CHAPTER I

HISTORICAL INTRODUCTION

Thailand nowadays facing the problem of public health deficiency in the rural area. With the suggestion of World Health Organization, the primary health care system has been introduced, which involved promotion of self sufficiency and self dependence of the community in term of medical cares. To cope with the system, the application of medicinal plants as a source of medicine is being recognized and a lot of research work on medicinal plants have been done recently in both pharmacological and phytochemical aspects. Some researches have been achieved and reported. As example of such work, Jirawongse *et al.* (1) worked on a mushroom known as Hed Dchig (*Lopharia papyracea* Jungh.). a folk medicine used in the northeastern part of Thailand, and reported the isolation of pure polyporic acid. Yupraphat and co-workers (2) investigated a Thai drug, Krung kha Mao, and reported the isolation of bisbenzylisoquinoline alkaloids. Kitazawa *et al.* (3) worked on Thai medicinal plant called "plaunoi" and reported the presence of plaunol, a novel diterpenelactone with antipeptic ulcer activity. Tantivatana and co-workers (4) reported a novel cytotoxic coumarin called "microminutin" from *Micromelum minutum* Wight & Arn.

The plant used in this investigation was found in the eastern part of Thailand where the usage about this plant was told by the local residents. The roots and leaves of this plant could cause vomitting effect and was used as antidote for poisoning. The specimen of this plant was identified to be *Aglaia pirifera* Hance, family Meliaceae. A preliminary study of this plant was done by the author and it was found that the leaf extract gave a positive test for alkaloid, the result was later confirmed by thin-layer chromatographic data.

According to Core (5), Meliaceae is composed of 50 genera 1,000 species with *Aglaia* containing 250 species (6). According to Craib (7) and Smitinand (8), it was found that there are about 25 species of *Aglaia* in Thailand. These species are: -

*** *Aglaia andamanica* Hiern
** *A. argentea* Bl.
** *A. caudata* Hiern
*** *A. chaudocensis* Pierre
*** *A. cordata* Hiern
** *A. domestica* Pelleg.
** *A. dookkoo* Griff
** *A. edulis* Gray
** *A. gigantea* Pelleg.
*** *A. hoaensis* Pierre
* *A. kunstleri* King
* *A. marginata* Craib

*** *Aglaia meliosmoides* Craib

* *A. merostela* Pelleg.

* *A. oblanceolata* Craib

*** *A. odorata* Lour.

*** *A. odoratissima* Bl.

*** *A. palembanica* Miq.

* *A. paniculata* Kurz.

*** *A. pirifera* Hance

*** *A. pyramidata* Hance

* *A. quocensis* Pierre

* *A. submonophylla* Miq.

* *A. tenuicaulis* Hiern

** *A. trichostemon* DC.

(* reported by Craib, ** reported by Smitinand, *** reported by both Craib and Smitinand)

The following pages contain a literature survey about the medicinal uses and poisonous properties of the plants in the family Meliaceae. In 1937, Volkonsky (9) studied the leaves of *Melia azedarach* L. for insecticidal effect, it was noticed that some types of the insects have never touched the leaves of this plant. Other plants sprinkled with extract of *Melia* leaves are equally protected against locust. In 1939, Carratala (10) reported the death of a 3 years-old child some days after eating the fruit of *Melia azedarach* L. An aqueous extract of the fruit when injected into rabbits (1 ml sc.) produced dyspnea, tremor, convulsions and death on the following day. When given by mouth, it also produced gastrointestinal symptoms. One

year later, Guevara (11) performed the pharmacodynamic study of lansone fruits (*Lansium domesticum* Corr.) and found that the peel of fruit contains a resin which checks diarrhoea and relieves intestinal spasm. A dilute aqueous suspension of the resin inhibits the contraction of rabbit intestine *in vitro*. In 1963, Sinha and Gulati (12) studied the seed cake of *Azadirachta indica* Juss. and found that the alcoholic extract of seed cake left after the oil expression was shown repellent action against migratory locusts, the marc was inactive. In 1965, Berndt (13) reported the use of margosa oil from *Azadirachta indica* Juss. in dermatological preparations in Indian pharmacy. During 1968-1972, Dhar *et al.* (14, 15, 16) performed the experiments on the biological activity screening of Indian plants including plants in family Meliaceae. The results were summerized in Table I.

Table I The biological activity screening of some Meliaceous plants

Plant	Part	Activity observed	Reference
Aglaia odoratissima Bl.	px	anticancer	16
Amoora wallichii King	st	anthelmintic	14
		antiviral	
		anticancer	
Aphanamixis polystachya (Wall.) Parker	st	anticancer, blood pressure	14
Cedrela microcarpa C.DC.	px	CNS effect	16

Table I (Cont.)

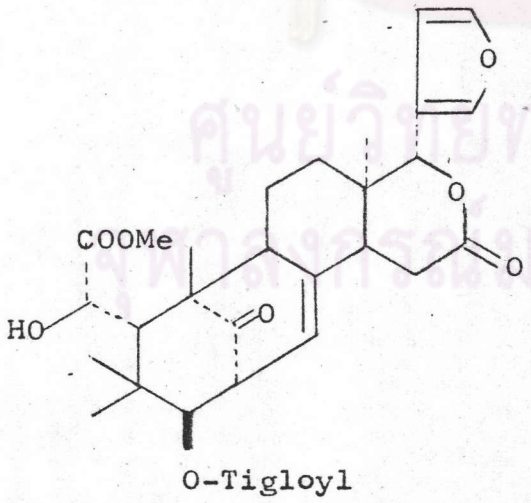
Plant	Part	Activity observed	Reference
Cedrela toona Roxb.	sb	spasmogenic, anticancer	14
C. toona Roxb.	lf	antiprotozoa, hypoglycaemic, spasmogenic, CNS effect	14
Cipadessa fruticosa Bl.	px	spasmogenic	15
Dysoxylum binectariferum Hook. f.	px	CNS effect	16
D. procerum Hiern	px	-	16
Melia azedarach L.	sb	antiviral, spasmogenic, anticancer	15

(px = plant excluding, st = stem, sb = stem bark, lf = leaves)

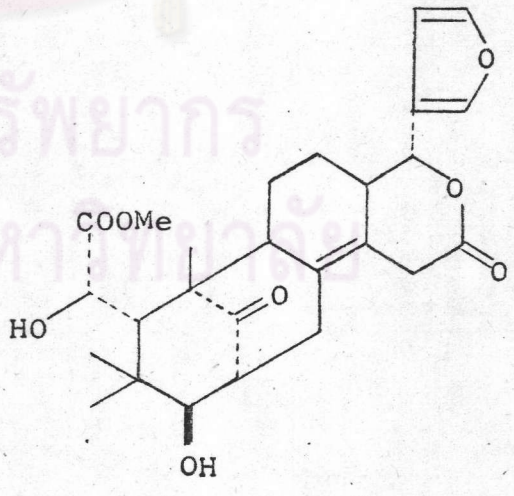
In 1973, Martinez Nadal *et al.* (17) investigated the toxicological effects of active principles of *Swietenia mahagoni* Jacq. and found that the precipitates obtained from the bark by diethyl ether extraction, petroleum ether extraction and an oil obtained from the seeds were sufficiently toxic to *Drosophila melanogaster* to warrant their use as pesticides. The rate of mortality was proportional to the concentration of active materials. The active materials were apparently non toxic to human. In 1977, Qadri and co-workers (18) studied the effect of combining some

indigenous plant seed extracts against household insects and found that neem (*Azadirachta indica* Juss.) extract showed synergistic action in combination with custard apple seed extract against pulse beetle, lesser grain borer, and housefly. This combination was half as toxic against lesser grain borer and equitoxic to DDT against housefly.

Further chemical characterization of this family has been reported as follows. In 1937, Volkonsky (9) studied the leaves of *Melia azedarach* L. and reported the presence of the alkaloid paraisine. In 1951, Sircar and Chakravarty (19) studied the seed of *Swietenia macrophylla* king. From this study, two crystalline substances were isolated, one non-bitter which they named swietenine, the other bitter, named swietenolide. The structure and stereochemistry of swietenine (I) and swietenolide (II) were determined later in 1965 by Connolly *et al.* (20, 21).

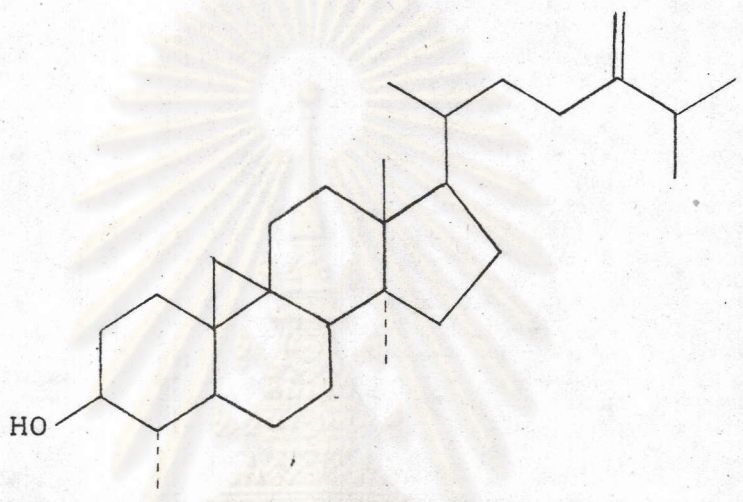


(I)



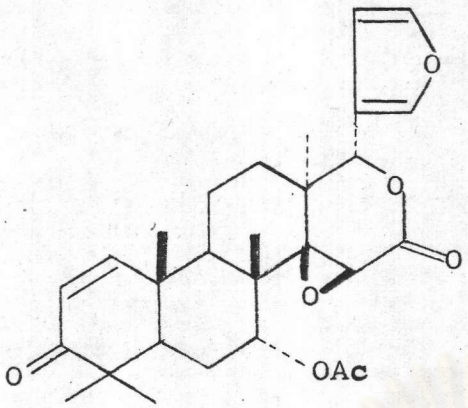
(II)

In 1959, Marin *et al.* (22) reported the isolation of cycloeucalenol (III) from the unsaponifiable fraction of the oil from West Indian mahogany wood (*Swietenia mahagoni* Jacq.).

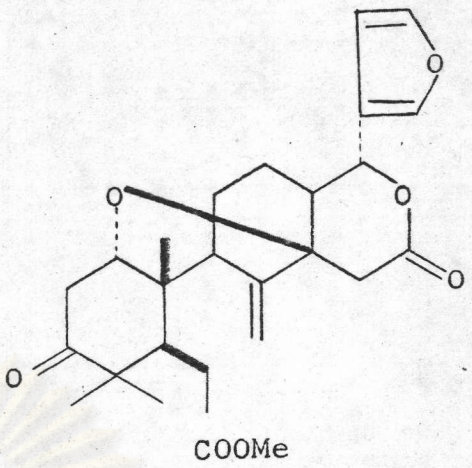


(III)

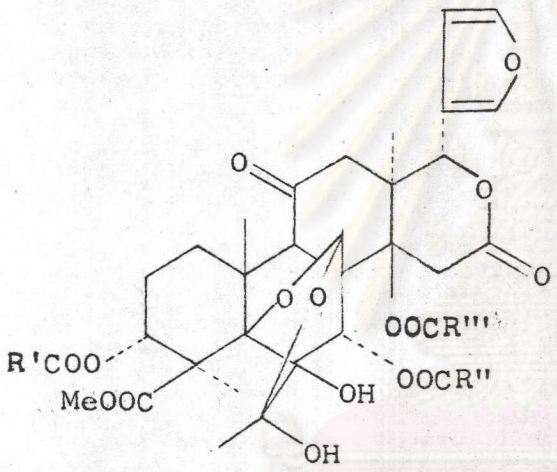
In 1960, Akisanya and co-workers (23) investigated some species of the genus *Entandrophragma* and the following results were reported. From the timber of *E. angolense* (Welw.) C.DC., two triterpenes, gedunin (IV), the structure was subsequently characterized by Akisanya *et al.* (24), and methyl angolensate (V) were reported. Another triterpene, entandrophragmin (VI), was isolated from *E. cylindricum* Sprague, of which structure was suggested by Taylor and Wragg (25).



(IV)



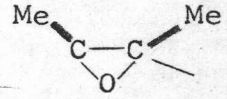
(V)



(VI)

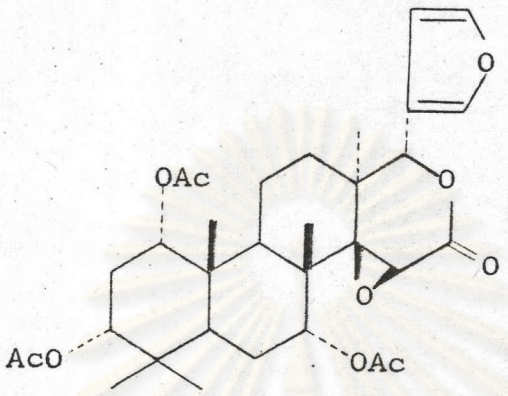
R' = Me_2CH

R'' = MeEtCH

R''' = 

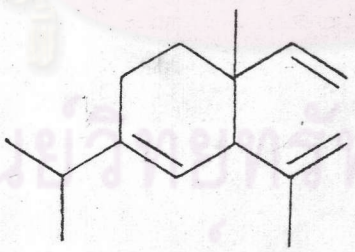
In addition, gedunin was also obtained from *Entandrophragma delevoyi* De Wild. and *Xylocarpus granatum* Koen. as well in 1965 (26). Besides these, there are some reports on the isolation of methyl angolensate (V) from the heartwood of *Cedrela odorata* L. (27) and the seed of *Swietenia mahagoni* Jacq. (28).

In 1962, a limonoid called khivorin (VII) was isolated from the heartwood of *Khaya ivorensis* A. Chevalier by Bevan *et al.* (29).



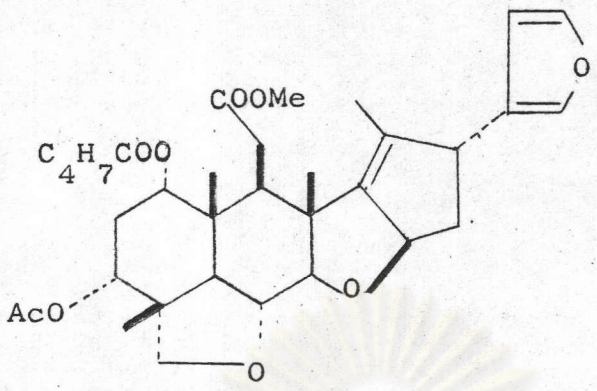
(VII)

In 1964, Gough and co-workers (30) described the structure of δ-elemene (VIII) which had been isolated from *Dysoxylum frazeranum* Benth. (31).



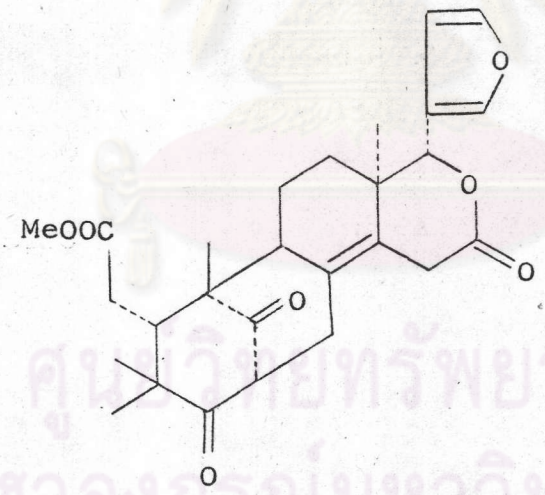
(VIII)

In the same year, Henderson *et al.* (32) investigated the seed oil of *Melia azadirachta* L. and found the presence of triterpenoid, salannin (IX). Five years later, this substance was isolated from *M. dubia* Cov. by Silva *et al.* (33).



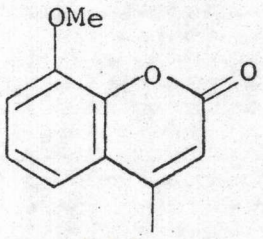
(IX)

In 1965, a crystalline lactone called mexicanolide (X) was isolated from *Cedrela mexicana* M. Roem. by Connolly *et al.*(34) and the constitution of this structure was proved by the same authors.



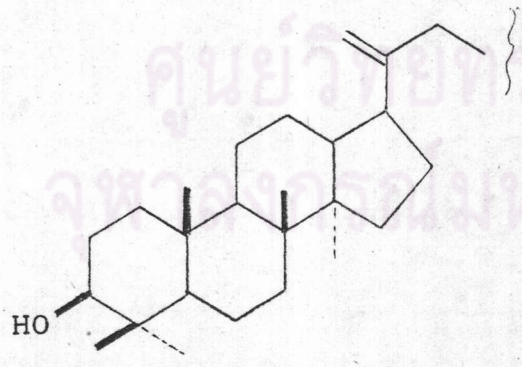
(X)

In the same year, Bevan and Ekong (35) extracted two specimens of *Ekebergia senegalensis* A. Juss from the Plateau Province of Northern Nigeria and found that the major crystalline product was 8-methoxy-4-methyl coumarin (XI).

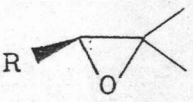


(XI)

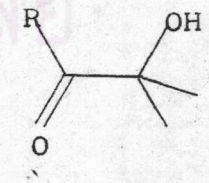
In addition, Shiengthong *et al.* (36) studied the leaves of *Aglaia odorata* Lour. and reported the presence of tetracyclic triterpene, aglaiol (XII). The configuration of aglaiol was further determined by Boar *et al.* (37, 38). The leaves of the same plant were further investigated in 1974 (39) and the presence of two more tetracyclic triterpenes, aglaiondiol (XIII) and aglaitriol (XIV), were reported.



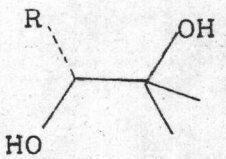
(XII)



(XIII)

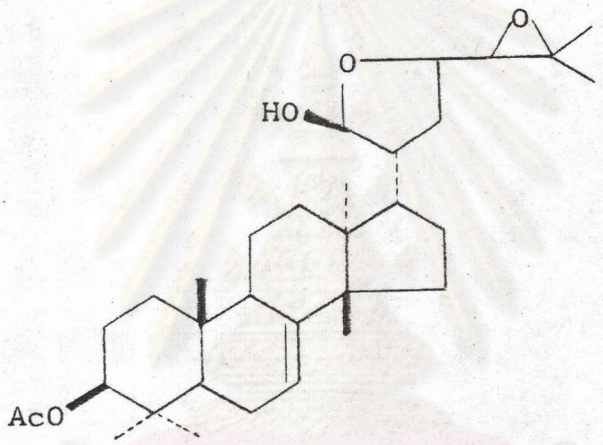


(XIV)



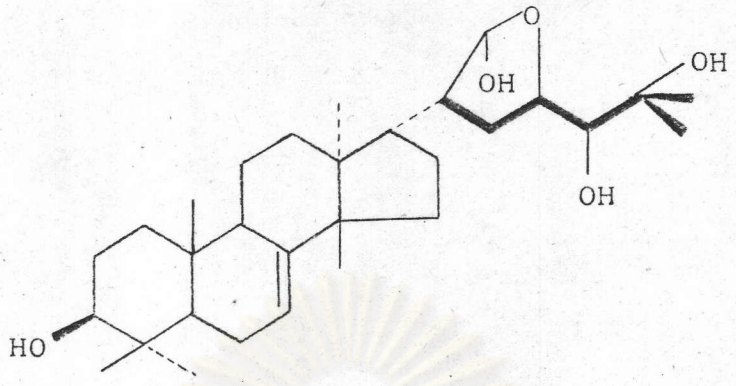
The year 1967 was one of the most exciting year in phytochemical study of family Meliaceae. Several activities were recorded as follows:

Chatterjee and Kunda (40) examined the fruits of *Aphanamixis polystachya* (Wall.) Parker and reported a new triterpene designated as aphanamixin (XV) from the petroleum extract.

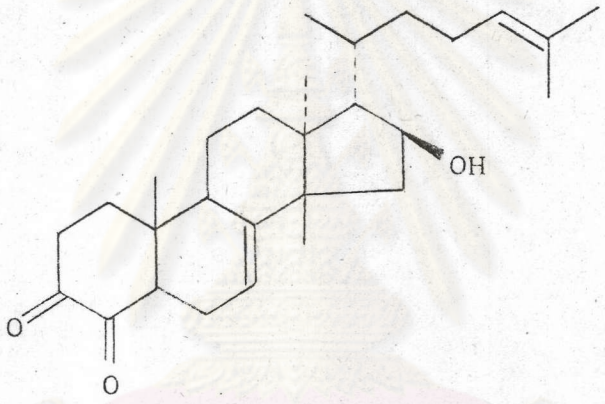


(XV)

Lavie and co-workers (41) obtained a crystalline compound with antifeeding activity identified as meliantriol (XVI) from the fruit of *Azadirachta indica* Juss. while a new triterpene of the euphane (20 β-H) series, kulinone (XVII), was isolated from the bark of *Melia azedarach* L. by Chang and Chiang (42).

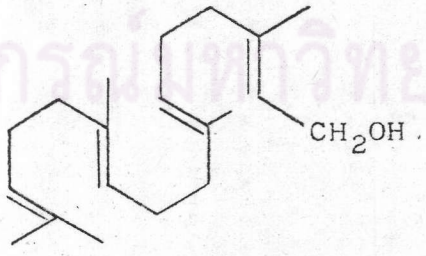


(XVI)



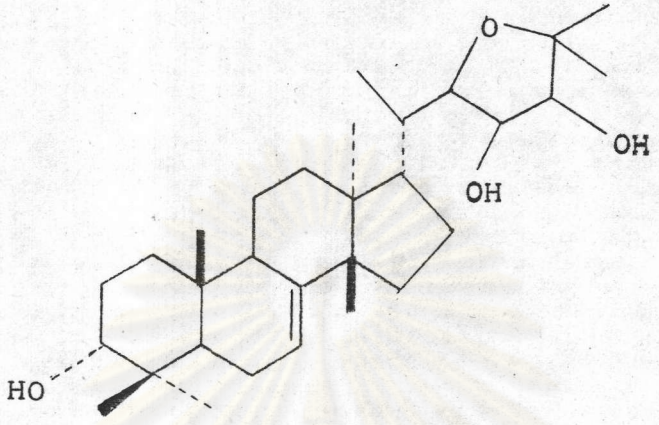
(XVII)

Nagasampagi *et al.* (43) isolated geranylgeraniol (XVIII) from the wood of *Cedrela toona* Roxb.



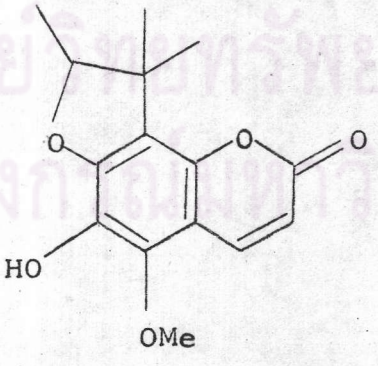
(XVIII)

Connolly and co-workers (44) isolated mexicanol (XIX) from the heartwood of *Cedrela glaziovii* C. DC. and *C. mexicana* M.Roem.



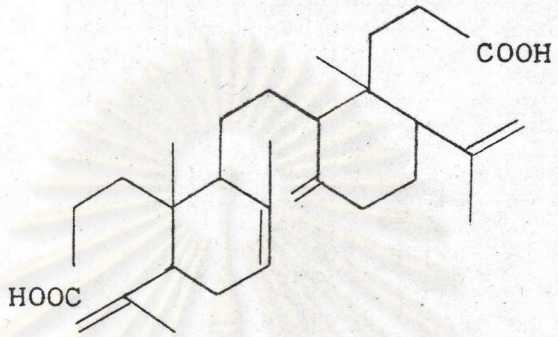
(XIX)

McCabe *et al.* (45) obtained nieshoutol (XX) from the heartwood of *Ptaeroxylon obliquum* Radlk. The structure was confirmed by Murray and Ballantyne (46).



(XX)

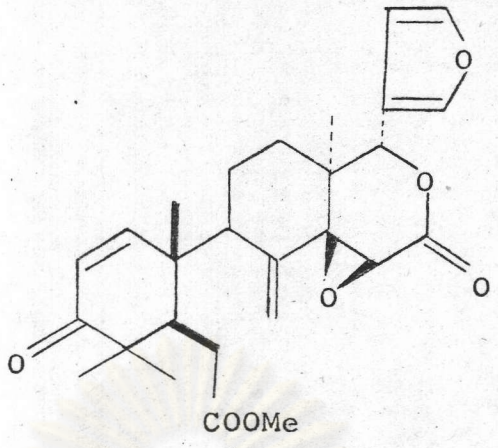
Kiang *et al.* (47) examined the peel of the fruit of *Lansium domesticum* Corr. and reported the isolation of triterpenoid acid, which they named lansic acid (XXI).



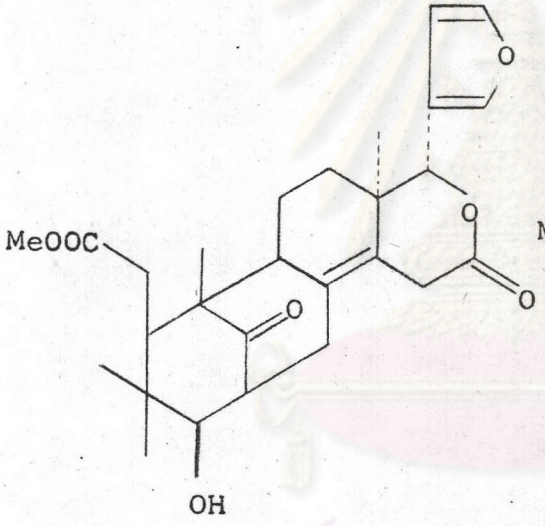
(XXI)

The history of phytochemical investigation of family Meliaceae became more interesting when it got to the year 1968 and several phytochemical works were reported at that time.

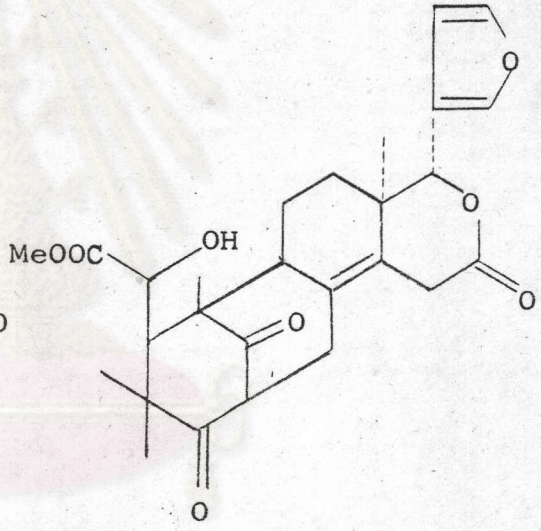
Okorie and Taylor (48) examined the seed of *Cedrela odorata* L. and reported that the seed of this plant contained the known limonoids mexicanolide (X), andirobin (XXII), and 6-deoxy swietenolide (XXIII), together with a new compound which had been identified as 6-hydroxy mexicanolide (XXIV).



(XXII)

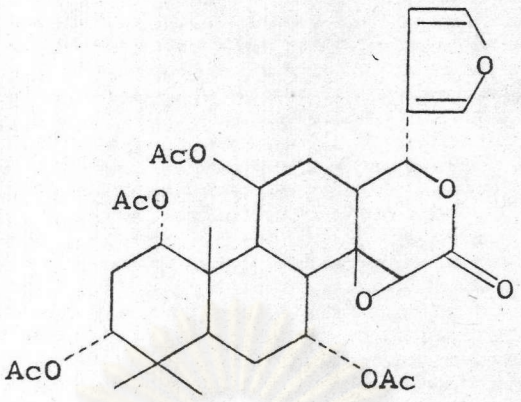


(XXIII)



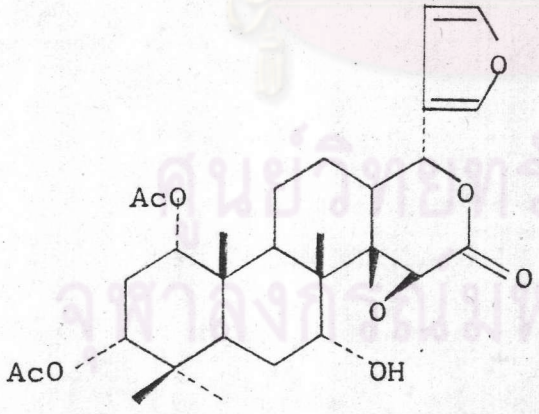
(XXIV)

Taylor (49) extracted the timber of *Khaya madagascariensis* Jumelle *et* Perrier and found that the main constituent of this extract was 11 β-acetoxykhivorin (XXV).

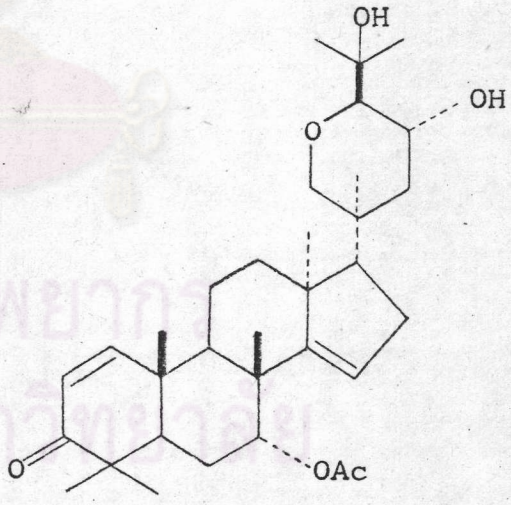


(XXV)

Connolly *et al.* (50) obtained grandifolione (XXVI) from the trunk wood of *Khaya grandifoliola* C.DC. Three years later (1971), grandifoliolenone (XXVII) was isolated together with grandifolione from this same plant by Connolly and McCrindle (51).



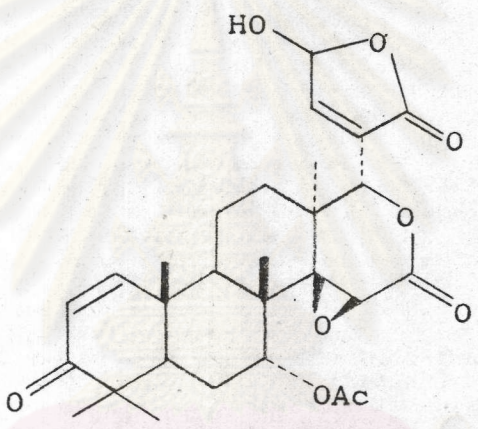
(XXVI)



(XXVII)

In 1969, Johns and Lamberton (52) performed phytochemical screening of some New Guinea plants for alkaloid and found positive results in several species of *Aglaia*.

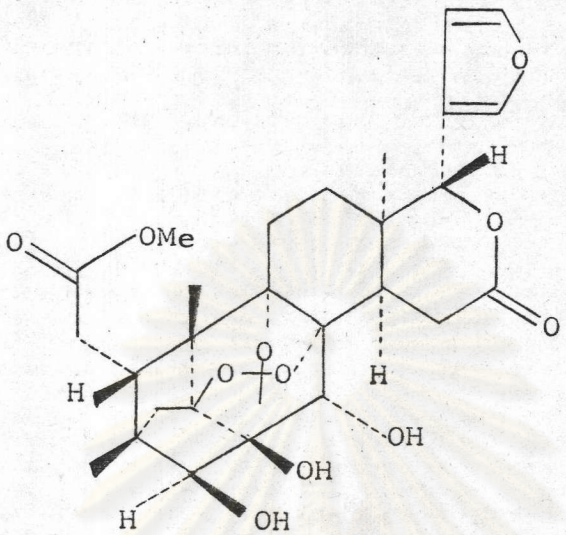
The leaves of one specimen was then further investigated but the result showed the presence of tiglamide as a major constituents in the crude alkaloid fraction. Buke and co-workers (53) examined the benzene extract of a specimen of *Cedrela odorata* L. growing in the Red Hills area of St. Andrew, Jamaica and reported the isolation of gedunin (IV) together with a non-furanoid tetranortriterpenoid, photo-gedunin (XXVIII).



(XXVIII)

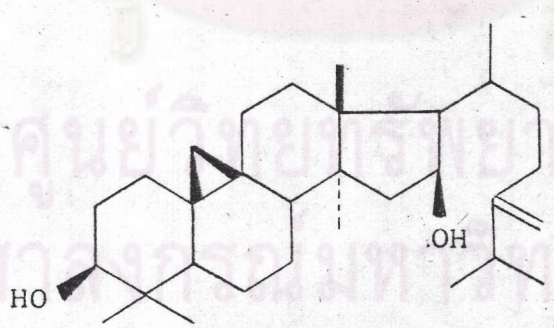
In 1971, several phytochemical studies of some Meliaceous plants were done and the results were reported as follows:

Arndt and Baarschers (54) extracted the bark of *Entandrophragma caudatum* Sprague by the conventional alkaloid extraction method and obtained a meliacin named phragmalin (XXIX).



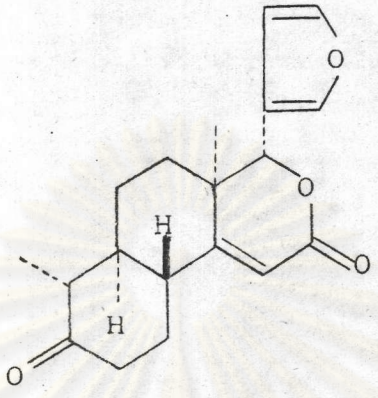
(XXIX)

Chakraborty and Basak (55) performed phytochemical work on the leaves of *Swietenia mahagoni* Jacq. and reported the isolation of cyclomahogenol (XXX).



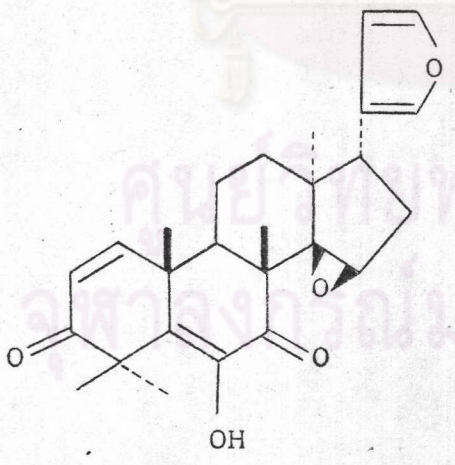
(XXX)

Chan *et al.* (56) investigated the specimen of *Cedrela odorata* L. obtained from St. Elizabeth, Jamaica and reported the presence of a new compound, odoratin (XXXI).

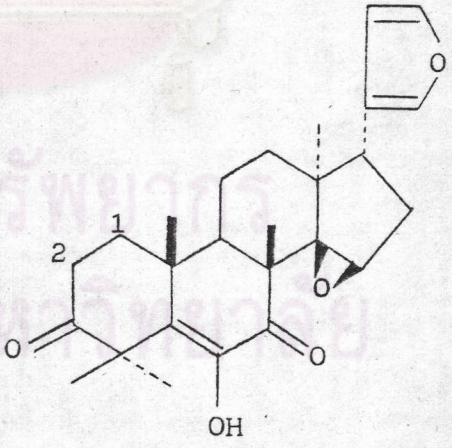


(XXXI)

Chatherjee and co-workers (57) reported the presence of cedrelone (XXXII), 1,2-dihydrocedrelone (XXXIII) in the seeds of *Cedrela toona* Roxb.



(XXXII)



(XXXIII)

During 1972-1975, the alkaloid screening of Meliaceous plants were undertaken by Farnsworth *et al.* and the results were shown in Table II.

Table II Alkaloid screening of some Meliaceous plants

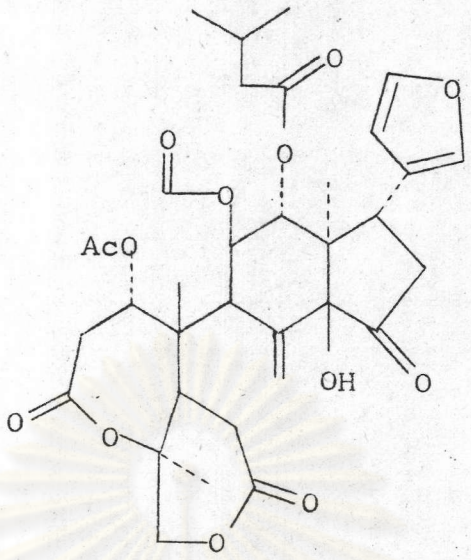
Plant	Part (s)	Result	Reference
Aglaia sp.	Lf, Sb	-	60
Aglaia sp.	Lf	++	58
Azadirachta indica Juss.	Lf, Fl, Rb, St, Sb, Wr, Ws	-	62
A. indica Juss.	Lf	+	60
A. indica Juss.	Sd, Fr	+	61
Cedrela toona Roxb.	Sd	+	60
Chickrassia tabularis A.Juss.	Sd	-	61
Dysoxylum chisochita	Lf, St	-	61
D. pettigrewianum F.M. Baill	Sb	+	59
D. pettigrewianum F.M. Baill	Sb	-	58
D. rufum Benth	Sb	-	58
D. spectabile Hook. f.	St, Lf	-	61
Ekebergia capensis Sparrman	Fr	+	58
E. capensis Sparrman	St, Lf, Fl	-	61
E. capensis Sparrman	Lf, Ws	-	58

Table II (Cont.)

Plant	Part (s)	Result	Reference
Guarea trichiloides L.	St, Lf, Fl	-	62
G. trichiloides L.	St, Lf, Fr	-	61
Lansium domesticum Jack.	St, Lf	-	61
Melia azedarach L.	Sd	++	61
M. azedarach L.	Ws, Sb	-	62
M. azedarach L.	St, Lf, Fr	++	60
M. azedarach L.	Lf	-	60
M. dubia Cav.	Sb	-	58
M. volkensii Gurke	Lf, St, Ws	+	62
M. volkensii Gurke	Rt	-	62
Owenia acidula F. Muell	Lf	-	58
Trichilia colimana DC.	Tw, Lf, Fr	-	62
T. dregeana Sond.	Ws, Sb	-	58
T. havanensis Jacq.	St, Lf, Fr Sb	-	60
T. pallida	St, Lf	+	59
Turraea mombassana Hiern	Ws, Sb	-	62

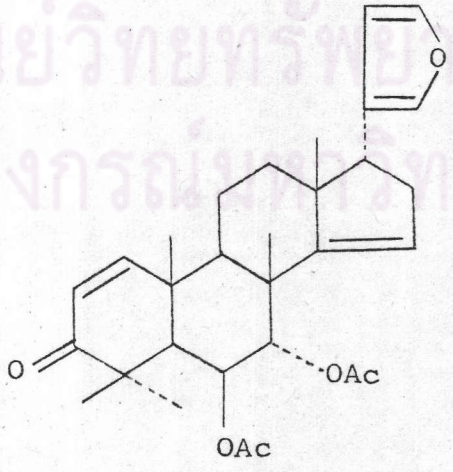
(+ = positive test, - = negative test, Fl = flower, Fr = fruit, Lf = leaf, Rb = root bark, Rt = root, Sb = stem bark, Sd = seed, St = stem, Tw = twig, Wr = root wood, Ws = stem wood)

In 1967, Connolly (63) investigated the seeds of *Aphanamixis polystacha* (Wall.) Parker and reported the presence of limonoid compound called rohitukin (XXXIV).



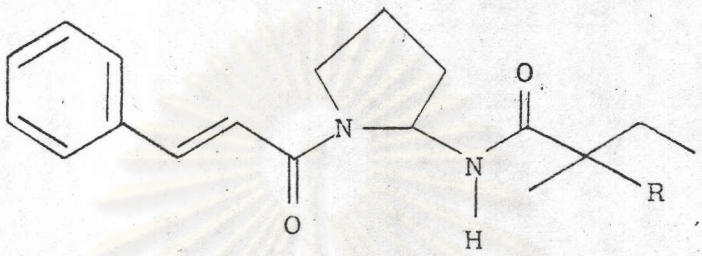
(XXXIV)

Singh *et al.* (64) extracted the fruits of *Dysoxylum binectariferum* Hook. f. and obtained a new tetranortriterpene of the meliacin group, dysobinin (XXXV). This substance showed general CNS-depressant action and mild anti-inflammatory activity.



(XXXV)

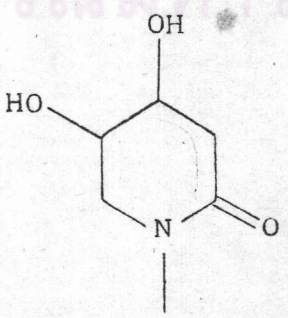
The alkaloid chemistry in family Meliaceae become more interesting in 1979 when Shiengthong *et al* (65) isolated two new alkaloids, odorine (XXXVI) and odorinol (XXXVII), from the leaves of *Aglaia odorata* Lour.



(XXXVI) R = H

(XXXVII) R = OH

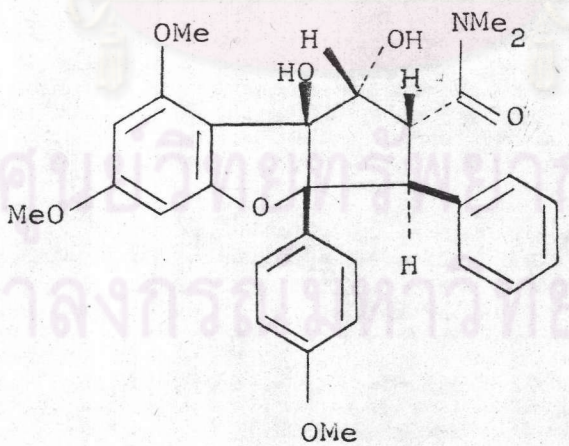
This result was supported by the work of Purushothaman *et al* (66) on the isolation of roxburghiline (XXXVI) which is subsequently found to be identical with odorine, from the close related species, *Aglaia roxburghiana* Hiern (Syn. *A. odoratissima* Bl.). Two years later, Techasauwapak (67) worked on the flower specimen of *A. odorata* Lour. and reported the isolation of new alkaloid called odoram (XXXVIII).



(XXXVIII)

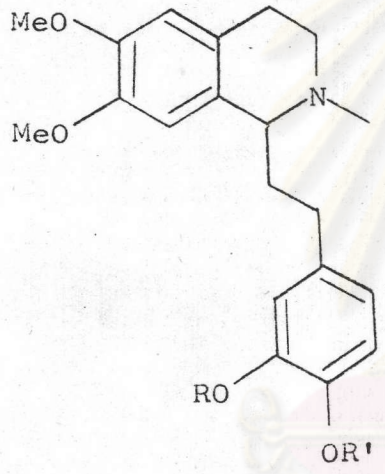
In 1981, Pillai and Santhakumari (68) reported the pharmacological study of nimbidin, a compound isolated from the oil of *Azadirachta indica* Juss. seeds, in comparison with two standard anti-inflammatory agents, phenylbutazone, a non-steroid and prednisolone, a steroid; against various experimental models of inflammation. The result showed that nimbidin was effective in both acute and chronic phases of inflammation and it was considered as a general anti-inflammatory agent.

In 1982, King *et al* (69) worked on the specimen of *Aglaia elliptifolia* Merrill and obtained a novel 1H-2,3,3a, 8b-tetrahydrocyclopenta(b)benzofuran, rocaglamide (XXXIX), with significant antileukemic activity against P-388 lymphocytic leukemia in CDF_1 mice.

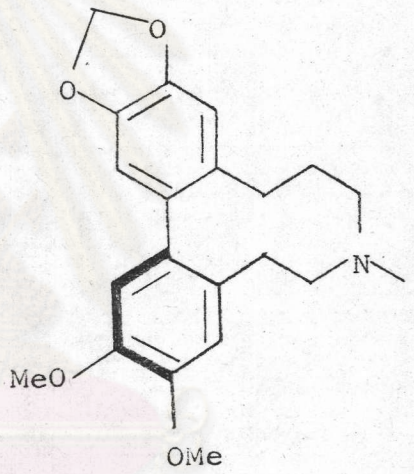


(XXXIX)

The recent work on Meliaceous plant is the work of Aladesanmi *et al.* (70) in 1983. The leaves of a Fiji plant, *Dysoxylum lenticellare* Gillespie, were studied and the presence of 5 alkaloids were reported. Of these, dysoxyline (XXXX), S-(+)-homolaudanosine (XXXXI), and dysazecine (XXXXII), are new natural products. The other two known alkaloids are 3-epischelhammericine (XXXXIII) and 2,7-dihydrohomoerysotrine (XXXXIV).

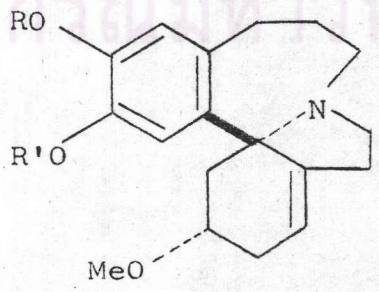


(XXXX) R, R' = $-CH_2-$



(XXXXII)

(XXXXI) R = R' = -Me



(XXXXIII) R, R' = $-CH_2-$

(XXXXIV) R = R' = -Me

The chemical studies of plants in the family Meliaceae have been meager, especially in the field of alkaloid chemistry. It was the purpose of this investigation to study the nature of alkaloid in the leaves of *Aglaia piri-fera* Hance. The result may serve as a piece of support to disclose the alkaloid chemistry in this family. Moreover, the chemical characterization of this plant may provide valuable information in the future in the field of chemotaxonomy.