CHAPTER 2

LITERATURES REVIEW

There are several hallmarks of cancer, one of hallmark is inflammation. In the first part of this chapter we introduced inflammation activity, mediators relate inflammation and finally how inflammation relates cancer. The second part gives details of plant ingredients of Ridsriduangmahakan preparation. The last section is literatures review about biological activities and chemical compounds of plants in the preparation.

2.1 Inflammation

2.1.1 Overview of inflammation

To understand the role of inflammation in the evolution of cancer, it is important to understand what the inflammation is and how it contributes to physiological and pathological processes such as wound healing and infection (Coussens and Zena Werb, 2002). Figure 2-1 illustrates wound healing (a) versus invasive tumour growth (b).

Inflammation is a part of complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells or irritants (Ferrero-Miliani et al., 2007). Components of inflammation are cells, mediators and immune system. For the first component, cells, they can be either fixed cells such as vascular cells or migratory cells such as polymorphonuclear leukocyte or PMNs. The second component, mediators, they are chemicals released into the body. Chemical mediators found in immune system should have the same action in all species where phenomenon occurs. They can be destroyed locally or systemically to avoid undue accumulation also can be blocked either directly or indirectly by inhibitors of inflammation. The last component is immune system which can be classified as innate and acquired.

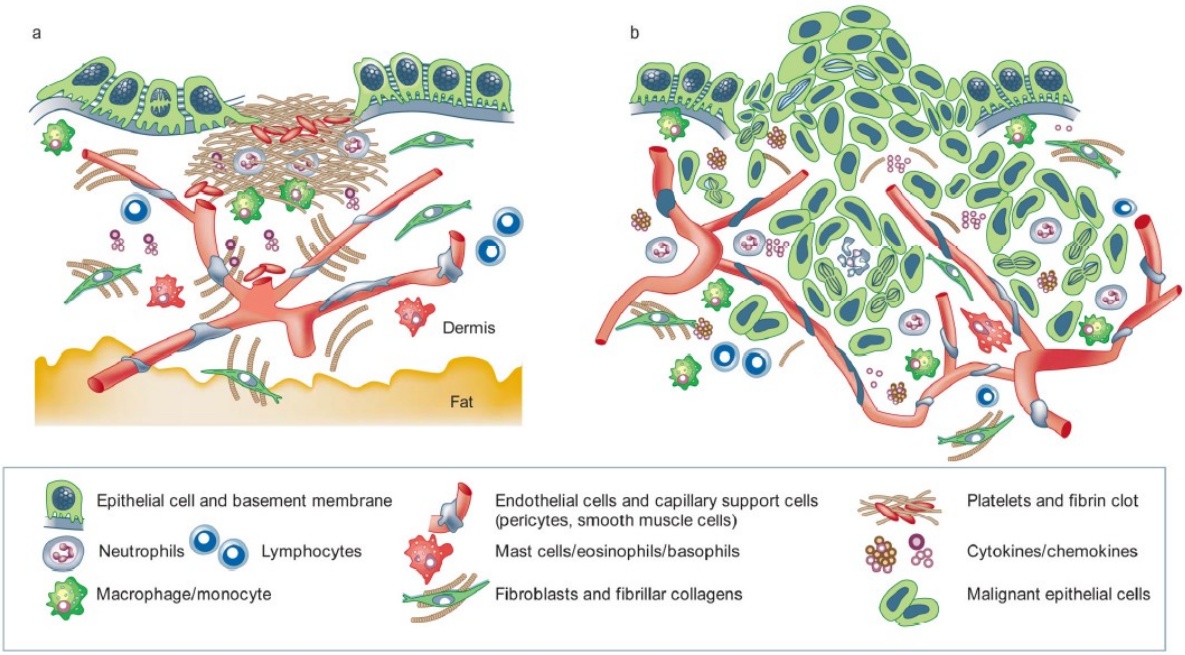

Figure 2-1

(a) Normal tissues have a highly organized and segregated architecture. Epithelial cells sit atop a basement membrane separated from the vascularized stromal (dermis) compartment. Upon wounding or tissue assault, platelets are activated and form a haemostatic plug where they release vasoactive mediators that regulate vascular permeability, influx of serum fibrinogen, and formation of the fibrin clot. Chemotactic factors such as transforming growth factor-β and platelet-derived growth factor, derived from activated platelets, initiated granulation tissue formation, activated fibroblasts, and induction and activation of proteolytic enzymes necessary for remodelling of the extracellular matrix. In combination, granulocytes, monocytes and fibroblasts are recruited, the venous network restored, and re-epithelialization across the wound occurs. Epithelial and stromal cell types engage in a reciprocal signalling dialogue to facilitate healing. Once the wound is healed, the reciprocal signalling subsides. **(b)** Invasive carcinomas are less organized. Neoplasia-associated angiogenesis and lymphangiogenesis produces a chaotic vascular organization of blood vessels and lymphatics where neoplastic cells interact with other cell types (mesenchymal, haematopoietic and lymphoid) and a remodelled extracellular matrix. Although the vascular network is not disrupted in the same way during neoplastic progression as it is during wounding, many reciprocal interactions occur in parallel.

Neoplastic cells produce an array of cytokines and chemokines that are mitogenic and/or chemoattractants for granulocytes, mast cells, monocytes/macrophages, fibroblasts and endothelial cells. In addition, activated fibroblasts and infiltrating inflammatory cells secrete proteolytic enzymes, cytokines and chemokines, which are mitogenic for neoplastic cells, as well as endothelial cells involved in neoangiogenesis and lymphangiogenesis. These factors potentiate tumour growth, stimulate angiogenesis, induce fibroblast migration and maturation, and enable metastatic spread via engagement with either the venous or lymphatic networks.

There are three stages of inflammation functions: initiation, progression, and metastasis. During the initiation phase, inflammation induces the release of a variety of cytokines and chemokines that promote the activation of inflammatory cells and associated factors. This causes further oxidative damage, DNA mutations, and other changes in the tissue microenvironment, making it more conducive to cell transformation, increased survival, and proliferation (S. Prasad et al*.,* 2010).

The key features of inflammation are redness, warmth, swelling, pain, and sometimes loss of movement or function. Inflammation is a necessary response to clear viral infections, repair tissue insults, and suppress tumor initiation/progression. However, when inflammation persists or control mechanisms are deregulated, disease may develop, including cancer.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increase movement of plasma and leukocytes from the blood into the injured tissues. Acute inflammation is a short-term process, usually appearing within a few minutes or hours and ceasing upon the removal of the injurious stimulus (Kumar and Collins, 1998).

The process of acute inflammation is initiated by resident macrophages, dendritic cells, histiocytes, kupffer cells and mastocytes. At the onset of an infection, burn, or other injuries, these cells undergo activation and release inflammatory mediators responsible for the clinical signs of inflammation. Vasodilation and its resulting increased blood flow causes the redness and increased heat. Increased permeability of the blood vessels results in leakage of plasma proteins and fluid into the tissue, which manifests itself as tumor. Some of the released mediators such as bradykinin increase the sensitivity to pain. The mediator molecules also alter the

blood vessels to permit the migration of leukocytes, mainly neutrophils, outside of the blood vessels into the tissue. The neutrophils migrate along a chemotactic gradient created by the local cells to reach the site of injury (Kumar and Collins, 1998). The loss of function is probably the result of a neurological reflex in response to pain. In addition to cell-derived mediators, several cellular biochemical cascade systems consisting of preformed plasma proteins act in parallel to initiate and propagate the inflammatory response. These include the complement system activated by bacteria, and the coagulation and fibrinolysis systems activated by necrosis (Kumar and Collins, 1998). The acute inflammatory response requires constant stimulation to be sustained. Inflammatory mediators have short half lives and are quickly degraded in the tissue. Hence, inflammation ceases once the stimulus has been removed (Kumar and Collins, 1998).

Prolonged inflammation or chronic inflammation leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. Inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation, and inflammation. It is now also becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, cell survival, and migration (Aravindaram and Yang, 2010).

Summary of acute inflammation and chronic inflammation is shown in Table 2-1.

Table 2-1

Comparison between acute and chronic inflammation

	Acute inflammation	Chronic inflammation
Causative agent	Pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions
Major cells involved	Neutrophils, monoclear cells (monocytes, macrophages)	Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts
Primary mediators	Vasoactive amines, eicosanoids	IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes
Onset	Immediate	Delayed
Duration	Few days	Up to many months, or years
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis, necrosis

2.1.2 Mediators associated inflammation

Mediators of inflammation are plasma proteins such as complement and antibodies, other proteins such as $sPLA_2$ and acute phase reactants, cytokines and chemokines, lipids such as prostaglandins and PAF, amines such as histamine, nitric oxide, kinins such as bradykinin, and neuropeptides. Mediators which suppress inflammation are ACTH, GCs, and products of HPA axis, some cytokines such as IL-10, some induced proteins such as antiproteases and lipocortin 1. Description and source of cell derived mediators are summarized and functions features of molecular mediators of inflammation and oncogenesis in Table 2-2 to 2-3 respectively.

Table 2-2

Description of cell derived mediators

Name	Type	Source	Description
Lysosome granules	Enzymes	Granulocytes	These cells contain a large variety of enzymes which perform a number of functions. Granules can be classified as either specific or azurophilic depending upon the contents, and are able to break down a number of substances, some of which may be plasma-derived proteins which allow these enzymes to act as inflammatory mediators.
Histamine	Vasoactive amine	Mast cells, basophils, platelets	Stored in preformed granules, histamine is released in response to a number of stimuli. It causes arteriole dilation and increased venous permeability.
IFN-γ	Cytokine	T-cells, NK cells	Antiviral, immunoregulatory, and anti-tumour properties. This interferon was originally called macrophage-activating factor, and is especially important in the maintenance of chronic inflammation.
IL-8	Chemokine	Primarily macrophages	Activation and chemoattraction of neutrophils, with a weak effect on monocytes and eosinophils.
Leukotriene B4	Eicosanoid	Leukocytes	Able to mediate leukocyte adhesion and activation, allowing them to bind to the endothelium and migrate across it. In neutrophils, it is also a potent chemoattractant, and is able to induce the formation of reactive oxygen species and the release of lysosome enzymes by these cells.

Table 2-2 (Continued)

Name	Type	Source	Description
Nitric oxide	Soluble gas	Macrophages, endothelial cells, some neurons	Potent vasodilator, relaxes smooth muscle, reduces platelet aggregation, aids in leukocyte recruitment, direct antimicrobial activity in high concentrations.
Prostaglandins	Eicosanoid	Mast cells	A group of lipids which can cause vasodilation, fever, and pain.
TNF-α and IL-1	Cytokines	Primarily macrophages	Both affect a wide variety of cells to induce many similar inflammatory reactions: fever, production of cytokines, endothelial gene regulation, chemotaxis, leukocyte adherence, activation of fibroblasts. Responsible for the systemic effects of inflammation, such as loss of appetite and increased heart rate.

Table 2-3

Functional features of molecular mediators of inflammation and oncogenesis

Mediators	Effect on inflammation	Role in tumorigenesis
Activated oncogenes	Pro-inflammatory, induce inflammatory gene expression, increase RONS	Oncogenic
Inactivated tumor suppressors	Pro-inflammatory, IL6/TNFa/IFNb-induced oncogenic miRNAs inactivate tumor suppressors	Oncogenic, accelerates activated RAS tumorigenesis
Toll-like receptor gene polymorphisms	Activating, sustain inflammation	Pro-neoplastic drive caused by chronic inflammation
Cytokine/cytokine receptor gene polymorphisms	Increased/sustained inflammation	Same
MicroRNA/microRNA-binding site gene polymorphisms		Oncogenic
Changes in microRNA expression patterns	Induced or repressed by inflammation Pro-or anti-inflammatory actions	Pro-or anti-tumorigenic actions
Oncogenic microRNA expression (e.g. miR-21 and miR-155)	Induced by inflammation	Oncogenic
Activated transcription factor NFjB	Inflammatory gene activation / acute inflammatory responses, including induction of NOd synthase; in itself activated by pro-inflammatory cytokines, e.g. TNFa	Oncogenic through anti-apoptotic effects, cell cycle and angiogenesis activation, promotion of tumor metastasis and through chronic inflammation
IjB gene mutations/activation of IjB kinase	Pro-inflammatory by allowing nuclear translocation of NFjB; activated by infections and by pro-inflammatory cytokines	Oncogenic through NFjB effects

Table 2-3 (Continued)

Mediators	Effect on inflammation	Role in tumorigenesis
RONS, including NOd	Microbial killing in acute inflammation Tissue damage if sustained/unregulated; NOd important signaling molecule in immunity	Anti-or pro-tumorigenic depending on cellular context; oxidative stress lead to DNA damage, genomic instability affecting tumor suppression and oncogenic activation; may also induce apoptosis, cellular senescence (anti-tumorigenic)
NOd and p53		Cooperate to inhibit tumorigenesis
Cytokines	Depends on balance between pro-and anti-inflammatory cytokines; tumors recruit inflammatory cells through secretion of chemokines	Sustained high-level expression of pro-inflammatory cytokines is oncogenic; anti-inflammatory cytokines (e.g. IL10 and TGFb) are anti-tumorigenic
PGE2 and cyclooxygenases	Increased concentration and activity in chronic inflammation	Oncogenic; increased COX-2 expression found in all tumors; PGE2 induces cellular proliferation

2.2 Nitric oxide and its roles related inflammation

Nitric oxide is an inorganic free radical gas, of formula *N=O (abbreviated as NO). NO is mediator that formed in many tissues from arginine. NO is a labile and highly reactive compound that plays a physiological role in blood pressure regulation, neurotransmission, tumor cell killing, immunity, and inflammatory processes (Hussain et al. 1994). NO is also an important component of the antineoplastic and antimicrobial armament of macrophages (Coleman et al., 2001). Upon inflammatory stimulation, macrophages produce NO and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6. Overproduction of these mediators is present in macrophage of many inflammatory diseases, including rheumatoid arthritis, atherosclerosis, and hepatitis (Isomaki and Punnonen, 1997; Libby et al., 2002; Tilg et al., 1992).

NO is synthesized by a family of enzymes referred as the nitric oxide synthases (NOS). Small amounts of NO produced by the constitutive nitric oxide (cNOS) are essential for maintaining the cellular function. Inducible NOS (iNOS) can sustainedly produce a high output of nitric oxide, which is believed as one of the most important inflammatory reactions in activated macrophage (Pokharel et al., 2007). In addition, the inducible cyclooxygenase-2 (COX-2) is believed to be the target enzyme for the anti-inflammatory activity of nonsteriodal anti-inflammatory drugs. Many studies have demonstrated that some inducible enzyme (COX and iNOS) cytokines and their reaction products are involved in chronic inflammatory disease (Abd-El-Aleem et al., 2001; Bruch-Gerharz et al., 1996, 2001). Improper up-regulation of iNOS and COX-2 is associated to pathophysiology of certain types of cancers as well as inflammatory disorders (Yang et al., 2006).

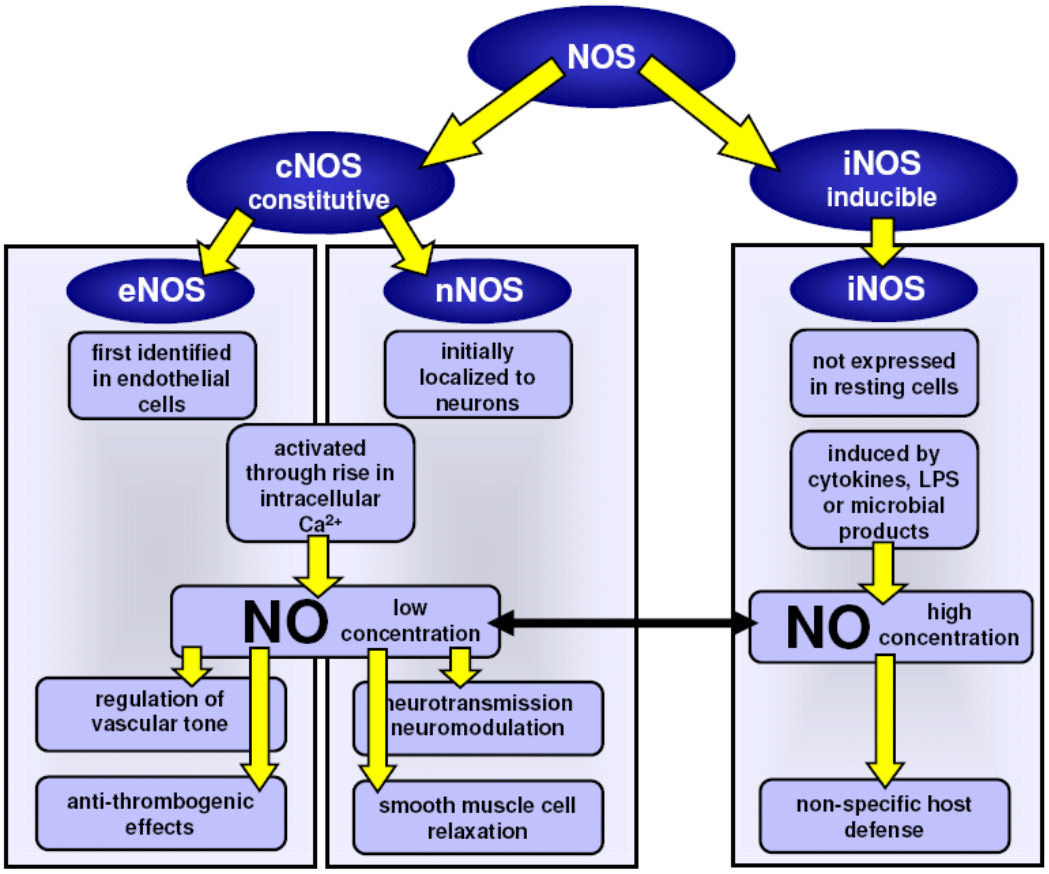

Figure 2-2

The isoforms of nitric oxide synthases. Two cNOS enzymes (eNOS, nNOS) are contrasted by a third, inducible NOS (iNOS) (Wibuloutai, 2006)

2.3 Tumor necrosis factor related inflammation

Tumor necrosis factor (TNF), cachexin or cachectin is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. There are two forms of TNF found. They are TNF-α and TNF-β. TNF-α are produced by many cells including monocytes. TNF-β are produced by T-cells. They are both widespread activation of cells; apoptosis, shock and cachexia.

TNF-α is a multifunctional cytokine mostly secreted by inflammatory cells and is involved in numerous pathological states (Muntané et al. 2000). TNF-α represents another pro inflammatory cytokine expressed by macrophages and KC

during inflammatory processes. TNF-α represents a key mediator in pathophysiological situations, such as endotoxin-, alcohol-, ischemia/reperfusion-, or virusinduced liver damage. (Keimer et al. 2002). TNF-α are known to produce fever, inflammation, tissue destruction, and sometimes induce shock and consequently death as being administered to humans (Yoon et al., 2009).

2.4 Relationship between NO and TNF-α

The pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-α) and the reactive free radical NO synthesized by iNOS are important macrophage derived inflammatory mediators and are also reported to be involved in the development of inflammatory diseases (Freeman and Natanson, 2000). Thus the inhibition of the excessive productions of TNF-and NO can be employed as criteria to evaluate anti-inflammatory effects of natural products (Sheeba and Asha, 2009).

2.5 Cyclooxygenase

Cyclooxygenase (COX) is the key enzyme for the conversion of arachidonic acid (AA) to prostaglandins (PGs) Vane et al., 1998). There are two iso-forms of COX; one is the COX-1, a constitutive enzyme, which is responsible for the production of PGs with general housekeeping functions such as maintenance of renal perfusion and a protective effect on the gastric mucosa against ulceration; and the other is the COX-2, an inducible enzyme, responsible for the production of PGs (Needleman and Isakson, 1998). COX-2 is expressed during inflammation by cytokines and bacterial products, such as lipopolysaccharide (LPS), and it produces PGs contributing to the pain and swelling of inflammation (Yoon et al., 2009).

Of the two isoforms of COX, COX-1 is a constitutively expressed form required for normal physiologic functions and the COX-2 is induced only during inflammatory processes (Herschman, 1996). Selective COX-2 inhibition can avoid these toxic effects (Sheeba and Asha, 2009)

COX-2 is an inducible enzyme catalyzing the conversion of arachidonic acid to prostaglandins. Recent studies have suggested that increased levels of prostaglandins and cyclooxygenase activity may play important roles in multiple epithelial cancers. COX-2-derived bioactive lipids, including prostaglandin E_2, are potent inflammatory mediators (Pan et al., 2006). Therefore, as chronic phases of inflammation and infection correlate strongly with the increased production of PGE_2, substances that inhibit PGE_2 production could be of therapeutic benefit (Yang et al., 2010).

An inflammatory immune response is pro- or antitumorigenic is a delicate balance between the adaptive and innate immune system as shown in Figure 2-2.

2.6 Inflammation and cancer

Inflammatory mediators can induce genetic instability which is a mechanism relate to cancer (Colotta et al., 2009). There are two relevant pathways; intrinsic pathway and extrinsic pathway. Intrinsic pathway relates to activate of various classes of oncogenes driven milieu inflammation. Extrinsic pathway relates to conditions which promote cancer development.

There is a strong association between chronic inflammatory conditions and cancer specific to the organ. Epidemiological evidence points to a connection between inflammation and a predisposition for the development of cancer. Various factors are known to induce chronic inflammatory responses that further cause cancer. These include bacterial, viral, and parasitic infections, chemical irritants, and non-digestible particles. It is mechanistically proven that inflammation produces reactive oxygen species (ROS) and reactive nitrogen species (RNS). In particular, ROS and RNS lead to oxidative damage and nitration of DNA bases, which increases the risk of DNA mutations and further leads to cancer (Prasad et al., 2010).

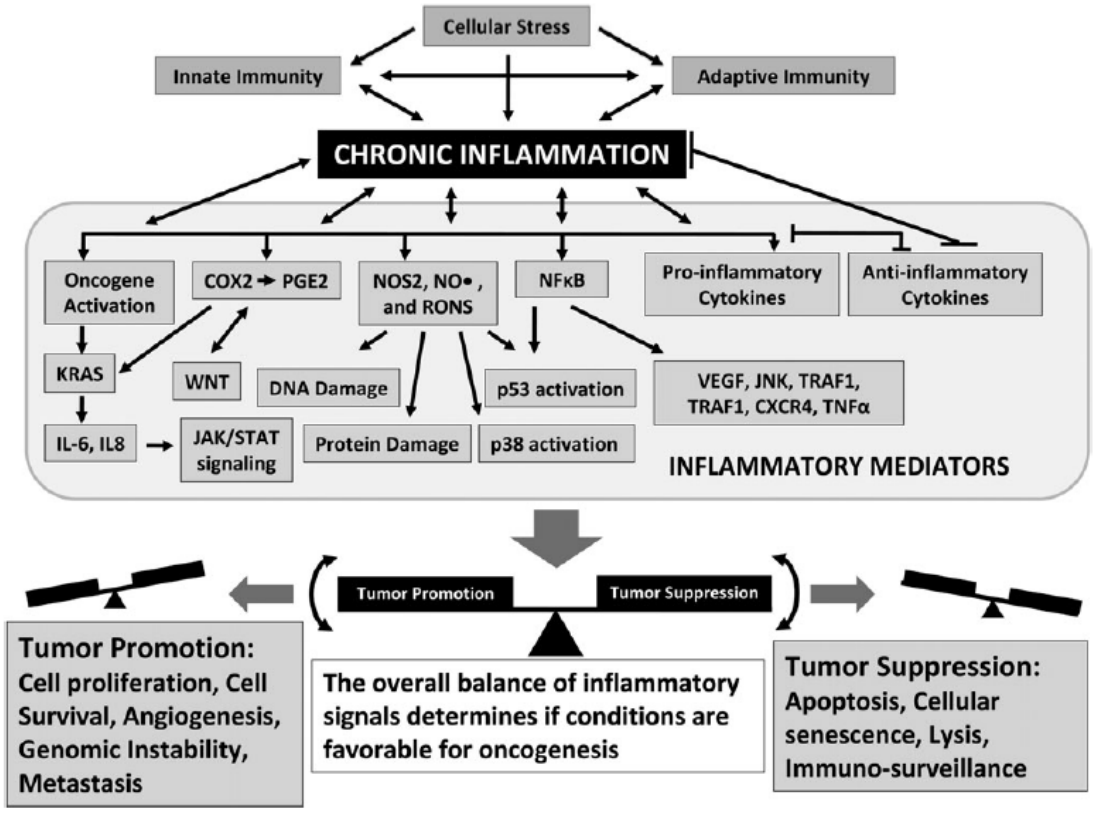

Figure 2-3

Chronic inflammation alters the cellular levels of inflammatory mediators, including COX-2, RONS and inflammatory cytokines and activates protooncogenes. Depending on the collective functions and balance of inflammatory mediators, an inflammatory response may be either pro- or anti-tumorigenic.

2.7 General data of the plants in Ridsriduangmahakal preparation

2.7.1 *Anacyclus pyrethrum* (L.) DC.

Anacyclus pyrethrum (Compositae), its common names in various countries are Kot kakkra (Thailand) and Pellitory (English) Pyrethrum, or pellitory, root (Pyrethum, U.S.P.) (Articlebase, 2010).

Description of *Anacyclus pyrethrum* is shown in Figure 2-4 (a,b) The root is about 5 to 10 centimeters long and is 12 millimeters in thickness, tapering towards the tip, and towards the crown. Tuft of grayish hairs can usually be seen. Fractured surface exhibiting a conspicuously radiate structure, narrow yellowish wedges of wood alternating with whitish medullary rays. Numerous yellow or brown oil glands occur both in the cortex and medullary, rays. Roots are long and finger like, length are about 7-10 centimeter and also have hair like root lets. Stem is possesses many hairs. Barks are brown in colour and bitter in taste. Leaves are bipinnatisect, with small hairs elliptic 20-40 millimeter long. Flowers are head inflorescence yellowish, white, pink in colour. Fruits are shallow and oval in shape (Articlebase, 2010).

2.7.2 *Anethum graveolens* Linn. or *Anethum sowa* Roxb. ex J.Fleming

Anethum graveolens L. or *Anethum sowa* Roxb. ex J.Fleming (Umbelliferae), its common names in various countries are Thian ta takkataen (Central), Phak chi lao (Nakkhon Ratchasima) (Thailand) and Dill (English) (Smitinand, 2001). It is native originally of southwestern Asia and now is naturalized in many parts of Europe and the northern US. It is also a very popular flavoring in northern, central and eastern European countries, but hardly used at all in France or Italy. It is almost indispensable in Russian and Scandinavian cookery (Floridata.com LC, 1996).

Anethum graveolens L. is an erect, freely branching annual herb with finely dissected, lacy, blue-green foliage as shown in Figure 2-5(a). Fruits are usually just called "dill" (Figure 2-5(b)) and "Dill weed" refers to the foliage. The leaves are about 0.3 meter long and divided pinnately three or four times into threadlike segments each about 2.5 centimeter long. Dill plant grows about 0.9 to 1.5 meter tall and sometimes gets top heavy and falls over. Dill flowers are yellow and borne in large, rounded,

compound umbels on stiff, hollow stems. The whole inflorescence can be 25 centimeter across, and several of them on a feathery blue-green framework can be showy indeed. The fruit is a flattened pod about 0.3125 centimeter long. All parts of the dill plant are strongly aromatic (Floridata, 1996).

2.7.3 *Angelica sylvestris* Linn.

Angelica sylvestris Linn. (Umbelliferae), its common names in various countries are Kot so (General) (Thailand) and Dahurian Angelica (English). It is found in eastern Siberia, Japan, and China. In Thai traditional medicine, the roots are used for antipyretic, antiasthmatic and anticough (Foundation of resuscitate and encourage Thai traditional medicine, 2005).

Angelica sylvestris is perennial 1–2.5 meter, stout as shown in Figure 2-6 (a,b). The root is cylindric, brown, 3–5 centimeter thick, strongly aromatic. The stem is purplish green, typically 2–5 centimeter (maximum is 8 centimeter) thick, ribbed, pubescent above. The basal and lower leaves are long-petiolate, sheaths oblong-inflated, glabrous; blade triangular-ovate, 30–50 × 25–40 cm, 2–3-ternate-pinnate; leaflets sessile, oblong-elliptic to oblong-lanceolate, 4–10×1–4 centimeter, base slightly decurrent, margin white-cartilaginous and coarse-cuspidate-serrate, apex acute, pubescent along nerves adaxially. The upper leaves are reduced, sheaths saccate-inflated, bladeless. The umbels are 10–30 cm across; peduncles 5–20 cm, scabrous; bracts absent or 1–2, like uppermost leaves; rays 18–40 (or 18-70), short-hairy; bracteoles many, linear-lanceolate, scarious; pedicels many, scabrous. Calyx teeth obsolete. The petals are white, obovate and notched. The ovary is glabrous or pubescent. The fruit is suborbicular, 4–7 × 4–6 mm; dorsal ribs prominent, obtusely thick-rounded, much wider than furrows, lateral ribs broad-winged; vittae 1 in each furrow, 2 on commissure (Flora of China, 2009a).

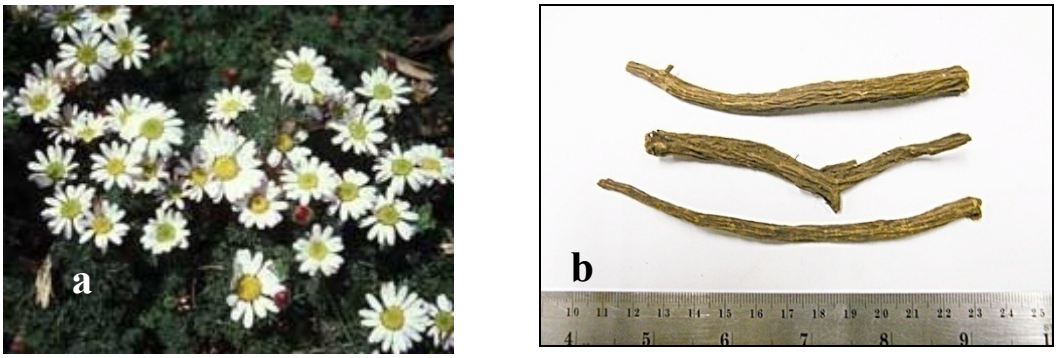

Figure 2-4

(a) *Anacyclus pyrethrum* (L.) DC.(Compositae)

(from : http://www.denverplants.com/perennials/html/anacy_pyr.htm)

(b) root of *A. pyrethrum*

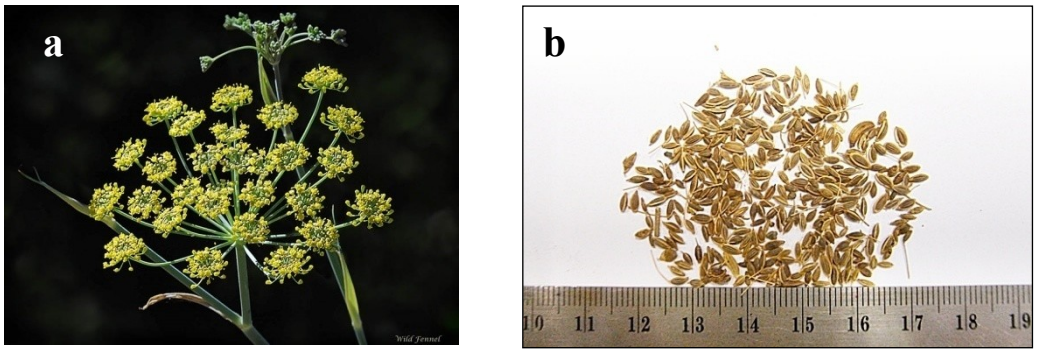

Figure 2-5

(a) *Anethum graveolens* Linn.(Umbelliferae)

(from : http://www.pbase.com/inaturalist/image/101906329)

(b) Fruit of *A.. graveolens*

2.7.4 *Artemisia vulgaris* Linn.

Artemisia vulgaris Linn. (Compositae), its common names is wormwood or Kot Julalumpa (Thailand). It is native in Europe, Asia, northern Africa and Alaska and also found in North America. It is a common plant growing on nitrogenous soils, like weedy and uncultivated areas such as roadsides.

Description of *Artemisia vulgaris* Linn. is shown in Figure 2-7(a,b). Its typically height is about 1–2 meter. It has a woody root. The leaves are 5–20 centimeter long, dark green and smooth. There are white tomentose hairs underside. The erect stem has a red-purplish tinge. The flowers have length about 5 millimeter and are radically symmetric with many yellow or dark red petals. The narrow and numerous capitula (flower heads) spread out in racemose panicles. It flowers from July to September. (Botanical, 2011)

2.7.5 *Cinnamomum bejolghota* (Buch.-Ham.) Sweet

Cinnamomum bejolghota (Buch.-Ham.) Sweet (Lauraceae), its common name is Samunlavang (Thailand). It is native in China and Vietnam but also found common in Asia (Flora of China 7, 2008).

Description of *Cinnamomum bejolghota* (Buch.-Ham.) Sweet is shown in Figure 2-8(a,b) . It has various sizes between 5 to 25 meter tall. The branches are always opposite and robust. Color is red-brown when dry. The buds are small and ovoid. The leaves are subopposite and 1-1.5 centimeter long. Leaf blade is greenish or yellow-green. Basal lateral veins are arising 0.5-1.5 centimeter above leaf base. Panicle axillary are on upper part of branchlet, 13-16 centimeter long. Pedicels is 4-6 millimeter and gray pubescent. The flowers are yellow. Their sizes are up to 6 millimeter. Perianth tube is short, obconical, ca. 1 mm; perianth lobes are 6, ovate-oblong, ca. 5 × 2.5 mm, acute, gray pubescent except apex subglabrous on both surfaces. Fertile stamens 9, ca. 3.5 mm (of 1st and 2nd whorls); filaments complanate, those of 3rd whorl each with 2 long stalked orbicular-reniform glands, others glandless; anthers of 1st and 2nd whorls ovate-oblong, those of 3rd whorl narrower, oblong, ca. 1.7 mm, with extrorse cells. Staminodes 3, conspicuous, sagittate-deltoid,

ca. 3 mm, long stalked. Ovary oblong, ca. 1.5 mm; style slender, up to 3 mm; stigma discoid. Fruit ellipsoid, ca. 1.3 × 0.8 cm, green when fresh; perianth cup in fruit yellow but purple-red tinged, somewhat dilated, obconical, apex up to 7 mm wide (Flora of China 7, 2008).

2.7.6 *Cinnamomum zeylanicum* Linn. or *Cinnamomum verum* J. Presl

Cinnamomum zeylanicum Linn. **(**Lauraceae) its common names in various countries are Ob chuey tet (Central) (Thailand) and Cinnamon (English). Ceylon cinnamon is indigenous tree of Sri Lanka and southwestern India. Cinnamon includes application as an astringent, germicide, and antispasmodic.

Description of *Cinnamomum bejolghota* (Buch.-Ham.) is shown in Figure 2-9 (a,b). It is large evergreen trees. Its young branches are smooth and brown. The leaves are opposite, leathery, ovate to broadly ovate with three. Young leaves are reddish and later turn dark green. Small, pale yellow flowers are borne in axillary or terminal panicles. The fruit is a fleshy, ovoid drupe, which contains one seed and turns dark purple or black when ripe (Lee et al*.,* 2005).

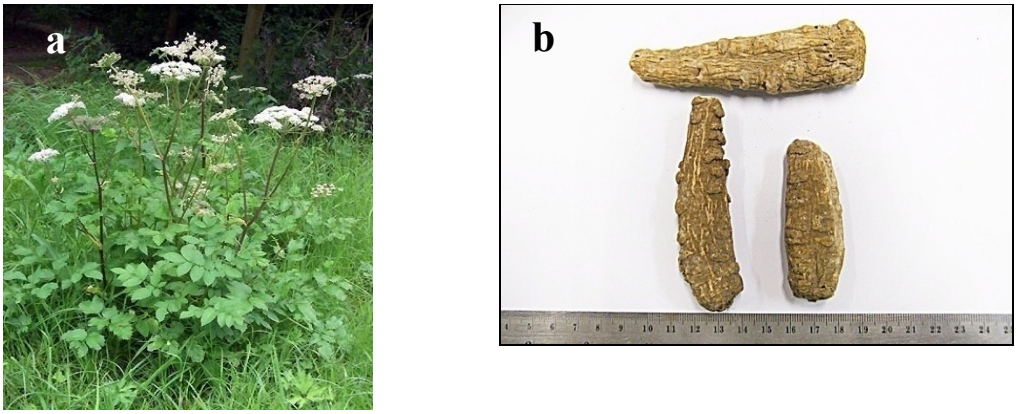

Figure 2-6

(a) *Angelica sylvestris* Linn. (Umbelliferae)

(from : http://www.ruhr-uni-bochum.de/boga/html/Angelica_sylvestris_Foto.html)

(b) Root of *A. sylvestris*

Figure 2-7

(a) *Artemisia vulgaris* Linn. (Compositae)**, (b)** All part of *A. vulgaris*

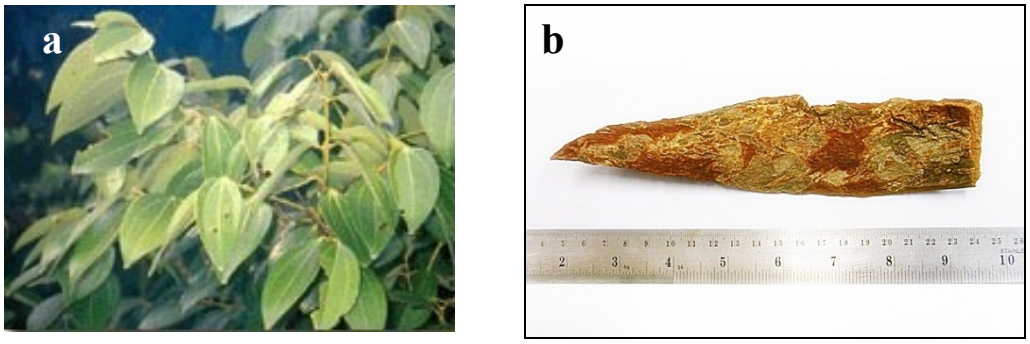

Figure 2-8

(a) *Cinnamomum bejolghota* (Buch.-Ham.) Sweet

(from : http://www.dnp.go.th/EPAC/Herb/29aobchey.htm)

(b) Bark of *C. bejolghota*

2.7.7 *Commiphora abyssinica*

Commiphora abyssinica (Burseraceae) its common name in Thai is Mod yob. *Commiphora abyssinica* is indigenous to Northeast Africa, and collected in Southern Arabia and Iran (Harley et al., 2005; Heywood, 1993). The three tribes can be linked to a specific region of the world although this is not obligatory. (Judd et al., 2008).

Description of *Commiphora abyssinica* is shown in Figure 2-10(a,b). The plants are dioecious (Judd et al., 2008; Heywood, 1993). The leaves are generally alternate, spiral, and odd-pinnately compound with opposite, frequently long-petiolulate, entire to serrate, pinnately veined leaflets whose symmetry is distinctive in some genera (Judd et al., 2008; Steven, 2001). The leaf and leaflet stalks and axis are brown and scurfy. The leaf base is swollen and concave adaxially (Steven, 2001). The family members tend to be without stipules (Judd et al. 2008; Heywood 1993). The determinate, axillary inflorescences carry small, radial, unisexual flowers. The flowers have 4-5 faintly connate but imbricate sepals with an equal number of distinct, imbricate petals (Judd et al., 2008; Heywood, 1993). The stamens contain nectar discs and also have distinct glabrous filaments that come in 1-2 whorls and in numbers equaling or twice the number of petals; the tricolporate pollen is contained within 2 locules of the anthers that open longitudinally along slits. The gynoecium contains 3-5 connate carpels, one style, and one stigma that is head-like to lobed. Each locule of the superior ovary has 2 ovules with axile placentation that are anatropous to campylotropous. The 1-5 pitted fruit is a drupe that opens at maturity. The endosperm is usually lacking in the embryo (Judd et al. 2008).

2.7.8 *Cuminum cyminum* Linn.

Cuminum cyminum L. (Umbelliferae), its common names in various countries are Thian khao, Yira (Central) (Thailand) and Cumin (English). It is native from the East Mediterranean to East India. Its seeds, which are actually dried fruits, are used in many spice mixtures such as chili and curry powders. Cumin is especially popular in Asian, North African and Latin American cuisines (Wikipedia, 2009).

Description of *Cuminum cyminum* L. is an herbaceous annual plant, with a slender branched stem 20-30 centimeter tall as shown in Figure 2-11(a). The leaves are 5-10 centimeter long, pinnate or bipinnate, thread-like leaflets. The flowers are small, white or pink, and borne in umbels. The fruit (shown in Figure 2-11(b)) is a lateral fusiform or ovoid achene 4-5 millimeter long, containing a single seed. Cumin seeds are similar to fennel and anise seeds in appearance, but are smaller and darker in color. Cumin used pant part of fruits often called seeds (Wikipedia, 2009).

2.7.9 *Foeniculum vulgare* Mill.

Foeniculum vulgare Mill. (Umbelliferae), its common names in various countries are Thian khao pluek (Thailand) and Sweet fennel (English). It is found in the Mediterranean countries, but it now can be found worldwide (Charters, 2009).

Description of *Foeniculum vulgare* Mill. var. *dulce* (Mill.) Thell is a tall, erect, glabrous, herbaceous perennial with glaucous, striate branching stems and a strong aroma of anise or licorice. The leaves are alternate and about a foot long, ovate to deltoid in outline, and pinnately dissected into many filiform divisions. The leaf stems are conspicuously sheathed at the base. The yellow flowers are in large compound umbels with 15-40 unequal rays on ± bare stems rising well above the leaves, and the five petals are wide with narrow tips as shown in Figure 2-12(a). There are five stamens. The calyx is rudimentary-vestigial or absent. The fruit (shown in Figure 2-12(b)) is a 3/4" long oblong to ovoid, slightly laterally flattened schizocarp with prominent ribs which splits into two 1-seeded compartments (Charters, 2009).

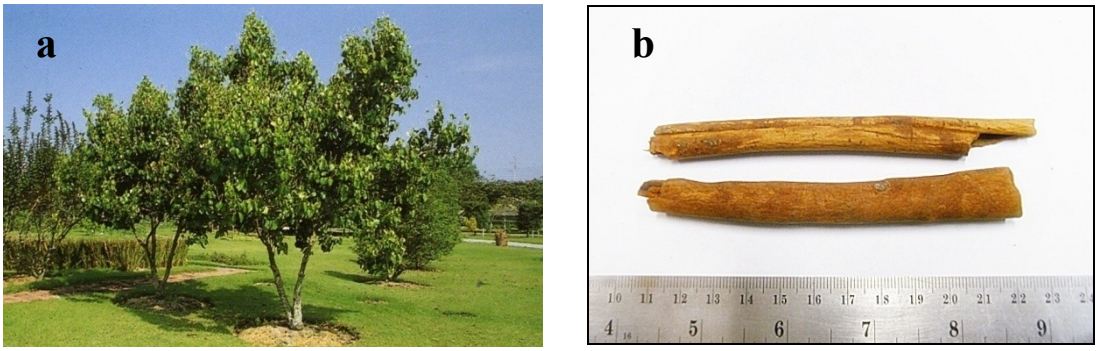

Figure 2-9

(a) *Cinnamomum zeylanicum* Linn. **(**Pichiensunthon et al., 2005)

(b) Bark of *C. zeylanicum*

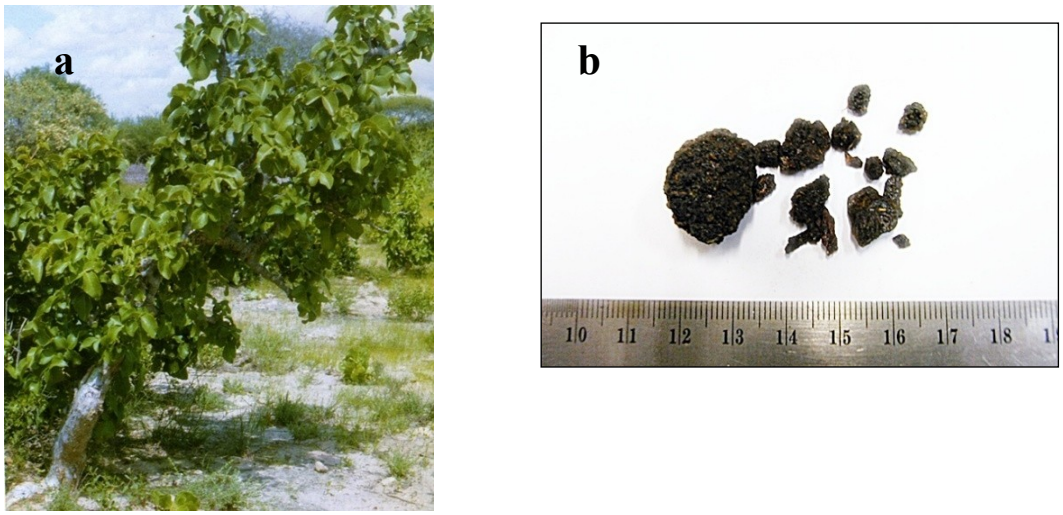

Figure 2-10

(a) *Commiphora abyssinica* (Berg.) Engel **(**Pichiensunthon et al., 2005**)**

(b) Myrrh of *C. abyssinica*

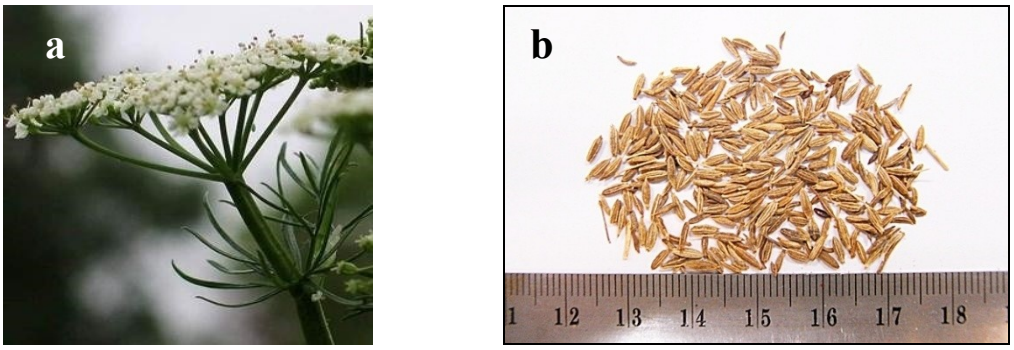

Figure 2-11

(a) *Cuminium cyminun* Linn.

(from : http://gstuff.co.nz/shop/garden/index.php?main_page)

(b) Fruit of *C. cyminum*

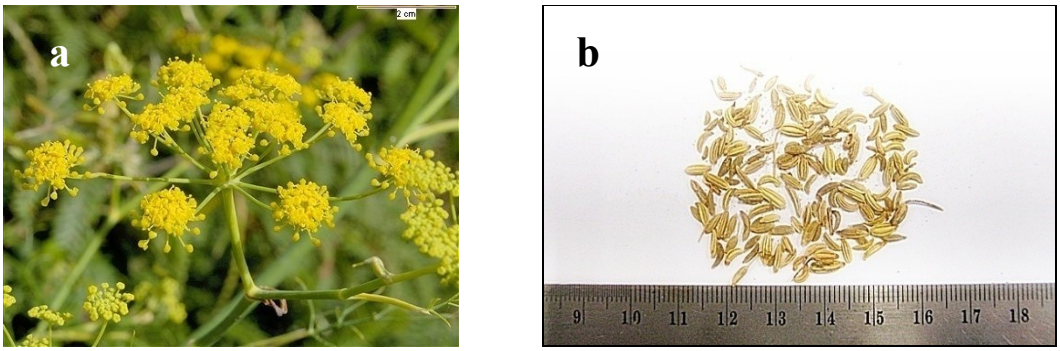

Figure 2-12

(a) *Foeniculum vulgare* Mill. (Umbelliferae)

(from : http://toxicopoeia.com/?get=plants&plant=Foeniculum)

(b) Fruit of *F. vulgare*

2.7.10 *Lepidium sativum* Linn.

Lepidium sativum L. (Cruciferae), its common names in various countries are Thian dang (Central) (Thailand) and Cress, Garden Cress (English) (Smitinand, 2001). *Lepidium sativum* is grown worldwide as a spicy salad herb. Its origin is not known, but is possibly Ethiopia or Iran (Brotonegoro & Wiharti, 2001).

Description of *Lepidium sativum* is an annual erect herbaceous plant, growing up to 30 cm. The leaves are alternate, membranaceous, ovate-oblong in outline, up to 12 cm x 9 cm, imparipinnati- or bipinnatipartite, with 2-4 pairs of lateral lobes, lobes linear, lanceolate or oblanceolate, up to 3 centimeter long, uppermost leaves sometimes simple, serrate, glabrous or sparsely pubescent; petiole up to 4 cm long in basal leaves; stipules absent. Inflorescence is arising from terminal or axillary raceme, 1-3 centimeter long, accrescent to 25 centimeter when fruiting. The flowers (shown in Figure 2-13(a) are bisexual, rather conspicuous, whitish to violet, pedicel 3-6 millimeter long in fruit, ascending; sepals 4, elliptical, 1-1.5 millimeter long, green, margins membranaceous; petals 4, spathulate to slightly clawed, 1.5-3 millimeter long, apex rounded; stamens 6, unequal in length, nectaries 6, alternating with filaments; ovary superior, flattened dorso-ventrally, apex emarginate, lateral margins wing-like, style up to 0.5 millimeter long, stigma capitate, finely pappilate. The fruit is an ovoid, flattened silique, 4.5-6.5 millimeter x 3-4 millimeter, pale green to yellowish, apical wings prominent, apex emarginate, dehiscing by 2 valves, leaving the replum with thin, white septum; 1 seed per locule. The seed is subovoid, flattened, 2-3 millimeter x 1.5 millimeter, wingless, reddish-brown as shown in Figure 2-13(b) (Brotonegoro & Wiharti, 2001).

2.7.11 *Myristica fragrans* Linn.

Myristica fragrans Linn. (Myristiceae), its common name in Thai is Luk jan. It is relatively widely cultivated crop *Myristica fragrans* (nutmeg and mace), the following three species, all native to the Philippines, are very locally cultivated in China for medicine (Iyer, 2007).

Description of *Myristica fragrans* Linn. is shown in Figure 2-14(a b and c) . Its height is up to 10 meter. The branches are slender, minutely pubescent, early glabrescent. The Petiole is 6–12 millimeter long. Leaf blade are elliptic or elliptic-lanceolate, 4–8 centimeter long, both surfaces glabrous. Lateral veins are 6–10 pairs. Male inflorescences are 2.5–5 centimeter long, glabrous, shortly peduncled, simple or forked, with 4–8 or more flowers on slender branches. Male flowers have pedicel 10–15 millimeter long; bracteole caducous; perianth trigonous-ovoid, 5–7 mm, lobes 3(or 4), with minute tomentum outside; anthers 9–12; synandrium ca. 5 mm, column ca. 2 mm, sterile apex ca. 0.5 mm. Female inflorescences is only 1- or few flowered. Female flowers have pedicel 8–12 millimeter long; bracteole inserted on base of perianth, leaving ringlike scar after abscission; perianth ca. 6 × 4 mm; ovary ellipsoid, with dense rusty pubescence; style extremely short; stigmas 2, minute. Fruiting pedicel is 10–15 millimeter long. Fruits 1 or 2, color are orange or yellow, pyriform or subglobose, 3.5–5 centimeter in diam. Seeds ellipsoid, 2–3 × ca. 2 cm; aril red, irregularly deeply lacerate; cotyledons short, curled, connate at base (Jukic et al., 2006).

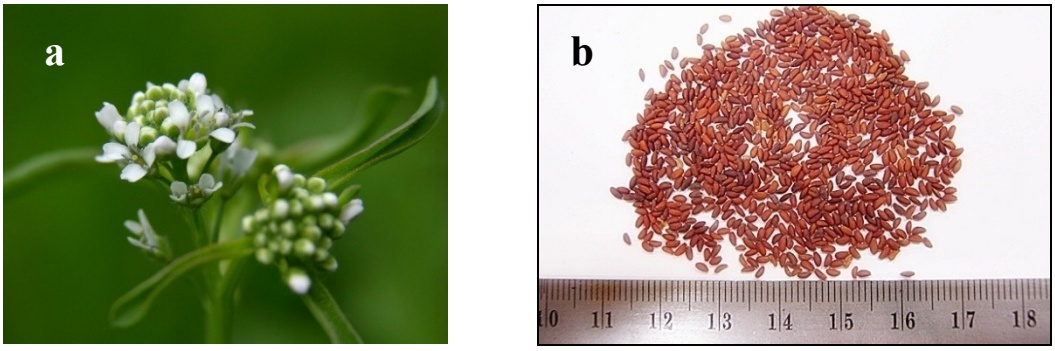

Figure 2-13

(a) *Lepidium sativum* L. (Cruciferae)

(from : http://todoplantas.blogspot.com/2010/09/mastuerzo.html)

(b) Fruit of *L. sativum*

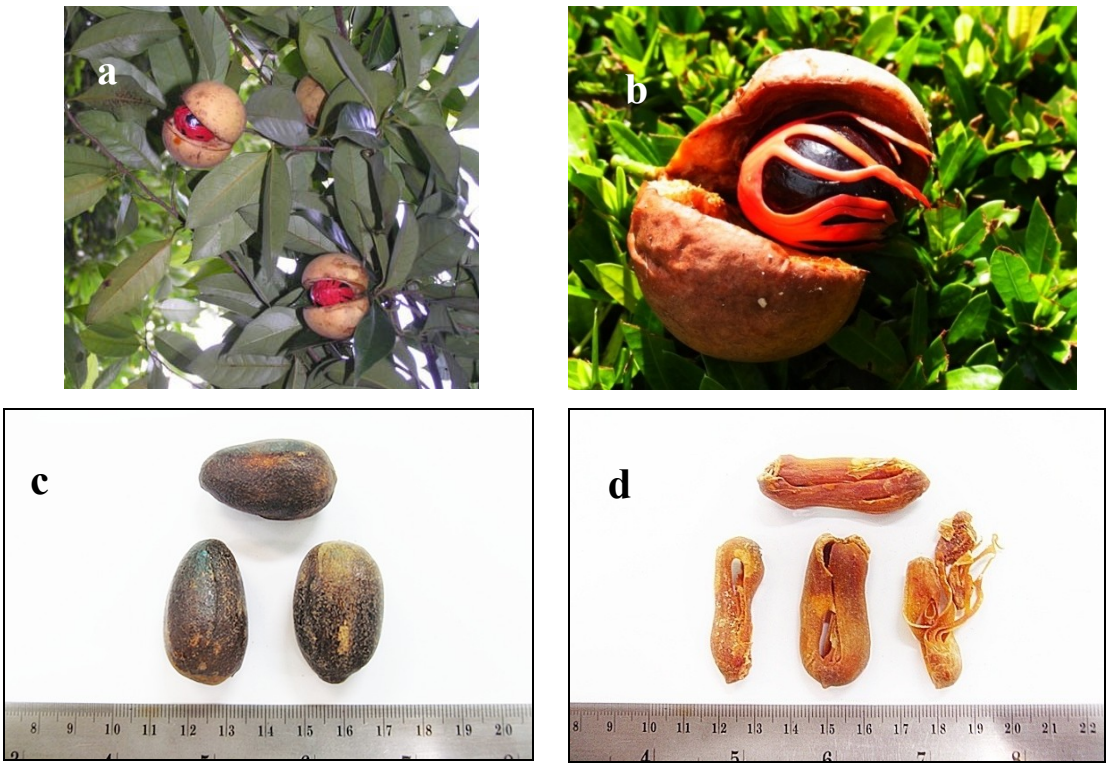

Figure 2-14

(a,b) *Myristica fragrans* Linn. (Myristiceae),

(c) Nutmeg of *M. fragrans* **(d)** Mace of *M. fragrans*

2.7.12 *Nigella sativa* Linn.

Nigella sativa L. (Ranunculaceae), its common names in various countries are Thian dum (Thailand) and Black cumin, Black Seed (English). It is widely used as spice condiments in vegetarian and nonvegetarian preparations along with other spices in India and Arabia (Thippeswamy & Naidu, 2005).

Description of *Nigella sativa* L is an annual herb. Its height is about 30-60 centimeter. The leaves are multiple pinnate and the leaflets are narrow and lanceolate to linear. The small flowers bear 5 white petals and numerous stamens with a circular arrangement of 5-10 nectorial petals in between, and 4-7 fused ovaries as shown in Figure 2-15(a). The ripe follicles contain numerous black seeds. The seeds are black and triagonal in shape as shown in Figure 2-15(b).

2.7.13 *Picrorrhiza kurroa* Royle. Ex Benth.

Picrorrhiza kurroa Royle ex Benth (Scrophulariaceae), its common names in various countries are Kot Kan Prow (Thailand) and Picrorhiza, Gentian (English). It is a hairy perennial herb growing wild in North Western Himalayan region (Mittal et al*.,* 1978; Ansari et al*.,* 1988).

Description of *Picrorrhiza kurroa* Royle ex Benth is shown in Figure 2-16 (a,b). It is a small perennial herb with short rootstock and fleshy thick, root fibers. The leaves are 5-8 centimeter long, ovate, and toothed. Leaf stalk are very thick. Cauline leaves are 1.3 - 4 centimeter long. Flowers are blue or purple in spikes.

2.8.14 *Piper chaba* Linn. or *Piper longum* Linn.

Piper chaba Linn. or *Piper longum* Linn. (Piperaceae), its common names in various countries are De plee**,** Prik-hang and Dipli-chueak (Thailand). It is considered a native of South Asia and India. It also found in Thailand, Myanmar, Malaysia and Singapore (Saralamp *et.al.,* 1996).

Piper chaba Linn is a monoecious. It is climbing so its stem is flexuous. Leaf stalk is 1-3 centimeter long. Leaves on creeping branch and epiphytic branches blade are ovate or elliptic. Leaves on free branches blade are ovate to ovate-oblong. Leaf blade is dark green, membranous and its size is about 3 to 5 centimeters wide and 7 to

10.5 centemeters long. Male spike is straight up and has diameter about 0.3-0.7 centimeter. Its length is about 5-8 centimeter. Its peduncle is 0.5 centimeter long. Female spike is erect. Its length is 0.6-2 centimeter and has diameter 0.2 centimeter. Peduncle is 0.5 centimeter long. Fruiting spike is straight up. Its length is 0.7-2.5 centimeter. Description of *Piper chaba* Linn. is shown in Figure 2-17(a,b).

2.7.15 *Piper nigrum* Linn.

Piper nigrum Linn. (Piperaceae), its common name in Thai is Prik tai. *Piper nigrum* Linn. is native to India and are extensively cultivated there and elsewhere in tropical regions

Description of *Piper nigrum* Linn. is shown in Figure 2-18(a,b). *Piper nigrum* Linn. is a perennial woody vine growing to 4 meters in height on supporting trees, poles, or trellises. Petiole is 1–2 centimeter long and glabrous. Leaf blade are ovate to ovate-oblong and size is about 10–15 × 5–9 centimeter, usually slightly oblique, apex acute. Veins are 5–7, apical pair arising 1.5–3.5 centimeter above base, alternate, others basal; reticulate veins prominent. Flowers are polygamous and usually monoecious. Spikes are leaf-opposed, to as long as leaves. Peduncle are nearly as long as petioles, glabrous; bracts spatulate-oblong, size is about 3–3.5 × ca. 0.8 mm, adaxially adnate to rachis, only margin and broad, rounded apex free, shallowly cupular. Stamens 2, 1 on each side of ovary; filaments thick, short; anthers reniform. Ovary globose; stigmas 3 or 4, rarely 5. Drupe red when ripe, drying black when unripe, globose, 3–4 mm in diam., sessile. (Flora of China 7, 2007)

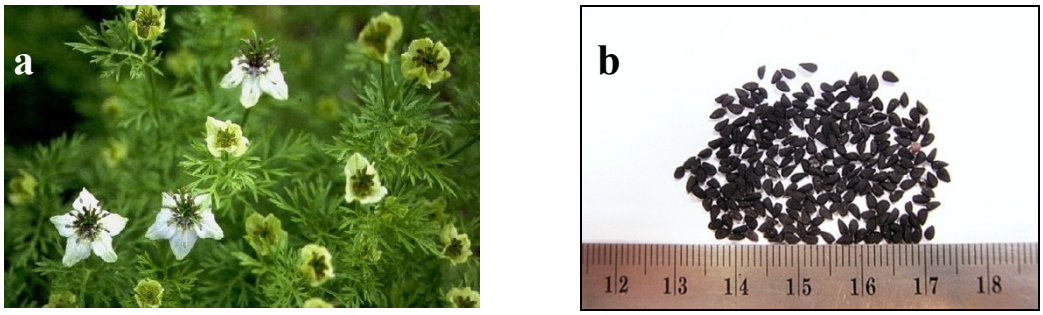

Figure 2-15

(a) *Nigella sativa* L. (Ranunculaceae)

(from : http://www.henriettesherbal.com/pictures/p09/pages/nigella-sativa-3.htm)

(b) Seed of *N. sativa*

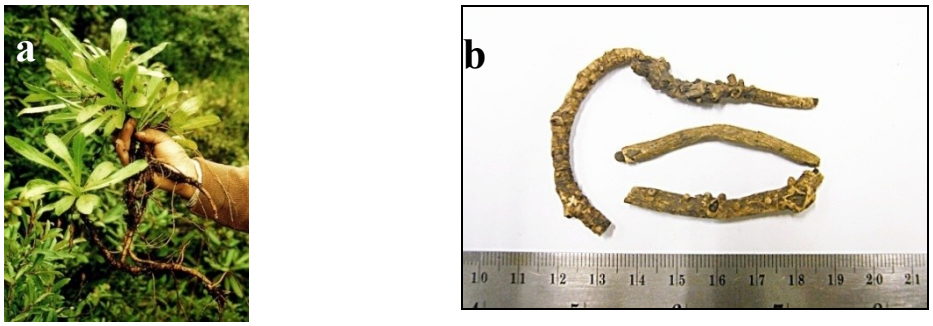

Figure 2-16

(a) *Picrorrhiza kurroa* Royle ex Benth (Scrophulariaceae)

(Pichiensunthon et al., 2005), **(b)** Rhizome of *P. kurroa*

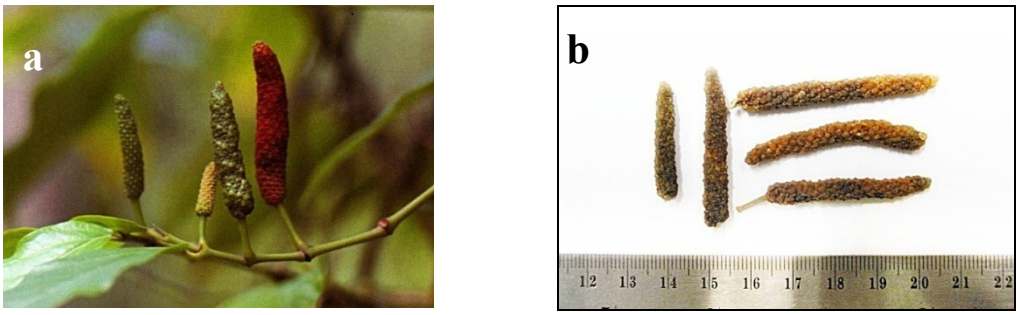

Figure 2-17

(a) *Piper chaba* Linn. or *Piper longum* Linn. (Piperaceae)

(Pichiensunthon et al., 2005), **(b)** Flower of *P. chaba*

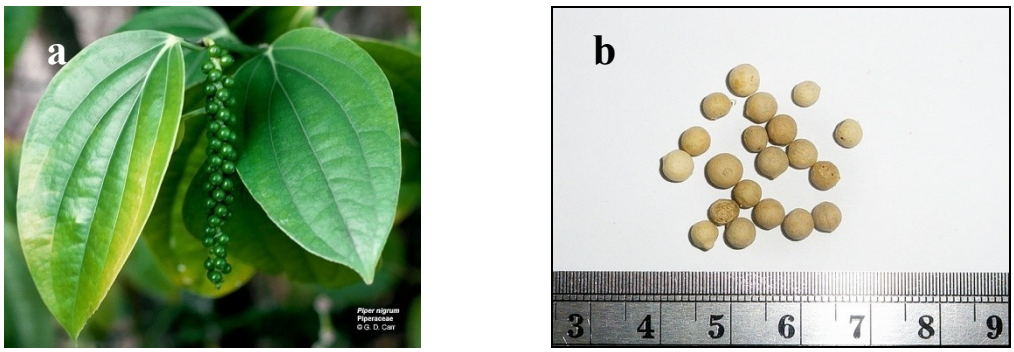

Figure 2-18

(a) *Piper nigrum* Linn. (Piperaceae)

(from : www.hunzaroma.com/produits/huiles_essentielles/fiches/Piper_nigrum.html)

(b) Seed of *P. nigrum*

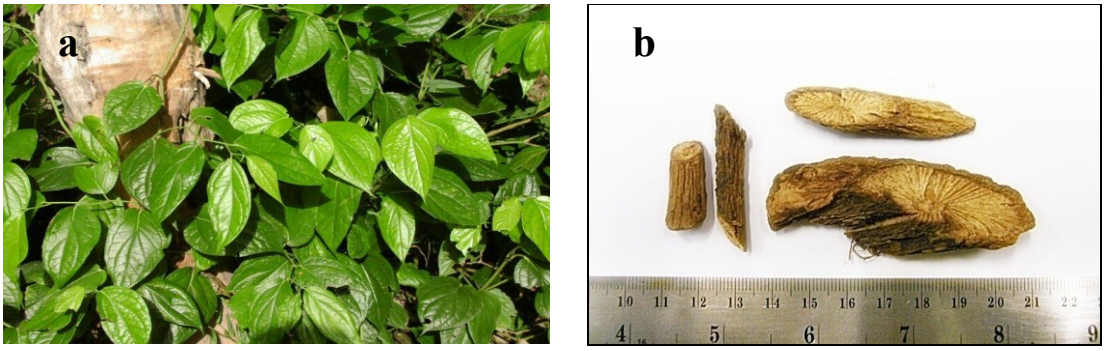

Figure 2-19

(a) *Piper ribesoides* Wall. (Piperaceae)

(from : home.hiroshima-u.ac.jp/shoyaku/photo/Thai/021205Piper.jpg, 2008)

(b) Stem of *P. ribesoides*

2.7.16 *Piper ribesoides* Wall. *or Piper interruptum* Opiz.

Piper ribesoides Wall. (Piperaceae), its common names in Thai are Sa kan, Sa-kan-lek and Sa-kan-youak. It is found in north and northeast Thailand from 200-1200 m altitude. In Thai traditional medicine, the stem is used as antiflatulant and carminative (Pichiensunthon and Jeerawongs, 2004).

Piper ribesoides Wall. is a climbers dioecious. Stems are glabrous, ridged and thickness is about 2-4.5 millimeter. Petiole is glabrous, 1-2.5(-4) centimeter long and sheathed at base only. Leaf blade is ovate to long ovate. Its size is 6-13 × 4-7 centimeter both surfaces are glabrous. and shortly acuminate. Veins are all basal. Male spikes are glabrous and their sizes are about 11-27 centimeter × 1.5-3 millimeter. Stamens are 2 or 3. Female spikes are 7-17 centimeter long. Flowers are sparse or interrupted in fruit. Ovary is distinct, apex acute and ovoid, stigmas 4 or 5. Drupe ovoid or ovoid-globose, 3-6 × 2-4 mm, smooth (Cheng *et.al.,* 1999). Description of *Piper ribesoides* Wall. is shown in Figure 2-19(a,b).

2.7.17 *Platycladus orientalis* (L.) Franco

Platycladus orientalis (L.) Franco or *Thuja orientalis* L. (Cupressaceae), its common names in various countries are Son tet, Son Phang or Son haang sing (Thailand) and Oriental arborvitae or Biota (English). It is native to northwestern China and widely naturalised elsewhere in Asia east to Korea and Japan, south to northern India, and west to northern Iran (Franco, 1949; Silba, 1996).

Description of *Platycladus orientalis* (L.) Franco is shown in Figure 2-20(a,b). *Platycladus orientalis* (L.) Franco is a small, slow-growing tree. Its height is 15 meters up to 20 meter. Its trunk has diameter about 0.5 meter. However, for very old tree could be found 30 meter tall and 2 meter diameter. Branchlets arranged in a plane, spreading or ascending, flattened. Leaves decussate, 4-ranked, scalelike, base decurrent, 1-3 millimeter long, apex bluntly pointed, with an abaxial resin gland, dimorphic along branchlets. Lateral leaves are overlapping facial ones, boat-shaped, ridged, apex slightly incurved, without conspicuous, white stomatal bands abaxially but with a median groove. Facial leaves are rhomboid, with a conspicuous, linear, glandular groove at center abaxially. Pollen cones with 8-12 microsporophylls, each with 3-6 pollen sacs; yellowish green, ovoid, 2-3 millimeter long. Seed cones

terminal, solitary, dehiscent when mature in first year, when immature bluish green, subglobose, ca. 3 millimeter in diameter, when ripe red-brown, subovoid, 1.5-2× 1-1.8 centimeter; cone scales 6 or 8, decussate, flat, thick, woody, only the middle 2 pairs fertile (proximal 2 fertile cone scales 2-seeded, distal 2 fertile scales 1-seeded); free bract apex a long, recurved cusp. Seeds wingless, rarely with a very narrow wing, grey-brown or purple-brown, ovoid or subellipsoid, size is about 5-7 × 3-4 millimeter, slightly ridged. Cotyledons 2. Pollination March to April, seed maturity October (Franco, 1949; Silba, 1996).

2.7.18 *Pouzolzia pentandra* J.J. Bennett

Pouzolzia pentandra J.J. Bennett (Urticaeae) its common name in Thai is Khob chanang khow and/or Khob chanang dang. They grow naturally in tropical and subtropical East Asia (Kapahi *et.al.,* 1993)

Description of *Pouzolzia pentandra* J.J. Bennett is shown in Figure 2-21(a,b). *Pouzolzia pentandra* J.J. Bennett is perennial, erect to decumbent. Its typical height is up to 1 meter. It is glabrous to sparsely hispid herb. Stem are cylindrical below, angular above. Leaves opposite below, alternate and gradually smaller above. Sessile or with up to 5 millimeter long petiole; lamina lanceolate or linear-lanceolate to oblong, 2-10 centimeter long, 0.5-1.8 (-2) centimeter broad, glabrous, subcordate or rounded at the base, margin entire, minutely spinulose, apex acute-acuminate or rarely obtuse. Stipules are ovate and length is about 1-2 millimeter and membranous. Flowers loosely clustered in upper leaf axils, greenish-white or pinkish-green; female sessile, male with 2.5-3.5 millimeter long pedicel. Calyx of male flowers 5-lobed, lobes shortly acuminate, abruptly incurved, ciliate, Stamens 5, c. 2 millimeter long. Achenes shining black, ovate, 1-1.5 millimeter long, acute, enclosed in 2-3-winged persistent calyx. (Flora of Pakistan, 2010)

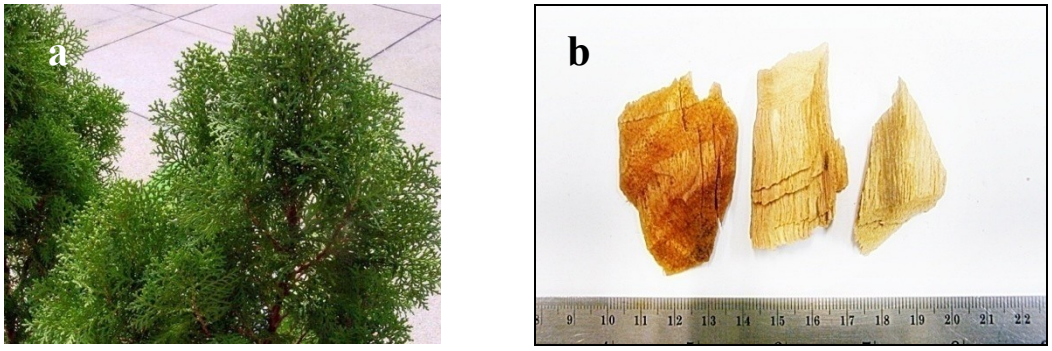

Figure 2-20

(a) *Platycladus orientalis* (L.) Franco or *Thuja orientalis* L. (Cupressaceae) (from : http://prathom.swu.ac.th/panmai/show_img.asp?ID=7-10110-002-020)

(b) Stem of *P. orientalis*

Figure 2-21

(a,b) *Pouzolzia pentandra* J.J. Bennett (Urticaeae) (Pichiensunthon et al., 2005) **(c)** All part of *P. pentandra*

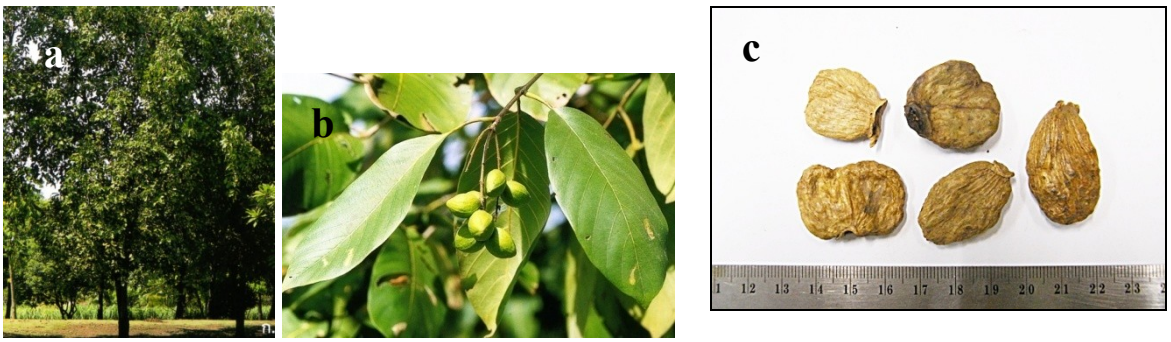

Figure 2-22

(a,b) *Terminalia chebula* Retz (Combretaceae) (Pichiensunthon et al., 2005),

(c) Gall of *T. chebula*

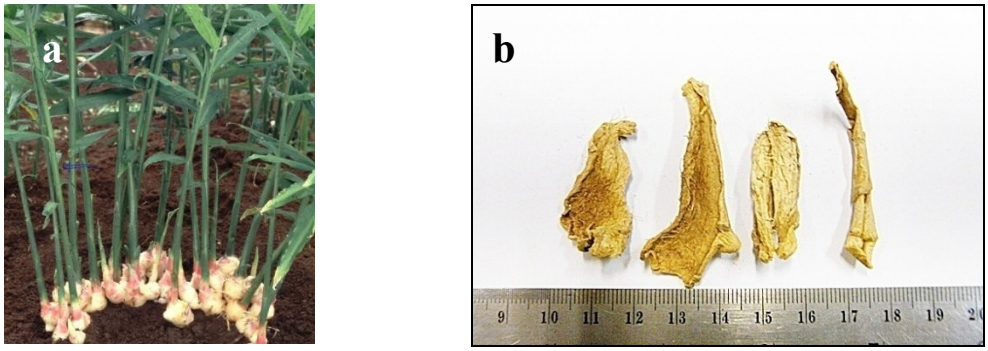

Figure 2-23

(a) *Zingiber officinale* Roscoe (Zingiberaceae) (Pichiensunthon et al., 2005)

(b) Rhizome of *Z. officinale*

2.7.19 *Terminalia chebula* Retz gall

Terminalia chebula Retz gall (Combretaceae), its common names in various countries are Kot pung pla (Thailand) and Terminalia gall, Myrobalan gall (English). It is native to southern Asia from India and Nepal east to southwestern China (Yunnan), and south to Sri Lanka, Malaysia and Vietnam (Flora of China 13, 2007; Germplasm Resources Information Network).

Description of *Terminalia chebula* Retz gall is shown in Figure 2-22 (a,b). *Terminalia chebula* Retz gall is a deciduous tree. Its height is up to 30 meter. The trunk has diameter up to 1 meter. The leaves are alternate to subopposite in arrangement, oval. It is about 7-18 centimeter long and is 4.5-10 centimeter wide with a 1-3 centimeter petiole. The fruit is drupe-like, 2-4.5 centimeter long and 1.2-2.5 centimeter broad, blackish, with five longitudinal ridges. (Flora of China 13, 2007) Branchlets are conspicuously white or yellowish long lenticellate, glabrous. Leaves are alternate or subopposite, spaced along branchlets; petiole 1-3 centimeter, moderately stout, with 2-4 glands 1-5 millimeter below apex; leaf blade elliptic, 7-18 × 4.5-10 centimeter, both surfaces glabrous., or appressed (and rarely silvery) villous at least when young, base obtuse-rounded or cuneate, oblique, apex mucronate; lateral veins in 6-12 pairs. Inflorescences axillary or terminal, simple spikes, 5-10 centimeter, numerous flowered, sometimes grouped at branchlet apex and forming a panicle; axis glabrous or sparsely hairy, with denser hairs near base of flowers. Flowers slightly fragrant, bisexual. Calyx tube distally cupular, 2.5-3.5 millimeter, abaxially glabrous, adaxially tawny tomentose; lobes 5, apex mucronate to aristate. Stamens 10, exserted, 3-4 millimeter. Fruit are not stipitate, blackish brown when ripe, ovoid or broadly and ellipsoid, or cylindric-ovoid, obtusely 5-ridged, 2-4.5 × 1.2-2.5 centimeter, rigid, becoming deeply wrinkled when dry, glabrous.

2.7.20 *Zingiber officinale* Roscoe.

Zingiber officinale Roscoe (Zingiberaceae), its common names in Thai is Khing. It is native to south-east Asia and is cultivated in the tropical regions in both the eastern and western hemispheres (WHO, 1999).

Description of *Zingiber officinale* Roscoe is shown in Figure 2-23(a,b). *Zingiber officinale* Roscoe is a perennial herb with a subterranean, digitately branched rhizome producing stems up to 1.50 m in height with linear lanceolate sheathing leaves, smooth and pale green. Its size is 5–30 centimeter long and 8–20 millimeter wide. Flower stems are surrounded by a thin bract and situated in axils of large, greenish yellow obtuse bracts. At end of flower stem forming collectively an ovate-oblong spike. Each flower shows a superior tubular calyx, split part way down one side. Orange yellow corolla is composed of a tube divided above into 3 linear oblong, blunt lobes and 6 staminodes in 2 rows. The outer row of 3 inserted at mouth of corolla. The posterior 2, is small and horn-like. The anterior petaloid is purple and spotted and divided into 3 rounded lobes; an inferior, 3-celled ovary with tufted stigma. Fruit a capsule with small arillate seeds (WHO, 1999). Rhizome of ginger is laterally flattened and has irregularly branching pieces. Its size is about 3–16 centimeter x 3–4 centimeter. Its thickness is about 2 centimeter. Sometimes they split longitudinally. It is yellowish brown in internal leading to show a yellow endodermis separating the narrow cortex from the wide stele, and numerous scattered fibrovascular bundles, abundant scattered oleoresin cells with yellow contents and numerous larger greyish points, vascular bundles, scattered on the whole surface (WHO, 1999).

2.8 Biological activity of plants in Ridsiduangmahakan preparation

Ridsriduangmahakan preparation consists of several ingredients. Some plants have been study various biological activities. Previous investigations on biological activity, or more specification, anti-inflammation and cytotoxic against cancer of plants in Ridsiduangmahakan Preparation are shown in Table 2-4

2.9 Chemical constituents of plants in Ridsiduangmahakan preparation

The reports of chemical constituents of several plants in Ridsiduangmahakan Preparation are shown in Table 2-5

Table 2-4

Biological activities of plants of Ridsiduangmahakan preparation

Botanical name	Activities	Results of biological activities	References
Cuminum cyminum L.	Anti-inflammation	The essential oil had no anti-inflammatory effect against formalin-induced edema	Sayyah et al., 2002
Cinnamomum zeylanicum Linn.	Anti-inflammation	Carrageenan in albino rats (400 mg/kg) exhibits significant reduction in the volume of inflammation	Maridass & GhanthiKumar ,2008
Commiphora abyssinica (Berg.)	Anti-inflammation	Xylene-induced ear oedema in mice and cotton pellet granuloma test in rats	Atta & Alkofahi 1998
	Toxic	No significant difference in both acute or chronic treatment between treatment and control (doses of acute were 0.5, 1.0, and 3g/kg and doses of chronic was 100 mg/kg per day for 90 days)	Rao et al. 2001
Foeniculum vulgare Mill.	Anti-inflammation	Methanolic extract exhibited inhibitory effects on the NO production in LPS-stimulated RAW 264.7 macrophages at concentration 50 and 200 μg/ml (%NO inhibition = 56.9±0.9 and 113.8±0.9)	Choi & Hwang, 2005
	Anti-inflammation	Methanolic extract exhibited inhibitory effects against acute and subacute inflammatory diseases and showed a central analgesic effect by oral administration (200 mg/kg)	Choi & Hwang, 2004

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Lepidium sativum Linn.	Anti-inflammation	The hydroalcoholic extract from *Lepidium sativum* leaves (300 μg/cm^2) showed an anti-inflammatory effect. Provoking oedema reductions 43%	Conforti et al., 2009
	Anti-inflammation	The ethanolic extract of *L. sativum* (500 mg/kg) exhibited inhibition of carrageenan-induced pedal oedema in rats and weak inhibition of cotton pellet-induced granuloma	Al-Yahya et al., 1994
Myristica fragrans Linn.	Cytotoxic	Screening of extracts against cancer cell lines as follow: P388, Molt4, Wehi 164, LL/2, Hep G2, SW620 and J82. Measurement by MTT assay showed that *Myristica fragrans* extract exhibited cytotoxic against Hep G2 and Molt4	Swamy & Tan, 2000
	Anti-inflammation (Aril)	The methanol extract inhibited the edema induced by carrageenin (1.5 g/kg). The increment of dye leakage induced by acetic acid (1 g/kg) and reduced the number of the writhings induced by acetic acid (0.3 and 1 g/kg)	Ozaki et al., 1989
Myristica fragrans Linn.	Anti-inflammation (Fruit)	Macelignan potently suppressed the expression of COX-2 and inducible nitric oxide synthase. The consequent resulted in the reduction of nitric oxide in LPS-treated microglial cells	Jin et al., 2005

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Nigella sativa Linn.	Anti-inflammation	The aqueous extract (500 mg/kg-body weight) showed inhibition of Carrageenan induced paw edema	Al-Ghamdi, 2001
	Anti-inflammation	The aqueous extract exhibited an inhibitory effect on NO production by murine macrophages	Mahmood et al., 2003
	Anti-inflammation	The *n*-hexane Soxhlet extract (100 μg/ml) showed strong inhibitory activity in COX-2 and COX-1 assays with 78.13% inhibition and 100% inhibition, respectively	Landa et al., 2007
	Anti-inflammation	Thymoquinone showed dose- and time- dependently reduced nitrite production by rat peritoneal macrophages with IC_{50} values of 1.4-2.76 μM	El-Mahmoudy et al., 2002
	Anti-inflammation	Thymoquinone (2.5 and 5 mg/kg) exerted anti-inflammatory effects on experimentally induced arthritis in rats	Tekeoglu et al., 2007
	Anti-inflammation	Thymoquinone showed inhibitory effect on COX-2 protein expression and PGD_2 production	El-Mezayen et al., 2006
	Anti-inflammation	Thymol exhibited the most active against COX-1 with the same IC_{50} value as indomethacin (0.2 μM)	Marsik et al., 2005

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Nigella sativa Linn.	Anti-inflammation	Thymohydroquinone and thymoquinone exhibited more inhibitory than indomethacin on COX-2 with IC_{50} values of 0.1, 0.3 and 0.6 μM, respectively	Marsik et al., 2005
	Cytotoxic	A decoction of *N. sativa* seeds and *N. sativa* plant extract were tested on Hep G2 cell line and found that plant extract showed inhibitory effect as 80±3.8%	Thabrew et al., 2005
Picrorrhiza kurroa Royle. Ex Benth.	Anti-tumour	Methanolic extract was studied in mice and 20-methylcholanthrene produced 100% induction of sarcoma in control mice, tumor incident and tumor related deaths were significantly inhibited by oral treatment of 150 and 750 mg/kg weight respectively	Joy et al., 2000
	Anti-inflammation	The anti-inflammatory activities of *P. kurroa* crude extract and purified compounds were compared in the croton oil mouse ear-swelling assay. The crude extract and picroside II (3) showed 65% and 46%, respectively, inhibition of mouse ear swelling at 6 h	Jia et al., 1999

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Piper chaba Hunt or *Piper longrum*	Anti-inflammation	Piperine inhibited adhesion of neutrophils to endothelial monolayer due to its ability to block the tumor necrosis factor-α (TNF-α) induced expression of cell adhesion molecules, i.e., ICAM-1, VCAM-1 and E-selectin	Kumar *et.al*., 2007
	Anti-inflammation	Chloroform extract was significantly blocking the TNF-α induced expression of CAMs at 17.5 µg/ml and E-selecting at 15 µg/ml concentration on human umbilical vein endothelial cells and also inhibited the NADPH catalyzed rat liver microsomal lipid peroxidation.	Singh *et.al*., 2008
	Anti-inflammation	(2E,4Z,8E)-N-[9-(3,4-methylenedioxyphenyl)-2,4,8-nonatrienoyl]piperidine inhibited the direct binding between sICAM-1 and LFA-1 of THP-1 cells, with IC_{50} values of 10.7, µg/mL.	Lee *et.al.,* 2008b
	Cytotoxicity	*Piper longum*, showed amoderate activity against ascitic and colon cancer cells, with IC_{50} at 100 and 250 µg/ml, respectively	Sunila & Kuttan, 2004

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Piper chaba Hunt or *Piper longrum*	Cytotoxicity	Alcoholic extract was 100% toxic for DLA cells (500 µg/ml) and EAC cells (250 µg/ml). Alcoholic extract was also found to produce cytotoxicity towards L929 cells in culture at a concentration of 100 and 50µg/ml, respectively.	Sunila & Kuttan, 2004
	Antitumor	Administration of alcoholic extract (10 mg/dose) as well as piperine (1.14 mg/dose) could inhibit the solid tumor development in mice induced with DLA cells (37.3%) and increase the life span of mice bearing EAC tumor (58.8%)	Sunila & Kuttan, 2004
Piper nigrum	Anti-inflammation	Piperine exhibited anti-inflammatory activity Piperine (1 or 5 mg/kg of body weight) also inhibited LPS-induced endotoxin shock in TNF-α knockout (KO) mice and type 1 IFN, but not IL-1β and IL-6; piperine also attenuates LPS-induced endotoxin shock via inhibition of type 1 IFN production.	Bae et al., 2010
	Anti-inflammation	The MeOH extracts of black pepper at 200 µg/mL and its compounds at 25 µg/mL inhibited COX enzymes by 31-80%	Yunbao et al., 2010

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Platycladus orientalis	Anti-inflammation	Methylene chloride fraction (10, 30, or 50 μg/ml) inhibited pro-inflammatory cytokines, e.g., TNF-α and IL-6. The expression of LPS-induced iNOS and COX-2 protein and their mRNA expression were inhibited by Western blotting method.	Kim et al., 2011
	Cytotoxicity	Methanol extract of stem and leafs against 4 human breast cancer cell lines (SKBR3, MCF7, T47D and MDA-MB435) and 2 human lung cancer cell lines (A549 and LU1) were determined proliferation by MTT assay. Results are reported methanolic extract againt SKBR3, MCF7, T47D and MDA-MB435 as ED_{50} values are 320 200 250 and 250 μg/ml., respectively.	Kummalue et al., 2005
Zingiber officinale Roscoe.	Anti-inflammation	[6]-gingerol inhibited the production of proinflammatory cytokines, i.e., TNF-α, IL-12, and IL-1β, produced by LPS stimulated macrophages.	Tripathi *et.al.,* 2007
	Anti-inflammation	[8]-paradol exhibited COX-1 inhibitory activity with IC_{50} value of 4±1 μM.	Tjendraputra *et.al.,* 2003

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Zingiber officinale Roscoe.	Anti-inflammation	Methanolic extract exhibited inhibitory effects on the NO production in LPS-stimulated RAW 264.7 macrophages at concentration 50 and 200 μg/ml. Percentage of NO inhibition were 89.9±0.9 and 112.8±0.9 respectively.	Choi & Hwang, 2005
	Anti-inflammation	The chloroform partition of Ginger roots inhibited COX-1 and COX-2 (20.0±0.4 and 7.5±0.6 μM respectively). Purified 10-gingerol, 8-shogaol and 10-shogaol from ginger roots inhibited COX-2 with IC_{50} values of 32, 17.5 and 7.5 μM, respectively. No inhibition of COX-1 was detected.	Breemen et al., 2011
	Cytotoxicity	[6]-gingerol induced cell death in HL-60 cells, caused DNA fragmentation and inhibited Bcl-2 expression.	Wang *et.al.,* 2003
	Cytotoxicity	[6]-gingerol and [6]-paradol were found to exert inhibitory effects on the viability and DNA synthesis of human promyelocytic leukemia (HL-60) cells.	Lee and Surh, 1998

Table 2-4 (Continued)

Botanical name	Activities	Results of biological activities	References
Zingiber officinale Roscoe.	Cytotoxicity	(3*R*,5*S*)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl) heptane, (3*R*,5*S*)-3-acetoxy-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane, 3-acetoxy-l,5-epoxy-1-(3,4-dihydroxy-5-methoxyphenyl)-7-(4-hydroxy-3-methoxy-phenyl) heptane, [6]-shogaol, [10]-shogaol and 1,7-bis(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one possess significant cytotoxicity against HL-60 cells (IC_{50} <50 μM) and that the cytotoxic activity is associated with the cell apoptosis.	Wei *et.al.,* 2005
	Cytotoxicity	[6]-shogaol exhibited potent cytotoxicity against human A549, SK-OV-3, SK-MEL-2, and HCT15 tumor cells. [6]-shogaol also inhibited proliferation of the transgenic mouse ovarian cancer cell lines, C1 (genotype:p53-/-, c-myc, K-ras) and C2 (genotype: p53-/-, c-myc, Akt), with ED_{50} values of 0.58 μM (C1) and 10.7 μM (C2).	Kim *et.al.,* 2008

Table 2-5

Chemical constituents found in plants of Ridsiduangmahakan preparation

Botanical name	**Chemical constituents**	**References**
Anacyclus pyrethrum	N-isoButyldienediynamide	Crombie, 1954
	Crystalline sialogogue	Gulland & Hopton, 1930
Anethum graveolens	Anethofuran	Zheng et al., 1992
	Carvone	
	Limonene	
	Carotenoids	Lisiewska et al., 2004
	Beta-carotene	
	Vitamin C	Lisiewska et al., 2006
	Chlorophylls	
	Polyphenols in dill	
Angelica sylvestris	Coumarins	Murphy et al., 2004
	Furanocoumarins	
	A-phellandrene	Bakkali et al., 2008
	Limonene	
	Carvone	
	Limonene	
Artemisia vulgaris	Casticin	Plant taxonomy, 2004
	Cirsilineol	
	Chrysoplenol-D	
	Chrysoplenetin	
	Terpenoids	Yin et al., 2008
	Flavonoids	
	Coumarins	
	Acetylenes	
	Caffeoylquinic acids	
	Sterols	

Table 2-5 (Continued)

Botanical name	Chemical constituents	References
Cinnamomum zeylanicum	Cinnamaldehyde	Barceloux, 2008
	Eugenol	
	Coumarin	
	α-pinene	Miyazawa et al., 2001
	Camphene	
	Limonene	
	1,8-cineole	
	Spathulenol	
	Santolina triene	
	Caryophyllene oxide	
	Terpene hydrocarbons	
	α-bergamotene	
Cuminum cyminum	Cuminlaldehyde	Hajlaoui et al., 2010
	Gamma-terpinene	
	O-cymene	
	Beta-pinene	
	2-caren-10-al	
	Trans-carveol	
	Myrtenal	
	Limonene	
Foeniculum vulgare	Trans-Anethole	Charles et al., 1993; Telci et al., 2009
	Estragole (Methyl chavicol)	
	α-Pinene	
	Fenchone	
	Camphene	
	Limonene	

Table 2-5 (Continued)

Botanical name	Chemical constituents	References
Lepidium sativum	Benzylcyanide Benzylthiocyanate Benzylisothiocyanate	Parekh & Chanda, 2008
Myristica fragrans	Myristicin Elemicin Isoelemicin Safrole Sabinene Terpinen-4-ol Terpineol α-Terpinene γ-Terpinene α-Pinene β-Pinene Eugenol Isoeugenol(*trans*-Isoeugenol) *cis*-Isoeugenol Methoxyeugenol Dehydrodiisoeugenol Macelignan β-Phellandrene Limonene Cuminol β-Myrcene Camphene α-Copaene β-Thujone	Morita et al., 2003; Singh et al., 2005; Tomaino et al., 2005; Chung et al., 2006; Jukic et al., 2006; Oussalah et al., 2006; Chirathaworn et al., 2007; Surveswara et al., 2007

Table 2-5 (Continued)

Botanical name	Chemical constituents	References
Myristica fragrans (continued)	*p*-Cymene Pulegone Linoleic acid Myristic acid Palmitic acid	
Nigella sativa	Thymoquinone Thylmohydroquinone Thymol Dithymoquinone *p*-Cymene Carvone Carvacrol γ-Terpinene All-*trans*-ratinol (Vitamin A) α-Tocopherol (Vitamin E)	Marsik et al., 2005; Nair et al., 2005; Salem, 2005; Thippeswamy & Naidu, 2005; Al-Saleh et al., 2006; El-Gazzar et al., 2006; Naeini et al., 2009
Picrorrhiza kurroa	Acetophenones Iridoid glycosides Triterpenoids Benzoic acid derivatives Picroside I Picroside II 6-feruloyl Catalpol	Jia et al., 1999

Table 2-5 (Continued)

Botanical name	Chemical constituents	References
Piper chaba Linn. or Piper longum Linn.	Piperrolein B	Lee et al., 2008 a
	Piperchabamide D	Lee et al., 2008 a
	Pellitorin	Wu et al., 2004; Lee et al., 2008 a
	Dehydropipernonaline	Lee et al., 2008 a
	Piperine	Park et al., 2007; Wu et al., 2004
	Piperlongumine	Wu et al., 2004; Park et al., 2007
	Piperoctadecalidine	Park et al., 2007
	Retrofractamides A	Zhang et al., 2008
	Retrofractamides B	Zhang et al., 2008
	Pipataline	Pullela et al., 2006
Piper nigrum	Piperine	Rho et al., 2007
	Retrofractamide A	
	Pipercide	
	Piperchabamide D	
	Pellitorin	
	Dehydroretrofractamide C	
	Dehydropipernonaline	
	Terpenes	
	Steroids	
	Lignans,	
	Flavones	
	Alkaloids/alkamides	Lee et al., 2008
	Guineensine	

Table 2-5 (Continued)

Botanical name	Chemical constituents	References
Piper nigrum	methylenedioxyphenyl)- 2,4,8-nonatrienoyl]piperidine Pipernonaline Piperrolein B Piperchabamide D Pellitorin Dehydropipernonaline	
Platycladus orientalis	α-pinene, α -pinene/3-carene, cedrol, and cedrol/terpinyl acetate. 14-dien-19-oic acid 12R,15-dihydroxylabda-8 14S,15-dihydroxylabda-8(17) 12Z-dien-19-oic acid 7a-hydroxysandaracopimaric acid Pinusolide Sandaracopimaric acid Isocupressic acid	Lei et al., 2010 Wang et al., 2008 Kuo & Chen, 1999; Kue et al., 2000 Kitajima et al., 1982 Chiang et al., 2003
Terminalia chebula	Chebulinic acid Tannic acid Gallic acid	Picheansoonthon et al., 2005

Table 2-5 (Continued)

Botanical name	Chemical constituents	References
Zingiber officinale Roscoe.	[6]-gingerol	Surh et al., 1999; Wei et al., 2005
	[6]-paradol	Surh et al., 1999; Wei et al., 2005
	[6]-gingerdiol	Wei et al., 2005
	(3*R*,5*S*)-3,5-diacetoxy-[6]-gingerdiol	
	[4]-gingerol	Wei et al., 2005; Kim et al., 2008
	[8]-gingerol	
	[10]-gingerol	
	5-acetoxy-[6]-gingerol	Wei et al., 2005
	Hexahydrocurcumin	
	[5]-Shogaol (96)	Jolad et al., 2005
	Methyl [6]-shogaol (97)	
	Methyl [8]-shogaol (98)	
	[12]-Shogaol (99)	
	[6]-Isoshogaol (100)	
	[6]-Gingerdione (101)	
	[8]-Gingerdione (102)	
	[10]-Gingerdione (103)	
	[5]-Gingerol (91)	

Table 2-5 (Continued)

Botanical name	Chemical constituents	References
Zingiber officinale Roscoe.	Methyl [4]-shogaol	Jolad et al., 2005
	[12]-Gingerdione	
	Acetoxy-[4]-gingerol	
	Methoxy-[4]-gingerol	
	[4]-Gingerdiol	
	[8]-Gingerdiol	
	[10]-Gingerdiol	
	Methyl 5-acetoxy-[4]-gingerdiol	
	3-Acetoxy-[4]-gingerdiol	
	5-Acetoxy-[6]-gingerdiol	
	Methyl 5-acetoxy-[6]-gingerdiol	
	Diacetoxy-[4]-gingerdiol	
	Methyl diacetoxy-[4]-gingerdiol	
	5-Acetoxy-3-deoxy-[6]-gingerol	
	1-Hydroxy-[6]-paradol	
	6-Hydroxy-[8]-shogaol	
	[10]-Gingerdiol, cyclic methyl orthoester	
	[7]-gingerol	Ali et al., 2008