamid HA, Ramli ANM, Zamri N, Yusoff MM. UPLC-QTOF/MS-based phenolic profiling of *Melastomaceae*, their antioxidant activity and cytotoxic effects against human breast cancer cell MDA-MB-231. *Food Chemistry*. 2018;**265**:253-259. DOI: 10.1016/j.foodchem.2018.05.033

[72] Tapondjou LA, Jenett-Siems K, Böttger S, Melzig MF. Steroidal saponins from the flowers of *Dioscorea bulbifera* var. *sativa*. *Phytochemistry*. 2013;**95**:341-350. DOI: 10.1016/j.phytochem.2013.07.020

[73] Wang GK, Zheng J, Sun YP, Jin WF, Liu HW, Yu Y, et al. New norclerodane diterpenoids from *Dioscorea bulbifera*. *Phytochemistry*. 2018;**27**:59-62. DOI: 10.1016/j.phytol.2018.06.025

[74] Nur RM, Nugroho LH. Cytotoxic activities of fractions from *Dioscorea bulbifera* L. chloroform and methanol extracts on T47D breast cancer cells. *Pharmacognosy Journal*. 2018;**10**(1): 33-38. DOI: 10.5530/pj.2018.1.7

[75] Mainasara MM, Abu Bakar MF, Md Akim A, Linatoc AC, Abu Bakar FI, Ranneh YKH. Secondary metabolites, antioxidant, and antiproliferative activities of *Dioscorea bulbifera* leaf collected from Endau Rompin, Johor, Malaysia. *Evidence-Based Complementary and Alternative Medicine*. 2021;**2021**:8826986. DOI: 10.1155/2021/8826986

[76] Wang JM, Ji LL, Branford-White CJ, Wang ZY, Shen KK, Liu H, et al. Antitumor activity of *Dioscorea bulbifera* L. rhizome in vivo. *Fitoterapia*.

2012;**83**(2):388-394. DOI: 10.1016/j.
fitote.2011.12.001

[77] Wang G, Zheng J, Yang J,
Yunpeng S, Zhang N. Liu Huiwen, Liu
Jinsong. Phenolic derivatives from
Dioscorea bulbifera. Records of Natural
Products. 2019;**13**(4):301-306.
DOI: 10.25135/rnp.114.18.10.1003