The Thai Journal of Pharmaceutical Sciences

Volume 11
Issue 4 *1986*

Article 6

1-1-1986

PLANTS AS SOURCES OF BIODYNAMIC COMPOUNDS

Payom Tantivatana

PLANTS AS SOURCES OF BIODYNAMIC COMPOUNDS

*Payom Tantivatana, Ph.D.**

Plants play an important role in human life since antiquity. In the old time the primary necessaries of man were food, cloth, shelter and medicine and all of these necessities were derived from plants. From generation to generation, plants have been used by mankind in an attempt to cure diseases or relieve physical suffering. All possible plants from surrounding areas were collected because survival being the intention of human race. Some of these were useless and hence only those discovered useful were ultimately reserved after thorough perusal. At the beginning their attempts at medicine were based on speculation and superstition. At that time most of them believed that illness was due to the presence of evil spirits in the body and could be driven out by employment of poisonous or disagreeable substances making the body to be unpleasant spot in which to remain.

Human cultures have always been influenced by plants and plant products. All indigenous remedies have their roots from folk medicines and ethnomedicobotany. Many of these remedies still have survived and have been used by people in certain regions of the world.

With the advancement of civilization of the human race, requirements began to increase. His necessities seemed to be complex. In order to meet the requirements, examination of new raw materials was started, from which useful articles and conversion products were prepared.

Although the present day market is flooded with drugs which are mostly synthetic but a large number of populations in the developed and/or developing countries still depend on drugs from natural sources. Some medicinally active substances of plant origin do not find suitable substitutes. For example, morphine, cocaine, quinine, reserpine, digoxin, etc. are all plant products, still holding a significant place among the list of drugs (1). Interesting in plant-derived drugs are both from developing and developed countries. In the U.S.A., for example, 25% of all prescriptions dispensed from community pharmacies from 1959 to 1980 contained plant extracts or pure compounds prepared from higher plants. This figure did not vary by more than ±1.0% in any of the 22 years surveyed. In 1980 consumers in the U.S.A. paid more than $ 8,000 million for prescriptions containing active principles obtained from plants (2).

Thailand is rich in natural resources and are usually available in abundance. Crude drugs are available in every town. After standardization, these materials may provide safe and effective galenical products or may lead to the discovery of new biologically active compounds. Moreover, some of known and novel compounds may reveal as models to organic chemists for synthesis of new drugs. Now we realize that in the realm of science, drug research belongs to the interdisciplinary group of sciences, since it involves a number of heterogenous technical fields which are united in the applications to a common object in order to seek for new drugs.

---

* Professor, Institute of Health Research, Chulalongkorn University.

Plant Kingdom represents as a pool of novel chemical compounds or of compounds with novel actions. The pharmacological action of compounds derived from plants is not narrow, infact is in wide ranging. Some pharmacologically active natural substances from plants which are prescribed in modern medicines are shown in the followings:-

Pharmacological activity (1)

Central nervous system	reserpine, caffeine, picrotoxin, strychine
Analgesic	morphine, codeine
Anti-inflammatory	colchicine, glycyrrhizin, bromelin
Muscle-relaxant	tubocurarine
Local anaesthetic	cocaine
Autonomic nervous system	
cholinergic	physostigmine, pilocarpine
cholinergic blocking	atropine, hyoscine
adrenergic	ephedrine
adrenergic blocking	ergotamine
ganglion blocking	nicotine
Hallucinogens	psilocin, psilocybin, LSD, THC
Chemotherapeutic	
anti-malaria	quinine
anti-amoebic	emetine
anti-cancer	vinblastine, vincristine
Cardiovascular	
vasodilator	papaverine, theophylline
hypotensive	reserpine, protoveratrine A & B
cardiotonic	digoxin, digitoxin
anti-arrhythmic	quinidine, ajmaline
anti-coagulant	coumarin
Carthartic	anthraquinone

In 19th century a number of alkaloids were isolated from plant drugs such as Opium (morphine, 1805), Ipecacuanha (emetine, 1817), Nux vomica (strychnine, 1819) and Cinchona (quinine, 1820). Apart from strychnine, these alkaloids are still prescribed in modern medicines and they continue to search for new alkaloids from plants because it is more economic than chemical synthesis. In fact, alkaloids were among the first natural products to be isolated from several potent drugs therefore scientists paid more attention to these compounds than any other groups of natural products. If investigators select to work on only alkaloids, then they will miss of other interesting groups of natural products. Now we realize that there are other groups of natural products provided interesting biological active compounds such as terpenes, saponins, etc.

Terpenes: Terpenes are active principal of some traditional plant medicines. Most volatile oils which are distributed widely in the plant kingdom consist largely of terpenes such as monoterpenes, diterpenes and sesquiterpenes. Formerly, not many terpenes have found clinical application in modern medicines but now these compounds reveal a wide range of biological activities. The number of mono-, di- and sesquiterpene from natural sources has increased rapidly. Now about 650 sesquiterpene lactones are known as natural products. This number is not constant as it seems to be increased from time to time. Biological activity of terpenes is given below (1, 3, 4, 5, 6, 7, 13).

Type of activity	Mono-terpene	Di-terpene	Tri-terpene	Sesqui-terpene
Anaesthetic	+			
Analgesic	+	+	+	
Anthelmintic	+	+		
Antibiotic	+	+	+	+
Anti-convulsant	+	+		
Anti-emetic	+			
Anti-fertility			+	
Antihistamine	+			
Anti-inflammatory	+	+	+	
Anti-malaria				+
Anti-spasmodic				+
Anti-tumour	+	+		+
Anti-ulcer and Anti-peptic	+	+	+	+
Antitussive	+		+	
Antihaemorrhagic (capillary)				+
Cardiotonic				+
Diuretic	+			
Hypotensive	+	+		+
Insecticide	+	+		
Spermicide		+	+	
Sweetening agent	+	+	+	
Uterine stimulant		+		

As shown on the above data, now we have learned that terpenes exhibit a wide range of biological activity. Today malaria is still considered as the world's most common tropical disease hence, new antimalarial drugs with novel actions are being sought. For many years *Cinchona* species have been used for the production of quinine as the major drug for the treatment of malaria but it causes vomiting, diarrhoea, problems of vision and hearing in high doses. With this situation the search for novel compounds from plants with antimalarial activity was begun. Artemisinin (quinghausu, QHS) was isolated as the active principle of Chinese traditional herbal remedy *Artemisia annua* (Compositae) and its structure was determined in 1979. Artemisinin is the novel sesquiterpene lactone. It contains an endoperoxide moiety which is a rare feature in natural products (3). A series of related terpenes, other terpenes, a flavonoid and scopoletin have also been isolated from the same Chinese medicinal herb (8). As a pure isolated compound, artemisinin suffers from some disadvantages, in particular it has low solubility in aqueous and oily solvents thus causing problems for clinical application. To solve this problem, derivatives of artemisinin were prepared. Among prepared derivatives, it is found that sodium artesunate (sodium dihydroartemisinin hydrogen succinate monoester) is readily water soluble and shows better therapeutic effect on chloroquine-resistant and chloroquine-sensitive strains of *Plasmodium berghei* and *P. knowlesi.* Furthermore, it is reported to be less toxic to the heart than chloroquine (3). The usefulness of artemisinin and its derivatives to treat malaria clinically has resulted in a flurry of scientific activity.

Sweetness is an important taste sensation to humans. The absence of suitable sweeteners as alternatives to cyclamates and saccharin has led to a renewed interest in natural, non-nutritive sweeteners. Stevioside, a constituent of *Stevia rebaudiana* Bert. (Compositae), is commonly used as a noncaloric sugar substitute and commercially available in Japan. The sweet principle, stevioside is bitter in high concentrations, but its intensely sweet taste is 150 to 300 times sweeter than sucrose and relatively high yield (6-10% from the leaves) stimulated further interest. Extracts of this plant and stevioside, its major

sweet constituent have been used for nearly a decade to sweeten a variety of foods including sea foods, prickled vegetables, dessert items, soft drinks and confectionery in Japan and Brazil (4,6). Stevioside one of sweet diterpene glycosides isolated from *S. rebaudiana* is not mutagenic as judged by utilization of *Salmonella typhimurium* strain TM 677, either in the presence or absence of a metabolic activating system. Similar negative results were obtained with several structurally related sweet-tasting glycosides. However, steviol, the aglycone of stevioside, was found to be highly mutagenic when evaluated in the presence of a 9000 × g supernatant fraction derived from the livers of Aroclor 1254-pretreated rats. Expression of mutagenic activity was dependent on both pretreatment of the rats with Aroclor-1254 and addition of NADPH. Unmetabolized steviol was not active but metabolite of an integral component of stevioside is mutagenic (14).

In continuing search for substance of plant origin with anti-peptic ulcer activity, has led to isolation of five novel furanoditerpenes namely plaunol A-E from Thai medicinal plant, *Croton sublyratus* Kurz (Euphorbiaceae) by Japanese investigators of Sankyo Co., Ltd. Furanoditerpenes are principles with anti-Shay ulcer activity in rats (9, 10). From the same plant, 18-hydroxygeranylgeraniol with activity against reserpine-induced ulcers in mice was also isolated (9). This finding has made great contributions in pharmacy and medicine.

The sesquiterpene diol namely cryptomeridiol was isolated from Egyptian desert weed, *Cymbopogon proximus* Stapf. (Gramineae) (7) and from Thai medicinal plant, *Blumea balsamifera* DC. (11) (Compositae), possessed a potent antispasmodic effect on the isolated rabbit ileum (7).

Cymbopogon proximus is highly reputed in the folk medicine of Egypt as an effective renal antispasmodic and diuretic agent (7).

Simaroubaceae contains a number of genera which are used in domestic medicine for a range of activities in several countries. The active ingredients are degraded triterpenes known collectively as quassinoids or simaroubolides. Recently, it is found that bruceantin from *Brucea amarissima* Desv. (Simaroubaceae) possesses anti-cancer property. Bruceantin is promising and has passed animal toxicology and formulation stages and has been considered for Phase II of clinical trial by the National Cancer Institute (12, 14).

The group of diterpenes includes some compounds of considerable physiological interest such as the group of plant hormones known as gibberellins. The best known of these is gibberellin A_3 (gibberellic acid) (13). The insecticide rayanodine of *Ryania speciosa* Vahl (Samydaceae) is a diterpenoid. Diterpenoids are toxic to higher animals including the grayanotoxins of Ericaceae, atractylate from *Atractylis gumifera* and gossypol of cotton seed. The latter two interfere with oxidative phosphorylation. Recently gossypol has shown promise as a male antifertility drug. In China, they claimed that gossypol is a reliable antifertility agent and is relatively safe to use. If the oral administration of gossypol is discontinued, fertility will gradually recover (13).

Considerable attention has been paid to a group of complex diterpenoid esters isolated from members of the Euphorbiaceae. These are powerful skin irritants but also act under various conditions both as tumour promoters and anti-leukemic substances. Many of them are esters of phorbol, but several other variant structures also occur.

Many species of the Euphorbiaceae and Thymelaeceae contain a highly irritant sap or latex. Recently, the irritant principles of these plants have been shown to be esters of closely related diterpene polyols based on tigliane, ingenane and daphnane hydrocarbon skeletons (16).

The first compound of this type to be isolated was ester of the tigliane polyol known as phorbol. Phorbol esters occur naturally in the esterified form, and a series of phorbol-12-13-diesters were isolated from *Croton tiglium* oil, followed by three further triesters known as "cryptic" irritants. More recently, phorbol di- and triesters have been isolated from *Croton sparciflorus, Sapium japonicum, Euphorbia tirucalli, E. coerulescens* and *E. franckiana.* All of these plants belong to Euphorbiaceae (15,16). Interest in these compounds has centered upon toxicological actions. In addition, the same type of compound namely 12-0-n-deca-2,4,6-trienoylphorbol-13-acetate with cytotoxic activity was isolated from

Aquilaria malaccensis (Thymelaeceae) (18). This plant is known in Thai as Mai hom or Krisna and the Infected *(Cytosphaera mangifera* Died*)* wood of this plant is prime source of the perfume agar (18).

Seeds of *Hura crepitans* Linn. and twig and bark of *Excoecaria agallocha* Linn. (Euphorbiaceae) contain toxic principles of daphnane diterpenes namely huratoxin and excoecariotoxin respectively. These substances cause irritation to skin, tumour promoters and anti-leukemic activity (17).

From seed oil of the Chinese tallow tree (*Sapium sebiferum* Roxb., Euphorbiaceae), diterpene esters of 12-deoxyphorbol, 13-monoesters of 12-deoxyphorbol, 12, 13-diesters of phorbol and of 6β, 7β-epoxyphorbol were isolated. All of these compounds exhibit skin irritant and tumour promoters (19). This tree is now spread world wide and often cultivated as an ornamental plant. Chinese vegetable tallow is obtained from the outer covering seeds and this stuff is utilized for candles, cosmetics and soaps. Root bark has been used in China as a purgative and diuretic and is reported to be effective against *Schistosoma japonicum.* The tree has never been reported to be generally toxic, but the latex to be acrid and a powerful vesicant. Chinese are not considered to this plant to be toxic (19).

Triterpenoids are widely distributed in plant resins, cork and cutin. Triterpenoid acids are resin acids which are frequently associated with polysaccharide gums in gum resin. Triterpenoid alcohols occur both free and as glycosides. Many of the glycosides are classed as saponins (13).

The only important acyclic triterpenoid is the hydrocarbon squalene which was first isolated from shark liver oil but is also found in some plant oils (e.g. olive oil) (13).

Monocyclic and dicyclic triterpenoids so far have never been found. Tricyclic ones are rare. Several tetracyclic triterpenoids are known. They probably have biogenetic relationship to the steroids. For a long time some of them were thought to be sterols, and this misconception is reflected in their name. The best known of this compound is lanosterol which occurs in wool fat, yeast and some higher plants (e.g. *Euphorbia electa*). Other tetracyclic triterpenoids are the alcohol euphol from *Euphorbia* spp. and the elemi acids of *Canarium commune* (Burseraceae) (13).

A tetracyclic triterpenoid, β-sitosterol is widely distributed in plant kingdom. It is present in unsaponifiable part of fixed oils. Soyabean oil is a good sources of β-sitosterol. It is used in therapy as cholesterol suppressing drug and acts by physiological competition with cholesterol. Atal *et al.* found that fixed oil of isabgul has cholesterol reducing property which is attributed to unsaturated acids and β-sitosterol present in the oil (12). In the screening programme of local plants as potential anti-inflammatory agents of India, β-sitosterol was isolated from *Cyperus rotundus* Linn. (Cyperaceae). This compound showed significant anti-inflammatory activity against carrageenin induced oedema and in granulation tissue formation induced by cotton pellet inplantation similar to hydrocortisone and oxyphenylbutazone in rats. Furthermore, β-sitosterol possesses antipyretic activity similar to acetylsalicylate on Brewer's yeast induced pyrexia (°C) in albino rats. Thus it may be concluded that β-sitosterol possesses potent anti-inflammation and antipyretic activities in experimental animals (20).

Gugglu or myrrh is the oleo-gum resin from *Commiphora mukul.* The drug has great reputation in Ayurveda in the treatment of rheumatoid arthritis, obesity, as internal anti-septic, anti-inflammatory and in several other disorders. According to chemical investigations the drug contains three sterols, gugglusterols I, II and III, two sterones one of them being called Z. guggulsterone and two diterpenes. Z. guggulsterone is the major pregnane type compound and has exhibited high degree of anti-cholesterolemic activity (12).

Withanolides are steroidal lactones obtained from *Withania somnifera* (Solanaceae). These compounds would be expected to elicit cytotoxic and/or *in vivo* anti-tumour activity. The compounds are withanolide Q, withanolide R, withanolide N, withanolide O, 27-hydroxywithanolide D, 14α-hydroxy-withanolide D and 17α-hydroxywithanolide. In addition, *Physalis peruviana* has also yielded 4β-hydroxy-withanolide E (29).

Several cucurbitacins have been found in many Cucurbitaceous plants. The fruit juice of *Ecballium elaterium* (Cucurbitaceae) has yielded three cucurbitacins which would be predicted to have

cytotoxic and possibly *in vivo* anti-tumour activity. The compounds are anhydro-22-deoxo-3-epi-isocucurbitacin D, hexanorcucurbitacin I and 16-deoxy-Δ16-hexanorcucurbitacin O. From the fruit of *Citrullus lanatus* var. *citroides*, cucurbitacin I 2-0-β-D glucoside and cucurbitacin E 2-0-β-D glucoside were isolated. Moreover, cucurbitacin IIa and cucurbitacin IIb were isolated from the roots of *Hemsleya amabilis* (Cucurbitaceae) and cucurbitacin S was isolated from *Bryonia dioica* (Cucurbitaceae). All of these compounds would undoubtedly be cytotoxic and possibly also have anti-tumour activity (29).

Saponins are widely distributed in the higher plants. They are plant glycosides with distinctive property of frothing, show haemolytic properties when injected into the blood stream. Their alcoholic solution are precipitate with cholesterol. They are toxic to lower organisms like earthworm and fish. According to the structure of the aglycone or sapogenin, two types of soponin are recognized, the triterpenoid and steroidal types.

Triterpenoid saponins are abundant in many dicotyledonous families, particulary the Caryophyllaceae, Sapindaceae, Polygalaceae, Leguminosae, Cucurbitaceae, Araliaceae, etc. Plant materials often contain triterpenoid saponins in considerable amounts. Glycyrrhizin or glycyrrhetic acid is the major saponin isolated from *Glycyrrhiza* species, possesses anti-inflammatory and anti-gastric ulcer effects. Another use of the anti-inflammatory action glycyrrhizin has been found in cosmetics. In 1970 a Japanese patent was granted to Fujiwara, Ishida and Nahamichi entitled Solid Skin Cosmetic. The patenters claim that glycyrrhizin, the base material for the cosmetic gel, has known skin-improving properties and provides a refreshing feeling, excellent transparency and consistency, together with anti-inflammatory value (21). Glycyrrhiza or Liquorice root has long been used in Western medicine for expectorant, antitussive and sweetening agents. It was official in the United State Pharmacopoeia from 1820 to 1975. It is retained in the current British Pharmacopoeia. The product from glycyrrhiza to be used in the treatment of peptic ulcer is carbenoxolone. Carbenoxolone sodium is available in Great Britain, but not in U.S.A. (21).

Glycyrrhiza is one of the most popular drugs in Chinese medicine and is often an ingredient in Chinese prescriptions (1). After over four thousand years of use in medicine, glycyrrhiza is still a viable medicine whose secrets are still being actively investigated and are not completely understood (21).

Senega root (Polygalaceae) is used as a stimulant expectorant in chronic bronchitis in Europe. The root contains crude triterpenoid saponins (senegin) about 10%. Hydrolysis of the crude saponin yields glucose, senegenin, senegenic acid and polygalic acid (22).

Ginseng, the well known ancient drug of East Asian countries, known for its properties of longevity or cure all is obtained from roots of *Panax ginseng* (Araliaceae). According to recent work. ginseng contains saponins which are called ginsenosides by Japanese and panaxosides by Russian workers. The Pharmacological activities of oriental ginseng are believed to be due to its saponins. Recently, it acquired popularity in the West. According to phytochemistry investigation, ginseng contains ginsenosides belong to two sapogenins 2-O-S-protopanaxadiol, 20-S-protopanaxatriol which are tetracyclic triterpene and of oleanosides which are pentacyclic triterpene derivatives known as chikusetsu-saponin. (12). Numerous pharmacological activities in humans and laboratory animals have been reported including general stimulatory effect, raising mental and physical capacity for work. Some members of the ginseng saponins produce effects directly opposed to those produced by others.

Chemical studies of *Panax pseudoginseng* Wall. have been performed in Japan recently. It was found that this plant contains saponin glycosides namely Pseudoginsenoside-RP_1 and RT_1 as the principal active agent along with minor components related to other ginseng saponins (23). Oleanolic saponins composed of glucuronic acid are unique group of compounds found only in *Panax* and other Araliaceous species (24). Interestingly, is the second discovery of pseudoginsenoside-RP_1 and RT_1 in *Randia siamensis* Craib which belongs to family Rubiaceae (25). In addition, a novel saponin named siamenoside has also been isolated from *Randia siamensis* (25). This finding reveals that ginseng saponins are not only restricted to Araliaceae (Polypetalae) but also occur in Rubiaceae (Sympetalae).

Consideration to reputed therapeutic, *Panax pseudoginseng* is a very effective agent in arresting haemorrhage in wounds, including snake and tiger bite. Internally, it has been prescribed in haematomesis, memorrhagia, etc. It is said that the secret formular of Yun-nan-Pai-yao, a famous antibleeding preparation made in Yun-nan province contains the active principles of this particular plant as effective constituent (23).

Randia siamensis fruit is claimed for inducing abortion, emenagogue and hemataenic. Crude ethanolic extract exhibits potent ichthyotoxic and spermacidal activities.

In India, six closely related triterpenes of friedelane derivatives (pentacyclic triterpene) are obtained from *Salacia prinoides* (Celastraceae). Alcoholic extract of the plant elicited hypoglycemic effect in experimental animals and man (12). Pentacyclic nortriterpene quinone methides such as celastrol and pristimerin are commonly isolated from several genera of the Celastraceae family. Pristimerin has been reported to have antitumour activity. An investigation of *Salacia madagascariensis* (Lam.) DC. guided by activity against the P-388 lymphocytic leukemia *in vivo* has yielded the new anti-leukemic pentacyclic bisnortriterpene quinone methide isoiquesterin (26).

There are many examples of saponin containing drugs. Aescin is present in the seeds of chesnut, *Aesculus hippocastanum* (Hippocastanaceae). The drug is popularly used in France in haemorrhoids and venous congestion. Aescin is β-amyrin derivative and is present up to 13%. It is also used as antiexudative, anti-inflammatory and in vericose veins (12). The product from aescin to be used in the treatment of imflammation is reparil which is available in West Germany.

Asiaticoside, a triterpene saponin is present in *Centella asiatica* Urban (Umbelliferae) which is widely distributed in tropical countries. The pharmacological study shows that asiaticoside is useful in leprosy and different types of skin tuberculosis. Only the samples of the plant collected from Lucknow and Madras contain brahmoside and brahminoside. Brahminoside and other two soponin compounds have great reputation as brain tonic in India. Preliminary pharmacological experiments show that drug has tranquilizing, sedative, spasmolytic and anti-amoebic properties (12).

Moreover, two novel triterpenoid saponins, dianosides A & B, showing analgesic activity, have been isolated from *Dianthus superbus* L. var. *longicalycinus* Williams (Caryophyllaceae). This plant has been employed as a diuretic and anti-inflammatory in Oriental medicine (27).

Steroidal saponins are less widely distributed in nature than triterpenoid saponins. Most of them are present in monocotyledonous families, particularly the Dioscoreaceae (e.g. *Dioscorea* spp.), Agavaceae (e.g. *Agave* spp.) and Liliaceae (e.g. *Yucca* and *Trillium* spp.) Steroidal saponins are of great interest and importance owing to their structures are chemically related to cortisone and sex hormones. Formerly, the total synthesis of sex hormones was lengthy and expensive. Now natural steroidal sapogenins such as diosgenin, hecogenin, sarsasapogenin and so on are in great demand for use in partial synthesis of sex hormones and cortisone. Additionally, diosgenin has been identified in other species such as *Costus speciosus* (Zingiberaceae) which is abundant in the tropical rain forest in South East Asian Countries but there is no evidence at present that it would be interesting commercially. Attention has been paid on the cultivation of several *Solanum* species for utilization of their berries as the source material for production of steroid.

Other interesting compounds from steroid saponin are Shatavarins I-IV from roots of *Asparagus racemosus* Willd. (Liliaceae). Shatavarin I has been found to possess anti-oxytocic activity (12).

Naturally occurring compounds exhibiting anti-tumour and/or cytotoxic activities represent a wide rang of chemical structures such as alkaloids, terpenes, steroids, lignans, quinones, flavonoids, etc.

Anti-tumour alkaloids are not limited only to the dimeric indole alkaloids and not even to indole alkaloids. Many types of alkaloids have shown anti-tumour and/or cytotoxic activities in experimental tumour test systems. Alkaloids exhibiting anti-tumour and/or cytotoxic activities are shown in the followings.

Two new diterpenoid alkaloids namely norerythrostachaldine and its 3β-diacetate were isolated from *Erythrophleum chlorostachys* (Leguminosae) by Loder and Nearn. Owing to low yields of both alkaloids therefore no data were reported with regard to the *in vivo* activity of them (29).

From *Nicotiana plumbaginifolia* (Solanaceae), two new steroidal alkaloid glycosides have been isolated and named solaplumbin and solaplumbinin. Both of them reduced tumour weight in the WM system (29).

Pyrrolizidine alkaloids from *Senecio* (Compositae) are potent hepatotoxins. According to the theory, carcinogens may also show anti-tumour activity at non-toxic dose. They are being further investigated. Monocrotaline, previously reported as the tumour inhibitor was isolated from *Crotalaria spectabilis* (Leguminosae). Recently, this alkaloid has been reported to isolate from *C. assamica* in the People's Republic of China and its anti-tumour activities were confirmed (29).

Apart from the genera *Senecio* and *Crotalaria,* plants containing pyrrolizidine alkaloids are so numerous and wide spread that they can be expected to be present in most environments. The main sources are the families Boraginaceae, Compositae (tribes Senecionae and Eupatorieae) and Leguminosae (genus *Crotalaria*). The potential number of alkaloid containing species are high or about 3% of the world's flowering plants (30). Even in technically advanced countries, herbs have remained in use without systematic testing for efficacy or safety therefore several herbs have recently been reported to contain hepatotoxic pyrrolizidine alkaloids, e.g. *Symphytum officinale* (Comfrey), *Emilia sonchifolia, Heliotropium* spp, etc. Contamination of food stuffs with pyrrolizidine alkaloids should be concerned. The levels of alkaloids 1-4 ppm of whole diet may cause chronic liver damage and tumour in experimental animals. The alkaloids of *Senecio jacobaea* have been found at the level of 1-4 ppm in milk and honey from cows and bees which have been foraging on this species. There are probably many regions in the world where the degree of observation is inadequate to ensure that cereal grains are not occasionally contaminated with these alkaloids at high level to cause hepatotoxic (30).

Thalicarpine, an isoquinoline alkaloid with a potent antileukemic agent has been isolated from *Thalictrum minuselatum* and *T. dasycarpum* (29). Tetrandrine, a bisbenzylisoquinoline alkaloid was reported to isolate from *Cyclea peltata* (Menispermaceae). Both the dl- and d- isomers of the compound showed enough activity in the WM system to be considered for preclinical toxiocological evaluation. Tetrandrine has a number of potent side effects. Hypotensive effect and hepatotoxicity were observed in dogs as well as nephrotoxicity in monkeys (29).

Another alkaloid of this group, liriodenine has been isolated from *Liriodendron tulipfera, Magnolia campbelii, M. mutabilis, Michelia formosana* and *Talauma mexicana* exhibiting cytotoxic activity (29).

Further interest has been paid to isoquinoline alkaloids with anti-leukemic activity of emetine from *Cephaelis ipecacuanha* (Rubiaceae) and other Rubiaceous species, pretazettine from *Narcissus tazetta* (Amaryllidaceae) and a number of other plants in the Amaryllidaceae (29).

Two potent tumour inhibitors benzophenanthridine alkaloids, nitidine and fargaronine have been isolated from several species of *Zanthoxylum* (Rutaceae) including *Z. flavum, Z. americanum, Z. dipeltalum, Z. myriacanthum* and *Z. dinklagei* (29). The isolation of these natural products has led to a number of synthetic programs with the aim of potentiating activity.

Berberine alkaloids are closely related to benzophenanthridine. Although berberine showed *in vitro* activity it was devoid of *in vivo* activity in the Ehrlich ascites test system. The phosphate of the related compound, berberoline did show antineoplastic activity. Derivatives of berberine, thiophosphamide have also been shown to exhibit anti-humour activity (29).

Tylophora asthmatica (Asclepiadaceae) contains phenanthroindolizidine alkaloids, tylophorine and minor alkaloid tylophoridine. Tylocrebine is related to tylophorine and is found in *T. crebiflora.* All the three alkaloids show significant anti-cancer activity (12).

Camptothecine has marked anti-leukemic and anti-tumour activities and is present in *Camptotheca acuminata* (Nyssaceae) of Republic of China only upto 0.005%. Later it was found in *Nothapodytes foetida* (Icacinaceae), a plant found in India, Thailand and others about 0.1% (12).

In Rutaceae, *Acronychia baueri* has yielded acronycine which has the broadest spectrum of *in-vivo* anti-tumour activity of any natural product known (29).

A number of alkaloid esters from *Cephalotaxus haringtonia* (Cephalotaxaceae) reveal significant activity in a variety of experimental leukemia systems (29).

Maytansine and the related maytansine esters are potent anti-leukemic agents obtained from *Maytenus ovatus, M. buchananii* (Celastraceae) and *Colubrina taxensis* (Rhamnaceae). As these compounds, particularly maytansine have approached clinical trials, so interest in these compounds has increased. As maytansine occurs in very low concentration, so its synthesis has been attempted. A serch for the new natural source of maytansine was performed. It was found that *Putterlickia verrucosa* (Celastraceae) yielded maytansine in high concentration (12 mg/kg). The same plant has also yielded two new maytansinoids, maytansinol and maytanacine (12, 29).

In addition, maytansine is a highly active inhibitor of cell division. It inhibits cell division in the eggs of sea urchins and clams. Maytansine is also potent inhibitor of murine sarcoma virus in mice (29).

Flavonoids : Flavonoids include may of the most common pigments and occur throughout the entire plant kingdom from the fungi to the angiosperms. As flower pigments they have a well known role in attracting pollinating birds and insects (13).

The vast majority of flavonoids are non-toxic to man and animals because they are widely distributed in foods. Their activities are weak when compared with other active plant substances such as alkaloids (33).

Anthocyanins and flavonol glycosides are among the most widespread and important flavonoids in foods. They also serve as colouring agents. It should be noted that no colour has been observed in the urine following ingestion of fruits or vegetables with high anthocyanin content. By contrast, it is interesting that the chemically unrelated betacyanins, such as betanin of the beet root red pigment, are occasionally recovered unchanged in the urine (33).

Rutin and the related flavonones hesperidin and eriodictyol were once thought to possess vitamin-like activity in humans and especially rutin was frequently added to multivitamin tablets. The therapeutic value of rutin in the treatment of blood pressure associated with capillary fragility has never been fully established. The claims that rutin and related flavanones are vitamin-P substances have never been substantiated. It is true that rutin in massive doses has pharmacological activity as an antioxidant towards adrenaline and ascorbic acid. It also relaxes smooth muscle and behaves as general enzyme inhibitor (33).

Phlorizidin is being restricted in the plant kingdom to apple bark. It does not even occur in apple fruit and thus does not present a dietary problem. In the mammalian body, phlorizidin causes glycosuria by interfering with the tubular readsorption of glucose from the small intestine (33).

According to systemic investigation of plants belonged to Compositae, has led to isolation of five flavonoids from a native plant of Brazil *Lychnophora affinis* Gardn. Two of these are novel compounds; one demonstrated acceptable cytotoxic activity when tested on cell cultures of a human carcinoma of the nasopharynx (31).

Silybin (silymarin) a flavolignan isolated from the seeds of *Silybum marianum* (Compositae) is used extensively in West Germany for the treatment of liver disorders. Although clinical evidence for the efficacy of this compound appears to be lacking. Silybin only shows a marked anti-hepatotoxic effect on laboratory animals when administered either before or after challenge by a known hepatotoxic substance such as phalloidin or bromobenzene.

Recently, a new method for assaying of anti-hepatotoxic has been reported. By this method, silybin has been shown to extend the survival rate of virus treated mice significantly in this assay. A recent patent has been issued which claims that a combination of silybin and cynarin is more efficaceous than either drug alone for the treatment of liver disorders (32).

Certain isoflavones act as estrogens for mammals and their structures bear a stearic resemblance to those of steroid hormones. Four isoflavones, daidzein, genistein, biochanin-A and mononetin and found in clover fodder (*Trifolium* sp.). All of them are weak oestrogens. There is little doubt that these substances increase the rate of growth of fattening stock and also have a beneficial effect on lactation in cows. Some isoflavones show activity in decreasing serum cholesterol levels. There is a fairly isoflavone content in soya bean, a staple diet in the Far East, but no untoward effects have been recorded in human female (33).

A new flavanone from *Sophora angustifolia,* 2′, 4′, 7-trihydroxy-5-methoxy-8-(5-hydroxy-5-methyl-2-isopropenylhexyl)-flavanone has been patented as a therapeutic agent for digestive ulcer (32).

Extracts of the fruits of *Prunus japonica* (Rosaceae) have been shown to elicit purgative activity. The active cathartic principle was subsequently isolated and shown to be the new flavonoid prunuside (32).

Coumarins occur in the plant kingdom either as simple hydroxy- and methoxy- derivatives or their corresponding glycosides. All of them are soluble in cell sap or non-glycosidic compounds. Scopoletin is the most common coumarin of higher plants. Simple coumarins may have toxic effects on microorganisms.

Much rarer than coumarins are isocoumarins. Bergenin from rhizomes of *Bergania crassifolia* was reported to be active against experimental ulcers induced by serotonin, reserpine, stress and fasting, with ED_{50} of 32, 64, 38 and 38 mg/kg respectively (32).

Several natural products are known which have a pyran or furan ring fused with the benzene ring of a coumarin. They are most common in Rutaceae and Umbelliferae (13).

Some furanocoumarins are of economic importance as the active ingredients of fish poisons used by some primitive peoples. Psoralen from *Psoralea carylifolia* seeds (Leguminosae) has been used to promote suntanning of the skin. This compound links to DNA on irradiaton with ultra-violet light. Some show toxic and repellant effects toward insects. Another furocoumarin angelicin the isolated compound from *Archangelisia officianalis* (Umbelliferae) caused a marked depression in mice and also potentiated the hypnotic effects of pentobarbital, hexobarbital and ether. Moreover, angelicin markedly inhibited amphetamine-induced hyper-activity, but failed to protect aggregated mice from amphetamine toxicity (13, 32).

Since most medicinal plants occur naturally in a large number of countries, a plant of potential importance in one country may have been studied by scientists elsewhere. Today there is probably more interest in drug derived from plants than at any time in history. Many factors are involved in this new interest in plant drugs. Among the more important and these :-

- The discovery of penicillin and other antibiotics has focused attention on the fungi and other lower plants as sources of physiologically active substances.
- Much of the research today is interdisciplinary in its scope, involving in many branches of science and medicine.
- The scope of present-day reseach is broadly international. Considerable time and effort could be saved if their findings could be made available to all interested people.

Now it is realized that there are more than 50 categories of secondary organic constituents known from higher plants but only small fraction of the higher plants have been investigated. Less than 10 percent of the angiosperms have been investigated for secondary organic constituents that fully 90 percent remain for discovery and investigation. A number of avenues are open in a search for new biodynamic plant constituents either concentrated on specific constituents-alkaloids, sapogenins, flavonoids and so on or on limited geography. These surveys are expensive in time and money. Combination of

informations indicating that a specific plant has been used in a local health care for centuries, together with efficacy and toxicity data published by several groups of scientists, can help in deciding whether it should be considered acceptable for medicinal use.

It is clear that plants have a great potential value for the development of new drugs. More research is needed for evaluation of natural products. In developing countries like Thailand, the information on medicinal plants is plentiful but most of these countries have neither a well organized pharmaceutical industry nor the manufacturing capacity to isolate large quantities of active principles from plants. Coordination among scientists in different lines is necessary for the goal in development of new drugs derived from plants. Finally, safety and efficacious drugs should be a prime of consideration.

References :

1. Phillipson, J.D. (1979). "The potential of the plant kingdom as a source for new biodynamic substances" presented at Regional Seminar on Medicinal Plants, September, 10-14, Bangkok, Thailand.
2. Farnsworth, N.R., Akerele, O., Bingel, A.S., Soejarto, D.D. and Guo, Z. (1985). Bulletin of the World Health Organization, 63(6), 965-981.
3. O'Neill, M.J., Bray, D.H., Boardman, P., Phillipson, J.D. and Warhurst, D.C. (1985). "Plants as sources of antimalarial drugs" Planta Medica, No. 3, 394-398.
4. Pezzuto, J.M., Compadre, C.M., Swanson, S.M., Dhammika, N.P. and Kinghorn, A.D. (1985). "Metabolically activated steviol, the aglycone of stevioside, is mutagenic" Proc. Natl. Acad. Sci. U.S.A. *82,* 2478-2482.
5. Kitazawa, E., Sato, A., Takahashi, S., Kuwano, H. and Ogiso, A. (1980). "Novel diterpenelactones with anti-peptic ulcer activity from *Croton sublyratus*" Chem. Pharm. Bull., *28,* 227-234.
6. Morris, J.A. (1976). "Sweetening agents from natural sources" Lloydia, *39,* 25-38.
7. Locksley, H.D., Fayez, M.B.E., Radwan, A.S., Chari, V.M., Cordell, G.A. and Wagner, H. (1982). "Constituents of local plants, XXV, Constitution of the antispasmodic principle of *Cymbopogon proximus*" Planta Medica, *45,* 20-22.
8. Tu You-You, Ni Mu-Yun, Zhong Yu-rong, Li Lan-na, Cui Shu-lian, Zhang Mu-gun, Wang Xiu-zhen, Ji Zheng and Liang Xiao-tain. (1982). "Studies on the constituents of *Artemisia annua*" Planta Medica, *44,* 143-145.
9. Kitazawa, E., Sato, A., Takahashi, S., Kuwano, H. and Ogiso, A. (1980). "Novel diterpenelactones with anti-peptic ulcer activity from *Croton sublyratus*" Chem. Pharm. Bull., *28,* 227-234.
10. Takahashi, S., Kurabayashi, M., Kitazawa, E., Haruyama, H. and Ogiso, A. (1983). "Plaunolide, A Furanoid Diterpene from *Croton sublyratus.* Chem. Pharm. Bull., *22,* 302-303.
11. Ruangrungsi, N., Tantivatana, P., Tappayuthpijarn, P., Borris, R.P. and Cordell, G.A. (1985). "Traditional Medicinal Plants of Thailand VI : Isolation of cryptomeridiol from *Blumea balsamifera*" J. Sci. Soc. Thailand, *11,* 47.
12. Shah, C.S. (1982). "Recent development of some natural products." In the cultivation & utilization of medicinal plants. Edited by Atal, C.K. and Kapur, B.M. Regional research labolatory, Jammu-Tawai (India)
13. Robinson, T. (1982). "The organic constituents of higher plants plants" Cordus Press, North Amherst, Mass. 01059.
14. Okano, M., Lee, K. and Hall, I.H. (1981). "Antitumor agents 39 Bruceantinoside-A and-B, novel antileukemic quassinoid glucosides from *Brucea antidysenterica.* J. of Nat. Prod. *44,* 470-474.
15. Evans, F.J. & Soper, C.J. (1978). "The tigliane, daphnane and ingenane diterpenes, their chemistry, distribution and biological activities, Lloydia *41,* 193-233.
16. Evans, F.J. & Schmidt, R.J. (1980) "Plants and plant products that induce contact dermatitis" Planta Medica, *38,* 289-315.
17. Wiriyachitra, P., Hajiwangoh, H., Boonton, P., Adolf, W., Opferkuch, H.J. and Hecker, E. (1985). "Investigation of medicinal plants of Euphorbiaceae and Thymelaeaceae occuring and used in Thailand: II Cryptic irritants of the diterpene ester type from three *Excoecaria* species. Planta Medica, *43,* 368-371.
18. Gunasekera, S.P., Kinghorn, D., Cordell, G.A. and Farnsworth, N.R. (1981). "Plant anticancer agents XIX : Constituents of *Aguilaria malaccensis*" J. of Nat. Prod. *44,* 569-572.
19. Seip, E.H., Ott, H.H. and Hecker, E. (1983). "Skin irritant and tumor promoting diterpene esters of the tigliane type from the Chinese Tallow tree *(Sapium sebiferrum).* Planta Medica, *49,* 199-203.
20. Gupta, M.B., Nath, R., Srivastava, N., Shanker, K., Kishor, K. and Bhargava, P. (1980). "Anti inflammatory and antipyretic activities of β - sitosterol" Planta Medica, *39,* 157-163.
21. Gibson, M.R. (1978). "Glycyrrhiza in old and new perspectives" Lloydia *41,* 348-354.

22. Trese, G.E. and Evans, W.C. (1975). "Pharmacognosy" Printed in Great Britain at The University Press, Aberdeen.
23. Tanaka, O., Morita, T. and Kasai, R. (1985). "Study on saponins of rhizome of *Panax pseudo-ginseng* subsp. *himalaicus* Collected at Tzatogang and Pari-la, Bhutan-Himalaya" Chem. Pharm. Bull. *33,* 2323-2330.
24. Chazan, J.B. "Repartition Des Sapogenines Triterpeniques Dans Quelques Genres D'Araliaceae De Madagascar" Phytochemistry, *10,* 2111-2116.
25. Ruangrungsi, N. (1986). Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand, Private communication.
26. Sneden, A.T. (1981). "Isoiguesterin, a new antileukemic bisnortriterpene from *Salacia madagascariensis*" J. of Nat. Prod. *44,* 503-507.
27. Oshima, Y., Ohsawa, T., Oikawa, K., Konno, C. and Hikino, H. (1984). "Structures of dianoside A & B, analgesic principles of *Dianthus superbus* var. *longicalycinus* herbs. Planta Medica 40-47.
28. Kunjithapadam, S. (1982). "Utilization of various raw materials for the production of steroids" In the cultivation & utilization of medicinal plants. Edited by Atal, C.K. and Kapur, B.M. Regional research laboratory, Jammu-Tawai (India).
29. Cordell, G.A. and Farnsworth, N.R. (1977). "Experimental antitumor agents from plants, 1974-76" Lloydia, *40,* 1-44.
30. Smith, L.w. and Culvenor, C.C.J. (1981). "Plant sources of hepatotoxic pyrrolizidine alkaloids" J. of Nat. Prod., *44,* 129-152.
31. LeQuesne, P.W., Pastore, M.P. and Raffuf, R.F. (1976). "The cytotoxic flavonoids of *Lychnophora affinis*" Lloydia, *39,* 391-394.
32. Farnsworth, N.R. and Cordell, G.A. (1976) "A review of some biologically active compounds isolated from plants as reported in the 1974-1975 literature" Lloydia, *39,* 420-455.
33. Harborne, J.B. (1967). "Comparative biochemistry of the flavonoids" Academic press, London and New York.