

## CHAPTER I

### INTRODUCTION

According to the World Health Organization, cancer is among the leading causes of death worldwide. There is a high incidence rate throughout the world, and the annual cancer cases are expected to reach 22 million within the next 20 years.

Despite advances in surgery and chemotherapy, research into new treatment strategies are still needed. A characteristic feature of cancer is the rapid creation of abnormal cells with uncontrollable growth, and which can then invade adjoining parts of the body and spread to other organs (WHO, 2014). This process is officially called as metastasis, which is accepted to be the cause of most cancer-related deaths.

Cancer therapeutic approaches can be comprised of surgery, radiation, and chemotherapy. Interestingly, some effective drugs which are used for the treatment of cancer nowadays were firstly obtained from natural sources, such as paclitaxel, vincristine and vinblastine. Unfortunately, cancer cells do not easily surrender. Rather, they fight the treatment back in an attempt to retain their immortality. Moreover, most of the chemotherapy-treated patients can not tolerate side effects of currently available drugs. Taken together, discovery of new drugs with higher efficacy and lower side effects for cancer treatment is still required.

Metastasis, which is considered as the most frequent cause of death for patients with cancer, is the dissemination of cancer cells from the originated tumor to a distant organ (Yamagushi *et al.*, 2005). The cancer metastasis is still remaining

even if the tumor is removed. So, searching for compounds with possess the antimetastatic activity is considered necessary (Chanvorachote *et al.*, 2013).

*Dendrobium* species, a member of Orchidaceae family, have been known as a potential source of several cytotoxic constituents. It has been widely accepted that the chemicals with this kind of activity may be the promising candidates for being cancer drugs. Previous pharmacological studies have reported many cytotoxic compounds from *Dendrobium* plants. Among them, moscatilin, a known cytotoxic compound isolated from various *Dendrobium* species, showed strong cytotoxicity against several cancer cell lines (Chanvorachote *et al.*, 2013).

Orchidaceae is the second largest family of angiosperms, with approximately 25,000 species (Singh *et al.*, 2012). They are mostly found in the tropical and sub-tropical region where their greatest diversity occurs. Apart from being ornamental, many orchid species have been used in different countries for therapeutic properties (Hossain, 2011). *Dendrobium* plants are widely distributed throughout Asian countries, including India, Nepal, Burma, Thailand, Laos, Vietnam and South-western of China, by more than 1,100 identified species (Seidenfaden, 1985; Chen *et al.*, 2008a; Guang hua *et al.*, 2009 ). They are primarily epiphytic with sympodial growth. Their sizes vary from very small to large. Their stems (Pseudobulbs) have various shapes, mostly spherical or cylindrical, with several segments. Each segment bears one or more leaves which are attached at the base. Their flowers bloom along the full length of stem in some species or from the apex of the stem in others with variable shapes and colors (สิทธิศักดิ์จรรยา, 2552). In China, *Dendrobium* plants have been used for thousand of years as a traditional medicine for many properties, such as, supplementing the stomach, promoting the production of body fluids, anti-aging,

antioxidant, antipyretic, eye-benefiting and immunoregulatory purposes (Zhang *et al.*, 2007a, Xiong *et al.*, 2013).

There are more than 74 species of *Dendrobium* found in China and about 30 species of them are currently used under the Chinese name “Shi-Hu” which is a commonly used Chinese medicine prepared from the dried or fresh stems of several *Dendrobium* species, such as, *Dendrobium nobile*, *D. chrysotoxum*, *D. fimbriatum* and other related *Dendrobium* species. This “Shi-Hu” is included in the Chinese Pharmacopoeia and considered as an important remedy for kidney, lung and stomach disorders, fever and hyperglycemia, etc (Hossain, 2011).

Among orchids, *Dendrobium* is the leading genus for phytochemical contents, so the chemical constituents of this genus have been extensively investigated. Previous studies have shown that many classes of secondary metabolites have been identified from this genus, including alkaloids, bibenzyl derivatives, coumarins, flavonoids, fluorenones, lignans, phenanthrenes, phenylpropanoids, sesquiterpenes, sesquiterpene glycosides and terpenoids (Zhang *et al.*, 2005, Zhang *et al.*, 2008a, Hu *et al.*, 2009).

In Thailand, more than 90 species of *Dendrobium* are identified as follows (Smitinand, 2001) :

<i>Dendrobium acerosum</i> Lindl.	กล้วยไม้มีอนาง Kluai mai mue nang (Chumphon)
<i>D. acinaciforme</i> Roxb.	เอื้องยอดสร้อย Ueang yot soi (Northern)
<i>D. albosanguineum</i> Lindl.	เอื้องตางัว Ueang ta ngua (Mae Hong Son)

<i>D. aloifolium</i> (Blume) Rchb.f.	เอื้องมณี Ueang mani (Bangkok)
<i>D. anosmum</i> Lindl.	เอื้องสาย Ueang sai (Chiang Mai, Peninsular)
<i>D. aphyllum</i> (Roxb.) C.E.C.Fisch.	เอื้องวงช้าง Ueang nguang chang (Mae Hong Son)
<i>D. bellatulum</i> Rolfe	เอื้องแซะภู Ueang sae phu
<i>D. bicameratum</i> Lindl.	เอื้องเข็ม Ueang khem (Northern)
<i>D. bilobulatum</i> Seidenf.	กล้วยไม้ก้างปลา Kluai mai kang pla (General)
<i>D. binoculare</i> Rchb.f.	เอื้องคำสาย Ueang kham sai (Northern)
<i>D. brymerianum</i> Rchb.f.	เอื้องคำฝอย Ueang kham foi (Northern)
<i>D. capillipes</i> Rchb.f.	เอื้องคำกิว Ueang kham kio (Lampang, Phrae)
<i>D. cariniferum</i> Rchb.f.	เอื้องกาจก Ueang kachok (Chiang Mai)
<i>D. christyanum</i> Rchb.f.	เอื้องแซะภูกระดิ่ง Ueang sae phu kradueng (Loei)
<i>D. chrysanthum</i> Lindl.	เอื้องสายมรกต Ueang sai morakot (Bangkok)
<i>D. chrysotoxum</i> Lindl.	เอื้องคำ Ueang kham (Northern)

<i>D. compactum</i> Rolfe ex Hackett	เอื้องข้าวตอก Ueang khao tok (Northern)
<i>D. concinnum</i> Miq.	หางเปีย Hang pia (Narathiwat)
<i>D. crepidatum</i> Lindl. & Paxton	เอื้องสายน้ำเขียว Ueang sai nam khiao (General)
<i>D. crocatum</i> Hook.f.	เอื้องนางนวล Ueang nang nuan (Peninsular)
<i>D. cruentum</i> Rchb.f.	เอื้องนกแก้ว Ueang nok kao (Bangkok)
<i>D. crumenatum</i> Sw.	หวายตะมอย Wai tamoi (Central, Peninsular)
<i>D. crystallinum</i> Rchb.f.	เอื้องนางพ่อน Ueang nang fon (Chiang Mai)
<i>D. cumulatum</i> Lindl.	เอื้องสายสีตอก Ueang sai si dok (Northern, Southeastern)
<i>D. dantoniense</i> Guillaumin	เอื้องเข็ม Ueang khem (Chiang Mai)
<i>D. densiflorum</i> Lindl.	เอื้องมอนไข่ Ueang mon khai (Northern)
<i>D. devonianum</i> Paxton	เอื้องเมียง Ueang miang (Chiang Mai)
<i>D. dickasonii</i> L.O. Williams	เอื้องเคี้ยะ Ueang khia (Chiang Mai)
<i>D. discolor</i> Lindl.	หวายกลัก Wai klak (Bangkok)
<i>D. dixanthum</i> Rchb.f.	เอื้องเทียน Ueang thian (Northern)

<i>D. draconis</i> Rchb.f.	เอื้องเงิน Ueang ngoen (Northern)
<i>D. ellipsophyllum</i> Tang & Wang	เอื้องทอง Ueang thong (General)
<i>D. exile</i> Schltr.	เอื้องเสียน Ueang sian (General)
<i>D. falconeri</i> Hook.	เอื้องสายวิสูตร Ueang sai wisut (Bangkok)
<i>D. farmeri</i> Paxton	เอื้องมัจฉาณู Ueang mat chanu (Bangkok)
<i>D. fimbriatum</i> Hook.	เอื้องค้ำน้อย Ueang kham noi (Chiang Mai)
<i>D. findlayanum</i> Parish & Rchb.f.	พวงหยก Phuang yok (Bangkok)
<i>D. formosum</i> Roxb. ex Lindl.	เอื้องเงินหลวง Ueang ngoen luang (Chiang Mai)
<i>D. friedericksianum</i> Rchb.f.	เอื้องเหลืองจันทบูร Ueang Lueang chantabun (Bangkok)
<i>D. fuerstenbergianum</i> Schltr.	เอื้องแซะภูกระดึง Ueang sae phukradueng (Loei)
<i>D. gibsonii</i> Lindl.	เอื้องค้ำสาย Ueang kham sai (Northern)
<i>D. grande</i> Hook.f	เอื้องแพงใบใหญ่ Ueang pheang bai yai (Peninsular)
<i>D. grotiosissimum</i> Rchb.f.	เอื้องกึ่งดำ Ueang king dam (Bangkok)
<i>D. gregulus</i> Seidenf.	เอื้องมะต่อม Ueang matom (Chiang Mai)
<i>D. griffithianum</i> Lindl.	เอื้องมัจฉาณู Ueang matchanu (Bangkok)

<i>D. harveyanum</i> Rchb.f.	เอื้องคำฝอย Ueang kham foi (Chiang Mai)
<i>D. hendersonii</i> Hawkes & Heller	หวายตะมอยน้อย Wai tamoi noi (Peninsular)
<i>D. hercoglossum</i> Rchb.f.	เอื้องดอกมะเขือ Ueang dok ma kuea (Bangkok)
<i>D. heterocarpum</i> Lindl.	เอื้องสีตาล Ueang si tan (Chiang Mai)
<i>D. indivisum</i> (Blume) Miq.  var. <i>indivisum</i>	ตานเสี้ยนไม้ Tan sian mai (Chumphon)
<i>D. indivisum</i> (Blume) Miq.  var. <i>pallidum</i> Seidenf.	ก้างปลา Kang pla (General)
<i>D. infundibulum</i> Lindl.	เอื้องตาเหิน Ueang ta hoen (General)
<i>D. intricatum</i> Gagnep.	เอื้องชมพู Ueang chom phu (Chanthaburi)
<i>D. jenkinsii</i> Wall. ex Lindl.	เอื้องฝั๋งน้อย Ueang phueng noi (Chiang Mai)
<i>D. kanburiense</i> Seidenf.	หวายเมืองกาญจน์ Wai muang kan (Kanchanaburi)
<i>D. leonis</i> (Lindl.) Rchb.f.	เอื้องตะขาบใหญ่ Ueang ta khap yai (General)
<i>D. lindleyi</i> Steud.	เอื้องฝั๋ง Ueang phueng (Northern)

<i>D. lituiflorum</i> Lindl.	เอื้องสายม่วง Ueang sai muang (Bangkok, Northern)
<i>D. moschatum</i> (Buch.-Ham.) Sw.	เอื้องจำปา Ueang champa (Northern)
<i>D. nathanielis</i> Rchb.f.	เกล็ดน้ยม Klet nim (Chantaburi)
<i>D. nobile</i> Lindl.	เอื้องเค้ากิว Ueang khao kio (Northern)
<i>D. ochreatum</i> Lindl.	เอื้องตะขาบ Ueang ta khap (Chiang Mai)
<i>D. oligophyllum</i> Gagnep.	ข้าวตอกปราจีน Khao tok prachin (General)
<i>D. pachyglossum</i>	เอื้องขนหมู Ueang khon mu (Mae Hong Son)
C.S.P.Parish & Rchb.f	
<i>D. pachyphyllum</i> (Kuntze) Bakh.f.	เอื้องน้อย Ueang noi (General)
<i>D. palpebrae</i> Lindl.	เอื้องมัจฉา Ueang mat cha, เอื้องมัจฉาณ Ueang mat chanu (Bangkok)
<i>D. parcum</i> Rchb.f.	เอื้องก้านกิว Ueang kan kio (Bangkok)
<i>D. parishii</i> Rchb.f.	เอื้องครั่ง Ueang khrang (Northern)
<i>D. pendulum</i> Roxb.	เอื้องไม้เท้าฤาษี Ueang mai thao ruesi (Bangkok, Chiang Mai)
<i>D. pensile</i> Ridl.	หวาย Wai (Narathiwat)



<i>D. porphyrophyllum</i> Guillaumin	เอื้องลั่น Ueang lin (Lampang)
<i>D. primulinum</i> Lindl.	เอื้องสายประสาธ Ueang sai prasat (Bangkok)
<i>D. pulchellum</i> Roxb. ex Lindl.	เอื้องคำตาควาย Ueang kham ta khwai (Mae Hong Son)
<i>D. pychnostachyum</i> Lindl.	เศวตสอดสี Sawet sot si (Chiang Mai)
<i>D. salaccense</i> (Blume) Lindl.	เอื้องใบไผ่ Ueang bai phai (Chiang Mai)
<i>D. scabrilingue</i> Lindl.	เอื้องแซะ Ueang sae (Mae Hong Son)
<i>D. secundum</i> (Blume) Lindl.	เอื้องแปรงสีฟัน Ueang preang si fan (Bangkok)
<i>D. seidenfadenii</i> Rchb.f.	เอื้องเกียะ Ueang kia (Chiang Mai)
<i>D. senile</i> Parish & Rchb.f.	เอื้องชะนี Ueang chani (Bangkok)
<i>D. signatum</i> Rchb.f.	เอื้องค้ำกัว Ueang khao kio (Chiang Mai)
<i>D. stuposum</i> Lindl.	เอื้องสาย Ueang sai (Chiang Mai)
<i>D. sulcatum</i> Lindl.	เอื้องจำปาน่าน Ueang champa nan (Bangkok)
<i>D. superbiens</i> Rchb.f.	หวายคิง Wai khing (Bangkok)
<i>D. sutepense</i> Rolfe ex Downie	เอื้องมะลิ Ueang mali (Chiang Mai)

<i>D. terminale</i> Parish & Rchb.f	เอื้องแผงโสภา Ueang phaeng sopha (Peninsular)
<i>D. thysiflorum</i> Rchb.f	เอื้องมอนไข่ไบมอน Ueang mon khai bai mon (Northern)
<i>D. tortile</i> Lindl.	เอื้องไม้ตั้ง Ueang mai tueng (Mae Hong Son)
<i>D. trigonopus</i> Rchb.f.	เอื้องคำเหลี่ยม Ueang kham liam (Chiang Mai)
<i>D. trinervium</i> Ridl.	เทียนลิง Thian ling (Chumphon)
<i>D. unicum</i> Seidenf.	เอื้องครั่งแสด Ueang krang saet (General)
<i>D. uniflorum</i> Griff.	เอื้องทอง Ueang thong (Pattani)
<i>D. venustum</i> Teijsm. & Binn	ข้าวเหนียวลิง Khao niao ling (Central)
<i>D. villosulum</i> Lindl.	กล้วยหุ้ยานา Kluai ya na (Bangkok)
<i>D. virgineum</i> Rchb.f.	เอื้องเงินวิลาศ Ueang ngoen wilat (Northern)
<i>D. wardianum</i> Warner	เอื้องมณีไตรรงค์ Ueang mani trai rong (Northern)
<i>D. wattii</i> (Hook.f.) Rchb.f.	เอื้องแซะ Ueang sae (Northern)
<i>D. ypsilon</i> Seidenf.	เอื้องแบนปากตัด Ueang baen pak tat (General)

*Dendrobium brymerianum* Rchb. f. has a Thai name as Ueang Kham Foi (เอื้องคำฝอย) or Ueang Kham Foi Pai (เอื้องคำฝอยพาย) (Figure 1). It is an epiphytic orchid with thin or fleshy throughout stems. Its flowers are characterized by golden colors with long dented and fimbriated lip in the size of 4.5 cm. This species is distributed in North and Upper Northeast of Thailand. Their flowering period is in August (Vaddhanaphuti, 2005).

Although *D. brymerianum* Rchb. f. has been known for a long time in Thailand, the chemical constituents of this plants have not been studied previously. In our preliminary screening of a methanolic extract of *D. brymerianum* for cytotoxic activity, the extract at 50 µg/mL concentration was found to exhibit significant cytotoxic activity against KB-Oral cavity cancer cell lines with 70% inhibition. Therefore, this study is the first attempt to investigate the chemical constituents and cytotoxic activity of *D. brymerianum*. The phytochemical data to be obtained in this study would broaden our knowledge on the chemotaxonomy of this plant family and would give us information on cytotoxic constituents of botanical origin.

The main objectives of this study are as follows.

1. To isolate and purify the chemical constituents from *Dendrobium brymerianum*.
2. To characterize the structures of the isolated compounds.
3. To evaluate the cytotoxic activity of the isolated compounds.

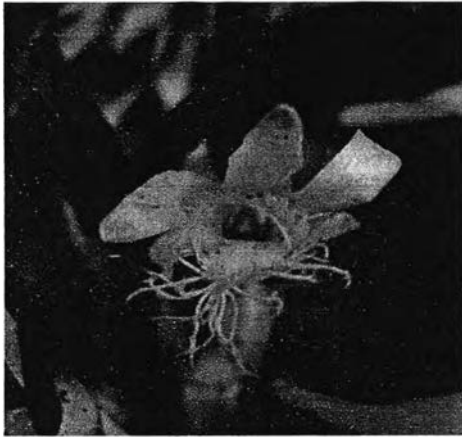


Figure 1 *Dendrobium brymerianum* Rchb.f.

