CHAPTER II

LITERATURE REVIEW

1. Traditional Thai medicine and Thai medicinal plants (The National Identity Office, 2004).

1.1 The Development of traditional Thai medicine and Thai medicinal plants.

Over the past decades, government agencies have renewed their interest in traditional Thai medicine and Thai medicinal plants. In 1979, the Ministry of Public Health, in response to the WHO's call for the revival of the indigenous medicines, recommended a strategy on the development of primary health care to be in clued to the Fourth National Economic and Social Development Plan (1977-1981). This resulted in the recommendation of the following strategies to be carried out:

1. The development of Thai medicinal plants for use in primary health care.
2. The development of Thai medicinal plants for use in traditional and modern drug industries.
3. The development of Thai medicinal plants as strategic supplies in case of war.
4. The development of Thai medicinal plants for export.

During the fifth National Committee on Thai Medicinal Plants (1982-1986), the Ministry of Public Health initiated a pilot project on the promotion of the use of medicinal plants under the sponsorship of UNICEF.

Following the success of the UNICEF-sponsored project, another project on the use of medicinal plants in primary health care was initiated in 1985. Funded by the Federal Republic of Germany through the GTZ program, this project concentrated on the formulation and clinical usage of five selected drug plants, namely *Curcuma longa* (*turmeric*), *Androgrphis paniculata, Cassia alata, Cilnacanthus mutans* and *Aloe vera*. The projected area of operation was on five community hospitals.

During the Sixth National Committee on Thai Medicinal Plants, further progress was made towards the development of Thai medicine plants and Thai medicinal plants. As the result of the GTZ funded project called "The Development of Thai Medicinal Plants into Drugs".

The government's endeavor to affect the advancement of Thai medicine and herbal drugs continues incessantly as is evident in its Seventh National Development Plan (1992-1996) whereby traditional Thai medicine, herbal drugs as well as other forms of indigenous health related technologies, such as traditional massage, were to be revived, promoted and integrated into the existing health service system.

The success of the government's efforts in the revival and preservation of an invaluable nation heritage in the form of traditional Thai medicine and herbal drugs for future generations will depend on the attitude and perception of the entire nation. It is not unreasonable to envisage public consensus in the use of herbal drugs for common ailments and as health foods. Herbal drugs should be made available to the general public both in traditional dosage forms, such as pills, fluid extracts and alcoholic macerates, and in modern dosage forms, for example capsules, tablets, and ointments.

1.2 The Art of drug compounding in traditional Thai medicine

The intrinsic principles of traditional Thai medicine are propounded on the knowledge of

1. **Drug matters.** This concerns the basic knowledge of each drug ingredient which may be derived form plant, animal or mineral. Traditional practitioners must be knowledgeable on the name, description, colour, odour and taste of each drug.
2. **Drug attributes.** In Thai medicine, drugs are divided into groups according to their pharmacological actions. The tastes ascribed to the formulated drugs are believed to be correlated to their ability to cure certain ailments. Individual drugs are recognized as possessing astringent, sweet, bitter, acrid, nutty, salty or sour tastes.

3. **Drug grouping.** To facilitate drug prescription in tradition Thai medicine where a recipe may consist of 30-40 ingredients, a number of drug ingredients are grouping together. These may be ingredients with similar nature or attributes or they may different drugs grouped together to form specific entities. Each of these drug groups may consist of two to nine ingredients.
4. **Drug dispensing or compounding.** In traditional Thai medicine, a drug refers to two or more ingredients mixed together into an appropriate dosage form. The ingredients contained in each recipe may be classified into three main categories, namely the principal drug(s), the adjuvant(s) and the flavouring agents. In general, twenty-five dosage forms are recognized. These include the more common preparations, such as pills, decoctions, alcoholic macerates, snuffs, poultices and suppositories. In addition to these traditional dosage forms, the Ministry of Public Health has permitted two more modern dosage forms for traditional drugs, for example tablets and capsules. Preservatives are also allowed to be used in traditional drug formulation.

Besides the main principles as outline above, other factors also have to be taken into consideration. These are

1. **Specific knowledge of drug ingredients.** Traditional practitioners must be able to identify the correct species and to differentiate between useful species and poisonous ones. The knowledge on the part or parts of medicinal plants to be used is also essential. Other pertinent information includes the forms in which the drug ingredients are required. Certain ingredients may need to be detoxified prior to use.
2. **Doses.** The appropriate amount of each ingredient is usually measured out using the old system of measurements, such as chang, baht, salueng. Traditional systems for measuring lengths and capacities also exist.
3. **Vehicles.** There are liquids used in drug formulation in order to dissolve or to extract active constituents from drug ingredients. Vehicles used in traditional drug formulation include water, spirit and lime water, for instance. The potency of the elixir may depend on the choice of vehicle used.
4. **Methods of preparation.** In practice only four or five are in common use and these are briefly described below.

1.3 Preparation of drug ingredients

1.3.1 Fluid extracts: The method is suitable for ingredients which are water soluble but may be unappetizing in their crude forms.

1.3.2 Infusion

1.3.3 Alcoholic macerates: This method is mostly used for extracting water-insoluble constituents from dried drug ingredients.

1.3.4 Pills: To prepare pills, binding agents such as honey or syrup are used.

Regulatory differences of medicine herb and drug showed in Table 1.

Table 1.Commerciallization of herbs and drugs: Regulatory differences(Chang, 1999).

Medicine herbs	Drugs
FDA approval not required	FDA approval required
Mixture of active constituents	Single-well characterized chemical
Efficacy based mainly on historical and anecdotal data	Prospective Phase I-II studies
Oral dosage form	All dosage form
No GMP guidelines	Well-established GMP guidelines
Difficult analytical methods	Well-established analytical methods
Environment factors influence level of active constituents	Chemical synthesis

2. *Butea superba* Roxb.

Butea superba Roxb. is a plant in the Family of Papilionaceae, with the localed name in Thai is "Kwao-krua-dang", "Jan-krua", "Than-jum-thong", "Thong-krua". It has the characteristics of the bring a crawler that cover itself around large trees. One branch has 3 leaves. The flowers are of a yellowish orange color and the plant grows at the outdoor. The long tuber root of the plant is hidden under the ground just as the tuber root of a cassava. When the skin of tuberous root is peeled off, red exudates with bloody appearance occur. Various parts of *Butea superba* Roxb were shown in Figure 1.The plant reproduces by seed, transfix branch, tissue culture and tuber root, growing in northern region and eastern region forest of Thailand (Smitinand, 1989).

Generally, *Butea superba* Roxb. and *Pueraria mirifica* Airy Shaw et Suvatabandhu. or "Kwao-krua-koa" have some morphology be parallel to the woody climbing plant, 3-foliate leaf, the tuberous root has starch granules and chemical compound can be found steroidal substance. The difference morphology described in the Table2.

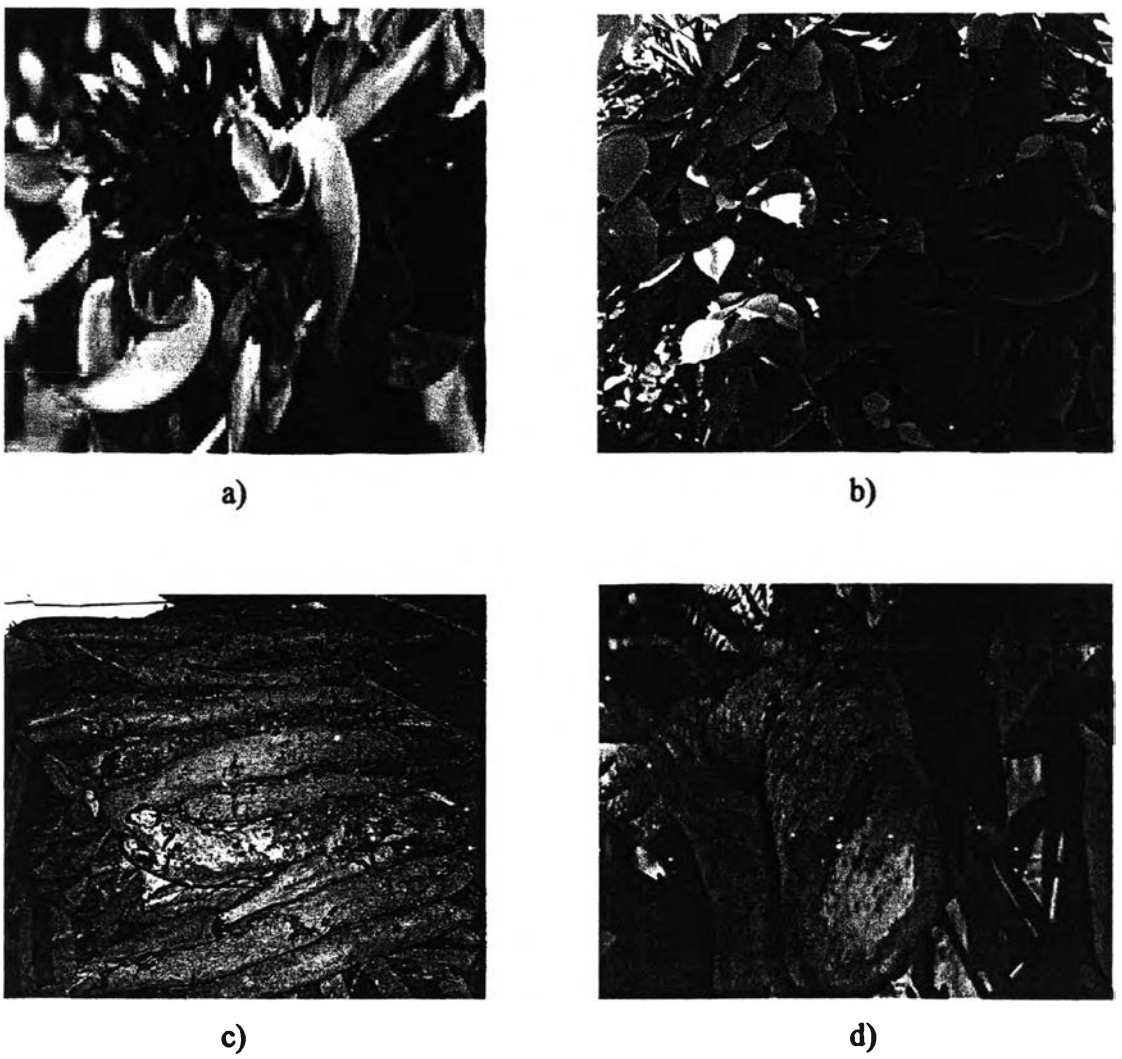

Figure 1. Various parts of *Butea superba* Roxb. a) Flower b) Leaves c) Tuber d) Tuberous root peeled off.

Table 2. Characterization of *Butea superba* Roxb. compared with *Pueraria mirifica* Airy Shaw et Suvatabandhu (Pisetpakasit, 1976).

Topic	*Pueraria mirifica*	*Butea superba*
1. Leaf		
1.1 Texture	Membraneous	Coriaceous
1.2 Size	Smaller	Large
1.3 Trichomes	Soft epidermal trichomes	Without trichomes
1.4 Apex	Acute	Retuse
2. Root		
2.1 Shape	Roundish or ellipsoid	Cylinderical,tapering
2.2 Sap	Whitish	Reddish
2.3 Pulp	White	Yellowish, turn brown after cut
2.4 Lumen	With lumen	Without lumen
2.5 Starch granule	Smaller	Larger
2.6 Chemical compound	Chromatographic pattern	Chromatographic pattern

From the textbooks of Thai folklore medicines as shown in Figure 2 describes the usage of *Butea superba* Roxb. as a natural product for physical, mental strength and prevention of age-related health problems. The tuber and stem of plan are used in medicines believed to give powerful, neurotonic, increase male sexual performance and prevent erectile dysfunction (ED) similar to current drug such as sildenafil citrate (Viagra®) and vardenafil HCl trihydrate (LEVITRA®). According to traditional use, recommended amount taken for an average body weight of 50 kg is approximate to a pepper-sized seed (*Butea superba* tuber powder mixed with honey), which is about 50 mg/day. (Loung–Anusarnsoontorn, 1931) As such, this plant has come to be known as one type of miracle herbs.

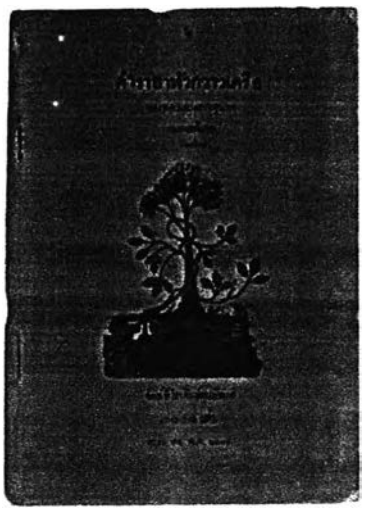

Figure 2. The Remedy Pamphlet of Kwao krua tuber of Loung – Anusarnsoontorn.

2.1 Phytochemistry

The flavonoids are members of a class of natural compounds that recently has been the subject of the considerable scientific and therapeutic interest. Many research about flavonoids in *Butea superba* Roxb. have been published, which impress by their comprehensiveness in the description of the structures and procedures of isolation for flavonoid content.

A new bio-active flavonol glycoside was isolated from the stems of *Butea superba* Roxb, and its was determined by spectral analysis and chemical degradations as 3,5,7,3',4'-pentahydroxy-8-methoxy-flavonol-3-O-ß-D-xylopyranosyl(1-->2)-alpha-L-rhamnopyranoside. The compound showed antimicrobial activity against plant pathogenic fungi *Trich viride, Asprgillus fumigatus, A. niger, A. terreus, Penicillium expansum, Helmitnhosporium oryzae, Botxitis cinerea, Rhizopus oligosporus, R. chinensis, Kelbsiella pneumoniae, Fusearium moniliforme* and gram-positive bacteria Streplococcus pyogenes, *Staphylococcus aureus, Bacillus subtilis* gram-negative bacteria *Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas aeruginosa.* The maximum inhibitory effect was shown by *H. oryzae, A. niger, B. cinera* and gram-positive bacteria (Yadava and Reddy, 1998).

From chemical constituents in methanol extract of *Butea superba* tuber root, isolation and identification of flavonoid is 3,7,3'-trihydroxy-4'-methoxyflavone and

of flavonoid glycoside is 3,3'-dihydroxy-4'-methoxyflavone-7-O-β-D-glucopyranoside. These compounds show higher inhibitory effects on cAMP phosphodiesterase than caffeine and theophyline (Roengsumran, et al., 2000).

The isoflavonolignans were also isolated and identified from *Butea superba* in ethanolic extract, designated as Butesuperin A and Butesuperin B. The structure as a common isoflavone unit for cAMP phosphodiesterase inhibition together with isoflavone derivatives (Chaichantipyuth et al., 2005).

Anti-oxidants compounds were found in tuber root of *Butea superba* in methanolic extract. They were separted by HPLC coupled on-line to ESI-MS and a DPPH-based method, that was successfully applied to the identification of flavonoids as procyanidin B2, (-)-epicatechin and procyanidin B5 (Nuengchamnong et al., 2005).

In the investigations of medicarpin(3-hydroxy-9-methoxypterocarpan) and 4 isoflavone as formononetin, 7,4'-dimthoxyisoflavone, prunetin and 7-hydroxy-6,4'-dimethoxyisoflavone were isolated and identified from tuber root of *Butea superba* in methanolic extract. Formononetin and prunetin showed moderate cytotoxic activity on KB cell line (Ngamrojanavanich, et al., 2006).

2.2 Pharmacology

Upon the vascular system in vitro experiment, *Butea superba* in ethanolic extract to assess the vasodilating effect and mode of action, isolated human umbilical vein was used. The ethanolic extract showed inhibitory on high concentration KCl and histamine induced vascular contraction. The inhibitory effect showed time and concentration dependent manners. Moreover, this action was required endothelium function and indicated that the vasodilating effect involved the Endothelium-Derived Relaxing Factors (EDRFs) and Endothelium-Derived Hyperpolarizing Factors (EDHFs). There are at least 3 pathways of EDRFs and EDHFs such as Nitric oxide (NO), Prostacyclin (PGI_2) and EDHFs in the inhibitory action by the extracts, whereas *Butea superba* in ethanolic extract was unable to inhibit the Serotonin (5-HT) induced vascular contraction (Boongapim, 2002).

In clinical trial study of *Butea superba* on erectile dysfunction (ED) in Thai males, a 3 months with randomized double-blind method was carried out in

volunteers with erectile dysfunction, aged 30-70 years, to evaluate the therapeutic effect of the crude drug preparation(250mg/capsule). The result as estimatation of the sexual record indicated that 82.4% of the patient exhibited noticeable improvement. Haematology and blood chemistry analysis revealed no appearance change (Cherdchewasart and Nimsakul, 2003).

The Thai traditional remedies known as rejuvenating and neurotonic agents have been popular in elderly. It is believed that remedies can prevent forgetfulness and improve memory. Acetylcholinesterase (AChE) inhibitor has been used a drug for the symptomatic treatment of Alzheimer's disease. The root bark of *Butea superba* in methanolic extract were tested for acetylcholinesterase (AChE) inhibitory activity using Ellman's colorimetric method. The result showed 56.87% in inhibitory activity (Ingkaninan,et al., 2003).

From another study, *Butea superba* in ethanolic extract was characterized as phytoestrogens. It was improved by the differential anti-proliferation effect of Kwao-krua plant on the growth of MCF-7 cells study. The ethanolic extract exhibited no proliferation and anti-proliferationeffect on the growth of MCF-7 cells from low and high concentrations with IC_{50} value of 370.91 µg/ml. It should be possible to the reason that plant did not show any estrogenic effect (Cherdchewasart, et al., 2004).

Naresuan University has investigated the effects of ethanol extracts of *Butea superba* in increasing intracavernous pressure (ICP) *in vivo*. Penile erection was induced in aged rats by electrical stimulation of the cavernous nerve. Cavernous smooth muscle relaxation was also observed *in vitro* in the presence of the extract, cGMP or isobutyl-methylxanthine (IBMX) alone or the extract together with cGMP or IBMX. The dried root core extract from Phrae province was the most effective in increasing the ICP. The dose-response relationship study revealed a bell-shape curve with the maximum effective dose at 1 mg/kg. The extract, cGMP and IBMX alone induced dose dependent muscle relaxation. *Butea superba* significantly enhanced the effects of cGMP and IBMX. The ethanol extracts were effective in enhancing penile erection. The dried root core extract from Phrae province was the most effective part with a maximal dose of 1 mg/kg. The *Butea superba* may act through cAMP/cGMP pathways (Torcharus, et al., 2004).

Recently, Chieng Mai University has investigated about the effect of *Butea superba* on the reproductive system in male *Wistar* rats in 8 weeks. The animals were fed daily with the powdered crude suspended in distilled water. The testis of the group fed with 1250 mg/kg was significantly different. The sperm count showed about 16% more than the control group. Hematology as well as the liver and kidney function showed no difference. *Butea superba* at 250 mg/kg which was 100 times more than the Thai FDA recommended dose for humans appeared to be safe in rats (Manosroi, et al., 2006).

In addition, *Butea superba* has been used for fishes. From the study the potential of red kwao kreua and compared the effect between two 17-alpha-methyltestosterone (MT) dosage regimens in terms of inducing sex reversal, survival rate, feed conversion ratio and gain in weight on red, Ghana and chitralada strains of Nile tilapia (*Oreochrimis niloticus* L.). Red kwao kreua did not have significant difference with the control and with the 17-alpha-Methyltestosterone treatment in some cases. A 72.2 ± 25.5% male sex ratio was obtained in treatment 3 dose *Butea superba* of the chitralada strain. As to the effect of the treatments on the three strains it was observed that they generally have comparable effects (Mengumphan, et al., 2006).

2.3 Toxicology

Chronic toxicity of *Butea superba* Roxb. was performed for six months with both sexes of *Wistar* rats. Significant changes in blood chemistry were shown in both sexes of animals particularly at doses 250 and 1000 mg/kg BW/day. The highest dose had significantly higher levels of aspartat amino transferase (AST), alanine aminotransferase (ALT), alkaline phoshatase(ALP), bilirubin and blood urine nitrogen (BUN). In contrast, the level of cholesterol, total protein, albumin and glucose were significantly lower. Histopathological had significant high rate of liver lesions which were hepatocyte megalocytosis, lymphoid aggregated periportal area and bile duct proliferation, that orally giving *Butea superba* at doses 250 mg/kg BW/day and higher was toxic to internal organs, particularly the liver of the *Wistar* rats (Chavalittumrong, et al., 2001).

Effects of chronic treatment of *Butea superba* on sperm motility and concentration in adult male Sprague-Dawley rat and ICR mice were in correlation with testicular damage by *Butea superba* alcoholic extract for 6 months. The testes were processed for histological examination show the long-term treatment with alcoholic extract significantly increased the sperm concentration and delayed the decreased motility with time. There were as signs of sperm anomalies and testicular damages. As chronic use of *Butea superba* increased the number of sperm, prolonged sperm motility in *vitro* while produced no changes on sperm morphology. *Butea superba* alcoholic extract may be useful in fertilization (Torcharus, et al., 2005).

2.4 Isoflavonoids

The isoflavonoids are a large and distinctive subclass of flavonoids. These compounds possess a 3-phenylchromam skeleton that is biogenetically derived by rearrangement of the 2- phenylchromam system by means of a 1,2-aryl rearrangement. The isoflavonoids enjoy only a limited distribution in the plant kingdom, and are almost entirely restricted to the subfamily Papilionoideae of the Leguminosae. Even in the Leguminosae subfamilies Caesalpinioideae and Mimosoidease, only a few plants have been reported to contain isoflavonoids. Among the non-legume dicotylendons, a number of families are knonw to produce isoflavonoid derivatives, but only isolated or genera seem to have this ability, and the range of structures produced is very much more limited than in plants of the Leguminosae (Havesteen, 2002).

Despite the restricted distribution of the isoflavonoids in the plant kingdom, the structureal variation encountered in the natural samples is surprisingly large. This arises not only from the number and complexity of substituents on the basic 3-phenylchromam system, but also from the different oxidation levels in this skeleton and the presences of extra heterocyclic rings (Harbone, 1994; Aoki et al., 2000).

2.5 Pterocarpans

After the isoflavonoves, the pterocarpans from the second largest group of natural isoflavonoids, with some 164 aglycones being characterized. Pterocarpans contain a tetracyclic ring system derived from the basic isoflavonoid skeleton by an ether linkage between the 4- and 2'-positions. The systematic numbering of figure 4

rather than that for simple isoflavonoves is used, however. Convenient subdivisions into pterocarpans, 6a-hydroxy pterocarpans and pterocarpenes are made for this group. The antifungal activity associated with all of these structures accounts for many of the pterocarpans functioning as phytoalexins in leguminous plants, and this has facilitated their discovery. Other constitutive pterocarpans have been detected by means of simple bioassay procedures.

The simple pterocarpans medicarpin and maackiain are reported almost as frequently as the isoflavones daidzein, formononetin, genistein and biochanin A, occurring both as constitutive materials and as phytolexins. Medicarpin has even been isolated from soil samples taken form near plants of alfalfa (*Medicago sativa*), where it appears to delay seed germination and seedling growth (Harbone, 1994).

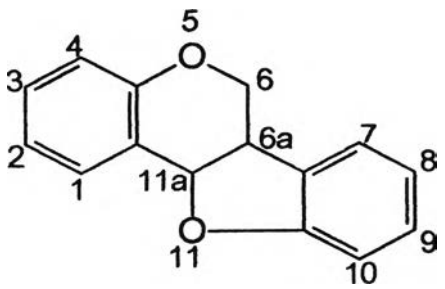

Figure 3. Chemical structure of pterocarpans

The pterocarpans contain two chiral centres, only the 6a*R*, 11a*R* and 6a*S*, 11a*S* configurations are sterically possible. Computational studies concur in that a *trans*-fused C/D-ring system is very much less favourable than the observed *cis*-fused one as shown in figure 3 (Harbone, 1994; Aoki et al., 2000).

3. Medicarpin

Synonyms	:	(6a*R*,11a*R*)-6a,11a-Dihydro-9-methoxy-6H-benzofuro[3,2-c][1]benzopyran-3-ol;(-)-3-hydroxy-9-methoxypterocarpan;demethylhomopterocarpin
Empirical Formula	:	$C_{16}H_{14}O_4$ as shown in figure 4
Molecular Weight	:	270.28. C 71.10%, H 5.22%, O 23.68%
Functional Category	:	Antifungal phytoalexin produced by leguminous species.

Description : Prisms from benzene, melting point 127.5-128.5°C, UV max at 207, 282, 287, 310 nm (Herath et al., 1998; Kalesh et al, 2001)

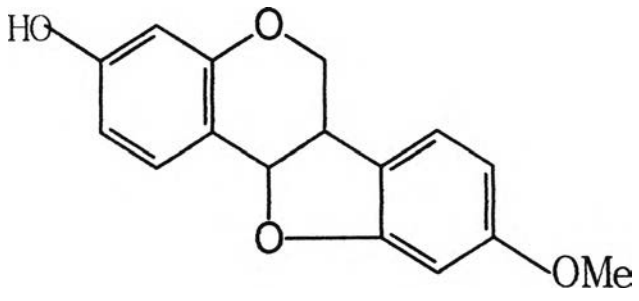

Figure 4 Chemical structure of medicarpin

In a search for new inhibitors of leukotriene formation, a methylene chloride extract of the plant *Dalbergia odorifera* (Jiangxiang) was found to be a potent inhibitor of luekotrienes C_4 (LTC_4) formation in AB-CXBG Mct-1 mastocytoma cells. Following LH-20 and reverse phase HPLC chromatography, two compounds were isolated that had potent LTC_4 inhibitory activity: medicarpin and 6-hydroxy-2-(2-hydroxy-4-methoxyphenyl) benzofuran (IV) with IC_{50}s of 0.5 and 0.05 μM respectively. IV was shown to be a specific inhibitor of 5-lipoxygenase with an IC_{50} against the soluble rat enzyme of 0.08 μM, whereas it was inactive against cyclooxygenase. In neutrophils IV inhibited luekotrienes B_4 (LTB_4) production at comparable concentrations but had no effect on neutrophil degranulation or adhesion (Miller D.K., et al. , 1989).

In the phytoalexin pathway were tested for antimicrobial activity against eight phytopathogenic fungi. Medicarpin were tested at concentrations from 0.1 mM to 0.5 mM in agar plate assays measuring inhibition of linear fungal mycelial growth. Medicarpin at 0.1 mM caused little or no inhibition of the growth of the four known alfalfa pathogens. The other alfalfa pathogens, *Phytophthora megasperma* f.sp. *medicaginis* (*Pmm*) was strongly inhibited by medicarpin at 0.5 mM. *Phoma medicaginis* was strongly inhibited by 0.5 mM medicarpin. Three strains of *Nectria haematococca*, varying in their phytoalexin detoxification capabilities, were inhibited to different extents by medicarpin and its precursors. The only growth inhibition observed at 0·1 mM was of strain 156-2-1 by medicarpin. At 0.5 mM medicarpin

greatly inhibited the growth of strain 156-2-1 compared to the other two strains (Jack et al., 1992).

Conversion of vestitone to medicarpin in Alfalfa (*Medicago sativa* L.). Medicarpin was identified by HPLC at 287 nm. HPLC system equipped with photodiode array detector for analysis. Compounds were separated on C-18 column using a gradient system (80% 1%H_3PO_4, 20%CH_3CN to 40% 1% H_3PO_4, 60% CH_3CN in 20 min, 1.5 ml/min). Medicarpin elutes at 16.6 min (Lining et al., 1994).

The antioxidant activities on oil of natural phenolic components extracted from *Dalbergia odorifera* T., were isolated medicarpin and eight known components. Their antioxidant activities compared with butylated hydroxytoluene (BHT) and alpha-tocopherol, were tested by an oxidative stability instrument (OSI) at 100°C. Medicarpin had antioxidant activity and for use in food, especially in oil (Wen et al., 2000).

Accordingly a reversed- phase liquid chromatographic method was developed for qualification of flavonoids, namely medicarpin and other compounds in the heartwood of *Dalbergia odorifera*. The optimal conditions were achieved on C-18 column using a gradient of acetonitrile and 0.3% (v/v) aqueous acetic acid, at a flow rate of 0.8ml/min, detected at 275nm. The complete separation would obtain medicarpin eluted at 50.50min (Rong-Xia et al., 2005).

4. Tablets (Bandelin, 1989)

Compressed tablets are the most widely used of all pharmaceutical dosage form a number of reasons. They are convenient, easy to use, portable, and less expensive than other oral dosage forms. They deliver a precise dose with a high degree of accuracy. Tablets can be made in a variety of shapes and sizes limited only by the ingenuity of the tool and die maker for example round, capsule-shaped, etc.

Generally drugs can not be compressed directly into the tablets because they lack the bonding properties necessary to form a tablet. The powdered of drugs, therefore, require additives and treatment to confer bonding and free-flowing properties on them to facilitate compression by a tablet press.

4.1 Properties of tablets

Whatever method of manufacture is used, the resulting tablets must meet a number of physical and biological standards. The attributes of an acceptable tablet are as follows:

1. The tablets must be sufficiently strong and resistant to shock and abrasion This property is measured by two tests, the hardness and friability tests.
2. The tablets must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation test and content uniformity test.
3. The drug content of the tablets must be bioavailable. This property is also measured by two tests, the disintegration test and the dissolution test.
4. Tablets must be elegant in appearance and must have the characteristic shape, color and other markings necessary to identify the product.
5. Tablets must retain all of their functional attributes, which include drug stability and efficacy.

4.2 Formulation of tablets

Formulation of the tablet requires the following consideration:

1. Size of dose or quantity of active ingredient(s)
2. Stability of active ingredient(s)
3. Solubility of active ingredient(s)
4. Density of active ingredient(s)
5. Compressibility of active ingredient(s)
6. Selection of excipients
7. Method of granulation (preparation for compression)
8. Character of granulation
9. Tablets press, type, size, capacity
10. Environmental conditions (ambient or humidity control)
11. Stability of the final product
12. Bioavailability of the active drug content of the tablet

The selection of excipients is critical in the formulation of tablets. Once the formulator has become familiar with the physical and chemical properties of the drug,

the process of selecting excipients is begun. The stability of the drug should be determined with each proposed excipient.

4.3 Tablet manufacture

There are three methods of preparing tablets granulations. There wet granulation, dry granulation (also called "slugging") and direct compression. Steps in different methods is described in Table 3.

Table 3 Steps in different methods of tablets manufacture.

Wet granulation	Dry granulation	Direct compression
1. Mixing of drug and excipients	1. Mixing of drug and excipients	1. Mixing of drug and excipients
2. Mixing of milled powder	2. Mixing of milled powder	2. Mixing of ingredients
3. Preparation of binder solution	3. Compression into large, hard tablets called slugs	3. Tablet compression
4. Mixing binder solution with powder mixture	4. Screening of slugs	
5. Coarse screening of wet mass using 6 to 12 mesh	5. Mixing with lubricant and disintegrating agent	
6. Drying moist granules	6. Tablet compression	
7. Screening dry granules with lubricant and disintegrant		
8. Mixing screened granules with lubricant and disintegrant		
9. Tablet compression		

Granulation is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates to render them into a free-flowing state similar to that of dry-sand.

Size enlargement, also called agglomeration, is accomplished by some method of agitation in mixing equipment or by compaction, extrusion or globulation. Because of the many possible approaches to granulation, selection of a method is of prime importance to formulator.

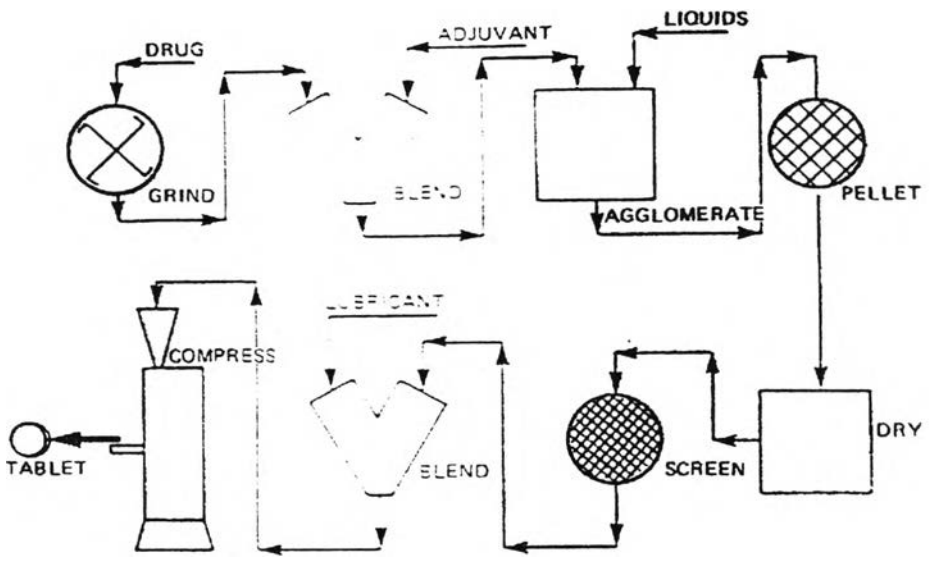

Figure 5. Wet granulation processes.

4.3.4 Wet granulation

It is the oldest and most conventional method of making tablets. Its processes are shown in Figure 5. Although it is the most labor-intensive and most expensive of the available method, it persists because of versatility. The possibility of moistening powders with a variety of liquids, which can also act as carriers for certain ingredients, thereby enhancing the granulation characteristics, has many advantages. In wet granulation, the bonding properties of the liquid binders available is usually sufficient to produce bonding with minimum additives.

The phenomena of adhesion and cohesion may be defined as follows: adhesion is the bonding of unlike materials, while cohesion is that of like materials. Identified mechanisms by which mechanical links are formed between particles. The following are involved in the bonding process. Wet granulation is a versatile process and its application in tablet formulation is unlimited.

4.3.5 Advantages of wet granulation

1. The cohesiveness and compressibility of powder is improved.
2. Suitable flow and cohesion for compression is obtained.
3. Good distribution and uniform content for soluble, low-dosage drugs and color additives are obtained.
4. Bulky and dusty powders can be handled without producing a great deal of dust and air bone contamination.
5. Wet granulation prevents segregation of components of a homogeneous powder mixture.
6. The dissolution rate of an insoluble drug may be improved.
7. Controlled release dosage form can be accomplished.

4.4 Excipients and Formulation

4.4.1 Fillers (Diluents)

Tablet fillers or diluents comprise a heterogeneous group of substances that are listed in Table 2. Since they often comprise the bulk of the tablet, selection of the candidate from this group as a carrier for a drug is of prime importance. Since combinations are also a possibility, consideration should be given to possible mixtures.

Table 4 Tablet filler (Gibbe, 2000).

Insoluble	Soluble
Calcium sulfate, dehydrate	Lactose
Calcium phosphate, dibasic	Sucrose
Calcium phosphate, tribasic	Dextrose
Calcium carbonate	Mannitol
Starch	Sorbitol
Modified starches (carboxymethyl starch, etc.)	
Microcrystalline cellulose	

Starch (Corn starch, Tapioca starch): It is a suitable diluent for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations.

Microcrystalline cellulose (Avicel®): It produces hard tablets with low pressure compression on the tablet press. It acts as an auxiliary wet binder promoting hard granules with less fines. Microcrystalline cellulose also serves as a disintegrant, lubricant and glidant.

4.4.2 Binders

Binders are the "glue" that hold powders together to form granules. They are adhesives that are added to tablet formulations to provide the cohesiveness required for the bonding together of the granules under compaction form a tablet. The quantity used and the method of application must be carefully regulated, since the tablet must remain intact until swallowed and must then release its medicament.

Binders of both types may be added to the powder mix and mixture wetted with water, alcohol-water mixture, or a solvent, or the binder may be put into solution in the water or solvent and added to the powder. Some materials used binders is given in Table 5.

Table 5 Binders commonly used in wet granulation (Gibbe, 2000).

Binder	Usual concentration
Cornstarch, USP	5-10% Aqueous paste
Starch 1500	5-10% Aqueous paste
Gelatin (various type)	2-10% Aqueous solution
Polyvinylpyrrolidone (PVP)	5-20% Aqueous, Alcoholic, Hydroalcohol solution
Microcrystalline cellulose (Avicel®)	20-90% Formulation

Polyvinylpyrrolidone (PVP) is inert and has the advantage of being soluble both in water and in alcohol. It is a versatile and excellent all-purpose binder used in approximately the same concentration as starch, but considerably more expensive.

4.4.3 Lubricants

Lubricants are used in tablet formulations to ease the ejection of the tablet from die, to prevent sticking of the tablets to the punches, and to prevent excessive wear on the punches and dies. Lubricants should be carefully selected for efficiency and for the properties of the tablet formulation.

Lubricant fall into two classes: water-insoluble and water-soluble that are listed in Table 6.

Table 6. Lubricants used in solid dosage form (Gibbe, 2000).

Lubrcants	Amount used in granulations (w/w%)
Hydrophobic	
Metal stearates, calcium, magnesium	0.5-2
Stearic acid, fine powder	1-3
Talcum	5-10
Water-soluble	
Sodium chloride	5-20
Sodium lauryl sulfate	1-3
Polyethylene glycol 4000 and 6000, fine powder	2-5

Stearic acid is a less efficient lubricant than the metal stearates. It melt at 69-70°C, so that it dose not melt usual conditions of storage. It should not be used with alkaline salts of organic compounds such as sodium saccharin or sodium bicarbonate. With these compounds it has a tendency to form a gummy, sticky mass that causes sticking to the punches.

4.4.4 Disintegrants

Disintegrants is the term applied to various agents added to tablet granulation for the purpose of causing the compressed tablet to break apart (disintegrate) when placed in an aqueous environment.

Disintegrant constitute a group of materials that, on contact with water, swell, hydrate, change in volume or form, or react chemically to produce a disruptive change in the tablet. This group includes various forms of starch, cellulose, aligns, vegetable gums, clays, ion exchange resin and acid-base combinations. A list of commonly used tablet disintegrants and amounts usually used are given in Table 7.

Microcrystalline cellulose (Avicel®) is a highly effective disintegrant. It has a fast wicking rate for water, hence, it and starch make an excellent combination for effective and rapid disintegration in tablet formulations.

Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®) is the intragranular and extragranular disintegrant so, that has a fast wicking and swelling rate for water.

Table 7 Disintegrant used in solid dosage form (Gibbe, 2000).

Disintegrant	Concentration in granulation(%w/w)
Microcrystalline cellulose (Avicel® PH101, PH102)	5-15
Sodium starch glycolate (Explotab®)	2-8
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®)	0.5-5
Starch USP	5-20

4.4.5 Glidants

Glidents are materials that improve the flow characteristics of granulation by reducing interparticulate friction. They increase the flow of materials from larger to smaller apertures, from the hopper into the die cavities of the tablet press.

In general, hydrophilic glidants tend to be more effective on hydrophilic powders, and the opposite is true for hydrophobic glidants. For any particular system there is usually an optimum concentration above with glidant may start to act as a antiglidant. This optimum depends, among other factors, on the moisture level in the granulation.

Some glidants commonly used and suggested concentrations for optimum glidant effect are shown in Table 8

Table 8 Commonly used glidants and usual concentration range (Gibbe, 2000).

Glidant	Percent(%)
Silica aerogels (Aerosil®, Cab-O-Sil®)	0.1-0.5
Magnesium stearate	0.2-2.0
Magnesium oxide, heavy	1.0-3.0
Talc	1.0-5.0

The silica-type glidants are the most efficient probably because of their small particle size. In one study, it was found that all silica-type glidants improved the flow properties of granulations as reflected in increased tablet weight and in decreased

weight variation in the tablets. Chemically, the silica glidants are silicon dioxide (Aerosil®, Cab-O-Sil®). They are available as two type, both insoluble.

Selection of glidants must be determined by formulator by trial and error since there is no way of predicting which will be effective in a specific granulation.

5. Tablets of herbal extract

The formulation of herbal extracts into dosage is complex operation which cannot be regarded only as a problem of pharmaceutical technology. Unlike pure active principle, whether synthetic or natural, extracts are raw materials that always contain, alongside variable but small amounts of the active principles, large quantities of secondary material that can appreciably affect the technology of preparation and the stability of the finished pharmaceutical form (Bonati, 1991). Herbal extracts with wet granulation method are wildely used as solid dosage forms.

Dried root powder of *Rhinacanthus nasutus*, Thong Phan Chang (Thai name) were extracted with methanol and made into 2 formulations of tablet containing the extract at 5% and 10% concentration. Due to the viscous and poor flow properties of the crude MeOH extract obtained, a wet granulation method was conducted in developing the tablets. The formulations were compounded with lactose, polyvinylpyrrolidone (PVP) K30 and stearic acid. Both formulas of prepared tablets had a smooth shiny surface with a round shape. Other physical properties of the tablets, such as weight variation, friability and disintegration time, met the requirements of the USP XX standard (Rongsriyam, et al., 2006).

In the investigation of *Anogeissus leiocarpus* extraxt tablets and *Prosopis africana* extract tablets. They were formulated into tablets using the wet granulation method of massing and screening. The Heckel equation was used to study the compaction characteristics of the extract formulated with lactose or magnesium carbonate as diluents. Granules prepared using magnesium carbonate were found to exhibit two stages of deformation - an initial fragmentation followed by plastic flow while those formulated with lactose consolidated mainly by plastic deformation. Compressibility profiles of the formulations were affected by the diluent type. Tensile strength of granules formulated with magnesium carbonate was found to increase as the compression pressure increased from 56.6 to 113.2 MN/m^2 while the tensile

strength of tablets formulated with lactose had its maximum at a compression force of 84.9 MN/m^2 (Isimi CY, et al., 2003).

From the formulation of *Garcinia kola* tablets dosage form with 2 source raw material, such as dry powdered seeds and crude aqueous extract of the seeds. The dry powdered seeds contain 0.003% of flavonoids while the crude extract contained 0.007% of flavonoids based on rutin used as the standard. The powdered material (50 mg) and crude extract (10 mg) were formulated into tablets using the wet granulation method. That the tablets had good disintegration time, dissolution and hardness/friability profiles. Tablets formulated with starch had the best disintegration properties but were consequently very friable. Tablets formulated from 10 mg of the crude extract needed a larger proportion of diluents, which affected the tablet properties (Onunkwo GC., et al., 2004).