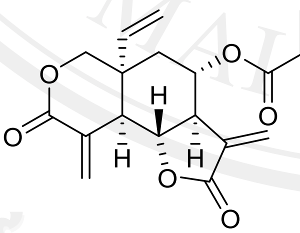
CHAPTER 2

LITERATURE REVIEWS

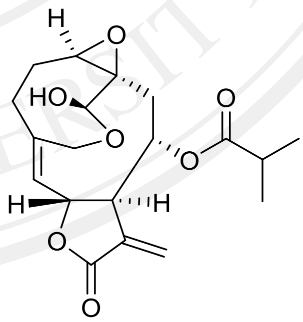
2.1 Previous Reports of *Vernonia* plants

Vernonia genus, which is composed of more than 1,000 species around the world, is one genus of plants characterized in Asteraceae or Compositae family. In Thailand, the plants of this genus were found more than twenty species such as *V. attenuata*, *V. cinerea*, *V. divergens*, *V. parishii*, and *V. sutipensis*, which are found at Doi Tung, Chaing Rai, Thailand.[22]

Although *Vernonia* genus includes a number of species, some plants have been investigated the phytochemistry and their bioactivities. For example, *V. amygdalina*, as known as "bitter-leaf" or "Onugbu" in Ibo, is a shrub which was found in Nigeria that was reported discovering many constituents. Vernolide (**1**) and vernomygdin (**2**), two cytotoxic sesquiterpene lactones, were isolated from the chloroform extract of *V. amygdalina* bark by Kupchan and coworkers.[23]



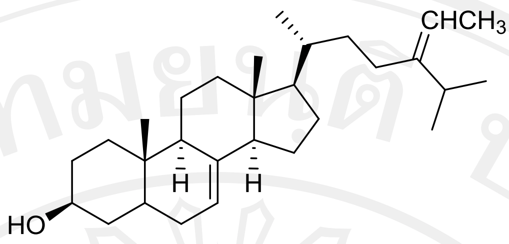
vernodalin (**1**)



vernomygdin (**2**)

Figure 2 Structures of compounds **1** and **2**

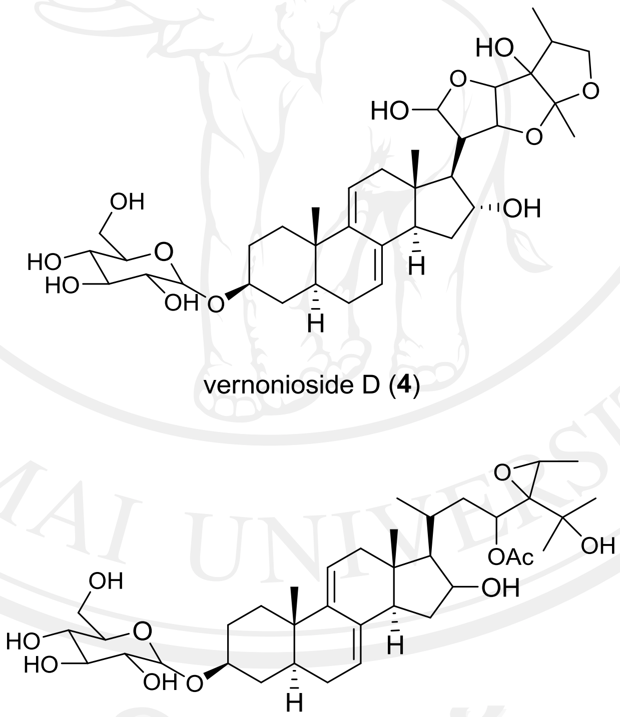
Additionally, 7,24(28)-sigmastadien-3β-ol (**3**) had been isolated from *V. amygdalina* stem as reported by Arene in 1972.[24]



7,24(28)-stigmastadien-3β-ol (**3**)

Figure 3 Structure of compound **3**

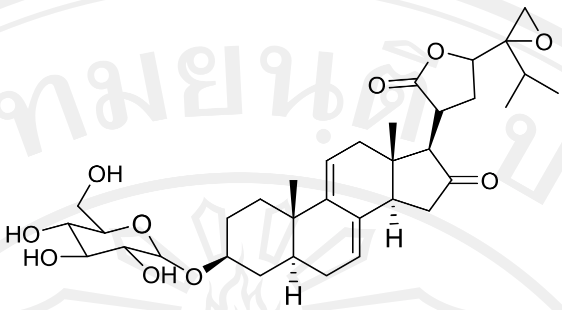
In 1995, Igile and members reported the data regarding three stigmastane-type steroid glycosides, vernonioside D (**4**), E (**5**), and A_3 (**6**), which were separated from the leaves of *V. amygdalina*.[7]



vernonioside D (**4**)

vernonioside E (**5**)

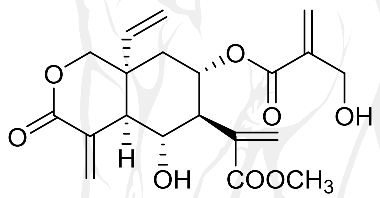
Figure 4 Structures of compounds **4** and **5**



vernonioside A_3 (**6**)

Figure 5 Structure of compound **6**

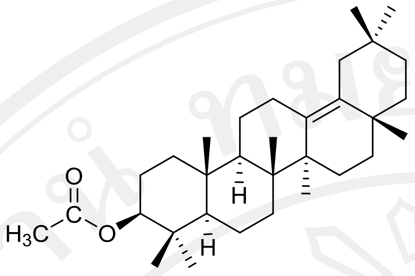
Two known compounds, vernolide (**1**) and vernodalol (**7**), which were isolated from *V. amygdalina* leaves and reported in 2006, also exhibited a significant bactericidal activity against Gram positive bacteria.[25]



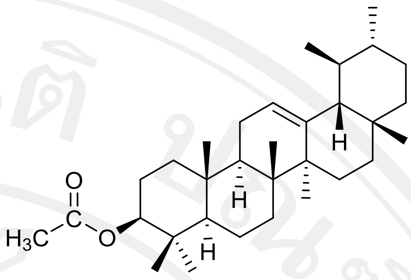
vernodalol (**7**)

Figure 6 Structure of compound **7**

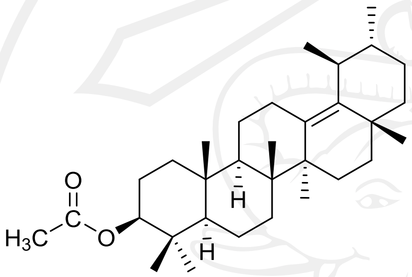
V. cinerea, which is called "Kbal Ruy" in Cambodia and substantially found in South-East Asia, is another plant that was investigated the chemical and bioactive compositions by several researchers. The roots of this plant were used in the study of chemical constituents by Misra and co-workers. They had isolated δ-amyrin acetate (**8**), α-amyrin acetate (**9**), 3β-acetoxyurs-13(18)-ene (**10**), β-amyrin acetate (**11**), β-amyrin (**12**), α-amyrin (**13**), and 24-hydroxytaraxer-14-ene (**14**) in 1984.[3, 26]



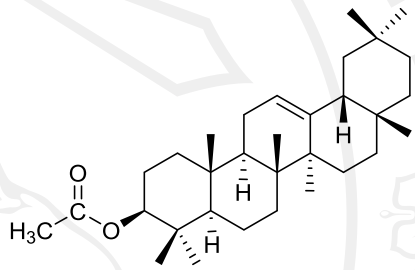
δ-amyrin acetate (**8**)



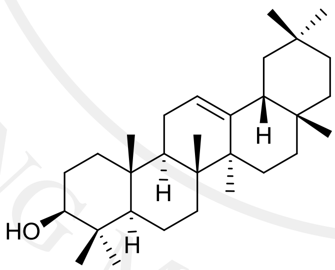
α-amyrin acetate (**9**)



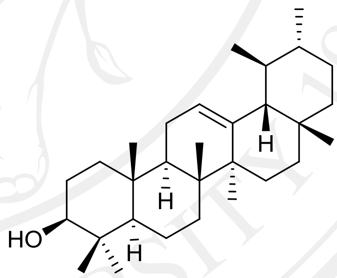
3β-acetoxyurs-13(18)-ene (**10**)



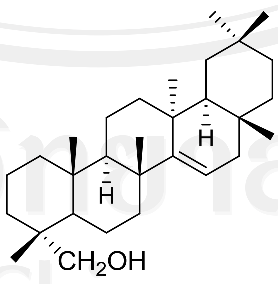
β-amyrin acetate (**11**)



β-amyrin (**12**)



α-amyrin (**13**)



24-hydroxytaraxer-14-ene (**14**)

Figure 7 Structures of compounds **8-14**

In 2006, vernolides C (**15**) and D (**16**), two novel sesquiterpene lactones, antimalarial compounds, were separated from the dichloromethane fraction of an aqueous extract of *V. cinerea* by Chea and colleagues.[4]

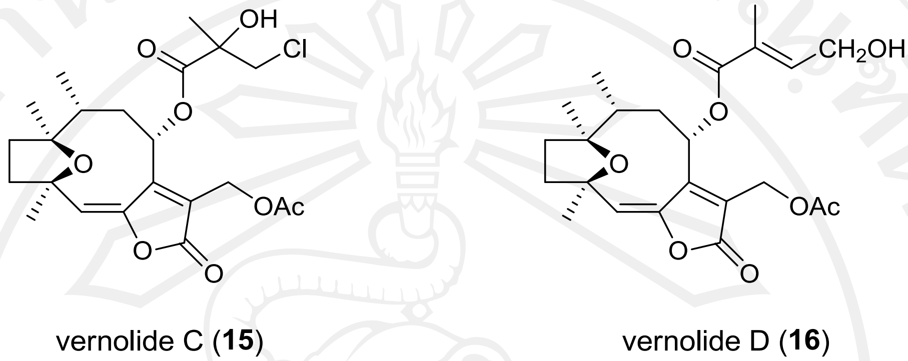


Figure 8 Structures of compounds **15** and **16**

Third species of *Vernonia* genus, *V. colorata* or "Kosafune" in Mali, was an interested subject for the investigation of the chemical compounds and their bioactivities by many scientists. The first study of this species was reported by Rabe's research group in 2002. They separated three antibacterial compounds, vernolide (**17**), 11*β*,13-dihydrovernolide (**18**), and vernodalin (**1**), from the ethyl acetate extract from leaves of this plant.[1]

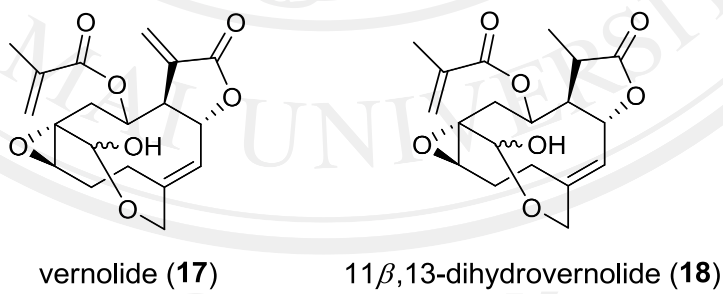
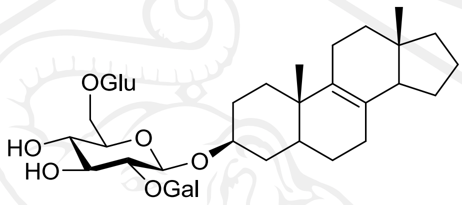
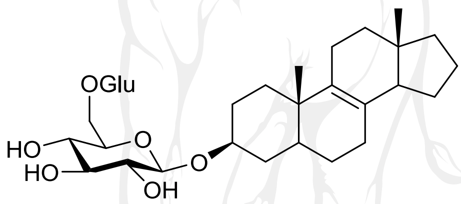


Figure 9 Structures of compounds **17** and **18**

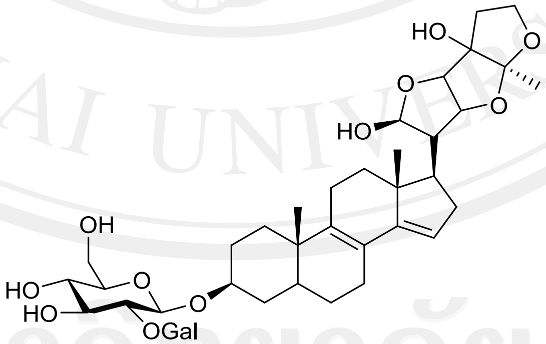
Previously, the chloroform-methanol (9:1) extract of leaves of *V. colorata* was also investigated for the chemical constituents by Cioffi and workers. This team reported six chemical new compounds, 3-*O*-{*β*-D-galactopyranosyl-(1-2)-[*β*-D-glucopyranosyl-(1→6)]-*β*-D-glucopyranoside}-5*α*,14*α*-androst-8-ene (**19**), 3-*O*-[*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside]-5*α*,14*α*-androst-8-enen (**20**), 3*β*-21,24-trihydroxy-21,23;22,28;26,28-triepoxy-5*α*-stigmasta-8(9),14(15)-dien-3-*O*-*β*-D-galactopyranosyl-(1→2)-*β*-D-glucopyranoside (**21**), 3*β* -21,24-trihydroxy-21,23;22,28;26,28-triepoxy-5*α*-stigmasta-8(9),14(15)-dien-3-*O*-*β*-D-galactopyranosyl -(1→2)-*β*-D-(6-acetyl)glucopyranoside (**22**), 3*β*,25,29-trihydroxy-5*α*-stigmasta-8(9),14(15),24*Z*(28)-triene (**23**), and 3*β*,23,25-trihydroxy-24,28-epoxy-5*α*-stigmasta-8(9),14(15)-diene (**24**), which were isolated from this extract.[2]



3-*O*-{*β*-D-galactopyranosyl-(1-2)-[*β*-D-glucopyranosyl-(1→6)]-*β*-D-glucopyranoside}-5*α*,14*α*-androst-8-ene (**19**)

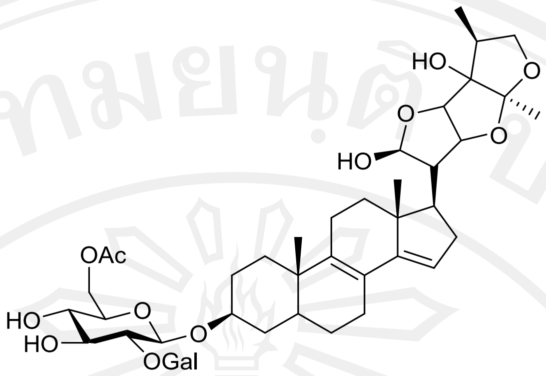


3-*O*-[*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside]-5*α*,14*α*-androst-8-ene (**20**)

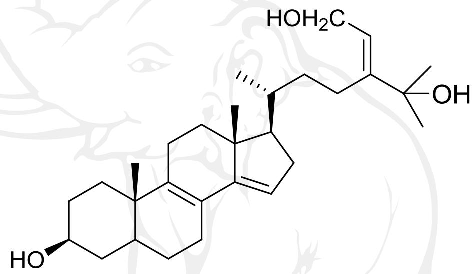


3*β*-21,24-trihydroxy-21,23;22,28;26,28-triepoxy-5*α*-stigmasta-8(9),14(15)-dien-3-*O*-*β*-D-galactopyranosyl-(1→2)-*β*-D-glucopyranoside (**21**)

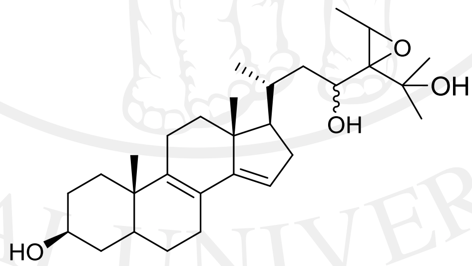
Figure 10 Structures of compounds **19-21**



3β-21,24-trihydroxy-21,23;22,28;26,28-triepoxy-5α-stigmasta-8(9), 14(15)-dien-3-*O*-β-D-galactopyranosyl-(1$\rightarrow$2)-β-D-(6-acetyl)glucopyranoside (**22**)



3β,25,29-trihydroxy-5α-stigmasta-8(9),14(15),24*Z*(28)-triene (**23**)

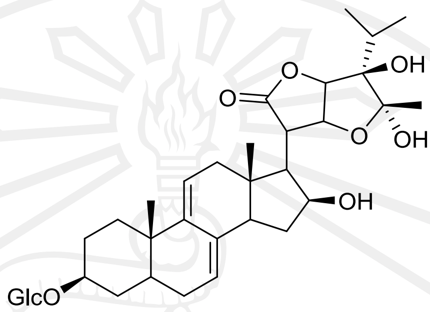


3β,23,25-trihydroxy-24,28-epoxy-5α-stigmasta-8(9),14(15)-diene (**24**)

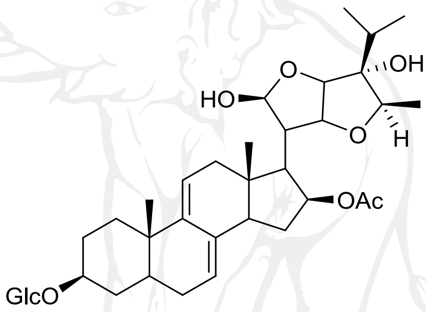
Figure 11 Structures of compounds **22-24**

In 2009, Chukwujekwu and his research group had isolated vernodalin (**1**) and vernolide (**17**), two known sesquiterpene lactones, from the acetone extract of *V. colorata* leaves. They also reported two isolated sesquiterpene lactones, compound **1** and **17**, against *Plasmodium falciparum*.[19]

The fourth plant of this genus studied and presented by researchers is *V. cumingiana*, a climber and shrub distributed in Guangxi, Yunnan, and Guangdong provinces in China. Liu and co-workers, firstly reported the discovering of a new steroidal saponin, named vernonioside G (**25**), with VE-1 (**26**), from the ethanol extract from the roots of this plant.[27]



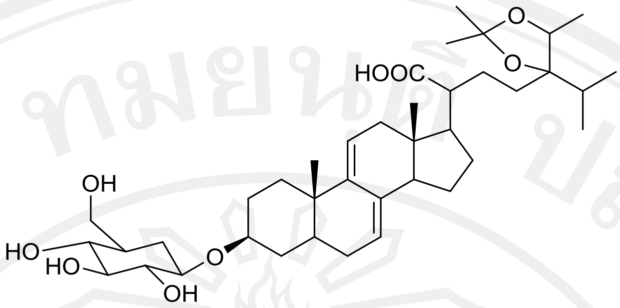
vernonioside G (**25**)



VE-1 (**26**)

Figure 12 Structures of compounds **25** and **26**

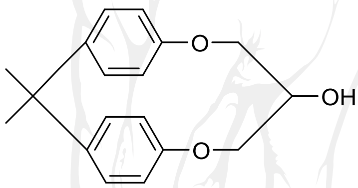
Besides, the second scientist team, Suo and coworkers, from China explored about the chemical constituents of *V. cumingiana* discovering two new compounds, vernonioside S (**27**) and vernoniether S (**28**) in 2008, isolated from the stem of this species.[28]



vernonioside S (**27**)

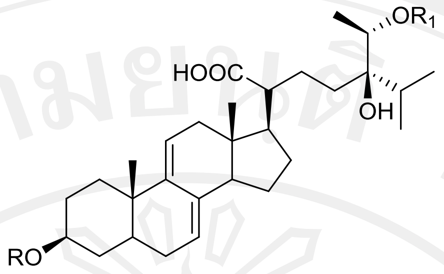
Figure 13 Structure of compound **27**

The third report about the investigation of *V. cumingiana* was recorded by Liu and his team in 2009. They had isolated seven new stigmastane-type steroidal glycosides, vernocuminosides A-G (**29-35**), which displayed promising anti-inflammatory and cytotoxicity activities.[29]



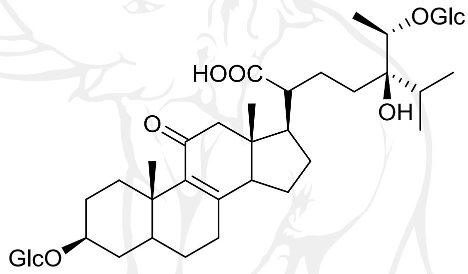
vernoniether S (**28**)

Figure 14 Structure of compound **28**



A (**29**) R = β-D-glc; R_1 = β-D-glc
B (**30**) R = β-D-gal-(1$\rightarrow$2)-β-D-glc; R_1 = β-D-glc
C (**31**) R = β-D-glc; R_1 = H
D (**32**) R = β-D-gal-(1$\rightarrow$2)-β-D-glc; R_1 = H
E (**33**) R = α-L-ara-(1$\rightarrow$2)-β-D-glc; R_1 = H
F (**34**) R = α-L-ara-(1$\rightarrow$2)-β-D-glc; R_1 = β-D-glc

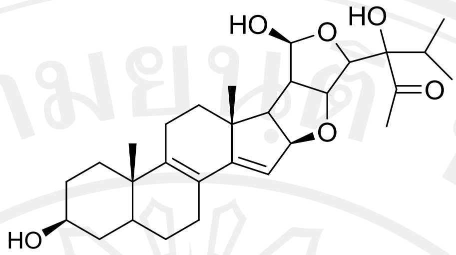
vernocuminosides **A-F** (**29**-**34**)



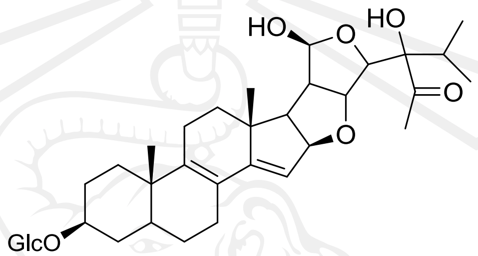
vernocuminoside G (**35**)

Figure 15 Structures of compounds **29-35**

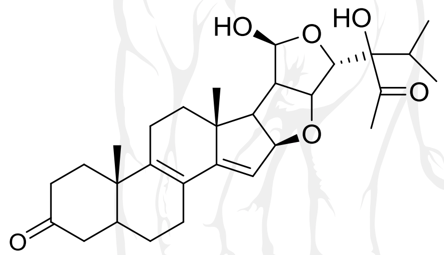
The fifth species of this genus is *V. guineensis*, a small tree found in the savannah region. A research group of Tchinda investigated the phytochemistry of this species, presented the constituents from the plant on two articles. The first report that was recorded in 2002 indicated two bitter stigmastane derivatives, vernoguinosterol (**36**) and vernoguinoside (**37**). The separated compounds were found in the stem bark of this species.[30]



vernoguinosterol (**36**)



vernoguinoside (**37**)

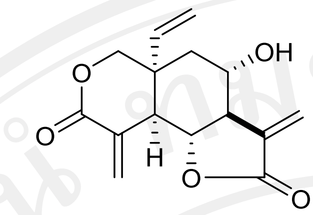


16*β*,22*R*;21,23*S*-diepoxy-21*S*,24-dihydroxy-5*α*-stigmasta-8,14-diene-3,28-dione (**38**)

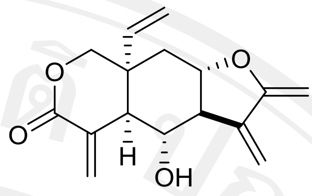
Figure 16 Structures of compounds **36-38**

In 2003, a new compound, 16*β*,22*R*;21,23*S*-diepoxy-21*S*,24-dihydroxy-5*α*-stigmasta-8,14-diene-3,28-dione (**38**) from the stem bark of *V. guineensis* was reported.[31]

Furthermore, the other species of *Vernonia* genus also provides the significant compositions in several parts of plants, for instance, *V. hymenolepis* leaves were extracted with chloroform to give two novel elemanolide dilactones, vernolepin (**39**) that showed significant *in vitro* cytotoxicity (KB) and *in vivo* tumor inhibitory activity against Walker intramuscular carcinosarcoma in rat, and vernomenin (**40**), were successfully separated.[8]



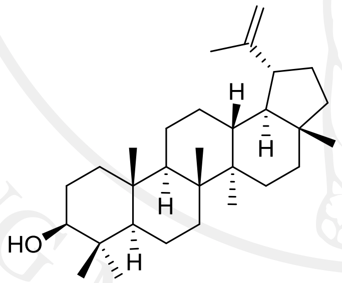
vernolepin (**39**)



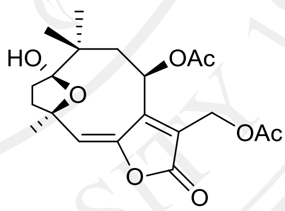
vernomenin (**40**)

Figure 17 Structures of compounds **39** and **40**

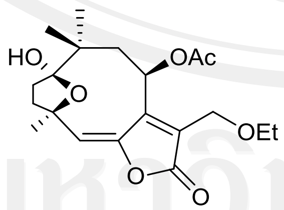
In addition, Catalan and his partner had studies the chemical compositions of two species of *Vernonia* plants, *V. mollissima and V. squamulosa*, found in Argentina. For first plant (*V. mollissima*), the researchers isolated five compounds, lupeol (**41**), diacetylpiptocarphol (**42**), 8-acetyl-13-ethoxypipotocarphol (**43**), piptocarphin D (**44**), and scopoletin (**45**), from the aerial parts of this tree. Another plant is *V. squamulosa*. They had separate six known compounds, β-amyrin (**12**), α-amyrin (**13**), lupeol (**41**), glaucolide A (**46**), glaucolide G (**47**), and piptocaphin A (**48**).[32]



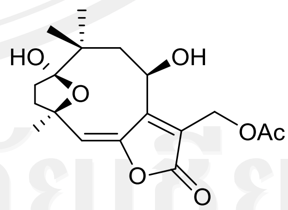
lupeol (**41**)



diacetylpiptocarphol (**42**)

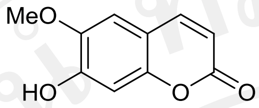


8-acetyl-13-ethoxypipotocarphol (**43**)

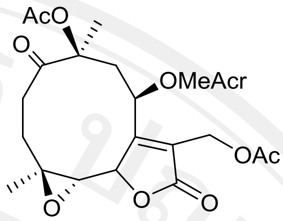


piptocarphin D (**44**)

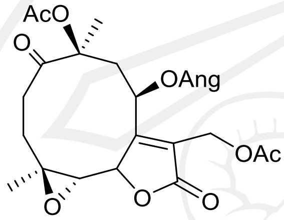
Figure 18 Structures of compounds **41-44**



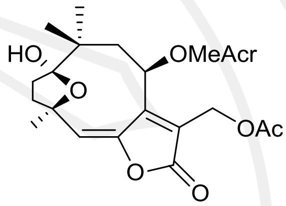
scopoletin (**45**)



glaucolide A (**46**)



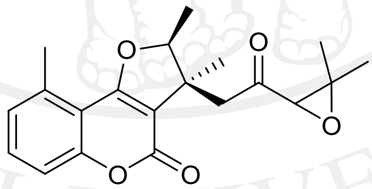
glaucolide G (**47**)



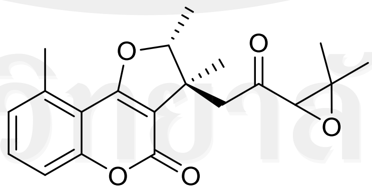
piptocarphine A (**48**)

Figure 19 Structures of compounds **45-48**

In 1997, Oketch-Rabah and colleagues had isolated two new antileishmanial and antimalarial compounds, containing 2'-epicycloisobrachycoumarinone epoxide (**49**) and cycloisobrachycoumarinone epoxide (**50**), from the roots of *V. brachycalyx*.[33]



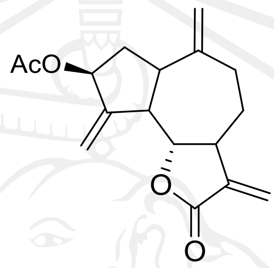
2'-epicycloisobrachycoumarinone epoxide (**49**)



cycloisobrachycoumarinone epoxide (**50**)

Figure 20 Structures of compounds **49** and **50**

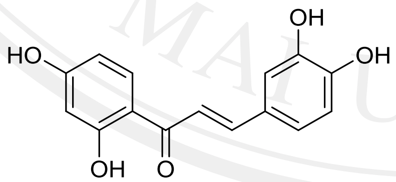
The discovery of zaluzanin D (**51**) showed an antifungal sesquiterpene lactone which was isolated from the leaves of *V. arborea* by Kumari and coworkers in 2003. They found that this compound showed good activity against six plant-pathogenic fungi, including *Botrytis cinerea*, *Curvularia lunata*, *Collectotrichum lindemuthianum*, *Fusarium oxysporum*, *Furarium equisetii*, and *Rhizoctonia solani*.[12]



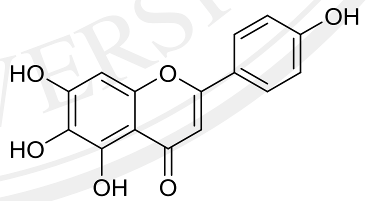
zaluzanin D (**51**)

Figure 21 Structure of compound **51**

The investigation about chemical components of the seeds of *V. anthelmintica* was reported by Tian and co-workers in 2004. They had been isolated several flavonoids, containing 2',3,4,4'-tetrahydroxychalcone (**52**), 5,6,7,4'-tetrahydroxyflavone (**53**), and 7,3',4'-trihydroxydihydroflavone or butin (**54**).[34]

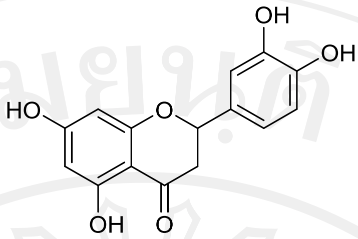


2',3,4,4'-tetrahydroxychalcone (**52**)



5,6,7,4'-tetrahydroxyflavone (**53**)

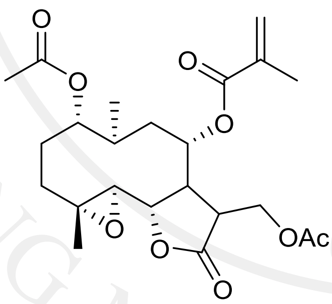
Figure 22 Structures of compounds **52** and **53**



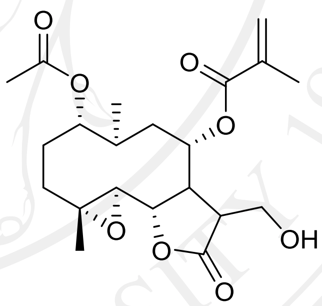
7,3',4'-trihydroxydihydroflavone (butin) (**54**)

Figure 23 Structures of compound **54**

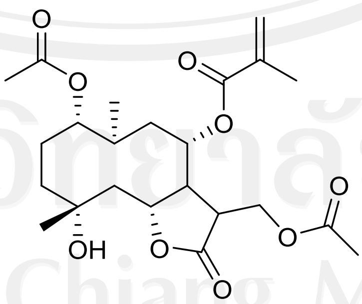
Recently, *V. pachyclada*, which is a species found in the rainforests of Madagascar, was studied for the phytochemical components by Williams and partners in 2005. They reported the three new sesquiterpene lactones, glaucolide K-M (**55-57**), from the leaves of this plant. Moreover, one compound of three isolated sesquiterpene lactones, glaucolide M (**57**), showed moderate activity against the A2780 human ovarian cancer cell line.[35]



glaucolide K (**55**)



glaucolide L (**56**)



glaucolide M (**57**)

Figure 24 Structures of compounds **55-57**

Even though several species in *Vernonia* genus were studied about chemical constituents and their bioactivities, a lot of *Vernonia* plants are not still thoroughly investigated. Therefore, *V. parishii*, a member in this genus, which is found in the northern region of Thailand, was chosen to research the chemical taxonomy and bioactive compounds.