CHAPTER I
INTRODUCTION

In the past, man has used animal, plant and mineral substances to ease pain, heal wounds and maintain health. The World Health Organization has estimated that at least 80 percent of the world's population relies mainly on natural medicines.[1] So in industrialized countries, up to 40 percent of all pharmaceuticals are derived from natural sources. In industrialized societies, medicines from natural sources were increasing in popularity as a remergence of an ancient and universal practice from behind the recent shadow of the phamaceutical industry. The last 100 years had orthodox medicine came to depend on man-made chemicals that did not occur in nature as well as modern drugs made a dramatic impact on infectious diseases, but they had not provided cures for common diseases liked breast, lung or bowel cancers, heart disease, rheumatism, or the common cold. Meanwhile, concern about the frequency and seriousness of drug side effects had grown the choice also reflected the wide range of conditions for which medicines from nature were used.

Medicinal plants had especially pharmacological active principles which could be used as therapeutic drugs or herbal medicine and they were used in agriculture e.g. antibacteria, antifeedant and used in industry for example perfume, because they were cheap and easily available.

Euphorbiaceae family had 800 genera and 5000 species. They were interesting medicinal plants because plants of Euphorbiaceae family were known to produce a variety of diterpenoids.[2,3] Diterpenoids compound constituted a large group of compounds derived from geranylgeranyl pyrophosphate. Chettaphangkhi was the medicinal plant in Euphorbiaceae family, used in popular Thai medicinal plant such as the roots of this plant had robotant properties and carminative. A decoction of the roots of Chettaphangkhi combined with the roots of *Styrax benzoides* had been used

as to cardiac or tonic drugs and the trunk of these had been used to treat anti-diarrheal and flatulence.

On literature search, up to the present time only two studies were reported on Chettaphangkhi until now[4,5] but they have not been reported biological activity of which they found. So it was main matter of this research to investigate the chemical constituents from the roots of *C. orientalis* and their biological activity. Consequently, it was decided to search for the active substances that could be applied to pharmaceutical and agricultural industries in future.

The scientific name of Chettaphangkhi is *Cladogynos orientalis* Zipp. ex Span. and its synonym is *Adenocleana siamensis* Ridl. [6] It was only one species in genus of Cladogynos in Euphorbiaceae family. This plants were also occasionally found in many provinces of Thailand, for example, Udawn, Nakarn sawan, Prachinburin. Additionally, it can also be found in China, Indo China and the Phillipines.

In Thailand, its common name was Chettapangkhi, Plao num-ngeon, Bai lung kaw. Plao num-ngeon also was the common name of *Croton classifulius*. So Thai people might be confuse, but in Thailand, the popular common name for *Cladogynos orientalis* Zipp. ex Span. was Chettapangkhi. In this study, this plant specimen was confirm with herbarium which had been deposited at the Royal Forest Department in Bangkok, Thailand.

Botanical Description [6-8]

General characterization of *Cladogynos orientalis* Zipp. ex Span. was a shrubly tree, 90-150 cm high. Leave had conspicuously white-tomentellous below, coarsely repand-dentate or lobulate. The ovate-elliptic leave were long about 10 cm Stalk was 7.5 cm long. Male flowers were small, dense, stalked slender piltillode but it was not overlapping no disc. They were stellate hairy. Female flowers were 5-7 big sepals, and leafy, ovary 3 chambered, styles joined at base. Flower heads are usually cernuous in the bug stage. Fruits were capsule, splitting in to bivalved part leaving a central column. Yellow root-bark were rigidly and smell. There were unmistakable features of this plant (Fig.1).

a)

b) c)

Fig. 1. *Cladogynos orientalis* Zipp. ex Span.

a). Fruit and leaving branch

b). Flowering

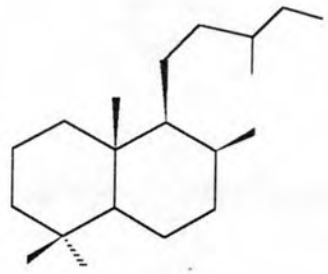
c). Dried-root

Ecology and Distribution [9-10]

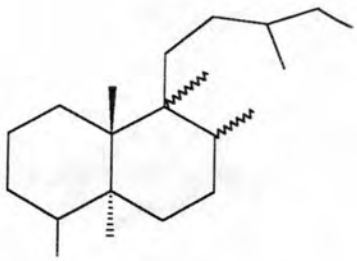
This plants are found in many country such as China, Indochina, North Malaya, Philippines and Thailand. In Thailand, it is common in dry evergreen or moist mixed deciduous forest, or it is scrub up to 450 m and frequently on limestone.

Research studies in Chemical Constituents of *Cladogynose orientalis* Zipp. ex Span.

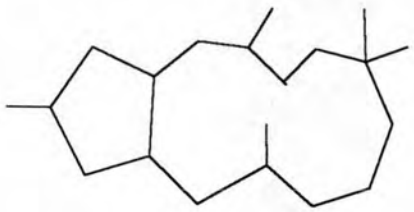
Family Euphorbiaceae contained various of diterpenoids such as clerodane, labdane, jatrophane and lathyrane diterpenoids and sesquiterpenoids as patchoulane and aromadendrane sesquiterpenoids.[11] Diterpenoids were twenty carbons, many skeletons. The sesquiterpenoids were C_{15} compound formed by the assembly of three isoprenoid units. They are found in many living systems but particularly in higher plants. There are a large number of sesquiterpenoid carbon skeletons, which all arise from the common precursor, farnesyl pyrophosphate, by various modes of cyclisation followed, in many case, by skeleton rearrangement (skeleton structure of diterpenoids and sesquiterpenoids from this family are shown in Fig. 2).



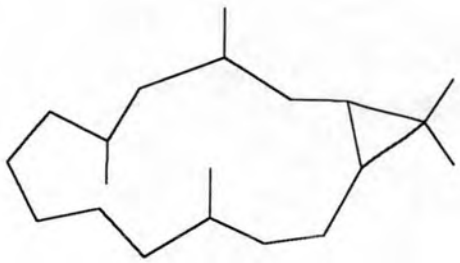
Labdane



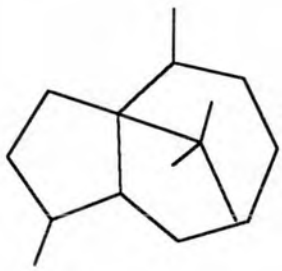
ent-Clerodane



Jatrophane



Lathyrane

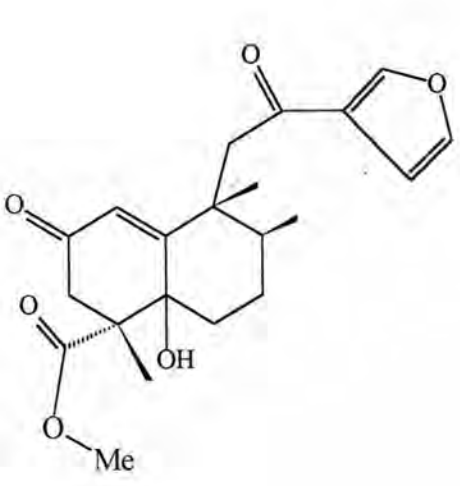


Patchoulane

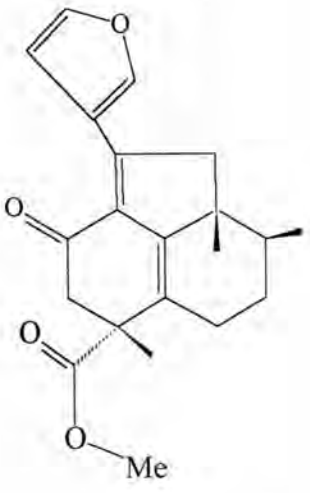
Aromadendrane

Fig. 2 The skeleton of some structures of diterpenoids and sesquiterpenoids

From the literature surveys, Aiyar Sato and coworker studied chemical constituents of this plant[4] and isolated two novel furanoditerpenoids which were chettaphanin I and chettaphanin II (Fig.2). Chettaphanin I was isolated from the roots of *C. crassifolius*[12] and determined the structure based on the basis of chemical and ^{1}H-NMR spectra. One year latter, the same group reported chettaphanin II (Fig. 2). The structure of chettaphanin II was established by X-ray diffraction analysis[5] but they did not show identical structural features and absolute configuration. However, they have not been reported about biological activity of isolated compounds.



Chettaphanin I



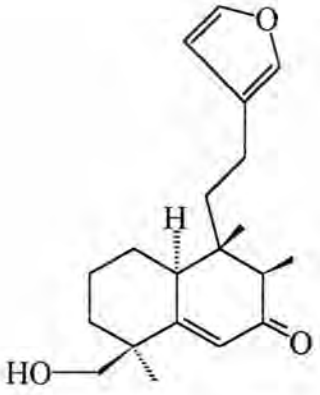
Chettaphanin II

Fig. 3 Organic compounds from the roots of *C. orientalis* [4,5]

Furanoditerpenes had a furan ring in skeleton structure of diterpene. They had 4 skeleton structure types as follows.

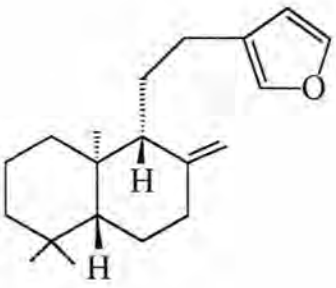
1. Labdanes formed a large group and occured in both enantiomeric series.

Example

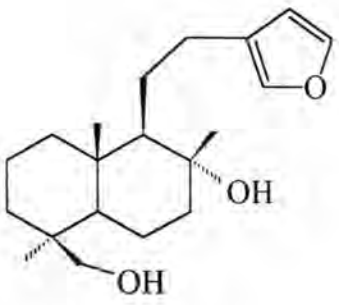


Friedolabdanes [13]

11-Dehydro-(-)-hardwickiic acid [14]



Labdane [15]

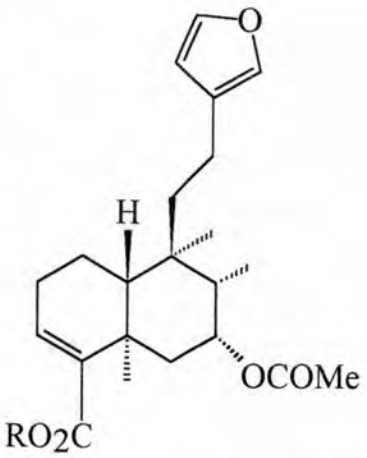


15,16-epoxylabda 13(16),14-diene-8α,19-diol[16]

2. Clerodane

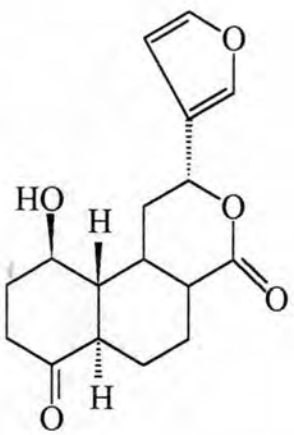
They are abundant and are founded particularly in *Teucrium spp.* where they were highly oxygenated. In the past, *ent*-clerodanes have been named as neoclerodanes and kolavanes but these names are not widly used.

Example

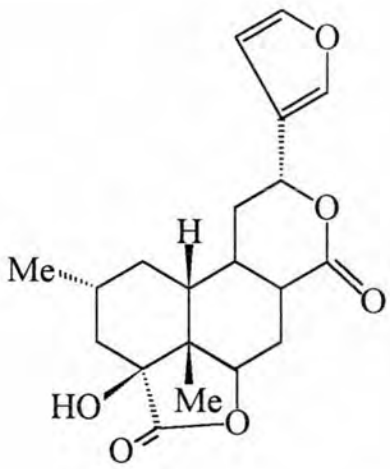


R= H 7-α-acetoxyhardwickii acid [17]

R= Me methyl ester derivertive [17]



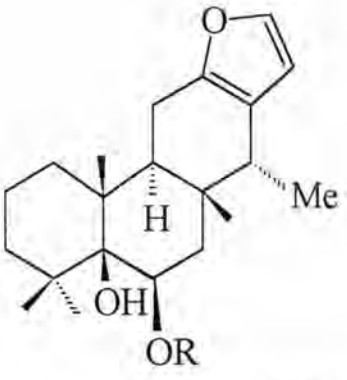
Malabarolide I [18]



Malabarolide II [18]

3. The cassanes presumably arise from methyl migration in the primarane skeleton from C-13 to C-14. Furanocassanes are called vouacapanes.

Example



Caesaldekarins a[19], R=OAc

Caesaldekarins b[19], R=H

From brine shrimp cytoxicity screening of ethanol extract of the roots of *C. orientalis* was moderate activity (LD_{50} =31.62μg/ml). The compound were cytoxic to brine shrimp had a broad range of activity such as brusatol. This compound showed high cytotoxic activity on brine shrimp so it also showed cytotoxicity against KB cell and *Plasmodium falciparum*.[20,21] Brine shrimp (*Artemia salina* Linn.) bioassay is rapid method, reliable, inexpensive and convenient as an in-house.

The objective of this research are summarized as follow.

1 To extract and isolate the chemical constituents from the roots of *C. orientalis*.

2 To identify the structure of the isolated substances.

3 To study biological activity of the isolated substances such as brine shrimp.