

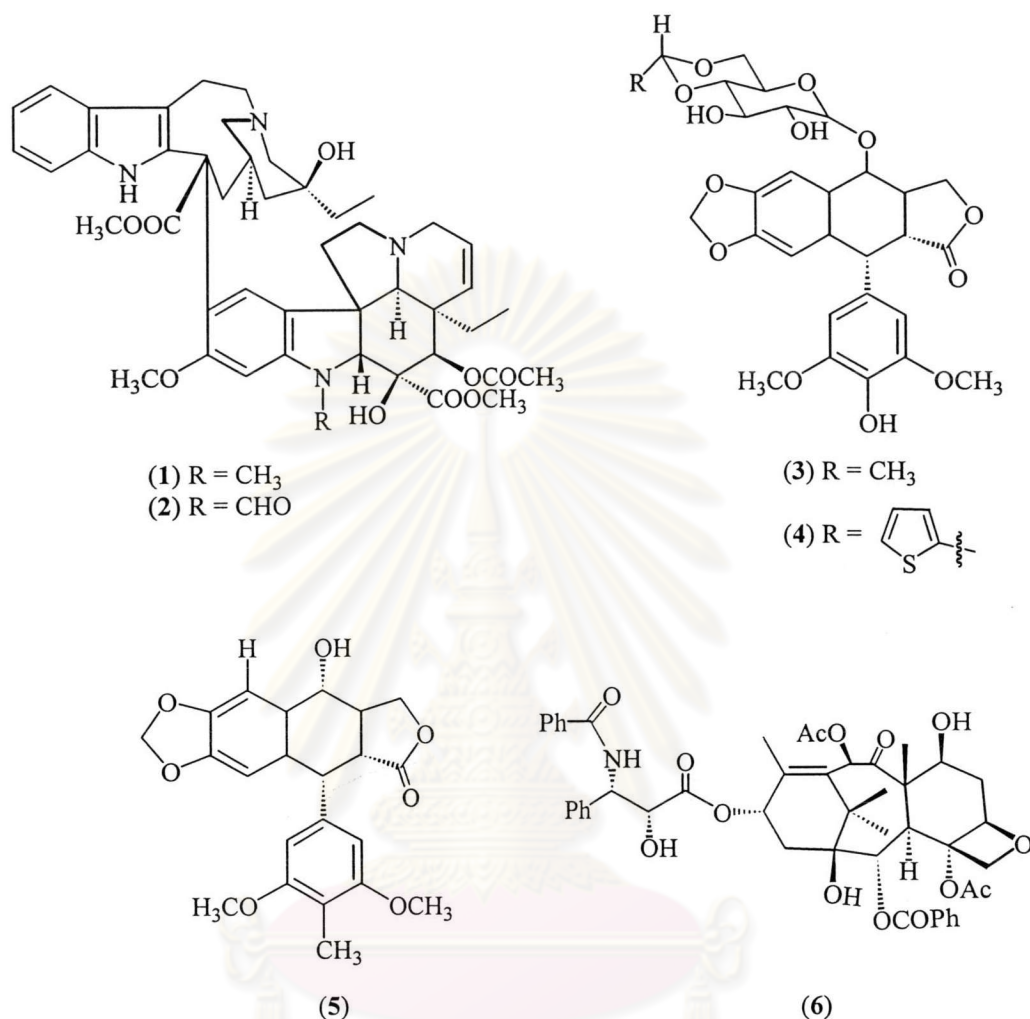
CHAPTER I

INTRODUCTION

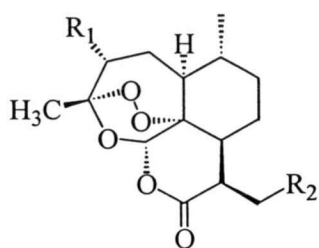
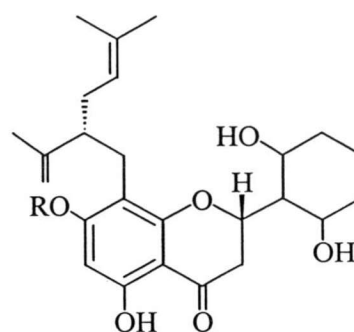
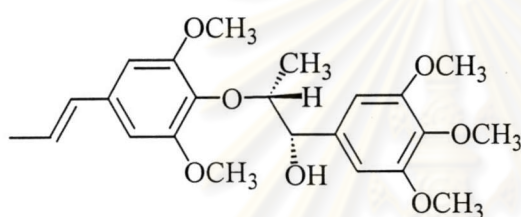
Medicinal plants play a key role in the human health care. About 80 percent of the world population rely on the use of traditional medicine which is predominantly based on plant material.^{1,2} Currently, about one-quarter to one-half of all pharmaceutical displayed in the United States having higher plant origins and at least 119 chemical substances derived from 90 plant species can be considered as important drugs currently in use in one or more countries. Of these 119 drugs, 74 percent were discovered as a result of chemical studies direct at isolating the active substances from plants used in traditional medicine.^{2,3} Many medicinal plants produce a large variety of biologically active substances representing a vast diversity of fascinating molecule architecture. Sometimes a novel bioactive compound had been found and often been employed as starting material for the preparation of a series of synthetic analog, which may have medicinal or economical values. For instance, local anesthetics posses the basic structure as cocaine; decongestant whose the basic structure is ephedrine and psychotropic whose the basic structure is ergot alkaloids and *etc.*⁴ In addition, almost all bioactive compounds from medicinal plants were found not to have side-effect for users. In the way of economical effect. Herbal medicinal plants are found to be cheaper than synthetic pharmaceutical medicine.

The plant derived a variety of bioactive compounds such as anticancer agent in clinical use, the best known are the alkaloids vinblastine (1) and vincristine (2) isolated from the Madagascar periwinkle *Catharanthus roseus*. The etoside (3) and teniposide (4), semisynthetic derivatives of the natural product epipodophyllotoxin, an isomer of the active antitumor agent podophyllotoxin (5) isolated from the roots of various species of the plant genus *Podophyllum*.^{2,4} The diterpenoid parlitataxel (6) isolated from the barks of *Taxus brevifolia*. and the other *Taxus* species have been added in recent years into the armamentarium of clinical therapeutic agents against

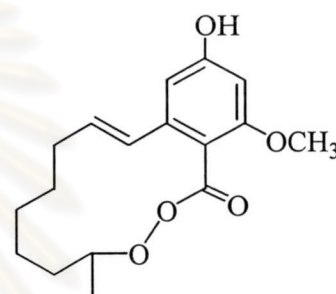
certain human solid tumors, such as ovarian and breast cancer, and is currently in clinical trial for the treatment of lung, colon and the others.^{5,6}



Plant products as antimalarial, artemisinin (7) and derivative analogs (8) which are currently established a clinical important drug against chloroquine resistant strains *Plasmodium falciparum*. Artemisinin, a sesquiterpene lactone bearing an endoperoxide moiety isolated from *Artemisia annua* L.⁷ The exiquaflavanone A (9) and B (10) isolated from *Artemisia indica*⁸ and polysyphorin (11) and raphidecurperoxide (12) isolated from the dried leaves and stems of *Rhaphidophora decursiva* showed activities against *Plasmodium falciparum*.⁹

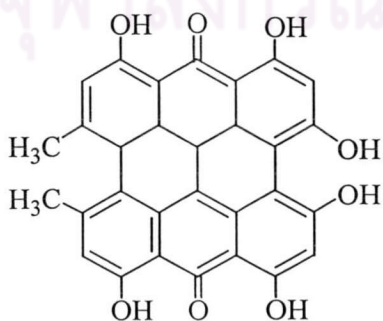
(7) $R_1 = H, R_2 = H$ (8) $R_1 = H, R_2 = CH_2NO_2$ (9) $R = H$ (10) $R = CH_3$ 

(11)

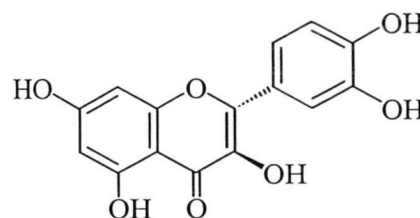


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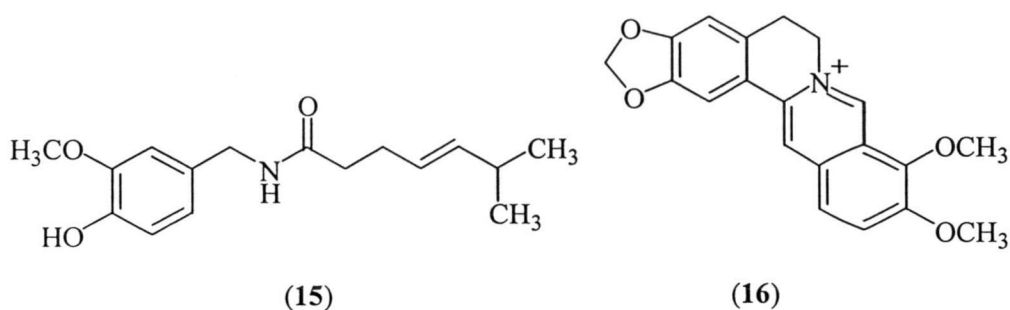
Plant products as antimicrobial: some quinones, flavones, flavonoids, terpenoids, coumarins, and alkaloids, these plant chemicals have been shown *in vitro* to be effective antimicrobial substances against a wide array of microorganisms. Such as anthraquinone (13) from Pakistani tree *Cassia italica*, catechin (14) isolated from green tea, the terpenoid capsaicin (15) from Chili Piper and berberine (16) was potentially effective against trypanosomes and plasmodia. These alkaloids, commonly isolated from the plants of the Menispermaceae.¹⁰



(13)



(14)



Nowadays, humans still suffer from many diseases such as AIDS, cancer, Parkinson, diabetes, malaria and *etc.* Although many pharmaceutical compounds are discovered to accomplish some infection diseases such as malaria and AIDS, it finally resisted to those compounds because of mutation. Some genetic diseases such as diabetes are also unachieved today. The investigation of novel biologically active compounds from herbal medicinal plants is important, especially plants in tropical forest where is plenty of medicinal plants. Thailand has a diversity of plants and living organisms. Many plants were used as drugs for native people to cure diseases such as *Diospyros mollis* Griff. (Ebenaceae) for anthelmintic, *Brucea antidysenterica* for antimalarial, *Catharanthus roseus* for anticancer and *etc.*⁴

Among the medicinal plants available in Thailand, plants belonging to Menispermaceae family are one of Thai medicinal plants, which widely used as traditional herbal medicine.

1.1 General Characteristic of *Coscinium fenestratum* (Gaertn.) Colebr.

Coscinium fenestratum (Gaertn.) Colebr. or “Heam” or “Khrueta hen” or “Khamim Khrueta” in Thai. The genus *Coscinium* belongs to the tribe Coscinieae of the family Menispermaceae. This genus comprises of two species which are stout woody climber growing in the tropical rain forest zones of Asia; Ceylon, India, Thailand, Indochina and West Malaysia (Malaya, Sumatra, Java, Borneo). These two species possess closely in character. The axillary flowers, extra-axillary or cauliflorous in racemiform or peduncled subumbellate aggregate, 20-50 cm in length, were characterized as *Coscinium* species. The floret is monochlamydeous with 6-9 tepals, unisexual. The leaves are subpeltate or ovate, large, hard-coriaceous, palmately, nerved, reticulate, densely hairy beneath. The fruits are drupelets 1-3, globose-

obovoid pubescent. According to the Index Kewensis, the genus *Coscinium* are recognized as *Coscinium blumeanum* Miers. and *Coscinium fenestratum* (Gaertn.) Colebr. (Synonym; *C. wallichianum* Miers., *C. usitatum* Pierre., *C. maingayi* Pierre. and *Menispermum fenestratum* (Gaertn)).¹¹

Coscinium fenestratum (Gaertn.) Colebr. (fig. 1.1) is a large liana with yellow wood and sap. Young twigs are hairy, their first leaves obviously peltate, the next ones ovate, with obtuse-truncate-subcordate, not or hardly peltate base with concave margins, mostly shortly acuminate, hard coriaceous, shining above, 12.5-30 cm by 10-25 cm. The petiole is 5-15 cm, with curved thickened base densely hairy, the inflorescences are axillary or cauliflorous with 6-12 florets.^{12, 13}

Various parts of *C. fenestratum* (Gaertn.) Colebr. have been used in pharmaceutical utilization for widely variety of diseases such as fever, colic, muscle pain, stomachic pain, gout, malaria, diabetes and as antibiotic, antidiarrhoea antihypertensive and antifungal purpose. In folkloric medicine people favor to use stems and roots more than leaves because of the alkaloid contents.

In India, *C. fenestratum* (Gaertn.) Colebr. has been widely used as a yellow dye and a medicine, aqueous or alcoholic extracts have been used to dress bruises and contusions. Darvi and Ayurvedic used against ulcers and affection of the eye. Studying the chemical constituent in this plant found that a major compound is berberine having been treated against the digestive tract like gastric ulcers and cure dermal leishmaniasis in the form of berberine sulphate.¹⁴

Moreover in Vietnam, the alcoholic extract of *C. fenestratum* (Gaertn.) Colebr. provided tablets named "Codan B" to combat dysentery. Having been analyzed by thin layer chromatography, only one alkaloid, berberine, could be detected.¹⁵

There are many researches concerned with the antimicrobial activity of protoberberine alkaloids. The berberine class alkaloids and their derivatives have been reported to exhibit a moderate, slow and selective antimicrobial activity with a low toxicity.^{15, 16} Furthermore, berberine has mentioned to be used for treating the cholera, amoebiasis and diarrhea.¹⁷



Fig. 1.1 *C. fenestratum* (Gaertn.) Colebr.

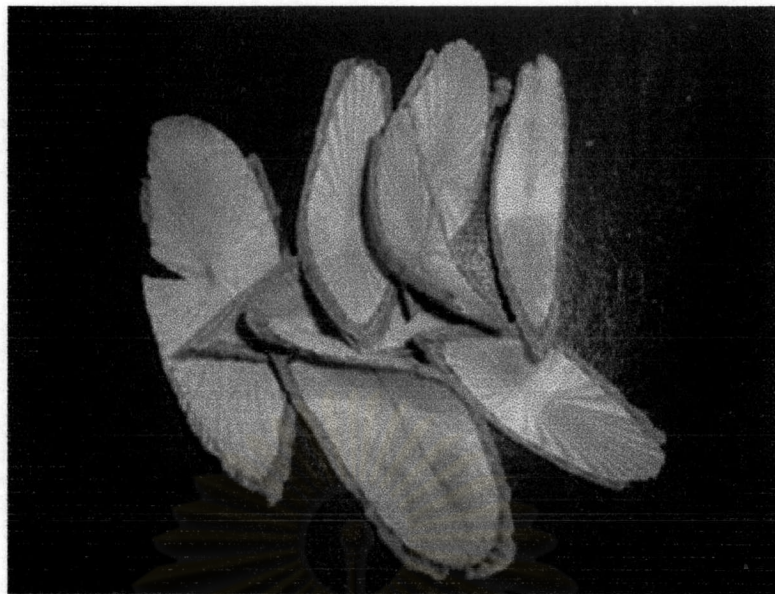
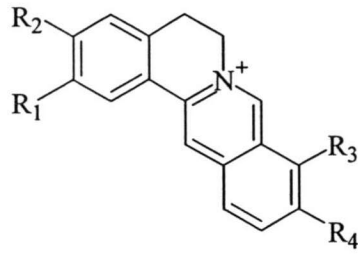


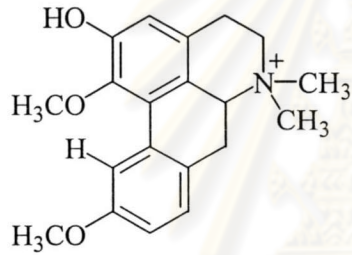
Fig. 1.2 The stems of *C. fenestratum* (Gaertn.) Colebr.

1.2 Chemical Constituents Studies of *C. fenestratum* (Gaertn.) Colebr.

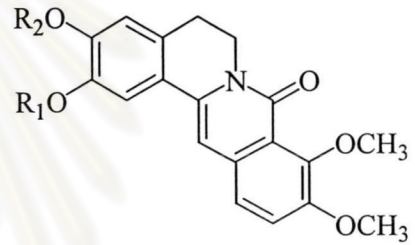
Photochemical work on the alkaloids of *C. fenestratum* (Gaertn.) Colebr. primarily originated from various pharmaceutical investigations of that by the Philippines which berberine (17), palmatine (18) and jatrorrhizine (19) have been isolated and characterized from roots and stems.¹⁸ Then quite an amount of work was carried out with *C. fenestratum* (Gaertn.) Colebr from South Kalimantan, Indonesia. Six alkaloids have been isolated, five of them were protoberberine alkaloids consisting of berberine, palmatine, jatrorrhizine, berberubine (20) and thalifendind (21) and the other is aporphine alkaloid: *N,N*-dimethylindcarpine (22).¹⁴ In 1989, minor alkaloids composing of oxyberberine (23), oxypalmatine (24), 8-oxocanadine (25), 8-oxotetrahydrothalifendine (26), tetrahydroberberine (27) and 12,13-dihydro-8-oxoberberine or 8-oxocanadine and two steroids; β -sitosterol (28) and stigmasterol (29) presented by Malhatra and collaborator.¹⁹ The stems of *C. fenestratum* (Gaertn.) Colebr. from Thailand furnished the new protoberberine alkaloids oxypalmatine, (-)-8-oxotetrahydrithalifendine, (-)-8-oxoisocorypalmatine (30) and either (-)-8-oxothaicanine (31) or (-)-8-oxo-3-hydroxy-2,4,9,10-tetramethoxyberberine (32) in addition to berberine which is a major alkaloid and (-)-8-oxocanadine.²⁰ Moreover, berberine, jatrorrhizine, tetrahydropalmatine (33) and crebanine (34) were reported by Kaewpradup.¹³



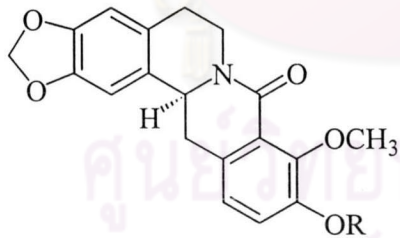
	R ₁	R ₂	R ₃	R ₄
(17)	O-CH ₂ -O		OCH ₃	OCH ₃
(18)	OCH ₃	OCH ₃	OCH ₃	OCH ₃
(19)	OCH ₃	OH	OCH ₃	OCH ₃
(20)	O-CH ₂ -O		OH	OCH ₃
(21)	O-CH ₂ -O		OCH ₃	OH



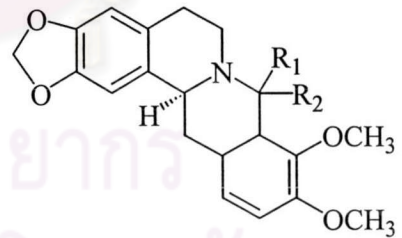
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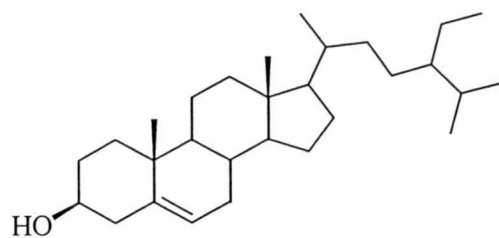


	R ₁	R ₂
(23)	—CH ₂ —	
(24)	CH ₃	CH ₃

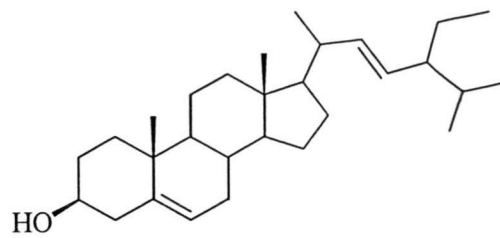


(25) R = CH₃
 (26) R = H

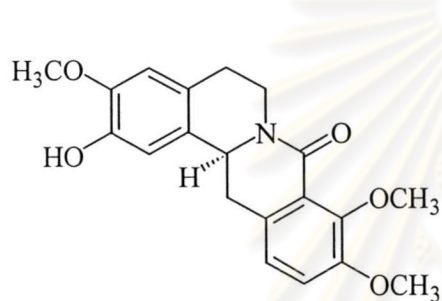
(27) R₁, R₂ = H



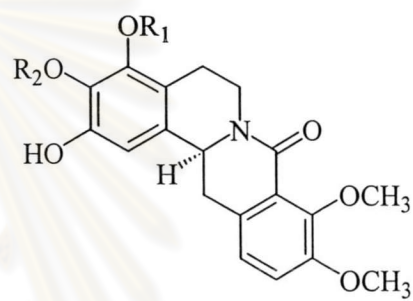
(28)



(29)

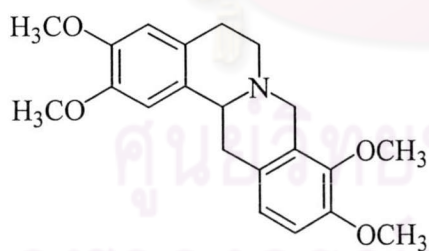
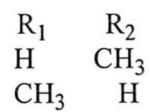


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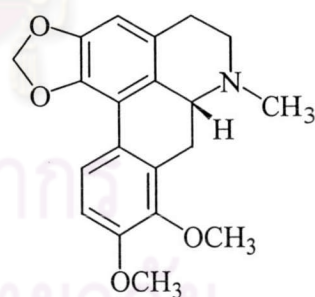


(31)

(32)



(33)



(34)

1.3 Chemical Constituents Studies of *Coscinium* Genus

Thank to plants in *Coscinium* genus having only two species, the one that is widely used as medicine is *C. fenestratum* (Gaertn.) Colebr. The other is not popular for using as medicine to cure ailments. Hence, chemical constituents studies have been reported, focusing on *C. fenestratum* (Gaertn.) Colebr. more than the other species. However, studying of chemical constituents of *Coscinium blumeianum* Miers. also found that berberine alkaloid was a major compound.²¹

1.4 The Goal of This Research

Presently, many people use *C. fenestratum* (Gaertn.) Colebr. as herb medicinal plant widely in order to treat a variety of disease such as fever, colic, muscle pain, stomachic pain, gout, malaria, diabetes and as the antibiotic, antidiarrhoea, antihypertensive and antifungal. Another point involves the fact that it has not been reported of biologically active compounds concerning anticancer, antifungal, cytotoxicity and antimalarial activity from this plant. The pharmaceutical aspects of this plant had not been thoroughly investigated. It is attractive to investigate the chemical constituents and search for bioactive compounds from the stem part of this plant. The received basic information of bioactive compounds from this plant will be utilized in pharmaceutical aspects. Therefore, the following goals can be summarized:

1. To isolate the bioactive substances from the stems of *C. fenestratum* (Gaertn.) Colebr.
2. To elucidate the chemical structure of isolated compounds.
3. To study the biological activities of isolated compounds.

จุฬาลงกรณ์มหาวิทยาลัย