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Investigation of some bioactive Thai medicinal plants*

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Abstract

It has been estimated that plants are the most important source of medicine for more than 80% of the world's population. Medicinal plants are a vital source of medication in developing countries. Despite the wealth of human experience and folklore concerning the medicinal uses of plants, proper scientific investigation has only been applied to a small fraction of the world's plants. This is a cause of grave concern as plant species continue to disappear. A rapid response to this situation is urgently needed to prevent the disappearance of the plant species and the ethnopharmacological knowledge that accompanies them. In this review, recent work on the investigation of selected bioactive Thai medicinal plants is presented. Their biological activities against infectious diseases including antimalarial and anti-HIV, are highlighted, as well as their anticancer, antiulcer and anti-inflammatory properties. The chemical transformations of some selected compounds are discussed.

Introduction

Throughout the ages humans have relied on nature for their basic needs for the production of foodstuffs, shelter, clothing, fertilizers, flavors and fragrances, and, not least, medicines. Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years. In industrialized nations at the present time, some fifty percent of all prescribed drugs are derived or synthesized from natural products, the only available sources for which are animals, marine species, plants, and microorganisms (Farnsworth and Morris, 1976, p. 46). The importance of natural products is also evidenced by the fact that in 1991 nearly half of the best selling drugs were either natural products or their derivatives (O'Neill and Lewis, 1993, p. 48). It is considered that because of the structural and biological diversity of their constituents, terrestrial plants offer a unique and renewable resource for the discovery of potential new drugs and biological entities (Balandrin et al., 1985; Hamburger et al., 1991; Cox and Balick, 1994; Cordell, 1995; Clark, 1996; Hostettmann et al., 1998; Cordell, 2000). However, only a small percentage of the world's estimated 250,000–400,000 flowering plants have as yet been analysed for their possible medicinal uses. Moreover, in developing countries, medicinal plants continue to be the main source of medication. It has been estimated that approximately 80% of the world's inhabitants and 88% of the inhabitants of underdeveloped countries rely mainly on traditional medicine for their primary health care (Farnsworth et al., 1985; Pezzuto, 1997).

Our country, Thailand, due to its unique geographical location has long enjoyed the luxury of an innumerable variety of plants. Evergreen forest is found in the southern part of Thailand, while the northern mountains have been penetrated with a number of the eastern Himalaya temperate taxa thus making this area one of the richest floristic regions of the world. Thailand is endowed with a great diversity of indigenous medicinal plants. The Thais have a long tradition of

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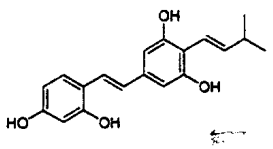
folklore medicine, utilizing alleged medicinal herbs and plants. Herbal drugs have been used in Thailand for centuries as an integral part of Thai culture. A great potential is foreseen for indigenous plants to be used as a source of new drugs. However, many of the claimed curative properties have neither been scientifically proved nor properly investigated. When screening for biologically active plant constituents, the selection of the plant species to be studied is obviously a crucial factor for the ultimate success of the investigation. Besides random collection of plant material, targeted collection based on consideration of chemotaxonomic relationships and exploitation of ethnomedical information is currently performed. Plants used in traditional medicine are more likely to yield pharmacologically active compounds. Research work on medicinal plants in Thailand mainly uses folklore medicine as a guideline in the selection of the plants for study.

In 1997, Cragg and Newman of NCI reported some interesting statistics. They found that during the period of 1983 to 1994, among new approved drugs for all disease types, those derived from synthesis are approximately twice the number of those derived from natural products, both modified and unmodified. However, of the 93 newly approved anti-infective drugs, 7 are unmodified natural products and 45 are modified natural products, giving 63% of drugs derived from natural sources. The same trend is observed in the cancer area where the number of anticancer drugs derived from natural products both modified and unmodified is higher than synthetic drugs, i.e., 62% of the 87 approved anticancer drugs. It is very interesting to note that for the pre-new drug application anticancer drugs, 50 compounds are from natural sources indicating the increasing importance of natural products as anticancer agents. It is obvious from the above statistics that natural products play a major role as drugs for the treatment of infectious diseases and cancer. In this review, phytochemical and biological investigations of some recent *selected* Thai medicinal plants will be discussed.

Anti-infectious diseases

New and reemerging infectious diseases for which no effective therapy is available and the development of resistance of many pathogens to currently used drugs are of utmost concern. In the developing countries, malaria, TB and HIV are the three major infectious disease threats. They account for approximately half of mortality caused by infectious diseases which is almost half of the mortality in developing countries. It is not at all an exaggeration to say that malaria has been responsible for much of the human suffering and misery accompanying the process of social and economic development. There are more than 300 million cases of malaria in the world every year and malaria kills more than one million people every year. Over the last ten years, the malaria situation has been worsening in many areas of the world. The need to find new antimalarials is pressing, due to the discovery of the resistance of the human malarial parasite, *Plasmodium falciparum* to the presently available common antimalarial drugs. Treatment has thus become both less effective and much more expensive. The problem is further aggravated by the resistance of vector anopheline mosquitoes to the most effective and least toxic insecticides which were used to kill them. The potential of natural products as therapeutic agents in the treatment of malaria is enormous and the research work in this area has been the subject of some recent reviews (Mahidol et al., 1997a; Ekthawatchai et al., 1999). Some further investigations include the isolation of an antimalarial stilbene from *Artocarpus integer*. Stilbene (**1**) exhibited *in vitro* antimalarial activity against *P. falciparum* with the EC_{50} value of 1.7 μg/ml (Boonlaksiri et al., 2000, p. 415). From *Artocarpus gomezianus*, a dimeric stilbene was isolated and this compound was found to have tyrosinase inhibitory activity (Likhitwitayawuid and Sritularak 2001, p. 1457).



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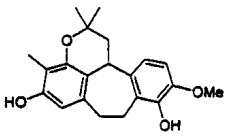

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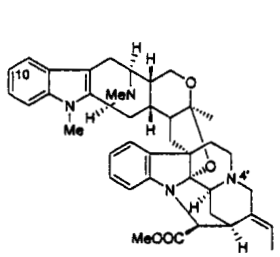
Racemosol (**2**) has been previously isolated from *Bauhinia racemosa* (Anjaneyulu et al., 1986, p. 2417) and *Bauhinia rufescens* (Maillard et al., 1991, p. 791). The compound has also been isolated from *Bauhinia malabarica* Roxb. and found to have antimalarial activity with EC_{50} of 0.9 μg/ml (Kittakoop et al., 2000, p. 349). Plants in the *Alstonia* species have been used as antimalarial remedies in traditional medicine. Investigations of three Thai *Alstonia* species, *A. scholaris*, *A. macrophylla* and *A. glaucescens*, have resulted in the isolation of thirteen indole alkaloids. Villalstonine (**3**) and macrocarpamine (**4**), the

macroline-pleiocarpamine bisindoles, exhibited significant antimalarial activity with IC_{50} values of 0.27 and 0.36 μM, respectively (Keawpradub et al., 1999, p. 690). Some coumarin and carbazole derivatives from *Clausena harmandiana* also exhibited antimalarial activity (Yenjai et al., 2000, p. 277).



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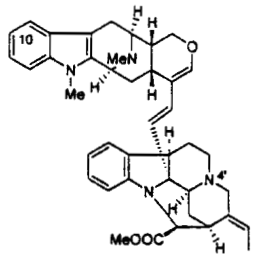

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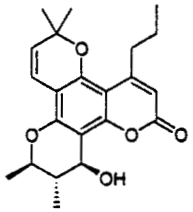
Anti-HIV drug discovery and development has been the subject of intensive study. The search for anti-HIV drugs, especially natural product-based anti-HIV reverse transcriptase inhibitors, has been the theme of recent reviews (Matthée et al., 1999; Yang et al., 2001). Many natural products have been found to be inhibitors of HIV-1-RT and these compounds are derived from various sources including terrestrial and marine plants, microorganisms, and marine animals. These compounds belong to diverse structural classes e.g. coumarins, flavonoids, tannins, alkaloids, lignans, terpenes and quinones. One of the most prominent compounds is calanolide A (**5**), a coumarin isolated from the tropical rainforest tree, *Calophyllum lanigerum* (Guttiferae) first collected from Sarawak, Malaysia (Galinis et al., 1996, p. 4507). Calophyllum species from Sri Lanka have recently been investigated (Dharmaratne et al., 2002, p. 86).



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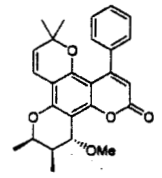
We have also undertaken the phytochemical investigation of Thai *Calophyllum inophyllum*. The methanol/dichloromethane (1:1) extract of the dried leaves of the plant was fractionated by vacuum liquid column chromatography and/or column chromatography and/or PTLC procedures to provide eight compounds **6–13** which were known and were identified by spectroscopic and/or chemical examinations as well as comparison with the published data (Harborne et al., 1965; Kawazu et al., 1972; Patil et al., 1993). These isolated compounds were identified as 12-methoxyinophyllum D (**6**), calophyllolide (**7**), inophyllum C (**8**), inophyllum E (**9**), calophyllic acid (**10**), isocalophyllic acid (**11**), kaempferol-3-*O*-α-L-rhamnoside (**12**), and quercetin-3-*O*-α-L-rhamnoside (**13**). Four new mammea coumarins as well as six known coumarins have recently been isolated from the flowers of *Mammea siamensis* (Mahidol et al., 2002a, p. 757).



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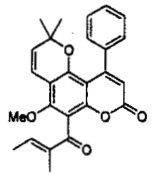

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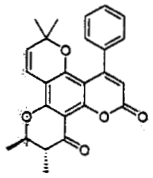

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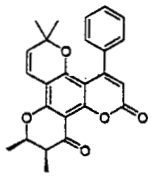

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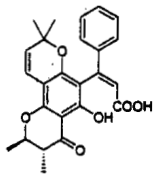

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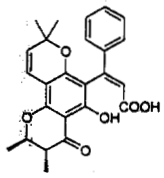

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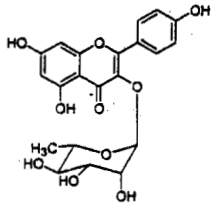

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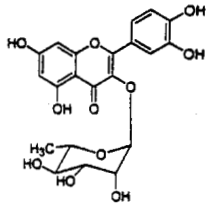

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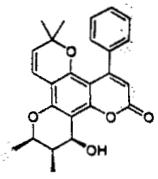

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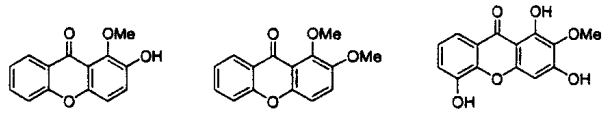
In addition, a hexane extract of the dried leaves of *C. inophyllum* was separated using vacuum liquid column chromatography. Further purification of the resulting fractions was carried out by PTLC leading to the isolation of known compound **14** which was identified by spectroscopic methods and comparison with the published data as inophyllum A. Furthermore, the dichloromethane extract was subjected to chromatography to give compounds **15–17**, which have already been isolated earlier from the same plant, and compounds **18–20** isolated from other plants. Structure elucidation of these compounds was accomplished by the use of 2D NMR technology and comparison with the literature data.



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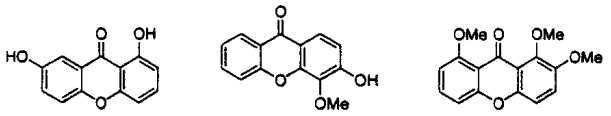
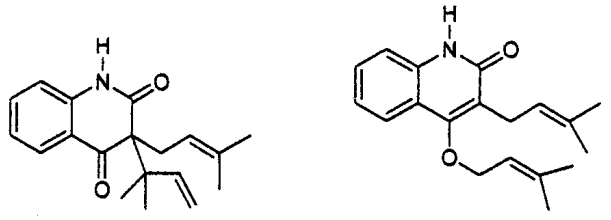


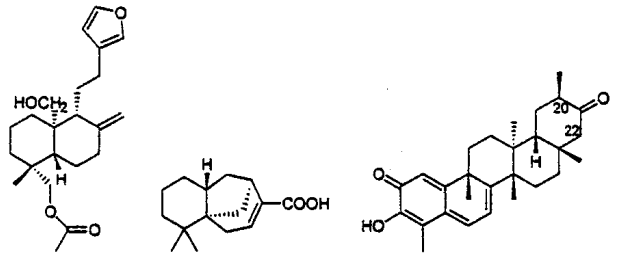
18 19 20

Buchapine (**21**) and a quinolone derivative (**22**) were isolated from *Euodia roxburghiana* collected in Surat Thani, the southern province of Thailand. These compounds were found to be active against infectious HIV-1 as well as inhibiting HIV-1-RT (McCormick et al., 1996, p. 469).

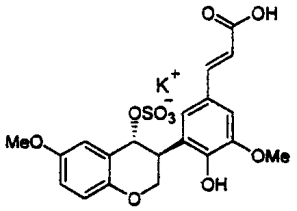


21 **22**

The fruits of *Momordica charantia* have been shown to contain many proteins with varying molecular weights and these proteins exhibit a ribosome-inactivating property. MAP30, a ribosomal inactivating protein, was isolated from this fruit and found to inhibit HIV-1 reverse transcription, viral core protein synthesis and syncytium formation between the infected and the new white blood cells. From the ripe fruit and seed of Thai *Momordica charantia*, a protein (MRK29) of molecular weight 28.6 kD was isolated and purified. MRK29 was found to inhibit HIV-1 reverse transcriptase with 50% of inhibitory ratio (IR) at a concentration of 18 μg/ml. The protein increased TNF activity 3-fold suggesting that the compound might have a modulatory role on immune cells (Jiratchariyakul et al., 2001, p. 350). *Potamogeton malaianus* is a high salt-tolerant water plant found in the northeast of Thailand. From this plant, potamogetonol (**23**), a furanoid labdane diterpene, was isolated and identified. The compound and other related compounds were found to exhibit antiviral (HSV-1) activity (Kittakoop et al., 2001, p. 385). Sclerocarpic acid (**24**), a sesquiterpene, and various quinone-methide triterpene derivatives (**25**) were isolated from the stem bark of *Glyptopetalum sclerocarpum* (Sotanaphun et al., 1998, 1999a). Sclerocarpic acid was also shown to exhibit antiviral (HSV-1 and 2) and antimicrobial activity while the triterpene derivatives were effective against *Bacillus cereus*, *B. subtilis*, *Sarcina lutea*, *Staphylococcus aureus*, *Microsporum gypseum* and a Gram-negative bacterium, *Klebsiella pneumoniae*. The quinone methide moiety was crucial for the biological activity (Sotanaphun et al., 1999b, p. 450). Some diterpenes, *ent*-abietadienolides, from *Euphorbia sessiliflora* also showed moderate antibacterial activities (Sutthivaiyakit et al., 2000, p. 947).



23 **24** **25**



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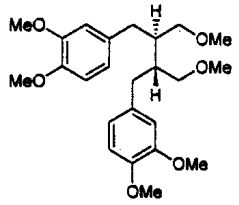
An antiviral isoflavonoid sulfate, torvanol (**26**), was isolated from the MeOH extract of the fruits of *Solanum torvum* (Arthan et al., 2002, p. 459). The compound exhibited activity against the herpes simplex virus type 1 with the IC_{50} value of 9.6 μg/ml. Water extracts of the plants *Maclura cochinchinensis* and *Mangifera indica* have been found to exhibit activity against herpes simplex viruses (HSV-1 and -2) in the plaque inhibition assay (Yoosook et al., 2000, p. 411).

Anticancer agents

As mentioned earlier, apart from being an excellent source of anti-infectious drugs, plants are also a good source of anticancer agents. These include paclitaxel (Taxol®) from *Taxus brevifolia*, vincristine (Oncovin®) from *Catharanthus roseus*, podophyl-

lotoxin, the natural product precursor of etoposide from *Podophyllum peltatum* and camptothecin from *Camptotheca acuminata*. The finding that taxoids act through the stabilization of microtubules has led to the search for new agents that function by a comparable mechanism. Towards this end, new compounds have been discovered. Epothilones are a new class of macrocyclic natural products which were first isolated from myxobacteria (Höfle et al., 1996, p. 1567). Epothilones are more potent than taxol in some cell lines and they hold great promise for further investigation (Bollag et al., 1995; Gerth et al., 1996; Finlay et al., 1997).

We have been interested in the screening of Thai medicinal plants for anticancer properties. The plant *Phyllanthus amarus* Schum. & Thonn. of the Euphorbiaceae family, locally known as *Look Tai Bai*, has been investigated for cytotoxicity activity. *Phyllanthus amarus* has been traditionally used for the treatment of jaundice and other hepatic diseases. Two major components, phyllanthin (**27**) and hypophyllanthin (**28**), were isolated from this plant (Somanabandhu et al., 1993, p. 233).



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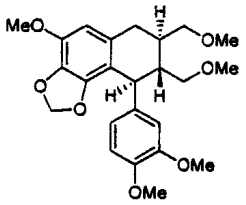

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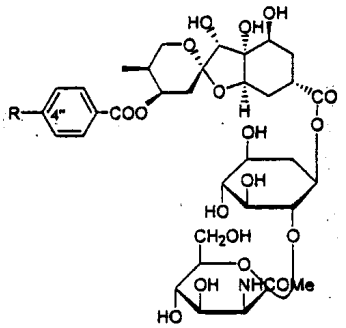
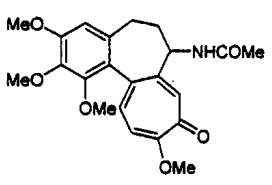
Apart from structural studies, the biological activities of these compounds have also been investigated. Evaluation of the cytotoxic potential of phyllanthin and hypophyllanthin was conducted with a battery of human tumor cell lines including P-388, BCA-1, HT-1080, LUC-1, MEL-2, COL-2, A-431, LNCaP, and ZR-75-1 cell lines. The ED_{50} values of both compounds exceeded the highest concentration tested which is 20 μg/ml. However, phyllanthin (**27**) demonstrated an ED_{50} value of 9.0 μg/ml with the drug-resistant cell line, KB-V1 in the absence of vinblastine, and very interestingly, this value was decreased to 2.1 μg/ml in the presence of vinblastine. Hypophyllanthin (**28**) did not mediate a cytotoxic response in the absence of vinblastine, but upon addition of this substance, an ED_{50} value of 3.8 μg/ml was obtained. However, neither compound demonstrated activity with the drug-sensitive cell line, KB-3. Recently another Thai phyllanthus plant, *Phyllanthus acidus*, was investigated (Vongvanich et al., 2000, p. 5420). The spirit extract of this plant has been reported to reduce the craving for alcohol. Two cytotoxic water-soluble norbisabolane glycosides, phyllanthusol A (**29**) and phyllanthusol B (**30**), were isolated from the methanol extract of the roots of this plant. Phyllanthusols A and B exhibited cytotoxicity against BC (EC_{50} at 4.2 and 4.0 μg/ml) and KB (EC_{50} at 14.6 and 8.9 μg/ml) cell lines. Apart from *Phyllanthus amarus*, we have also investigated *Gloriosa superba* Linn., for anticancer activity. *Gloriosa superba* Linn. is known in Thai as '*Dong Dueng*' or '*Dao Dueng*', a climber plant in the family 'Colchicaceae', which is widely distributed in the tropical parts of Asia and Africa, with many varieties present in Thailand. The active principle of *Gloriosa superba* is the alkaloid colchicine which is isolated from the dried tubers of the plant. Colchicine has long been used for the treatment of arthritis. From the dried tubers of Thai *Gloriosa superba*, four tropolone alkaloids, colchicine (**31**), lumicolchicine (**32**), 3-demethyl-N-formyl-N-deacetylcolchicine (**33**), and 3-demethylcolchicine (**34**) were isolated (Mahidol et al., 2000, p. 6).



29 R = OH; **30** R = H



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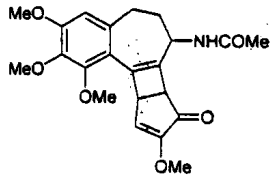

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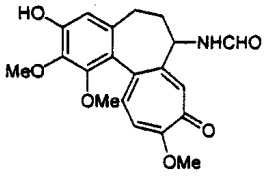

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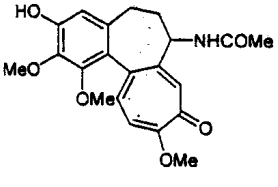
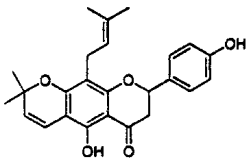


34

Another cancer cell line of interest to us is the cholangiocarcinoma cell line. Cholangiocarcinoma, a form of bile duct cancer, is a rare type of cancer in the Western world but it is highly prevalent in Thailand and in many other Asian countries. The cause of the disease is believed to be associated with infestation of *Opisthorchis viverrini* (O.V.) or liver fluke and exposure to a chemical carcinogen in food or in the environment, presumably, dimethylnitrosamine (DMN). We have conducted the evaluation of the effectiveness of some new anticancer agents against cholangiocarcinoma.

The ED_{50} for the cholangiocarcinoma cell line for 3-demethyl-*N*-formyl-*N*-deacetylcolchicine (**33**) was found to be 0.0625 μg/ml, in contrast with the ED_{50} of about 0.02 μg/ml for colchicine (**31**) itself. These values were approximately two times higher than the ED_{50} values for the KB cell line. These results showed that the cholangiocarcinoma cell line is highly susceptible to the derivatives of the tropolone alkaloids, at least when testing *in vitro*, whether or not these agents will be effective *in vivo* remains to be determined in further experiments. We have synthesized various analogues of colchicine with the goal of improving the therapeutic index of the target compound by enhancing the potency of these analogues. Modification of the aromatic ring of colchicine was first studied. Colchicine could be selectively demethylated at C-2 by the action of sulfuric acid. Ester and ether analogues of 2-desmethylcolchicine were synthesized. The biological testing indicated that the longer chain of the alkyl or ester group attached to the aromatic ring of colchcine did not improve the biological activity in the cholangiocarcinoma cell line. Modifications of the tropolone ring and the peripheral functional groups of the tropolone ring have also been studied. The results of the biological testings of these compounds using the cholangiocarcinoma cell line showed very low biological activities as compared to colchicine; these results clearly illustrated the importance of the tropolone ring in the activity. Even though the results of the above biological testing have been very discouraging, the results clearly indicated to us that modifications of the aromatic ring and the tropolone ring of colchicine molecule will not yield any compound with higher biological activity than colchicine itself. At this point there is only one alternative left, that is the modification of the nitrogen side chain. Many colchicine derivatives with modification at the nitrogen atom have been synthesized and these compounds have been subjected to biological testing for anti-cholangiocarcinoma activity and found to be more potent than colchicine itself. Some derivatives exhibited very impressive activity, 20–30 times more potent than colchicine.

We have also investigated a plant named *Derris reticulata* Benth. (Leguminosae), it is a well known Thai herbal medicine used for the relief of thirst and as an expectorant. The Leguminosae is known to be a rich source of flavonoids and most of the prenyl derivatives have been found in this family (Harborne and Williams, 1998, 2001). The flavonoids exhibit diverse biological activities and recent interest has been focussed on their medicinal and nutritional values (Harborne and Williams, 2000, p. 481). Recently, some biologically active prenylated flavonoids have been reported (Manfredi et al., 2001; Sekine et al., 1999; Tseng et al., 2001) and, significantly, it was found that the prenyl groups on the flavonoid skeleton play an important role in anti-HIV activity (Meragelman et al., 2001, p. 546). Initially, we reported the isolation and structural characterization of four prenylated flavanones, lupinifolin (**35**), 2‴,3‴-epoxylupinifolin (**36**), dereticulatin (**37**), and 1‴-hydroxy-2‴,3‴-epoxylupinifolin (**38**) from the stems of *Derris reticulata* (Mahidol et al., 1997b; Prawat et al., 2000). The structures of these compounds were deduced from various spectroscopic analyses, especially 1D and 2D NMR as well as chemical transformations.



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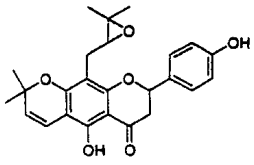

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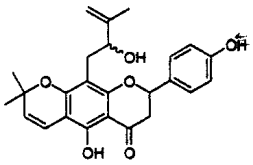

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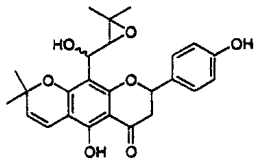

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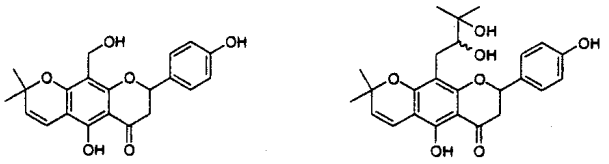
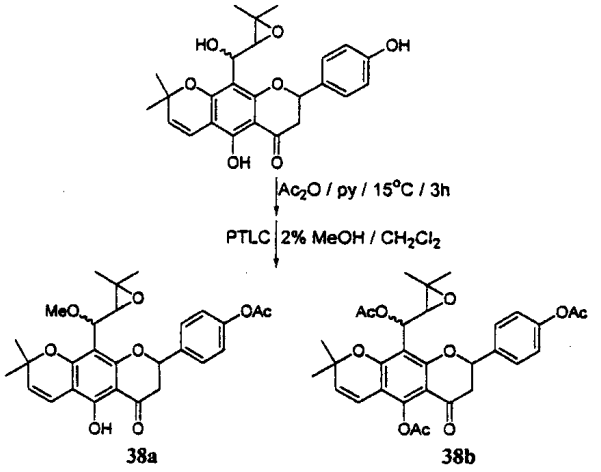
Further investigation of this herb has led to the isolation of two new cytotoxic flavonoids, 4′,5-dihydroxy-8-hydroxymethyl-6″,6″-dimethylpyrano [2″,3″:7,6]flavanone (**39**), and 2‴,3‴-dihydroxylupinifolin (**40**) (Mahidol et al., 2002b, p. 1287).



39 40

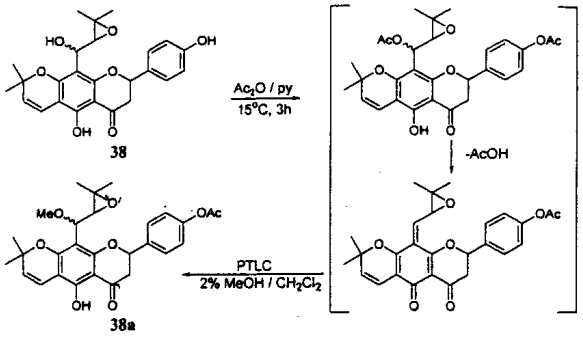
We have also investigated the chemistry of some of these compounds. For example, epoxidation of lupinifolin (**35**) with magnesium monoperoxy-phthalate hexahydrate (MMPP) gave epoxylupinifolin (**36**). Acetylation of 1‴-hydroxy-2‴,3‴-epoxylupinifolin (**38**) with acetic anhydride in pyridine was attempted. After general workup, the crude was chromatographed on silica gel by PTLC using 2% MeOH in CH_2Cl_2 as developing solvent to give two compounds **38a** and **38b** in 50% and 31% yields respectively as shown in Scheme 1.



38a 38b

Scheme 1. Acetylation of compound **38**.

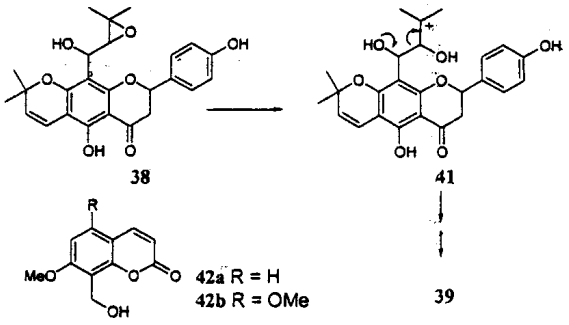
The formation of the abnormal methoxy derivative under these acetylation conditions can be explained by the mechanism as shown in Scheme 2. Partial acetylation of the hydroxyl group leads to the acetoxy derivative. Loss of the acetic acid with the help of the hydroxyl group can lead to the quinone methide intermediate which could then react with methanol to give the methoxy compound. Apparently, the compound was formed during PTLC purification when methanol was used as developing solvent.



38 38a

Scheme 2. Proposed mechanism for the formation of methoxy derivative **38a**.

The co-occurrence of hydroxymethyl compound **39** with 1‴-hydroxy-2‴, 3‴-epoxylupinifolin (**38**) and compound **40** lends support to the proposal in Scheme 3 that the hydroxymethyl group in compound **39** could be derived from this compound by acid catalyzed opening of the epoxide ring or protonation of the hydroxyl group in compound **40** to give the corresponding stable carbonium ion followed by carbon-carbon bond cleavage as shown in **41** to give the aldehyde, an immediate precursor to compound **39**. This biosynthetic route apparently could be applied to rationalize the biosynthesis of the extremely rare hydroxymethyl coumarins, murrayacarpin-A and -B, **42a** and **42b**, which also co-occur with the prenyl derivatives (Wu et al., 1989, p. 293).

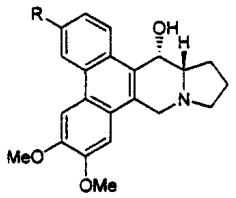


38 41 39

Scheme 3. The proposed biosynthesis of compound **39**.

We have also carried out the *in vitro* bioassay evaluation of lupinifolin, epoxylupinifolin and dereticulatin triacetate. They inhibited the P-388 cell line at 0.4–0.5 μg/ml while hydroxymethyl compound (**39**) and 2‴,3‴-dihydroxylupinifolin (**40**) inhibited at 6.4 and 1.3 μg/ml. All compounds were inactive against the KB cell line. Other flavonoid compounds including the calycopterones, a new class of biflavonoids, which exhibited novel cytotoxicity in a diverse panel of human tumor cell lines (Wall et al., 1994, p. 1465). Labdane

diterpenes from *Croton joufra* (Sutthivaiyakit et al., 2001, p. 811) and *Croton oblongifolius* (Roengsumran et al., 2001, 2002) collected from various parts of Thailand have found to possess cytotoxicity which is also found in clerodane derivatives from the same plant. *O*-methyltylophorinidine (**43**), a phenanthroindolizidine alkaloid, has been reisolated from *Ficus hispida* collected in Chiang Rai in the northern part of Thailand (Peraza-Sánchez et al., 2002, p. 186). The compound was shown to be highly cytotoxic in many cell lines tested (Col2, ED_{50} = 0.02 μg/ml; Lul, ED_{50} = 0.018 μg/ml; KB, ED_{50} = 0.02 μg/ml; and LNCaP, ED_{50} = 0.03 μg/ml). Interestingly, a related phenanthroindolizidine (**44**) was isolated from the Danaid butterfly, *Ideopsis similis*. The compound was found to have a potent cytotoxic property against a human gastric cancer cell line, TMK-1 (IC_{50} = 0.5 ng/ml) (Komatsu et al., 2001, p. 1833).

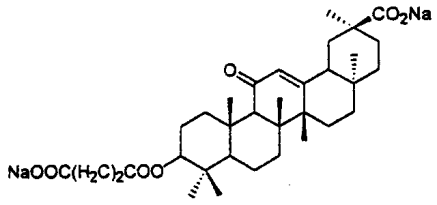


43 R = OMe

44 R = OH

Antiulcer agents

It has been estimated that about 10–20% of people in the West suffer from a peptic ulcer at some stage of their lives, and the treatment of this condition has long been of interest to the medical community.



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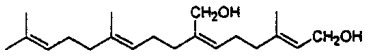
Plants are also a good source of antiulcer drugs. The modern treatment of peptic ulcers started in the 1960s with the use of a drug called carbenoxolone (**45**) which is a sodium salt of a triterpenic acid. The drug was discovered after the intensive investigation of the roots and rhizomes of liquorice (*Glycyrrhiza glabra*). It is a transformation product of glycyrrhizic acid, a natural product found in this plant.

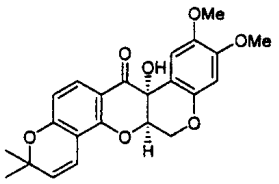
As far as the discovery of antiulcer drugs is concerned, the highlight must be the discovery of plaunotol (**46**) from the plant from Thailand called *Plao-Noi*, *Croton sublyratus* Kurz. (Euphorbiaceae) by Japanese scientists at the Sankyo company.



46

The structure of compound **46** was proved to be the diterpene as shown by spectroscopic methods and synthesis (Ogiso et al., 1978, p. 3117). The compound was proved to be a potent antiulcer drug. The mechanism of the action of this drug is probably that it raises the defensive factors since it enhances prostaglandin levels in gastric mucosa. Prostaglandins are known to inhibit acid secretion and stimulate the secretion of mucus, and of bicarbonate. This compound is now commercially available under the trade name of Kelnec. The antiulcerative effect of Thai bananas of different varieties have also been recently investigated (Pannangpetch et al., 2001, p. 407).

It is now generally accepted that *Helicobacter pylori* infection is the major cause of chronic active gastritis and peptic ulcer disease. It was found that rotenoids from the roots of *Derris malaccensis* exhibited selective activity against *Helicobacter pylori*. Tephrosin (**47**) and toxicarol (**48**) gave the best result with minimum inhibitory concentrations (MIC) of 0.3 mg/ml. The toxicity of the rotenoids as insecticides and piscicides is caused by the inhibition of NADH oxidation in the respiratory chain. It is thus likely that the selective anti-*H. pylori* activity in these rotenoid compounds might be due to the inhibition of NADH oxidation (Takashima et al., 2002, p. 611). *Derris malaccensis* also grows in Thailand and is locally known as '*haang lai kaow*'. The plant is used for pest control and as a fish poison. We have recently reported the isolation and structural elucidation of a new rotenoid, 12a-hydroxyelliptone (**49**), and the known rotenoid, 12-deoxo-12α-acetoxyelliptone (**50**), from this plant (Thasana et al., 2001, p. 1121).



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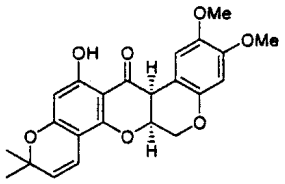

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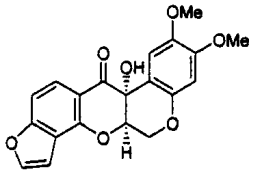

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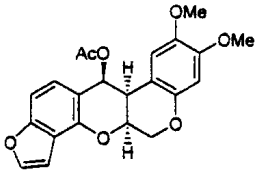
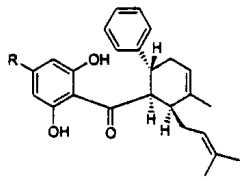


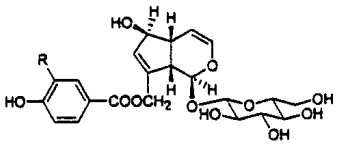
50

Anti-inflammatory agents

Some Thai medicinal plants have recently been investigated for anti-inflammatory activity. (–) Hydroxypanduratin A (**51**) and panduratin A (**52**) have been isolated from the chloroform extract of a red rhizome variety of *Boesenbergia pandurata*. Both compounds showed significant topical anti-inflammatory activity in the TPA-induced ear edema assay in rats (Tuchinda et al., 2002, p. 169). Iridoids (**53**) and (**54**) were isolated from the polar fractions of the butanol extract of *Vitex peduncularis* Wall. (Verbenaceae) and were tested for inhibition of cyclooxygenase (COX, prostaglandin H synthase)-1 and COX-2 regulated prostaglandin biosynthesis using COX deficient murine cell lines. Iridoid (**53**) showed preferential inhibition of COX-2 over COX-1 (COX-2 $IC_{50} = 0.026 \pm 0.015$ mg/ml and less than 10% inhibition of COX-1 at this concentration). Similarly, iridoid (**54**) had a COX-2 IC_{50} value of 0.15 ± 0.21 mg/ml while having almost no effect on COX-1 activity as indicated by less than 10% inhibition at this concentration (Suksamrarn et al., 2002, p. 72).



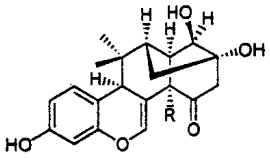
51 R = OH; **52** R = OMe



53 R = H; **54** R = OMe

Miscellaneous agents

The plant '*Kwao Keur*', *Pueraria mirifica*, has captured the interest of local newspapers during the past years because of its rejuvenating properties. Miroestrol (**55**) was previously isolated and found to exhibit potent estrogenic activity. It was regarded as the compound with the highest estrogenic potency among the known phytoestrogens. Recent investigation resulted in the isolation of deoxymiroestrol (**56**) and it was found that deoxymiroestrol was 10 times more potent than the previously isolated miroestrol in terms of their growth-promoting effects on MCF-7 human breast cancer cells in the presence of an estrogen antagonist, toremifene. Due to the facile aerial oxidation of deoxymiroestrol to miroestrol, it is likely that miroestrol was an artifact (Chansakaow et al., 2000, p. 173).



55 R = OH

56 R = H

8-Isopentenylnaringenin, a prenylflavonoid, isolated from a methanol extract of the heartwood of *Anaxagorea luzonensis*, has been found to exhibit estrogen agonist activity (Kitaoka et al., 1998, p. 511). Similar agonist activity has also been reported for retrodihydrochalcone derivatives isolated from *Dracaena loureiri* (Ichikawa et al., 1997, p. 540).

In conclusion, at present there are a large number of chronically debilitating or life-threatening diseases that urgently require improved or new medical treatments. Chemotherapy is a well-established approach for the remedy of these diseases. With new diseases and increasing resistance to existing drugs, there is a pressing need to discover and develop new innovative drugs with diminished side-effects to combat cancer cells, viruses and other threats. The research on natural products will be essential for the discovery of lead compounds in the future because of the incredible diversity of chemical structures that are produced by living organisms.

Acknowledgements

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บทคัดย่อ

การค้นคว้าวิจัยพืชสมุนไพรไทยที่มีฤทธิ์ทางชีวภาพ

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พืชนับเป็นแหล่งที่มาของยาที่สำคัญที่สุดสำหรับประชากรโลกมากกว่าร้อยละ ๘๐. สมุนไพรเป็นแหล่งที่มาของยาที่สำคัญในประเทศกำลังพัฒนา. ถึงแม้ว่ามนุษย์จะมีประสบการณ์การใช้สมุนไพรเป็นยาพื้นบ้านมานาน แต่สัดส่วนของพืชในโลกที่มีการศึกษาวิจัยทางวิทยาศาสตร์อย่างเหมาะสมมีน้อยมาก ซึ่งเป็นเรื่องที่น่าเป็นห่วงเป็นอย่างมาก เพราะพืชหลายชนิดได้สูญพันธุ์ไปเรื่อย ๆ. ดังนั้น จึงจำเป็นต้องเร่งตอบสนองต่อสถานการณ์นี้อย่างรวดเร็ว เพื่อป้องกันการสูญหายของพืชพันธุ์ต่าง ๆ ไปพร้อม ๆ กับองค์ความรู้เกี่ยวกับสรรพคุณยาพื้นบ้านของสมุนไพรเหล่านั้น. บทปริทัศน์นี้ได้นำเสนอการศึกษาวิจัยสมุนไพรไทยบางชนิดที่มีฤทธิ์ทางชีวภาพ โดยเน้นการนำเสนอฤทธิ์ทางชีวภาพในการต้านโรคติดเชื้อ, ต้านเชื้อมาลาเรียและเอชไอวี, ต้านมะเร็ง, ต้านการเกิดแผล และต้านอักเสบ, รวมทั้งได้กล่าวถึงผลของการเปลี่ยนแปลงสูตรเคมีของสารบางชนิดในสมุนไพรด้วย.

คำสำคัญ: **ฤทธิ์บำบัดโรคมะเร็ง, ฤทธิ์ต้านเชื้อเอชไอวี, ฤทธิ์ต้านโรคติดเชื้อ, ฤทธิ์ต้านอักเสบ, ฤทธิ์ต้านเชื้อมาลาเรีย, ฤทธิ์ต้านการเกิดแผล, สมุนไพรไทย**