CHAPTER I
INTRODUCTION

A large number of plants in Thailand have been used as traditional medicine for a long time. Chemical constituents of plants were widely studied in order to use in medicines. Medicinal plants have been the primary treatment in the health care system. In addition, there are numerous medicinal plants that were clinically used in Thailand because they are easily available, inexpensive, have good efficiency and has less side effect in contrast to synthetic drugs.

Piper betle Linn. is a medicinal plant belonging to the Piperaceae family, *Piper* genus. This plant is commonly known as Phluu[1] which is used as herbal medicine. The family Piperaceae includes nine genera and about 1400 species, more than one-half of which belong to the genus *Piper*[2]. The *Piper* genus has 14 species in Thailand; they are:[3]

1. *P. aurantiacum* Miq.
2. *P. betle* Linn.
3. *P. chaba* Hunter (*P. retrofractum* Vahl.)
4. *P. chuvya* Roxb.
5. *P. flavimarginatum* C.DD.
6. *P. kurzii* Ridl.
7. *P. longamentum* C.DC.
8. *P. longrum* Linn.
9. *P. nigrum* Linn.
10. *P. porphyrophyllum* N.E.Br.
11. *P. ribesoides* Wall.
12. *P. sarmentosum* Roxb.
13. *P. subpeltatum* Kunth (*P. umbellatum* Linn.)
14. *P. subpenninerve* Ridl.

Fig. 1 Leaves and stems of *Piper betle* Linn.

The general characteristics of *Piper betle* Linn.[4] is a stout creeper, claiming by adventitious roots at the nodes, quite glamorous. Leaves are simple, alternate, broadly ovate or rounded, 5-18 by 2-10 cm, having apex acute or acuminate, unequally rounded at the base or broadly heart-shaped. Flowers are very minute, in cylindrical male or female spikes, pendulous, male spikes are 2-12 cm long, having peduncle 1.5-3 cm long; female spikes are long-peduncled, without calyx and corolla. Fruit is a berry, small, round, pulpy; containing one globose seed .

In the past, *Piper betle* Linn. has been used in traditional medicine. The claimed efficacy in Thai traditional medicinal text books[4] are as follows: roots have been found to be efficient as an antifertility activity. Leaves have been found to be efficient as an antimitotic, growth inhibition, mutagenic, antimutaginic, antifertility, antimicrobial, smooth muscle relaxant, toxicity assessment and insect attractant activity. Fruits have been found to be efficient as carcinogenic activity. Essential oil has been found to be efficient as hypotensive, skeletal muscle relaxant, antipassmodic and anthelmintic activity. From a literature survey of this plant, it was found that it is very interesting and useful in many ways.

According to a preliminary study involving a collaborative research between the Natural Products Research Unit of the Department of Chemistry and Department of Biology, Chulalongkorn University with the aim of screening for bioactive compounds possessing cytotoxicity against brine shrimp (*Artemia salina* Linnaeus), the ethanol crude extract of the leaves of *Piper betle* Linn. gave attractive results. Therefore, the leaves of this plant were selected for further investigation.

1.1 Chemical Constituents Studies on *Piper* Genus

Literature surveys of chemical constituents of the plants belonging to *Piper* genus revealed that there have been a variety of organic substrates isolated from this plant which were summarized by Pimporn Montienart [5] as shown in Table 1. The structures of some isolated compounds are shown in Fig. 2.

Table 1 The chemical constituents of some plants in Piper genus

Scienctific name	Plant parts	Organic Compounds	Ref.
P.aborescens Roxb.	leaves	piplartine **(22)**	6
		piplartine dimer A **(23)**	
		N-(3-methoxy-4,5-methylene di-oxydihydrocinnamoyl)-Δ^3-pyridin-2-one	
	stems	(+)-diayangambin	7,8
		(+)-epiexcelsin	
		N-(3,4-dimethoxycinnamoyl)- - Δ^3 -pyridine-2-one	7,17
		N-(3-methoxy-4,5-methylene di-oxycinnamoyl)-Δ^3-pyridin-2-one	
		N-(3,4,5-trimethoxycinnamoyl)-Δ^3 -pyridin-2-one	
		1,2,3-trimethoxy-4,5-dioxo-6a,7-dehydroaporphine	7,9
		1,2-dimethoxy-4,5-dioxo-6a,7-dehydroaporphine	7
P. aduncum Linn.	leaves	aduncin A	14
		aduncin B	
		aduncin C	
		aduncin D	
		aduncin E	
		piperiton	13
		stigmasterol **(61)**	
		α- tocopherol =**Vitamin E (64)**	14
		trans-phytol	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. aduncum Linn.	leaves	1-{6-hydroxy-4-methoxy-4-(1-isopropylspiro-[benzo-furan-2-(3H),1'cyclohex-2-en] -7-yl]-3-phenyl-1-propanone	12
		2-hydroxy-4-methoxy-6-[1-(1-isopropy)-4-methylcyclohex-3-en-1-yloxy] dihydrochalcone	
		4-hydroxy-3,5-bis(3-methyl-2--butenyl) benzoic acid	10
		4-hydroxy-3(2-hydroxy-3-methyl-2-butenyl) benzoic acid methyl ester	
		8-hydroxy2,2-dimethyl-2H-chromene-6-carboxylic acid methyl ester	11,13
		2,6-dihydroxy-4-methoxy-3-[6-(1-isopropy)-3-methylcyclohex-2-en-1-yl] dihydrochalcone **=methyllindaretin**	12,14
		3-geranyl-4-methoxybenzoic acid methyl ester	11
		4,5-dimethoxy-6-(2-propenyl)-1,3-benzdioxole = **dillapiol**	10
		2,2-dimethyl-8-(3-methyl-2-butenyl) -2H-chromene-6-carboxylic acid	13

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. aduncum Linn.	leaves	methyl-2,2-dimethyl-2H-chromene-6-carboxylate	13
		methyl-3-(2-hydroxy-3-methyl-2-butenyl) -4-hydroxy -benzoate	
	fruits	4-methoxy-3,5-bis(3-methyl-2-butenyl) benzoic acid	10
		methyl-3-(6-hydroxy-3,7-dimethyl-2,7-octadienyl)-4-methoxy benzoate	13
		methyl(6S)-2-trans-hydroxy-2,6-dimethyl-2,7-octadienote	
		pseudodillapiol **(34)**	
P. amalago Linn.	stem bark	β-amyrin **(59)**	
	leaves	dopamin **(30)**	
	roots	ishwarol	15
		2-methoxy -4,5-methylene-dioxy-trans-cinnaoyl piperi-dide **(18)**	16
		2-methoxy -4,5-methylene-dioxy-trans-pyrollidide	
P. attemuatum Ham	roots	N-isobutyl-deca-trans-2-trans-4-dienamide **(3)**	18
		guineensine **(4)**	
		piperlonguminine **(6)**	
		piperine **(14)**	
	leaves	8-hentriacontanol	19
		(-) galbelgin	21,22

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. attenuatum Ham.	leaves	pipoxide chlorohydrin **(53)**	21
	whole plant	crotepoxide **(33)**	75
		10-amino-2-hydroxy-3,4-dimethoxyphenanthrene-1-carboxylic acid lactam = **piperolactam D**	20
P. aurantiacum Miq. and Wall	seeds	dl-N-benzoylphenylalanine	24
		N-(N′-benzoyl-S-phenyl-alaninyl)-S-phenylalaninol = **aurantiamide (27)**	23
		aurantiamide acetate **(27)**	23,82
		auranamide **(27)**	
		vanillic acid	24
P. auritum Kunth.	leaves	β-bisabolene	25
		borneol **(55)**	
		borneol acetate **(55)**	
		β-bourbonene	
		cadina-1,4-diene	
		Δ-cadinene **(57)**	25,27
		camphene **(56)**	25
		camphor **(55)**	
		Δ^3-carene **(56)**	
		β-caryophyllene **(57)**	25,27
		β-caryophyllene oxide **(57)**	
		1,8-cineol	25
		α-copaene **(57)**	
		α-cubenene **(57)**	
		ρ-cymene **(56)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. auritum Kunth	leaves	ρ-cymen-8-ol	25
		Δ-elemene (57)	
		elemicin (32)	
		eugenol (32)	
		n-hexadecane	
		humulene (57)	
		limonene (56)	
		linalool (57)	
		monanone-2	
		muurolene (57)	25,27
		myristicin (32)	25
		myrcene	
		parraffin	
		α-phellandrene	
		β-phellandrene	
		α-pinene (56)	
		β-pinene (56)	
		piperochromanoic acid	
		piperochromenoic acid	
		piperoic acid	
		sabinene (56)	
		cis-sabinene hydrate	
		safrole (32)	
		sitosterol (60)	
		spathulenol	
		spathulenol isomer	
		α-terpinene (56)	
		γ-terpinene (56)	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. auritum Kunth.	leaves	terpinolene	25
		α-thujene	
		trans-phytol	27
		7,4′-dimethoxy-3′-hydroxy-	
		-flavone	
		4-hydroxy-5-(E,E-farnesyl)	
		benzoic acid	
	roots	androstenol	26
		cepharadiones A and B **(25)**	
		cholesterol **(62)**	26
		dillapiole **(32)**	
		1-propenal-3,4-	
		(methylenedioxy)-5-	
		methoxybenzene	
		1-allyl-2,3-(methylenedioxy)-5-	
		methoxybenzene	
		safrole **(32)**	
		stigmasterol **(61)**	
P. banksii Miq.	leaves,stem	dillapipole **(32)**	32
		elemicin **(32)**	
		N-isobutyl-trans-2-trans-4-	
		octadienamide **(3)**	
P. betle Linn.	roots	β-sitosterol **(61)**	
	leaves	allylpyrocatechol **(32)**	29
		allylpyrocatechol-	
		diacetate **(32)**	
		camphene **(56)**	
		cadinene **(57)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. betle Linn.	leaves	β-caryophyllene **(57)**	64
		chavibetol **(32)**	
		chavibetol acetate **(32)**	29
		chavibetol methyl ether **(32)**	
		chavicol **(32)**	64
		1,8-cineol	
		ρ-cymene **(56)**	29
		eugenol **(32)**	64
		eugenol methyl ether **(32)**	
		limonene **(56)**	29
		safrole **(32)**	
		β-sitosterol **(60)**	
		stigmasterol **(61)**	
	stems	crotepoxide **(53)**	31
		methyl piperbetol	
		piperbetol	
		piperol A	
		piperol B	
P .brachystachyum C.DC.	fruits	asarinin **(40)**	30
		brachystinebrachyamide A	
		brachyamide	
		cinnamic acid **(34)**	
		longamide	
		methyl ploviatitol =**fargesine**	
		pipataline **(54)**	
		pipercide **(4)**	
		retrofractamide A	
		sesamine **(40)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P . brachystachyum C.DC.	fruits	sitosterol **(60)** N-isobutyl-13-(3,4-methylene-dioxyphenyl) trideca-2,4-12-trienamide = **guineensine** (4) 3,4,5-trimethoxy cinnamic-acid **(34)**	30
P. callosum Opiz	leaves leaves,stems roots	safrole **(32)** dillapiole **(32)** elemicin **(32)** pipercallosidine **(5)** pipercallosine **(5)** piperovatine **(5)**	28
P. capense	roots	Δ^8-3′,6′-dihydro-3,4,3′,4′-bis-methylenedioxy-6′-oxo-8,3′-neolignan Δ^8-1′,2′--dihydro-3,4,3′,4′-bis-methylenedioxy-2′-oxo-8,1′-neolignan iso-Δ^8-1′,2′--dihydro-3,4,3′,4′-bis-methylenedioxy-2′-oxo-8,1′-neolignan	34,35
P. clarkii C.DC. & Linn.	leaves,stems fruits	(+)-cretepoxide **(53)** β-sitosterol **(60)** 3-(4-hydroxyphenyl)propyltetra-cosanoate (+)-(2S,3R,4R,5R)-1-benzoyl-oxy methylcyclohex-1(6)-ene-2,3,4,5-tetrol-3-benzoate	39 38

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. clarkii C.DC. & Linn.	fruits	(+)-(2S,3R,4R,5R)-5-acetyl-1-benzoyloxy methylcyclohex-1(6)-ene-2,3,4,5-tetrol-3-benzoate =(+) **acetyl piperenolA**	38
	leaves,stems	asaronaldehyde	40
		(-) cubebin **(37)**	
		(-) deoxypodorhizon	
		(-) dihydrocubebin **(39)**	
		2-furanol-4-(1,3-benzo-dioxol-5-ylmethyl) tetrahydro-3-(3,4,5,-trimethoxyphenyl) = **clusin(37)**	
		2S,3R,4R,2-ethoxy-3-(3,4,5-trimethoxyphenyl) methyl -4-(1,3-benzodioxol-5-yl) methyl -tetrahydrofuranol	41
		3R,4R-bis-3,4-(3,4,5-trimethoxy-phenyl) methyl -tetrahydrofuran-2-one	
	leaves,stem	2R,3R,2-(7-methoxy-1,3-benzodioxol-5-yl) methyl -3-(3,4,5-trimethoxyphenyl) methyl -butan-1,4-diol	
		2R,3R,2-(1,3-benzodioxol-5-yl) methyl -3-(3,4,5-trimethoxy-phenyl) methyl -butan-1,4-diol	
		sitosterol **(61)**	40
		(-) cubebin **(37)**	42
		clusin **(37)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P.clusii C.DC. & Linn.	fruits	deoxypodorhizon **(36)** (-) O-ethylcubebin **(37)** hinokinin **(36)** 5''-methoxy hinokinin **(36)** (-) ledol (-) (3R,4R)-bis-4-[(3,4,5-trimethoxyphenyl) methyl]-tetrahydrofuran-2-ol 1-(2,4,5-trimethoxyphenyl) -1,2-diacetoxypropane 1-(2,4,5-trimethoxyphenyl) -1,2-dihydropropane 1-(2,4,5-trimethoxyphenyl) -2-acetoxy-1-hydroxypropane	42
P. cubeb C.DC.	fruits	(+) crotepixide **(53)** (+) piperanol A (+) piperanol B (-) zeylenol	38
P. cubeba Linn.	fruits	bicyclosesquiphellandrene (-) clusin **(37)** (-) cubebin **(37)** (-)cubebininolide (-) cubebinone **(36)** (-) cubebinin **(37)** (-) dihydroclusin **(39)** (-)dihydrocubebin **(39)** 1-epibicyclosesquiphellandrene α-O-ethyl cubebin **(37)**	43 44 45 44 45

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. cubeba Linn.	fruits	β-O-ethyl cubebin **(37)**	46
		hemiariensin **(39)**	
		heterotropan	
		(-)hinokinin **(36)**	
		magnosalin	
		(-)-5-methoxyhinokinin **(36)**	
		(-)di-o-methyl thujaplicatin-	45
		methyl ether **(36)**	
		(-)isoyatein **(36)**	
		2,4,5-trimethoxybenzaldehyde	
		(2R,3R)-2-2 (3,4methylene	
		dioxybenzyl)-3-dimethoxy	
		benzyl) butyrolactone	
		(-)yatein **(36)**	
P. fadyenii C.DC.	roots	fasyenolide **(49)**	47
P. falconeri C.DC.	leaves,stem	(2E,4E) N-isobutyl-7-(3,4-	55
		methylenedioxyphenyl)-hepta-	
		2,4-dienamide	
P. futokadzura Sieb	leaves	isodihydrofutoquinol A **(44)**	50
		isodihydrofutoquinol B **(44)**	
		isofutoquinol A **(44)**	
		isofutoquinol B **(44)**	
		piperinone **(42)**	51,53
	leaves,	camphene **(56)**	48
	stems	crotepoxide **(53)**	
		futoamide	
		futoenone **(43)**	48,49

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. futokadzura Sieb	leaves,stem	futoquinol **(44)**	48
		isoasarone	48,54
		limonene **(56)**	48
		α-pinene **(56)**	
		β-pinene **(56)**	
		sabinene **(56)**	
		β-sitosterol **(60)**	
		stigmasterol **(61)**	
	stem	kadsurenone **(42)**	52
		kadsurin A **(42)**	
		kadsurin B **(42)**	
P. guayranum C.DC.	leaves,stem	alatamide	56
		tembamide acetate	
P. guineense Schum	leaves	dihydrocubebin **(39)**	58,59
& Thonn.	seeds	$\Delta^{\alpha\beta}$-dihydrowasanine **(17)**	63
		$\Delta^{\alpha\beta}$-dihydrowisanidine **(11)**	65
		wisanine **(16)**	66,67
		wisanidine **(11)**	65
	fruits	eicosa-2,4-dienoic	66
		$\Delta^{\alpha\beta}$-dihydropiperine	59,71
		$\Delta^{\alpha\beta}$-dihydropiperlonguminine	59
		4,5-dihydro-2′methoxy-piperine **(17)**	64
		dihydrowisanine **(17)**	67
		guineensine **(4)**	57
		piperine **(14)**	
		N-isobutylhexadeca-trans-2-trans-4-dienamide	57

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. guineense Schum & Thonn.	fruits	N-isobutyleicosa-trans-2-trans-4-dienamide	57,71
		N-isobutyloctadeca-trans-2-trans-4-dienamide	57,59
		13-(3,4-methylenedioxyphenyl)-undeca-2,4-12-trienoic	57
		trichostachine **(11)**	57,67
	roots	$\Delta^{\alpha\beta}$-dihydropiperine	59
		4,5-dihydropiperine	64,67
		dihydrowisanine **(17)**	67
		N-isobutyl-trans-2-trans-4-eicosadienamide **(3)**	70
		pellitorine **(1)**	68
		piperine **(14)**	67,70
		wisanidine **(11)**	70
		wisanine **(16)**	60,69
P. hispidum H.B.K. & Sw.	leaves, twig	2,3-dihydro-4,6-dimethoxy-chalcone	72
		4-(5-E-n-hexadecenyl) phenol	
		8-hydroxy-5,7-dimethoxy-flavanone **(52)**	
		2-hydroxy-3,4,6-trimethoxy-chalcone **(51)**	
		6-hydroxy-5,7-dimethoxy-flavanone **(52)**	
		5,7,8-trimethoxy flavanone **(52)**	
	fruits	2,6-dihydroxy-4-methoxy-dihydrochalcone **(52)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. hispidum H.B.K. & Sw.	fruits	pinostrobin **(52)**	73
		pseudo-dillapiole **(34)**	
		4-methoxy-3,5-bis(3-methyl-2-	
P. hookeri Miq.	leaves	butenyl)-benzoic acid	
		1-phenylethanol benzoate	74
		β-sitosterol **(60)**	
		triacontane	
		triacontanol	
	whole	crotepixide **(53)**	75
	plant	pipoxide chlorohydrin **(53)**	
P. hostmannianum	stems	linalool **(57)**	76
		sitosterol	
		5-hydroxy-7-methoxy-6,8-	
		dimethylflavanone	
		methyl-2,2-dimethyl-2H-1-	
		benzopyran-6-carboxyrate	
		methyl-4-hydroxy-3(2-	
		hydroxy-3-methylbut-3-enyl)	
		benzoate	
P. kadsura Ohrvi	whole plant	pinocembrin	
	stems	germacrene D	29
		kadsuranin A	77
		kadsuranin B	
		kadsuranin C	
		kadsuranin D	
		kadsuranin E	
		kadsuranin F	
		kadsurenone **(55)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. longum Linn.	fruits	asarinine **(40)**	30
		eicosadienamide	80
		eicosatrienamide	30,80
		guineensine **(4)**	80
		dihydropiperlonguminine **(6)**	80
		longamide	30
		methyl pluviatiol	
		octadecadienamide	80
		pipercide **(4)**	
		piperine **(14)**	
		piperlonguminine **(6)**	
		pipernonaline **(21)**	
		piperundecalidine **(21)**	
		pluviatiol	30
		sesamin **(40)**	
		3,4,5-trimethoxy cinnamic acid	
	seeds	(+) diaeudesmin	84
		sesamin **(40)**	
		sylvatin **(28)**	
	roots	aristolactam A II	81,83
		cepharadione A	81
		cepharadione B	
		cepharanone B	
		norcepharadione B	
		piperlongine	79
		piperlongumine **(22)**	
		piperlonguminine **(6)**	
		piperadione	81

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. longum Linn.	roots	piperine **(14)**	79
		piperolactam A	81
		piperolactam B	
		β-sitosterol **(60)**	79
		2-hydroxy-1-methoxy-4H-dibenzo(de,g) quinoline-4,5-(6H) -dione	81
	stems	piplatine **(22)**	78
P. marginatum Jacq.	leaves	anethole **(34)**	28
		1,8-cineol **(56)**	29
		ρ-cymene	28
		β-eudesmol	
		eugenol methyl ether **(32)**	
		2-hydroxy-4,5-methylenedioxy-propiophenone	86
		isoeugenol methyl ether **(34)**	28
		limonene **(56)**	29
		maginatoside **(52)**	85
		2-methoxy-4,5-methylenedioxy-propiophenone	86
		3,4-methylenedioxypropio-phenone **(54)**	
		β-pinene **(56)**	28
		piperonal **(54)**	86
		safrole **(32)**	
		stearic acid	
		vitexin **(52)**	85

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. marginatum Jacq.	whole plant	3-faresyl-4-hydroxybenzoic acid	87
P. methysticum Forst.	leaves	cepharadione A	97
		dihydrokawain	89,96
		dihydromethysticin	
		demethoxyyangonin	96
		kawain	89,96
		methysticin	
		yangonin	
		pipermethysticin	
	leaves, stems	dihydrokawain	95
		dihydromethysticin	
	roots	dihydrokawain	90,95
		dihydromethysticin	95,96
		11,12-dimethoxydihydro-kawain	92
		11-hydroxy-12-dimethoxy-dihydrokawain	
		(+)-5,6,7,8-tetrahydroyan-gonin	91
		kawain	95,96
		methysticin	93
		tetrahydroyangonin	95
		yangonin	95,93
	stems	dihydrokawain	95,96
		dihydromethysticin	
		desmethoxyyangonin	
		kawain	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. methysticum Forst.	stems	methysticin **(46)**	95
		pipermethysticin **(24)**	
		tetrahydroyangonin **(47)**	
		yangonin **(47)**	95,96
P..nepalense Miq. & Forst.	leaves	caryophyllene oxide	98
		N-isobutyl-deca-trans-2-trans-4-dienamide	
		piperlonguminine **(6)**	
		piperine **(14)**	
		sitosterol **(60)**	
		triacontanol	
P. nigrum Linn.	leaves	δ-cadinene **(57)**	105
		euginol **(32)**	
		α-humulene **(57)**	
		methyl eugenol **(32)**	
	whole plant	crotepoxide **(53)**	75
		pipoxide chlorohydrin **(53)**	
	stems	n-hentriacontane	29
		hentriacontan-16-ol	
		hentriacontan-16-one	
	fruits	bergamotene	
		bisbolene	
		caffeic acid **(34)**	28
		camphene **(56)**	29
		car-3-ene	
		carvel	
		carvone	
		α-caryophyllen **(57)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. nigrum Linn.	fruits	coumaperine	102
		crytone	29
		ρ-cymen-8-ol	
		citronellol	
		dihydrocarveol	
		dihydropipercide	106,107
		elemene	29,28
		eugenol nethyl ether	29
		β-farnesene	104
		guineensine **(4)**	29
		isoquercitrin **(52)**	
		kaempferol glycoside	
		linalool **(56)**	
		limonene **(56)**	
		myrcene **(56)**	28
		myristicin **(32)**	29
		nerolidol **(58)**	
		ocimene	104,106
		pellitorine **(1)**	29
		α-phellandrene	
		piperanine **(17)**	101
		pipercide **(4)**	
		piperoleine A&B **(19)**	
		piperettine **(21)**	29
		quercitrin **(52)**	
		quercitrin glycosides	
		rhamnetin glycosides	
		rutin **(52)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. nigrum Linn.	fruits	safrole **(32)**	28
		sesquisabinene	99
		α-terpineol **(56)**	29
		γ-terpinene **(56)**	
		α-thujene	
		N-5-(4-hydroxy-3-methoxy-phenyl)-2E-pentenoyl - piperdin **(17)**	103
		N-isobutyl-2E,4E,8Z,eicosa-trienamide **(3)**	104
		N-isobutyleicosa-trans-2-trans-4-dienamide **(3)**	100
		N-trans-feruloyl piperidine **(18)**	104
		N-trans-feruloyl tyramine **(26)**	102
		N-isobutyl-12-(3,4-methylene-dioxyphenoxy)-3-methyl-(2E,-4E)-2,4-dodecadienamide	106
		N-isobutyl-2E,4E-octadeca-dienamide	104
		N-isobutyl-trans-2-trans-4-eicosadienamide	28
		N-isobutyl-trans-2-trans-4-octadecadienamide	
		sesquibinene	99
P. peepuloides Roxb.	leaves	2-methoxy-4,5-methylenedioxy-Z-cinamoyl **(18)** piperidide	109,110
		peepuloidine **(9)**	111

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. peepuloides	leaves	β-sitosterol **(60)**	111
Roxb.		β-sitosterol glucoside	
		trichostachine **(11)**	94
	leaves,	(+)-diaeudesmin	109,112
	fruits	5-hydroxy-4,7-dimethoxy	
		flavone	
		5-hydroxy-3,4,7-trimethoxy -	
		flavone	
		N-isobutyldodeca-trans-2-	108,109
		trans-4-dienamide	
	fruits	1-(3,4-methylenedioxy	112
		benzene)-dodec-1-ene	
		peepuloidine **(9)**	
		pellitorine **(1)**	
		pipataline **(54)**	109,112
		piperine **(14)**	108
		sesamine **(40)**	108,109
P. retrofractum	leaves,	N-isobutyl-9-(3,4-	117
Vahl.	stems	methylenedioxyphenyl)-2E,4E,	
		8E-nonatrienamide =	
		retrofractamide A (7)	
		pipercide =	
		retrofractamide B (4)	
		retrofractamide C (7)	
		retrofractamide D	
		sesamin **(40)**	
		3,4,5-trimethoxydihydro-	
		cinnamic acid **(34)**	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. retrofractum Vahl.	fruits	pipercide **(4)**	19
		pipereicosalidine	118
		piperlonguminine **(6)**	
		pipernonaline	
		piperine **(14)**	
		retrofractamide C **(7)**	
(*P. chaba* Hunter)	roots	piperlonguminine **(6)**	37
		piperine **(14)**	
		β-sitosterol **(60)**	
		sylvatine **(28)**	
	stems	piplartine **(22)**	36
		piperine **(14)**	
		β-sitosterol **(60)**	
(*P. officinarum*	fruits	guineensine **(4)**	28,114
C.DC.)		N-isobutyldocosa-trans-2-trans-4-cis-10-trienamide	28,116
		methyl piperate	19,113
P. ribesoides Wall.	fruits	bornyl-ρ-coumarate	61
		elemol	
		hinokinin **(36)**	
		β-sitosterol **(60)**	
	stems	crotepoxide **(53)**	
		futoamide	33,120
		4-hydroxy-3-methoxy-N-methylaristolactum = **N-methylaristolactam**	61
		2-isobornyl-4-hydroxy cinnamate	33

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. ribesoides Wall.	stems	N-isobutyl-5-phenyl penta-2,4-dienamide	33
		guineensine **(4)**	
		methyl-7-phenyl-2E,4E,6E-heptatrienoate	61
		methyl piperate	33,61
		methyl piperettate	33
		piperlonguminine **(6)**	
		piperic acid	
		senediol	61
		β-sitosterol **(60)**	33,61
	whole plant	(-)-cubebin **(37)**	62
		(-)-hinokinin **(36)**	
		3,7-dimethyl-3-hydroxy-4-(ρ-coumaryloxy)-1,6-octadiene	
		N-isobutyl-2E,4E-deca-2,4-dienamide	
		methyl-2E,4E,6E,7-phenyl-2,4,6-heptatriene	
		methyl piperateoat	
		palmitic acid	
		stearic acid	
P. rugosum	whole plant	8,9-dihydropiplartine	121
		piplartine dimer **(23)**	
P. saltuum C.DC.	aerial part	prenylated hydroxybenzoic acid 1	122
		prenylated hydroxybenzoic acid 2	

Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. saltuum C.DC.	aeril part	prenylated hydroxybenzoic acid 3	122
P. sanctum Schlecht. ex Miq.	fruits	cepharadion A	81,125
		cepharadion B	
	roots	5-(-methoxy)-cinnamylidine-4-methoxybut-3-enolide = piperolid (III) **(48)**	123
		methylenedioxypiperolid **(48)**	
P. sarmentosum Roxb.	leaves	asaricine	
		α-asarone	
		-asarone	126,127
		1- ally-2,6-dimethoxy-3,4-methylenedioxybenzene	126
		hydrocinnamic acid **(35)**	
	fruits	1-(3,4-methylenedioxyphenyl)-1E-tetradecene	128
		N-(3-phenylpropanoyl)-pyrrole **(29)**	128
		pellitorine **(1)**	
		sarmentine **(13)**	
		sarmentosine **(13)**	
		β-sitosterol **(60)**	
P. schmiditii Hook.f.	leaves, stems	(+) calopiptin	129
		friedelin **(63)**	130,131
		futoquinol **(44)**	129
		galgravin	130
		β-o-glucoside	
		isodihydrofutoquinol-A **(43)**	129

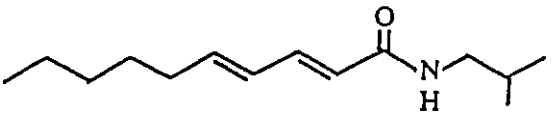
Table 1 (cont.)

Scienctific name	Plant parts	Organic Compounds	Ref.
P. schmiditii	leaves,stems	isodihydrofutoquinol-B	129
Hook.f.		**(43)**kadsurin A **(42)**	129,133
		(+) machilin G	
		octacosanoic acid	130
		β-sitosterol **(60)**	
		1-triacontanol	
		(-) zuionin A	129,132
P.sumatranum Var.	leaves,stems	andamanicin	134
& C.DC.		asaralaldehyde	42,134
		asarinin **(40)**	134
		asarone	42,134
		3-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-1,2-dihydroxy propane	134
		1(2,4,5-trimethoxyphenyl)-1-hydroxy-2-methoxy propane	42
		β-sitosterol	42,134
		tricontane	
P. sylvaticum Roxb.	seeds	aurantiamide acetate **(26)**	24
		3,5-dihydroxy-4,7-dimethoxy-flavone = pilloin	139
		N-isobutyl-4,5-dihydroxy-2-(E)-decenamide = sylvamide **(2)**	137,138
		sesamin **(40)**	24
		sylvatesmin **(41)**	139
		sylvone **(38)**	88
	roots	guineensine **(4)**	135
		piperlongumine **(22)**	135,136

Table 1 (cont.)

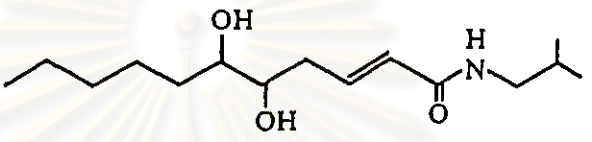
Scienctific name	Plant parts	Organic Compounds	Ref.
P.sylvaticum	roots	piperine **(14)**	135,136
Roxb.		sesamin **(40)**	
P. trichostachyon	leaves	trichostachine **(11)**	94
		N-pyrrolidinyl-eicosa-trans-2-trans-4-dienamide = trichonine **(10)**	
	stems	cyclopiperstachine **(7)**	144
		cyclostachin A **(12)**	144,145
		cyclostachin B **(12)**	144
		piperstachine **(7)**	143,146
		trichostachin **(11)**	147
P. tuberculatum	roots	piplartine **(22)**	141
Facq.		piplartine dimer A **(23)**	
		3,4,5-trimethoxy cinnamic acid **(34)**	
P. villiramulum	leaves	villiramulin A	142
		villiramulin B	

(1)



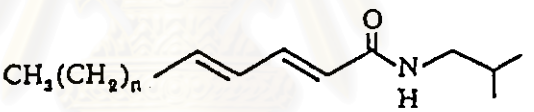
pellitorine

(2)



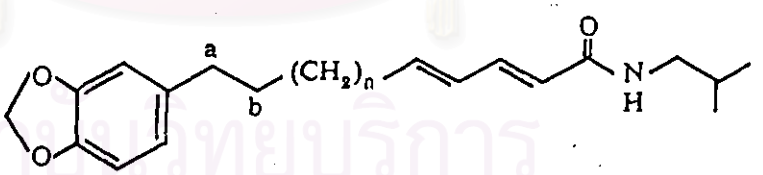
sylvamide

(3)



isobutylamide dienes (E, E) n = 2, 6, 10, 12, 14

(4)

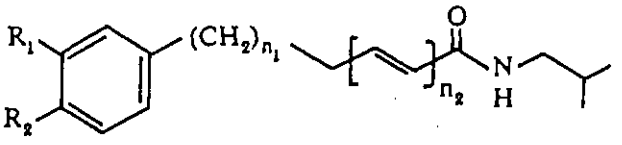


pipercide : n = 4, ab = unsaturated bond

dihydropipercide : n = 4, ab = saturated bond

guineensine : n = 6, ab = unsaturated bond

Fig 2 The chemical constituents of some plants in *Piper* Genus

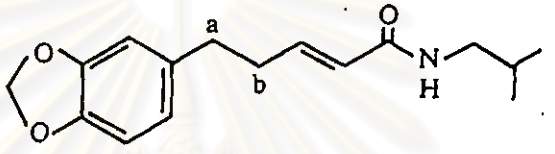


(5)

pipercallosidine R_1 and $R_2 = OCH_2O$, $n_1 = 3$, $n_2 = 1$

pipercallosine R_1 and $R_2 = OCH_2O$, $n_1 = 3$, $n_2 = 2$

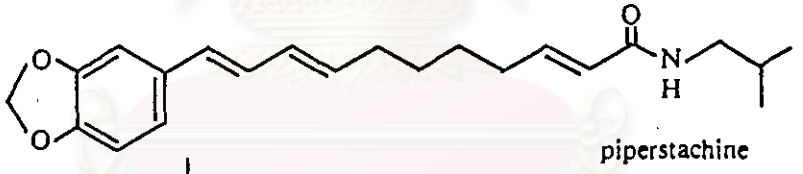
piperovatine $R_1 = H$, $R_2 = OCH_3$, $n_1 = 0$, $n_2 = 2$



(6)

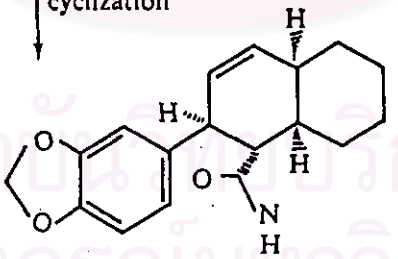
piperlonguminine ab = unsaturated bond

dihydropiperlonguminine ab = saturated bond



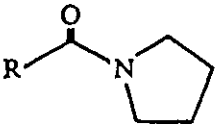
piperstachine

cyclization



(7)

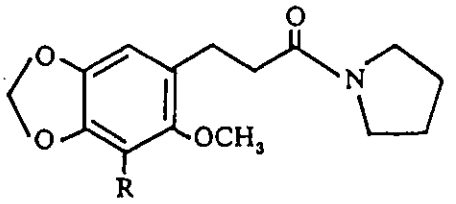
cyclopiperstachine



(8)

pyrrolidides

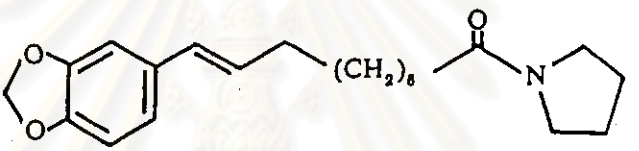
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



(9)

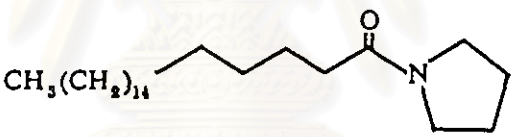
peepuloidine : R = OCH_3

3'-desmethoxypeepuloidine : R = H

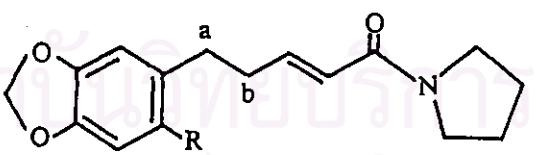


tricholeine

(10)



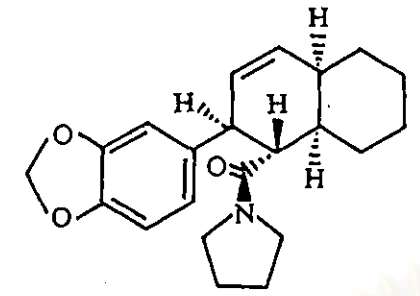
trichonine



(11)

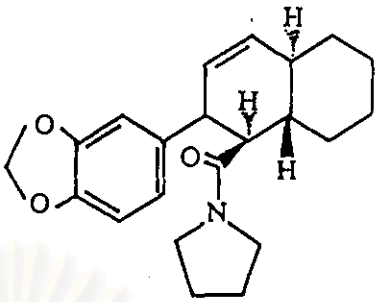
	R	ab
trichostachine	H	unsaturated bond
wisanidine	OCH_3	unsaturated bond
$\Delta^{\alpha\beta}$-dihydrowisanidine	OCH_3	saturated bond

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus

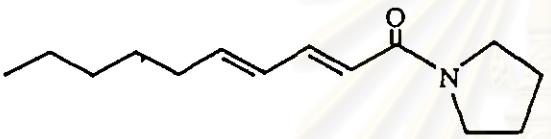


cyclostachine A

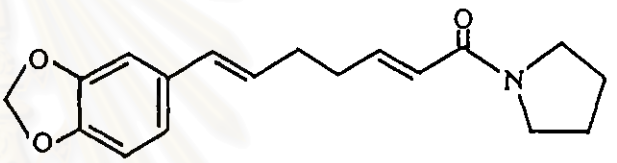
(12)



cyclostachine B

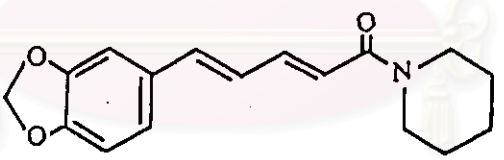


sarmentine

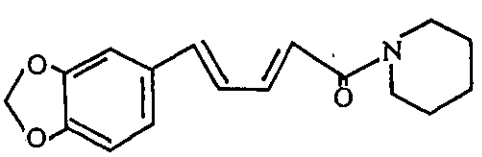


sarmentosine

(13)



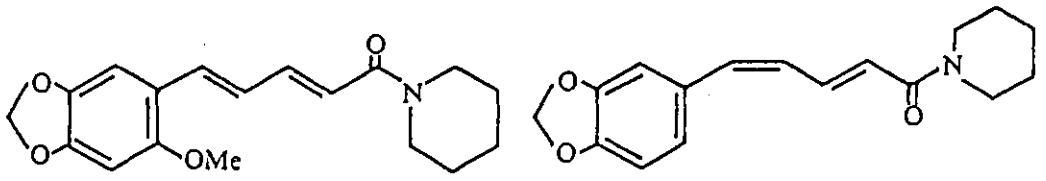
(14) piperine



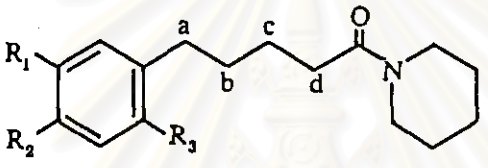
(15)

chavicine

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



wisanine $C_{18}H_{21}NO_4$ **(16)** *trans*-2-*cis*-4-wisanine $C_{18}H_{21}NO_4$

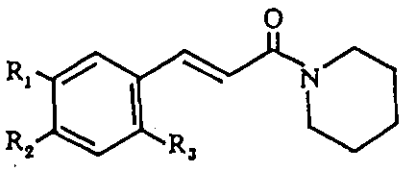


(17)

derivative of piperine

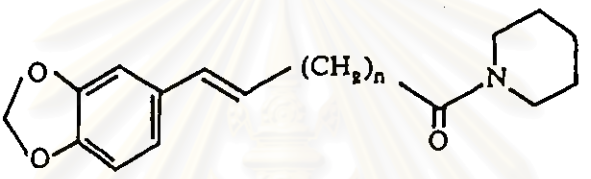
	R_1	R_2	R_3	ab	cd
piperanine	-OCH_2O-		H	sat.	unsat.
tetrahydropiperine	-OCH_2O-		H	sat.	sat.
4,5-dihydro-2'-methoxypiperine	-OCH_2O-		OCH_3	sat.	unsat.
dihydrowisanine	-OCH_2O-		OCH_3	sat.	unsat.
coumaperrine	H	OH	H	unsat.	unsat.
N-5-(4-hydroxy-3-methoxyphenyl)-penta-*trans*-2-*trans*-4-dienoyl piperidine	OCH_3	H	H	unsat.	unsat.

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



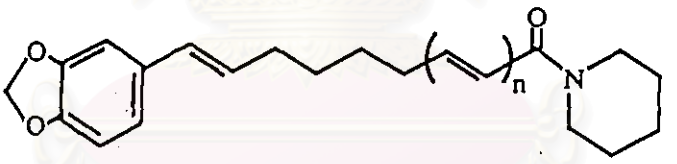
(18)

	R_1	R_2	R_3	
I	$-OCH_2O-$		OCH_3	2-methoxy-4,5-methylenedioxycinnamic acid piperidide
II	OCH_3	OH	H	N-*trans*-feruloyl piperidine
III	$-OCH_2O-$		H	3,4-methylenedioxycinnamic acid piperidide



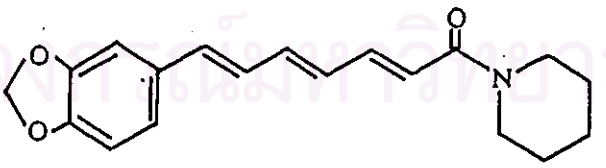
(19)

piperoleine A : n = 4 piperoleine B : n = 6



(20)

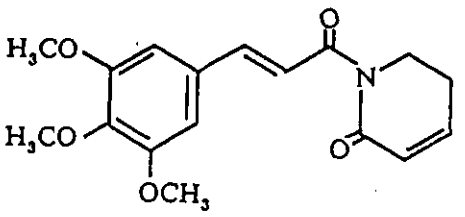
pipernonaline : n = 1 piperundecalidine : n = 2



(21)

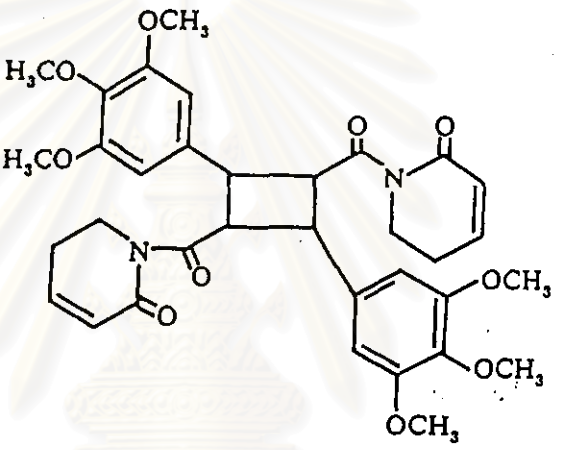
piperettine

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



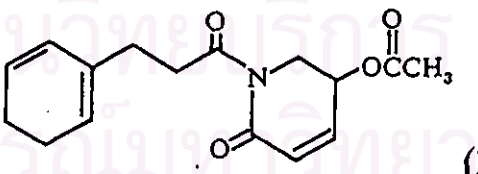
(22)

piplartine



(23)

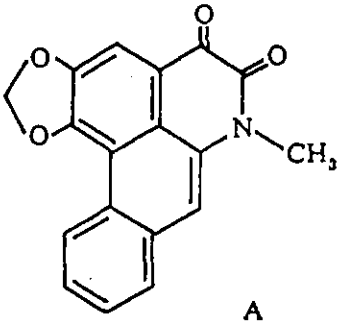
piplartine dimer A $C_{34}H_{38}O_{10}N_2$



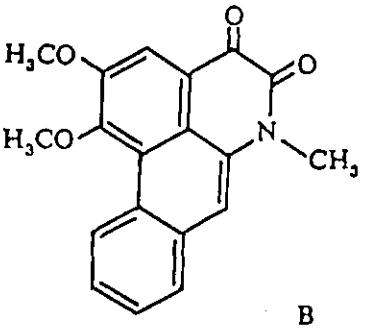
(24)

pipermethystine $C_{16}H_{17}NO_4$ M.W. 287.1157

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



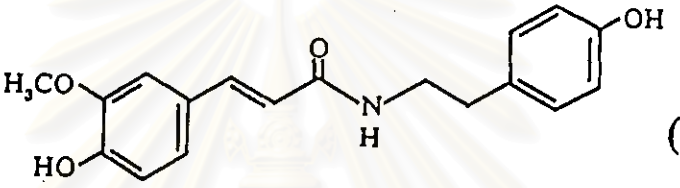
A



B

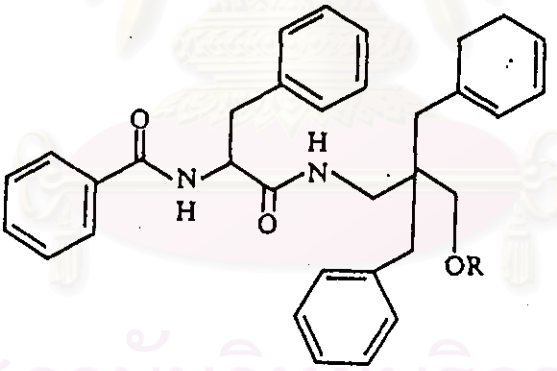
(25)

cepharadiones A and B



(26)

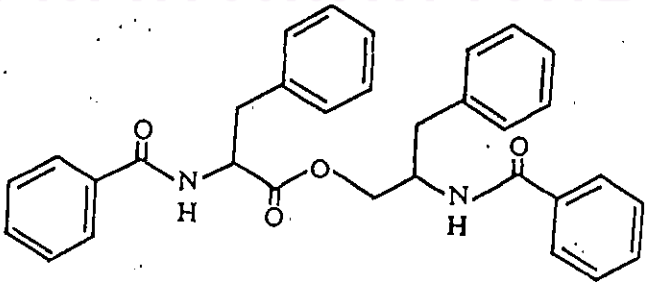
N-*trans*-ferulyl tyramine



(27)

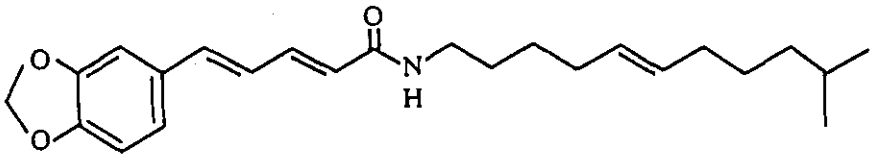
R = H, aurantiamide

R = CH_3CO, aurantiamide acetate

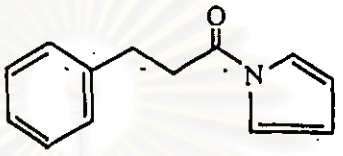


auranamide

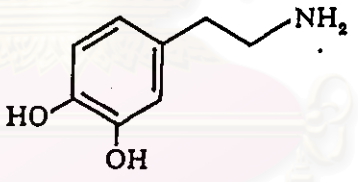
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



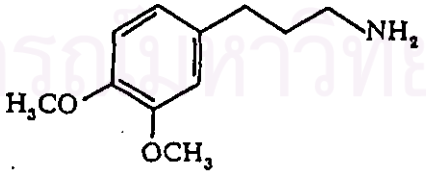
sylvatine (28)



N-(3-phenylpropanoyl) pyrrole (29)



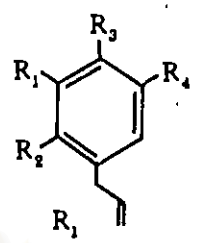
dopamine (30)



3,4-dimethoxyphenylpropylamine (31)

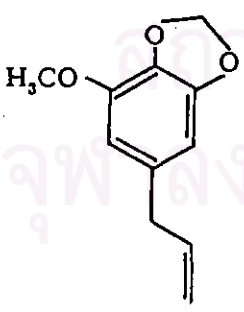
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus

derivative of allylcatechol in *Piper*

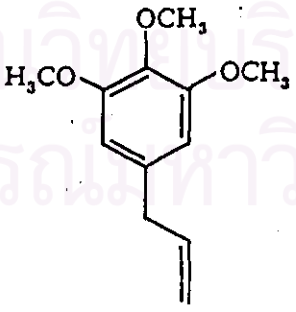


(32)

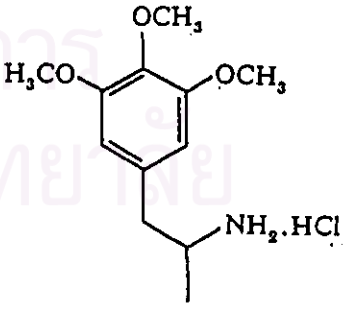
	R_1	R_2	R_3	R_4
allylpyrocatechol	H	H	OH	OH
chavibetol	H	H	OCH_3	OH
chavibetol acetate	H	H	OCH_3	OAc
chavibetol methyl ether	H	H	OCH_3	OCH_3
chavicol	H	H	OH	H
dillapiol	OCH_3	OCH_3	$R_3 + R_4 =$	OCH_2O
elemicin	H	OCH_3	OCH_3	OCH_3
estragole	H	H	OCH_3	H
eugenol	H	H	OH	OCH_3
eugenol methyl ether	H	H	OCH_3	OCH_3
myristicin	H	OCH_3	$R_3 + R_4 =$	OCH_2O
safrole	H	H	$R_3 + R_4 =$	OCH_2O



myristicin



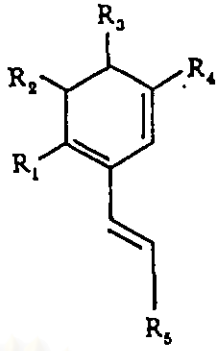
elemicin



amphetamine HCl

(33)

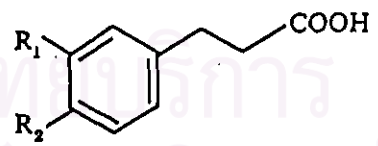
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



(34)

derivative of 1- propenyl benzene

	R_1	R_2	R_3	R_4	R_5
anethole	H	H	OCH_3	H	H
caffeic acid	H	H	OH	OH	COOH
cinnamic acid	H	H	H	H	COOH
3,4-5-trimethoxycinnamic acid	H	OCH_3	OCH_3	OCH_3	COOH
methyl 3,4,5-trimethoxy-cinnamate	H	OCH_3	OCH_3	OCH_3	$COOCH_3$
3,4-methylenedioxycinnamic acid	H	H	$R_3 + R_4 = OCH_2O$		COOH
isoeugenol methyl ether	H	H	OCH_3	OCH_3	H
ω-hydroxyisodillapiol	OCH_3	OCH_3	$R_3 + R_4 = OCH_2O$		OH
pseudodillapiol	$R_1 + R_2 = OCH_2O$		OCH_3	OCH_3	H

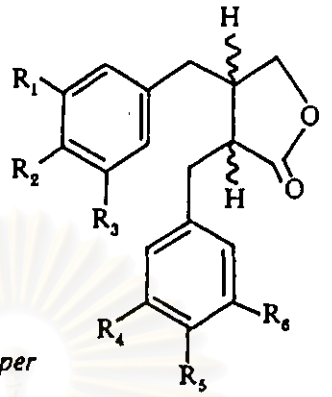


(35)

	R_1	R_2
hydrocinnamic acid (phenylpropionic acid)	H	H
3,4-dimethoxyphenylpropionic acid	OCH_3	OCH_3

phenylpropionic acid

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



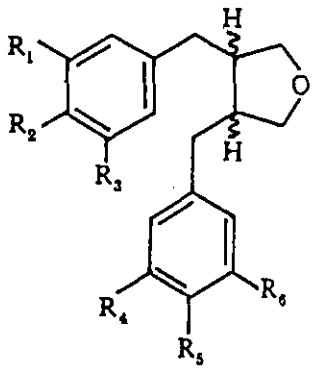
(36)

Butanolides in *Piper*

	R_1	R_2	R_3	R_4	R_5	R_6
I	-OCH_2O-		H	OCH_3	OCH_3	OCH_3
II	OCH_3	OCH_3	OCH_3	-OCH_2O-		H
III	OCH_2O		H	-OCH_2O-		H
IV	OCH_3	OCH_3	H	-OCH_2O-		H
V	-OCH_2O-		H	-OCH_2O-		OCH_3
VI	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
VII	-OCH_2O-		H	OCH_3	OCH_3	OCH_3
VIII	OCH_3	OCH_3	OCH_3	-OCH_2O-		OCH_3
IX	OCH_3	OCH_3	H	OCH_3	OCH_3	OCH_3

	Butanolides
I	yatein
II	isoyatein
III	hinokinin (cubebinolide)
IV	
V	5"-methoxyhinokinin
VI	
VII	deoxypodorhizon
VIII	cubebinone
IX	di-O-methylthujaplicatin methyl ether

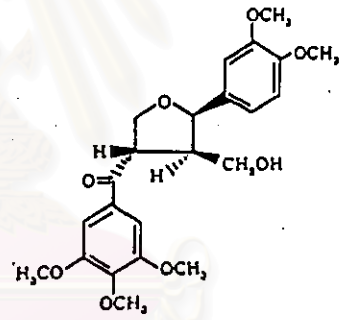
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



(37)

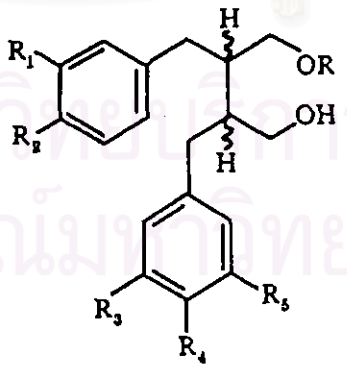
Tetrahydrofuranols

		R_1	R_2	R_3	R_4	R_5	R_6
I	cubebin	-OCH_2O-		H	-OCH_2O-		H
II	clusin	-OCH_2O-		H	OCH_3	OCH_3	OCH_3
III		OCH_3	OCH_3	OCH_3	OH	H	OH
IV	α-O-ethyl cubebin	-OCH_2O-		H	-OCH_2O-		H
V	cubebinin	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3



(38)

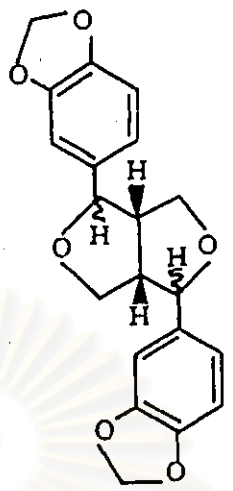
sylvone



(39)

		R	R_1	R_2	R_3	R_4	R_5
I	dihydroclusin	H	-OCH_2O-		OCH_3	OCH_3	OCH_3
II	dihydrocubebin	H	-OCH_2O-		-OCH_2O-		H
III	hemiariensin	OAc	-OCH_2O-		-OCH_2O-		H

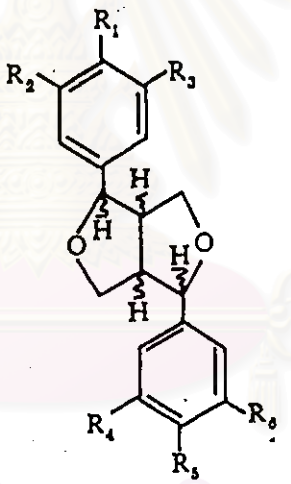
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



(40)

H = α : sesamin

H = β : asarinin

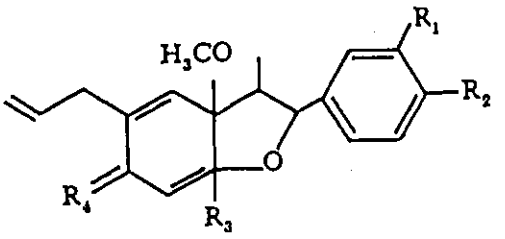


(41)

bisepoxy lignans

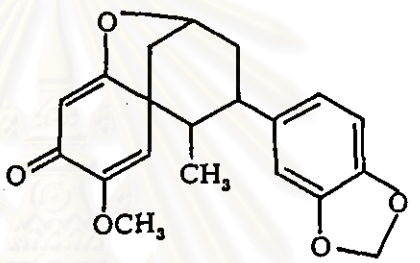
		R_1	R_2	R_3	R_4	R_5	R_6
I	yangambin	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
II	sylvatesmin	OCH_3	OCH_3	H	H	OH	OCH_3
III	eudesmin	OCH_3	OCH_3	H	H	OCH_3	OCH_3
IV	aschantin	$-OCH_2O-$		H	OCH_3	OCH_3	OCH_3

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



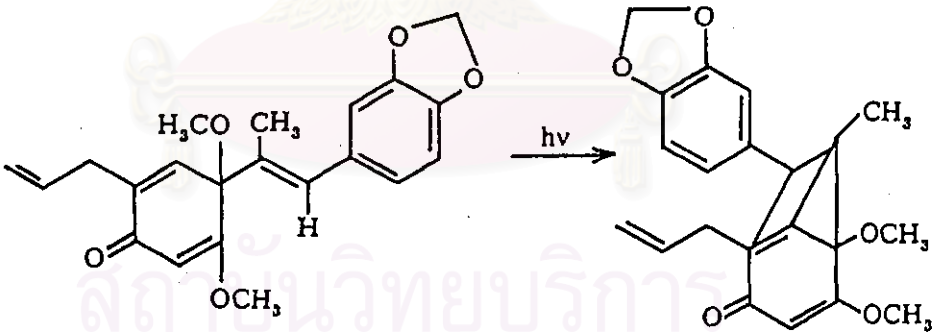
(42)

	R_1	R_2	R_3	R_4
piperenone	OCH_3	OCH_3	OCH_3	O
kadsurenone	OCH_3	OCH_3	H	O
kadsurin A	$-OCH_2O-$		OCH_3	O
kadsurin B	$-OCH_2O-$		OCH_3	$<^{OH}_{H}$



(43)

futoenone



(44)

futoquinol

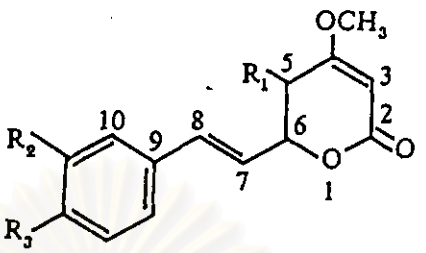
isofutoquinol A

isofutoquinol B

dihydrofutoquinols A and B

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus

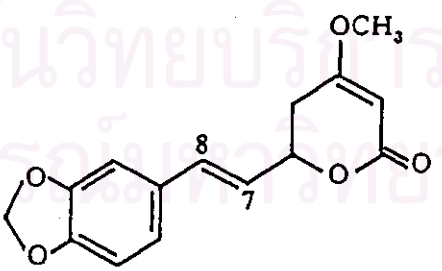
derivative of kawain



(45)

kawains

	R_1	R_2	R_3	5-6	7-8
kawain	H	H	H	sat	unsat
dihydrokawain	H	H	H	sat	sat
dehydrokawain	H	H	H	unsat	unsat
dihydrokawain-5-ol	OH	H	H	sat	sat
11-hydroxy-12-methoxy-dihydrokawain	H	OH	OCH_3	sat	sat
11,12-dimethoxy-dihydrokawain	H	OCH_3	OCH_3	sat	sat

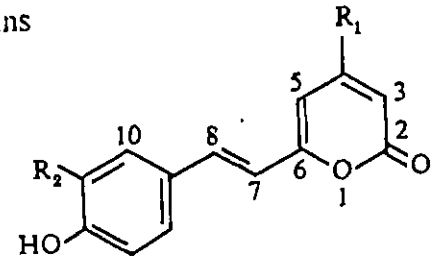


(46)

methysticin and
dihydromethysticin (7-8 = sat)

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus

derivative of yangonins

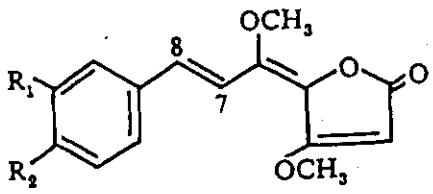


(47)

yangonins

	R_1	R_1	5, 6	7, 8
yangonin	OCH_3	H	unsat	unsat
4-demethoxyyangonin	H	H	unsat	unsat
11-methoxyyangonin	OCH_3	OCH_3	unsat	unsat
5,6,7,8-tetrahydroyangonin	OCH_3	H	sat	sat

Butenolides	R_1	R_2	7, 8
piperolide	H	H	unsat.
7,8-epoxypiperolide	H	H	epoxy
methylenedioxy piperolide	$-OCH_2O$		unsat.



(48

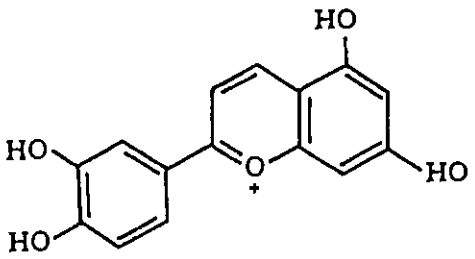
butenolide I

fadyenolide

(49)

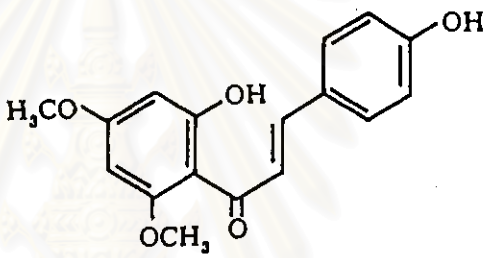
Z and E fadyenolides

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



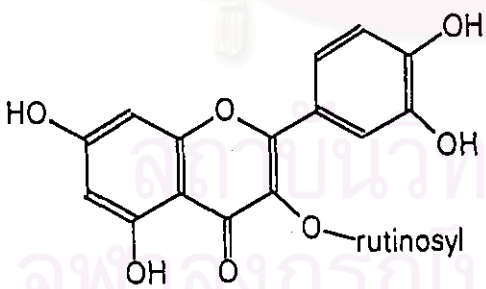
(50)

luteolinidin



(51)

flavokawain C



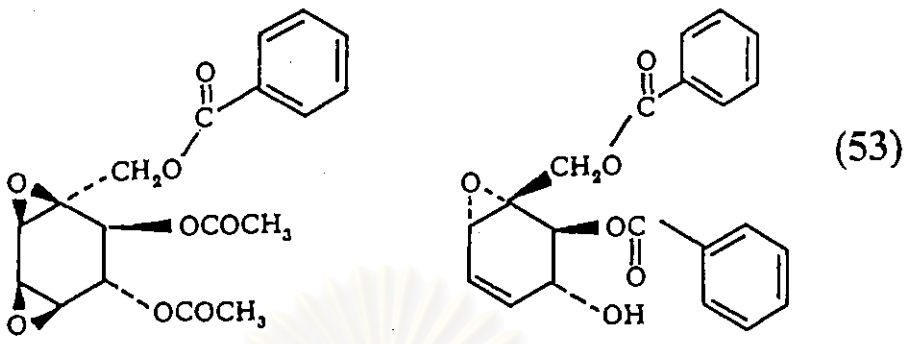
(52)

Rutin ($C_{27}H_{30}O_{16}$)

R, R' = OH หรือ OCH_3

flavones in *Piper*

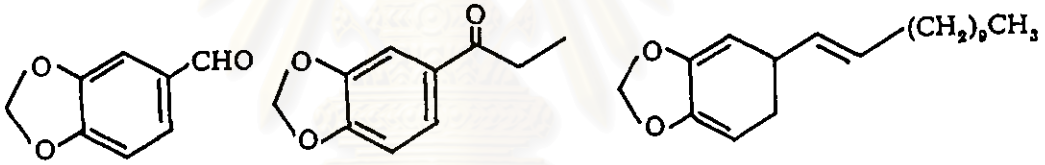
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



(53)

crotepoxide

pipoxide

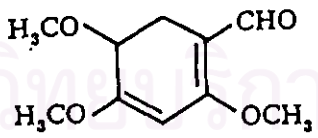


piperonal

methylenedioxy-
propiophenone

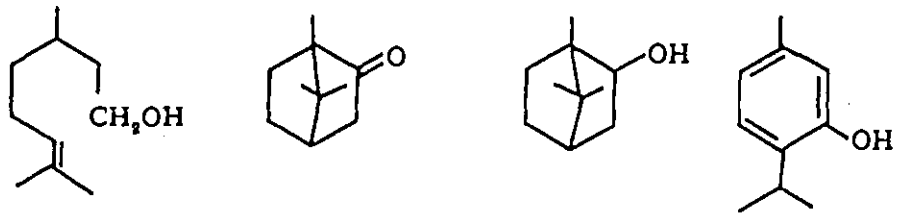
pipataline

(54)



asaronaldehyde

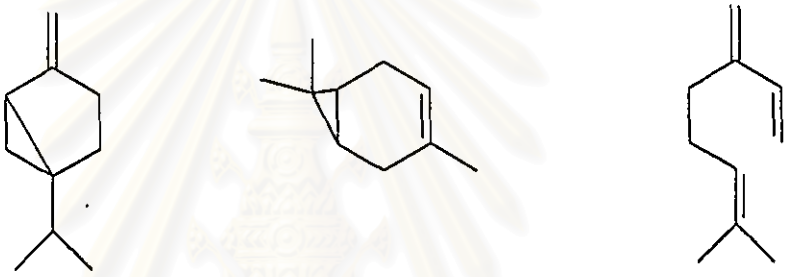
Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



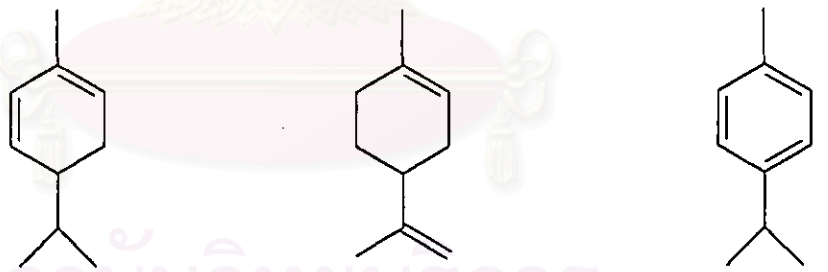
(55)

citronellol camphor borneol thymol

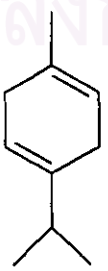
Pinene Camphene Pinene



Sabinene Carene Myrcene



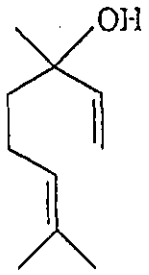
Phellandrene Limonene Cymene



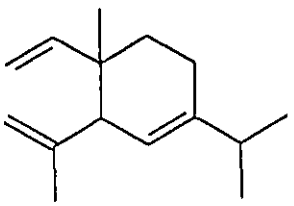
(56)

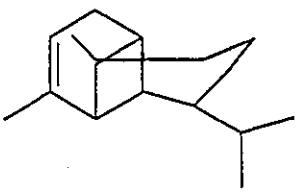
Terpinene

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus

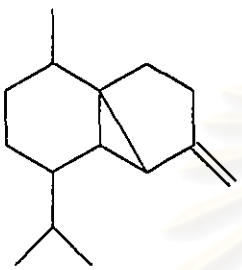


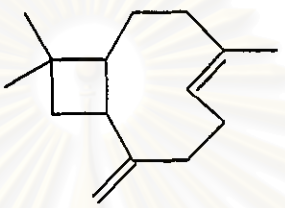
(57)

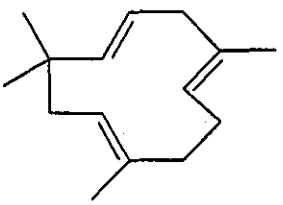




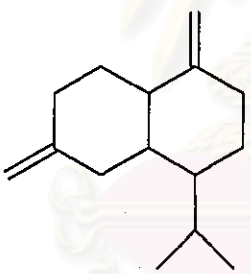
Linalool Elemene Copaene

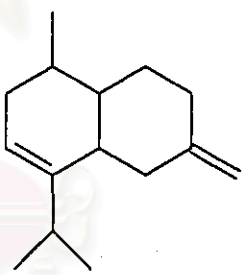




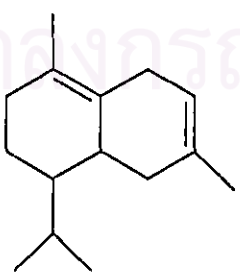


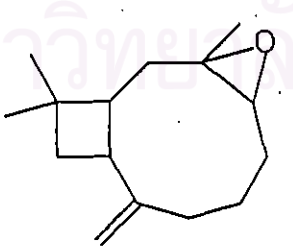
Cubebene Caryophyllene Humulene





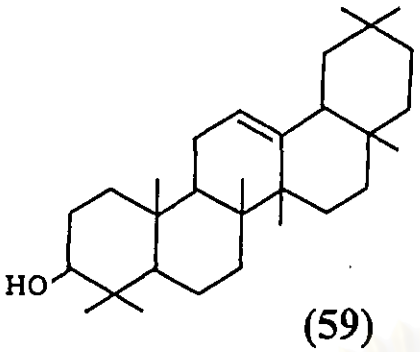
Muurolene Cadinene





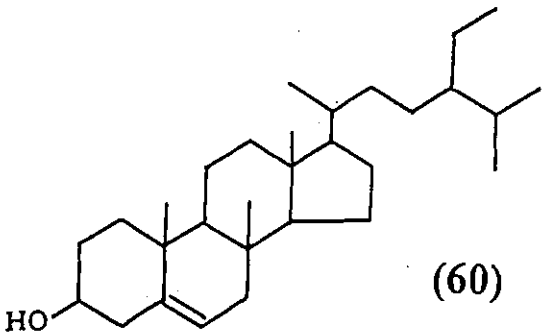
Cadinene Caryophyllene oxide (58)

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus



(59)

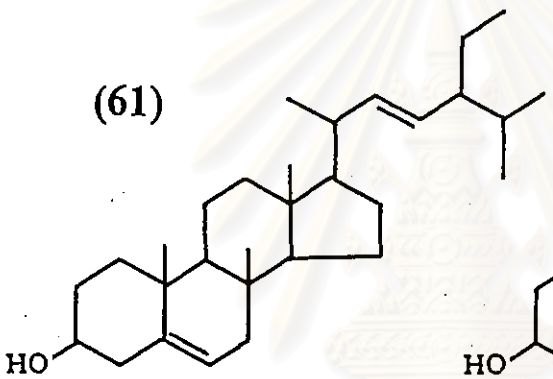
β-amyrin



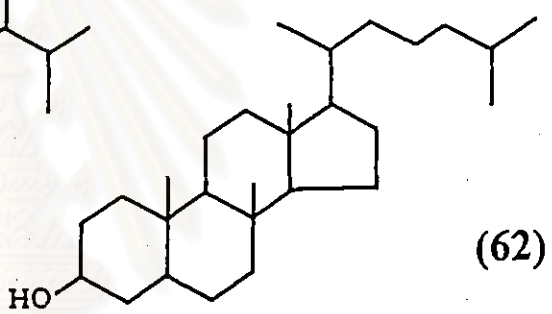
(60)

β-sitosterol

(61)



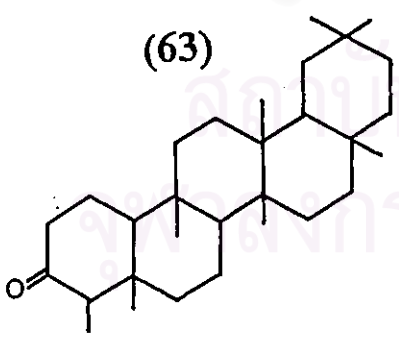
stigmasterol



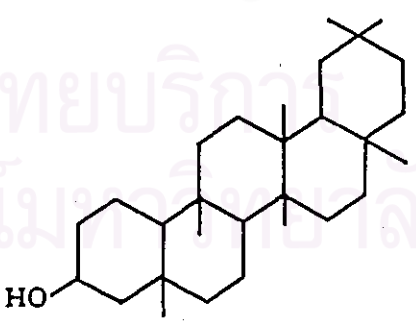
(62)

cholesterol

(63)



fridelin



(65)

epi-fridelinol

Fig 2 (cont.) The chemical constituents of some plants in *Piper* Genus

1.2 Research in pharmacology study and chemical constituents of *Piper betle* Linn.

In 1957, Airan and Sheth studied on chemical composition of leaves of *Piper Betle.* Banarsi betel leaves. Crude extract of diethyl ether found : leucine, phenyl alnine, alanine, arginine, throenine, setine, aspatic acid, glutamic acid, methinonine, valine, tyrosine, γ-aminobutaric acid and glycine. [149]

In 1962, Nigam and Purohit studied on chemical examination of the essential oil of the leaves of *Piper betle.* found chavicol , carvacrol , eugenol , chavibetol , polymerized oil , terpinene , cineole , estragol , caryophyllene , cadinene ,and γ-lactone (sesquiterpene) . [150]

In 1970, Despande, Upadhyay and Singh studied on the leaves of *Piper betle.* Crude extracts of petroleum ether, benzene and alcohol. were found pentatriacontane, *n*-triacontanol, hentriacontane, steric acid, chavicol, β- and γ-sitosterol . [151]

In the same year, Ali and Mehta studied on preliminary pharmacological and anthelmintic studies of the essential oil of *Piper betle* Linn. The essential oil of *Piper betle* showed hypotensive, cardiac and respiratory depressant effects and in the isolated smooth and skelatal muscles, relaxant actions were studied in the frog, dog, rat, and rabbit. It exhibited anthelmintic activity on earth worms.[152]

In 1971, Khosa and Dixit studied on preliminary study of the root of *Piper betle*, freshly collected major roots were dried and extracted with petroleum ether and the extract chromatographed on Al_2O_3. β-sitosterol was isolated. [153]

In 1972, Nanda and Krishna studied on fluoride content of *Piper betle* and its constituents. Betel chewing, eating suparis (Arica catechu) and tobacco (chewing varieties) is a common habit in India. To determine how much fluoride may be consumed through this source, betel and its various constituents were analyzed for

fluoride content. A significant amount of fluoride is ingested through this chewing samples indicating and additional source of fluoride. [154]

In 1975, Ganguly and Choudhury studied on Bangla varity of betel leaf was found β-sitosterol and stigmasterol.[155]

In 1982, Kapoori, Sharma, Rawat and Singh studied on essential oil of betel leaf. The major components of the oil were : terpinyl acetate 21.98%, eugenol 15.83 %, and 1-8 cineole 5.95%.[156]

In 1984, Evan,William and Evangeline studied on chloroform extracts of the leaves of *P.betel* possessed significant fungicidal activity against the fungus *Cladosporium cucumerinum.* They have isolated five fungicidal compounds from the fresh frozen leaves. The compound are identified as chavicol, chavibetol, allylpyrocatechol, chavibetol acetate, and allylpyrocatechol diacetate .[157]

In 1986, Huang and Chang studied on the main antioxidative components of betel vines. The oleoresin extracted by MeOH-Et_2O from betel (*Piper betle)* vines and rhizomes afforded 4 antioxidant components by TLC. In order of increasing activity these were as follows: tocopherol < eugenol < a mixture of 2 unidentified compounds < hydroxychavicol. Hydroxychavicol was quantitative the most important antioxidant representing 0.3 % of the dry wieght of betel vine powder.[158]

In 1989, Rawat, Tripathi, Khan, Balasubrahmanyam, studied the constituents of the essential oil of *P. betle* leaves. It was found to contain eugenol, 1,3-benzodioxole (5)-2-propenyl, anethole, cis-caryophyllene, α-thujene, trans-β-ocumene, terpinolene, allo-ocimene, Δ-cadinene, terpinen-1-ol, α-costol, Δ-cardinol, methel-2-hexadecan-1-ol, geraniol and hexadeconic acid.[159]

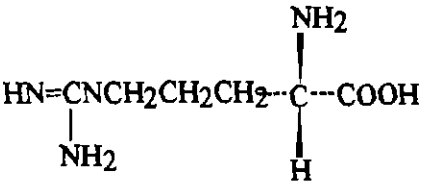
In 1996, Suhaila, Saleh, Suzana, Abdul and sepiah studied on ethanolic extracts of *P. betle* were tested for antifungal activity against 7 plant pathogens using the filter

paper disc diffusion technique. Considering that the yield of the extracts from the *P. betle* leaves are quite high (26 ± 2g/100 g dry weight) and the activity of the extracts is very strong, this plant is probably worth cultivating, for extraction of antifungal compound on a commercial scale. *P. betle* has antifungal, antiseptic and anthelmintic activity. In addition, it is effective against other plant phathogens such as *Pyrucularia oryzae* Cav., *Cochliobolus miyabeanus*, Drechsler ex. Dasture, *Phizoctonia solani* Kuhn. *B. theobromae* and Thanatephorus cacumeris (Frank) Donk which are responsible for collar rot.[160]

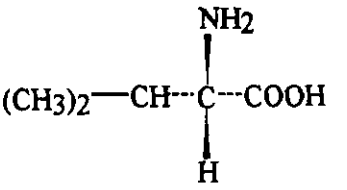
The chemical constituents of *Piper betle* Linn. are summarized in Table 2 and the structure of some isolated compounds are shown in Figure 3.

Table 2 The chemical constituents of *P. betle* Linn.

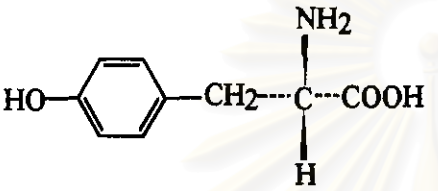
year	extracts	Isolated compound	Ref.
1957	Et_2O (leaves)	leucine, phenylalanine, alanine, arginine, threonine, setine, aspatic acid, glutamic acid, metheonine, valine, tyrosine, γ-aminobutyric acid	149
1962	essential oil (leaves)	chavicol 5.1%, carvacrol 4.4%, eugenol 40.5%, chavibetol 3.5%, polymerized oil 1.1%, cadinene 9.1%, γ-lactone 7.5%.	150
1970	petroleum ether, alcohol and benzene (leaves)	β-sitosterol, γ-sitosterol, hentriacontane, n-triacontanol, pentatriacontane, chavicol, steric acid	151
1971	petroleum ether (roots)	β-sitosterol	152
1982	essential oil (leaves)	terpinyl acetate 21.98%, eugenol 15.8%, 1-8 cineole 5.95%	153
1984	$CHCl_3$ (leaves)	chavicol, chavibetol, allylpyrocatechol diacetate, allylpyrocatechol, chavibetol acetate	157
1986	MeOH-Et_2O (vine)	tocopherol, eugenol, hydroxy chavicol, mixture of 2 unidentified compound	158
1989	essential oil (leaves)	*trans*-β-ocumene, terpinolene, allo-ocimene, Δ-cadinene, terpinene-1-ol, α-costol, Δ-cadinol, methyl-2-hexadecan-1-ol, geraniol, hexadeconic acid and methylbenzoate.	159



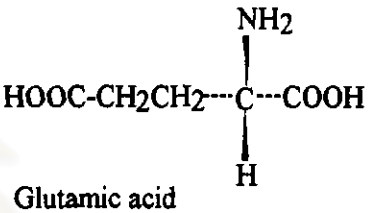
Arginine



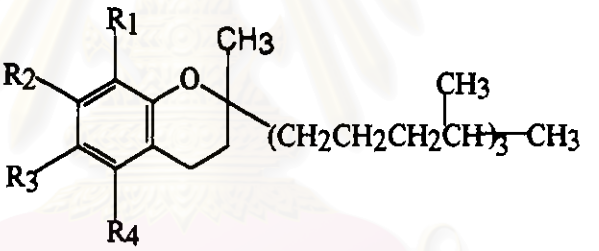
Valine



Tyrosine



Glutamic acid



Tocopherol

	R_1	R_2	R_3	R_4
β-tocopherol	CH_3	H	OH	CH_3
γ- tocopherol	CH_3	CH_3	OH	H
δ- tocopherol	CH_3	H	OH	H

Fig. 3 Some chemical constituents of *Piper betle* Linn.

The objective of this research

The goal of this research can be summarized as follows

1. To extract and to isolate the organic constituents from the leaves of *Piper betle* Linn.
2. To elucidate the structures of the isolated substances.
3. To search for bioactive compounds that can possibly be used as a cytotoxic agents against brine shrimp (*Artemia salina* Linnaeus) by using bioassay results as a guide.