CHAPTER I

INTRODUCTION

Andrographis paniculata **Nees.** is one of nineteen species of *Andrographis* belong to the family Acanthaceae. This plant is available abundantly in India,Pakistan, Sri lanka growing in warm and shady places. It is also cultivated in certain parts of India East and West Indies and Mauritius (Hooker, J. D.1885).

Hooker, J.D. described the characters of Acanthaceae in the Flora of British India, volume 4 (1885) as follow :

Annual herb or very small shurbs ; **Stems** quadrangular, base not pubescent. **Leaves** 2 ½ by ¼ in., narrowed at both ends, never spathulate, ovate at base, paler beneath; petiole ¼ in. ; Racemes 1-4 in.; pedicels 0- 1/16 in., distant, usually pubescent ; bract 1/16 in., linear; bracteols smaller or O ; **Inflorescence** terminal mostly sympodal, the pedicel jn the axil one of each pair of bracts suppressed. Sepals 1/8 in., linear-lanceolate, pubescent corolla ½ in., 2-lipped for at least half its length, hairy; white, spotted rose-purple. **Filaments hairy** upwords. **Ovary** and base of style subglabrous or very thinly hairy. **Capsule** ¾ by 1/8 in., young slightly glandular hairy, mature glabrous. **Seeds** subquadrate, rugose without hairs or scales at any period, wet or dry, yellow or deep brown.

In Thailand, 2-3 species of *Andrographis* are found (Smithinand, 1980):

Andrographis paniculata Nees.	ฟ้าทะลายโจร	Fa	thalai joan	(Bangkok)
	น้ำลายพังพอน	Nam	lai pangpon	(Bangkok)
	หญ้ากันงู	Yaa	kannguu	(Songkhla)
	ฟ้าสาง	Fa	sang	(Chonburi)

เมฆทะลาย	Mekh thalai	(Yala)
ฟ้าสะท้าน	Fa sa tan	(Phatthalung)
สามสิบดี	Sam sib dee	(Roy-ed)

Andrographis paniculata Nees. grows widely throughout the plains of India. The place is assumed to be its native land (Bremekamp, C.E.B.1961).

The characteristic features of *A. paniculata* Nees. are described in Thai Herb of Pharmacopoeia v.1 (Subcommittee on The Establishment of The Thai Herbal ,1995).

Annual herb, up to1 m high, erect, stem acutely quadrangular. **Leaves** simple, opposite, lanceolate, acute, glabrous, entire-slightly undulate, 2 to12 cm long and 1 to 3 cm wide, upper ones often bracteiform; petiole short. **Inflorescence** patent, in panicle, 10 to 30 cm long; terminal and axillary, bract small, pedicelshort. **Calyx** 5- partite, small, linear. **Corolla tube** narrow about 6 mm long; limb not shorter than the tube, bilabiate; upper lip oblong, white with a yellowish top; lower lip broadly cuneate, trifid white with violet marking. **Stamens** 2, inserted in the throat and far exserted, anthers basally bearded. **Superior ovary**, 2-celled, style far exserted. **Capsule** erect, linear-oblong, 1 to 2 cm long and 2 to 5 mm wide, compressed, longitudinally furrowed on the broad faces, thinly glandular-hairy. **Seeds** small, subquadrate.

In Bengal similar to Pakistan. It is used as a bitter tonic, antispasmodic, anti-peristaltic, stomachic and also as an anthelmintic. It has been employed with benefit in cases of general debility in convalescences after fever, disorders of liver and advanced stages of dysentery (Bentley, R. and Trimen, H.1983; Dastur, J.F.1959). The juice of fresh leaves was used as a domestic remedy in the treatment of colic pain, loss of appetite, irregular stools and diarrhoea. A decoction of the same is administered in bowel complaints of children. Usefulness of the juice is increased by the addition of aromatics like clove, cardamom and cinnamon. The household

medicine known as "alui" is made from its leaves and is given to children suffering from stomach complaints and typhoid fever.(Singh ,U. et al .1983)

In India, this herb is well known under the name of "kalmegh" (Chakravarti, D. and Chakravati, R.N.1952) and form the principle ingredient of an extensively used household medicine call "Alui", The herb was dried and made into little globules The globules are prescribed for infant to relieve griping irregular stools and loss of appetite. The crude extract of the leaves of this herb could afford significant protection against alcohol and carbontetrachloride induce hepatic injury at the level of serum and liver glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT) and NADPH - mediated hepatic lipid peroxidation. It was also found to produce a remarkable resistance against carbontetrachloride induce changed in the hepatic cellular and subcellular lipid profile (Choudhury, B.R. and Poddar, M. K.1984) Hepatoprotective activity studies of andrographolide of this herb could protected on carbontetrachloride-induce hepatic toxicity and galactosamine 800 mg/ kg., ip / paracetamol 3 g / kg., po-induced hepatic toxicity (Honda S.S. et al., 1990). The alcoholic extract exhibited significant antidiarrhoel activity against *E. coli* enterotoxins in animal models. The activity was further located in *n*- butanol fraction which led to the isolation of four diterpenes, andrographolide, neoandrogra pholide, deoxyandrographolide and andrographiside. Among the four diterpenes, andrographo- lide and neoandrographolide showed similar activity to loperamide against *E. coli* LT and LT / ST enterotoxin. Andrographolide was found to be superior against ST enterotoxin, the most common cause of epidemics of neonatal diarrhoea.

In China, this herb is used by herb doctors in treatment of a large varity of illness which include acute hepatitis, bacillary dysentery, meningitis, choriocarcinoma and many other acute inflammatory (Chang R, S.et al.1991)

On the survey of Thai medicinal plants, this herb has been promoted to be the primary health care medicinal herb. Fine powder of this herb was mixed with honey

to formulate pills which had been prescribed for treatment of sorethroat, common cold and fever in seven community hospitals (Nuntakan, M. 1990).

250 mg of fine powder of the leaves of this herb has been packed in capsule and named Fa thalai joan capsule. The recommended dose for sorethroat and fever is 3-5 capsules in 3-4 times a day.

Pharmacological studies of leave powder of this herb about inhibition of gastric ulcer induced by stress, aspirin and 30 % acetic acid in albino rat revealed that gastric ulcer induced by aspirin and stress was effectively cured(ศิริมา พรสุวัฒนา, ประสาน ธรรมอุปกรณ์ และ อุมา กิติยานี , 2532).

In vitro study of pharmacological effects of three members in the diterpene lactone group (andrographolide, neoandrographolide and 14-deoxy-11,12-didehydro andrographolide) which were extracted from this herb. In the dose of 1.5×10^{-5} and 1.5×10^{-6} M. They had antispasmodic effect on isolated rat and mice stomach smooth muscle preparation. Their effects on rat stomach strips showed non-competitive antagonism to spasmogenic activity of acetylcholine and in rat stomach strips depolarized by potassium chloride in high concentration, they showed competitive antagonism to spasmogenic activity of calcium chloride. In depolarizing condition, their competitive antagonistic effects were the same as those obtained from 5×10^{-8} M. verapamil. The inhibitory potencies were dose-dependent. In whole isolated mice stomach, the extracts reduced phasic and tonic contraction, especially in tonic phase, induced by acetylcholine and calcium chloride. The results of the present study indicated that the extracts were non-specific antagonist. Although several mechanisms are possible, the results suggest that they may act as calcium-entry blocker. The antispasmodic effect supports the clinical use of this native plant in diarrheal disorder of the gastrointestinal tract (วนิดา แสงอลังการ, ประสาน ธรรมอุปกรณ์, อุมา กิติยานี และ ชัยโย ชัยชาญทิพยุทธ , 2533).

Pharmacological studied of this herb revealed that aqueous extract, 50% and 85% ethanol extract of the aerial part in concentration 200 mg / ml of physiological solution could decreased the spasm of guinea pig ileum activated with acetylcholine,

barium chloride, histamine and serotonin. The ethanol extract was more effective than aqueous extract (กมล สวัสดิมงคล และ คณะ, 2533).

In vitro studied by Agar dilution method revealed that of 70 % and 80 % ethanol extract could inhibit microbials causing diarrhea such as *Shigella dysenteriae, Vibrio chlolarae* 01, *Escherichia coli* and *Salmonella typhi.* The 10 mg/ml extract could inhibit microbial causing respiratory tract infection such as β-streptococcus gr.A and *Staphyllococcus aureus* (ธิดารัตน์ ปลื้มใจ และ นาถฤดี สิทธิสมวงศ์ , 2533).

85% ethanol extract in the dose of 2 g / kg could decrease the swelling of the carageenan-induced hind paw edema in albino rat. The inflammatory effect did not find in aqueous extract and 50% ethanol extract (กองวิจัยและพัฒนาสมุนไพร , 2533).

The methanolic extract of the leaves of this herb could be significant cytotoxi city against KB and P 388 cells. Three diterpenes from isolation of this herb androgra pholide, a major constituent have been potent cytotoxic activity against KB culture as well as P 388 lymphocytic leukemia, whereas 14-deoxy-11,12-didehydroandrographolide and neoandrographolide have shown no cytotoxicity in the tumor cell lines (Siripong, P. et al.1992).

Clinical studied by comparative study between 250 mg capsules of fine powder of this herb and tetracyclin given in 2 regimens, 500 mg every 6 hours for 3 days or 1 g every 12 hours for 2 days, to 200 diarrhea or dysentery patients revealed that the herb capsules could decrease symtom more effectively than tetracyclin (ปัญจางค์ ธนังกูล และ ชัยโย ชัยชาญทิพยุทธ , 2528).

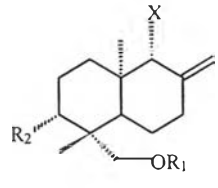
Comparative studied between this herb and paracetamal in 152 pharyngotonsilitis patients revealed that paracetamol or this herb in regimen 6 g per day could decrease fever and sorethroat to 80-90 % in 3 days (คณิต สุวรรณบริรักษ์ และ ชัยโย ชัยชาญทิพยุทธ, 2534).

Although there were many studies about pharmacological activities of this herb, but there were a few explanation about the components in this herb which

exhibited the pharmacological activities, mode of actions of the compounds and structure activity relationship.

The main components of this herb are the diterpene lactones of which andrographolide is the major component. The structures of andrographolide and several related diterpene lactones have been recently deduce. Nowadays, have to try to isolate new compounds as same as to synthesize chemical transformation products of andrographolide and of interesting diterpene lactones to study the suitable pharmacological of action.

This research was aimed to synthesize novel andrographolide liked compounds containing diterpene lactone moiety. The derivatives as 14-deoxy-11,12-didehydroan drographolide-3,19-diester (di-acyl derivatives of dehydroandrographolide) and 14-deoxy-11,12-didehydroandrographolide-19-monoester (mono-acyl derivatives of dehydroandrographolide) were synthesized as follow (See figure 1).



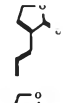
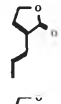
Compound	X	R_1	R_2
A1&A2		$COCH_3$	$OCOCH_3$
A3&A5		$CO(CH_2)_2CH_3$	$OCO(CH_2)_2CH_3$
A4		$CO(CH_2)_2CH_3$	OH
A6&A8		COC_6H_5	$OCOC_6H_5$
A7		COC_6H_5	OH
A9&A10		$CO(CH_2)_5CH_3$	$OCO(CH_2)_5CH_3$
A11&A12		$CO(CH_2)_{16}CH_3$	$OCO(CH_2)_{16}CH_3$

Figure 1. The chemical structures of target compounds in this research