

Review

Thai medicinal plants: Potential sources of anti-cholangiocarcinoma drugs

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Accepted 04 March, 2013

Cholangiocarcinoma (CCA), the bile duct cancer, is a major public health problem in several parts of the world particularly in Southeast Asia. The incidence of CCA in northeastern Thailand is high. The most effective treatment is surgical removal in early stage patients. However most patients present to the hospital in advanced stage, which is inoperable. There is no standard chemotherapy regimen for advanced stage. The life expectancy after being diagnosed is 12 weeks. The existing chemotherapeutics are not effective. There is an urgent need to explore other effective agents to combat with this devastating disease. Several medicinal plants used in traditional medicine have been demonstrated to exhibit promising anti-CCA activities either in *in vitro* and/or *in vivo* models. These include triptolide from *Tripterygium wilfordii*, the ubiquitous tannic acid, *Atractylodes lancea* (Thunb) DC., *Zingiber officinale* Roscoe, Prasa-Prao-Yhai formulation, and curcumin, the pure compound isolated from *Curcuma longa* Linn. Their mechanisms of anti-CCA activities are either through direct activities on cancer cells (induction of apoptosis, stimulation of cell cycle arrest, and cytotoxicity, etc.) or through indirect activities through promotion of host immune system (inhibition of inflammation caused by liver fluke infection, inhibition of NF- κ B-regulated gene products expression involved in DNA damage, etc.). The candidate leads from these plants for CCA treatment are awaited. Their potential roles in CCA either when using alone or as adjunct therapy should be further investigated.

Keywords:Cholangiocarcinoma, anticholangiocarcinoma, medicinal plants, pure compound, chemotherapy Cholangiocarcinoma, anti-cholangiocarcinoma, medicinal plants, pure compound, chemotherapy.

INTRODUCTION

Cholangiocarcinoma (CCA), the bile duct cancer, is a major public health problem in several parts of the world particularly in Southeast Asia. High incidence of CCA is reported from the northeastern Thailand, where the liver fluke *Opisthorchis viverrini* is endemic (Sripa et al., 2011). Combination of liver fluke infection and nitrosamine is a risk factor of CCA in Thailand, whereas primary sclerosing cholangitis (PSC) is a common risk factor of CCA in other parts of the world. Most of the patients are asymptomatic and are presented to the hospitals in advanced stage, which limits its effective treatment. Surgery, liver transplantation, radiation therapy, photodynamic therapy and chemotherapy are commonly

applied treatment approaches for CCA. While surgery is a major choice, several patients are present with unresectable tumors. Liver transplantation is an alternative choice for these unresectable patients, but unfortunately, early recurrence rate of more than 50% with a 5-year survival of <35% to 45% has been reported (Aljiffry et al., 2009; Rosen et al., 2012). With regard to CCA chemotherapy, the goal is to control disease progression, prolong survival and improve quality of life rather than to achieve complete cure. Monotherapy with 5-fluorouracil (5-FU), the common chemotherapeutic drug is rather unsatisfactory, with the overall response rate and median survival of only 10% and 26 weeks, respectively (Falkson et al., 1984). Combination therapy using gemcitabine, 5-FU, oxaliplatin, docetaxel, irinotecan, cisplatin, or capecitabine provides less than one year survival with the maximum response rate of 50%

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Table 1. Medicinal plants and a herbal formulation which showed promising anti-CCA activities in the *in vitro* and/or *in vivo* models (Rh = Rhizome, Fl = Flower, St = Stem, Ba = Bark, Rt = Root, Fr = Fruits, Sd = Seed, and Lf = Leaves).

Family	Plant	Part used	References
Zingiberaceae	<i>Zingiber officinale</i> Roscoe.	Rh	Plengsuriyakarn et al., 2012a,b
Compositae	<i>Atractylodes lancea</i> (Thunb.) DC.	Rh	Plengsuriyakarn et al., 2012a,b
Zingiberaceae	<i>Curcuma longa</i> Linn.	Rh	Plengsuriyakarn et al., 2012a,b
Pra-Sa Prao-Yhai formulation (composition):			Plengsuriyakarn et al., 2012a,b
Compositae	<i>Artemisia annua</i> Linn.	Rh	-
Cruciferae	<i>Asclepias curassavica</i> Linn.	Fl	-
Dracaenaceae	<i>Dracaena loureiri</i> Gagnep.	St, Ba	-
Guttiferae	<i>Mammea siamensis</i> Kosterm	Fl	-
Guttiferae	<i>Mesua ferrea</i> Linn.	Fl	Mahavorasirikul et al., 2010
Myristicaceae	<i>Myristica fragrans</i> Houtt.	Sd	-
Myrtaceae	<i>Syzygium aromaticum</i> Linn.Merr. & L.M. Perry	Fl	-
Nelumbonaceae	<i>Nigella sativa</i> Linn.	id	-
Sapotadeae	<i>Mimusops elengi</i> Linn..	Fl	Mahavorasirikul et al., 2010
Umbelliferae	<i>Angelica dahurica</i> Benth.	Rt	-
Umbelliferae	<i>Angelica sinensis</i> (Oliv.) Diels	Rh	-
Umbelliferae	<i>Anethum graveolens</i> Linn.	Rt, Fr	-
Umbelliferae	<i>Cuminum cyminum</i> Linn.	Sd	-
Umbelliferae	<i>Foeniculum vulgare</i> Mill. var. dulce Alef.	Sd	-
Umbelliferae	<i>Ligusticum sinense</i> Oliv. cv. Chuanxiong	Rh	Mahavorasirikul et al., 2010
Zingiberaceae	<i>Amomum testaceum</i> Ridl.	Sd	-
Zingiberaceae	<i>Curcuma longa</i> Linn.	Rh	Prakobwong et al., 2011a,b
Zingiberaceae	<i>Kaempferia galangal</i> Linn.,	Lf	Mahavorasirikul et al., 2010

(Giuliani et al., 2006). Several factors contribute to such high failure rates following treatment with conventional chemotherapeutics. These include resistance of CCA to drugs and host-related factors. These necessitate the identification of resistance mechanisms and effective alternative chemotherapeutics including delivery methods for treatment of CCA.

Throughout history, natural products have afforded a rich repository of remedies with diverse chemical structures and bioactivities against several health disorders including cancer. Attempts have been made to identify candidate leads from natural products including those from bacteria, fungi, marine organisms, animals, and plants with promising anticancer activities. It is estimated that 122 drugs from 94 plant species have been discovered through ethnobotanical leads (Gao and Watanabe, 2011). Additionally, the use of herbs as complementary and alternative medicine has increased dramatically in the past decades. According to the World Health Organization (WHO), traditional medicines are relied upon by 65-80% of the world's population for their

primary health care needs (Gao and Watanabe, 2011). For cancer chemotherapy, plant-derived compounds or dietary phytochemicals have emerged as an accessible and promising approach to cancer control and management (Surh, 2003). A growing trend among cancer patients especially those living in the rural areas, is to combine conventional therapy with some forms of complementary therapy (Vapiwala et al., 2006). There are strong evidences supporting folkloric medicine, in particular those having a historical reputation as anticancer agents that represent promising candidates for chemotherapeutic research and development. Examples of plant-derived compounds that have been registered for use as anticancer drugs include vincristine, vinorelbine, etoposide, teniposide, paclitaxel, navelbine, taxotere, topotecan, and irinotecan (Dholwani et al., 2008). For CCA, a number of plant-extracted and plant-derived compounds have been investigated for their anticancer activities against CCA, notably triptolide from *Tripterygium wilfordii* (Tengchaisri et al., 1998), the ubiquitous tannic acid (Naus PJ, 2007), the ethanolic

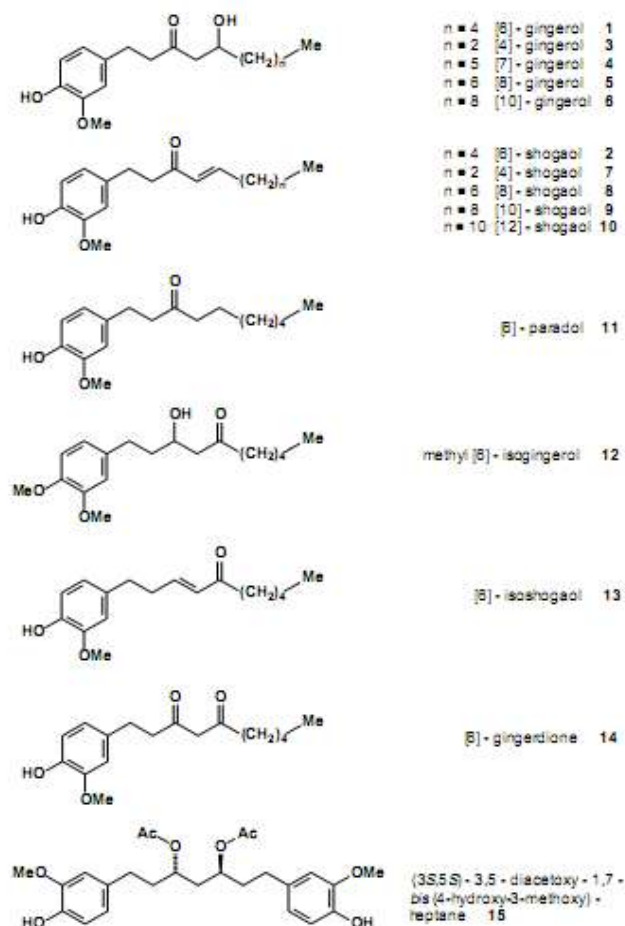


Figure 1. Major chemical components of *Zingiber officinale* Roscoe (Jolad et al., 2004).

extracts of *Atractylodes lancea* (Thunb) DC., *Zingiber officinale* Roscoe, Prasa-Prao-Yhai formulation, and curcumin, the pure compound isolated from *Curcuma longa* Linn. (Plengsuriyakarn et al., 2012a, b). This review focuses on the potential role of Thai medicinal plants in the treatment of CCA. Table 1 summarizes information on plants (including their parts used) which show promising anti-CCA activities in different *in vitro* and *in vivo* models.

Zingiber officinale Roscoe

Zingiber officinale Roscoe (ZO) in the family Zingiberaceae, is a herbaceous, rhizomatous perennial plant widely distributed throughout the tropical and subtropical regions. The rhizome of ZO, commonly known as ginger, is a common condiment for various foods and beverages, and is used in folk medicine in Asia and other tropical countries for various purposes such as for the relief of cold, fever, and for treatment of inflammation, rheumatic disorder, gastrointestinal discomfort, loss of appetite, motion sickness,

hypercholesterolemia, and high level of triglyceride (Chrubasik et al., 2005). The US Food and Drug Administration (FDA) recommends ginger as “generally recognized as safe” list, although it can interact with some medications such as warfarin (Wilkinson, 2000).

Chemical composition

The major composition of fresh ginger is gingerols (mostly in the form of [6]-gingerol), while that of dry ginger is shogaols (mostly in the form of [6]-shogaol). Other constituents include 3-dihydroshogaols, paradols, dihydroparadols, acetyl derivatives of gingerols, gingerdiols, mono- and di-acetyl derivatives of gingerdiols, 1-dehydrogingerdiones, diarylheptanoids, and methyl ether derivatives of these compounds (Jolad et al., 2004) (Figure 1).

Biological and pharmacological activities

The rhizome extracts (ethanolic and aqueous) of ZO and

their active components have been shown to possess several pharmacological and physiological activities including anti-inflammatory (Podlogar and Verspohl, 2012), anti-oxidant (Sabina et al., 2011), antimicrobial (Chen et al., 1985; Wang and Ng, 2005; Mostafa et al., 2011), analgesic (Ozgoli G, 2009), cardiovascular (Ghayur et al., 2005) and anti-ulcer (al-Yahya et al., 1989; Ko et al., 2010) activities. An oily extract of ZO was shown to possess anti-inflammatory activity in human bronchial epithelial cells (BEAS-2B cells) *via* its effect on lipopolysaccharide (LPS)-induced secretion of the pro-inflammatory chemokine interleukin 8 (IL-8), and RANTES (regulated upon activation, normal T-cell expressed and secreted) (Podlogar and Verspohl, 2012). The anti-oxidative effect of [6]-gingerol was reported to be through the depletion of anti-oxidant status in the liver of acetaminophen-intoxicated mice (Sabina et al., 2011). ZO and its active compounds were shown to exhibit antibacterial (*Escherichia coli*, *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus*, *Salmonella typhimurium*, *Proteus vulgaris*, *Staphylococcus aureus*, *Mycobacterium phlei*, *Streptococcus faecalis*, and *Bacillus cereus*), antifungal (*Botrytis cinerea*, *Fusarium oxysporum*, *Mycosphaerella arachidicola*, and *Physalospora piricola*), and antiparasitic (*Schistosoma mansoni*) (Chen et al., 1985; Wang and Ng, 2005; Mostafa et al., 2011) activities. Moreover, result from a double-blind comparative clinical trial conducted in primary dysmenorrheal students showed that ZO was as effective as mefenamic acid and ibuprofen in relieving pain (Ozgoli et al., 2009). The aqueous extract of ZO was shown to decrease blood pressure through a dual inhibitory effect mediated *via* stimulation of muscarinic receptors and blockade of calcium channels (Ghayur et al., 2005). In previous studies (al-Yahya et al., 1989; Ko et al., 2010), the gastroprotective effect of 50% ethanolic extract of ZO was assessed in rats in the ethanol- and acetic acid-induced ulcer models. It prevented the oxidative damage of the gastric mucosa by blocking lipid peroxidation, and by a significant decrease in superoxide dismutase and increase in catalase activity.

A number of mechanisms that may be involved in the chemopreventive activities of ZO and its components have been reported from a wide range of experimental models (Shukla and Singh, 2007). Several studies demonstrated their inhibitory activities on the production of nitric oxide, inflammatory cytokines and enzymes prostaglandin synthase, and arachidonate-5-lipoxygenase in a dose-dependent manner. The latter in turn, ZO has been shown to inhibit the synthesis of leukotrienes from both cyclo-oxygenase-1 (COX-1), cyclo-oxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX) (Srivastava and Mustafa, 1989; Grzanna et al., 2005). 5-LOX, COX-1, and COX-2 are the key enzymes involved in the metabolism of arachidonic acid, either to prostaglandins and thromboxanes or to leukotrienes, which play a central role in the regulation of different

physiological processes, but it also causes pain, inflammation, and hypersensitivity. ZO was also shown to produce a significant reduction of inflammation in animals compared to conventional drugs (Thomson et al., 2002; Young et al., 2005).

The potential roles in cholangiocarcinoma and other types of cancer


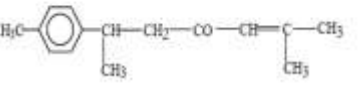




Several lines of evidence suggest that the pungent vallinoid of ZO, [6]-gingerol, is effective in the suppression of the transformation, hyperproliferation, and inflammatory processes that initiate and promote carcinogenesis, as well as the later steps of carcinogenesis, *i.e.*, the angiogenesis, and metastasis (Suzuki et al., 1997; Bode et al., 2001; Kim et al., 2005a; Kim et al., 2005b; Lee et al., 2008).

The anti-CCA activity of the crude ethanolic extract of ZO was investigated both *in vitro* and *in vivo* model. ZO inhibited cell viability, tube formation and cell invasion in the CCA cell line, CL-6 (Plengsuriyakarn et al., 2012b). ZO produced a significant tumor growth inhibition in CCA-xenografted nude mouse model by reducing tumor volume (by 35.8%), prolonging survival time (by 161.5%) and inhibiting pulmonary metastasis (by 50%) compared with the control group (Plengsuriyakarn et al., 2012a). Both [6]-gingerol and [6]-paradol exhibited antiproliferation activities in liver, pancreatic, prostate, gastric, and leukemic cancer cells (Lee and Surh, 1998; Chen et al., 2007; Shukla and Singh, 2007). Furthermore, [6]-shogaol was also shown to exhibit anticancer activity against breast cancer (inhibition of cell invasion by suppressing matrix metalloproteinase-9 expression *via* blockade of nuclear factor activation), antiproliferation activity (disruption of microtubule network of non-small lung epithelium cancer), and anti-invasion on human hepatocellular cell (Choudhury et al., 2010; Ling et al., 2010; Weng et al., 2010).

***Curcuma longa* Linn**

Curcuma longa Linn. (CUR) or turmeric belongs to the family of Zingiberaceae. Its active ingredient is curcumin that has a distinctly earthy, slightly bitter, slightly hot peppery flavor, and a mustardy smell. Its rhizome is ovate-oblong, pyriform, and often short-branched in shape (Eigner and Scholz, 1999). The orange powder, called "turmeric" has been in continuous use for its flavoring as a spice in both vegetarian and non-vegetarian food (Govindarajan, 1980). CUR has long been used as an herbal remedy for a variety of diseases and has been used in Indian and Chinese traditional medicine as early as 700 AD. Traditional Indian medicine claims the use of its powder against biliary disorders, anorexia, hepatic disorder, cough, rheumatism, coryza,

Table 2. Curcumin and its derivatives (Araújo and Leon, 2001).

Compounds	Chemical structure
Curcumin	
Ar-turmerone	
Methylcurcumin	
Demethoxy curcumin	
Bisdemethoxy curcumin	
Sodium curcumin	

diabetic wounds, and sinusitis (Ammon et al., 1992). In Chinese traditional medicine, CUR is used for treatment of abdominal pains (Govindarajan, 1980). Due to its vast number of biological targets and virtually no toxicity, CUR has achieved the potential therapeutic interest to cancer (Weisberg et al., 2008).

Chemical compositions

The major constituent of CUR is curcumin (diferuloylmethane) (Roughley and Whiting, 1973). Curcumin is soluble in ethanol, alkalis, ketone, acetic acid, and chloroform, but is insoluble in water with the melting point at 176-177°C and forms red-brown salts with alkali. Chemical structures of curcumin and derivatives are shown in Table 2 (Araújo and Leon, 2001).

Biological and pharmacological activities

The toxicity and carcinogenic properties of curcumin that is commonly added to food were evaluated in rats and mice and results showed that curcumin was not toxic to humans up to 8,000 mg/day when taken by oral route for 3 months (Cheng et al., 2001). On the contrary, the toxic effect of curcumin was demonstrated in hamster cells, of which it enhanced gamma-radiation-induced chromosome aberrations in Chinese hamster ovary cells (Araujo et al., 1999).

The chemopreventive effect of curcumin on DNA damage

in human normal cell but not in hepatoma G2 cells was reported (Cao et al., 2006). The anti-oxidant activity on lipid peroxidation of curcumin was investigated in rat liver microsomes, erythrocyte membranes, and brain homogenates (Reddy and Lokesh, 1994). Curcumin acted as an inhibitor of RANKL-induced NFATc1 which is a downstream event of NF-κB signal pathway through suppression of ROS generation (Moon et al., 2012).

The anti-inflammatory activities of curcumin were investigated in both acute and chronic models of inflammation. Results showed that the administration of curcumin significantly reduced the inflammatory swelling compared to control in rats with Freud's adjuvant-induced arthritis (Srimal and Dhawan, 1973). It also potentiated the anti-inflammatory activity of various COX inhibitors in the cotton pellet granuloma pouch model in rats (Nandal et al., 2009).

The immunosuppressive activity of curcumin has recently been reported to be through blocking of T-cell activation-induced Ca^{2+} mobilization, and preventing NFAT activation and NFAT-regulated cytokine expression (Kliem et al., 2012). Curcumin inhibited IFN-γ signaling in human and mouse colonocytes, including CII-TA, MHC-II genes (HLA-DRα, HLA-DPα1, HLA-DRβ1, and T cell chemokines (CXCL9, 10, and 11) (Midura-Kiela et al., 2012).

Curcumin exhibited antiprotozoal activity against *Leishmania amazonensis* with LD₅₀ (concentration that inhibits growth by 50%) of 24 μM (9 mg/ml). This observation supports results of the *in vivo* study in mice which showed 65.5% inhibition of the lesion size from the footpad of the animals when compared with the group

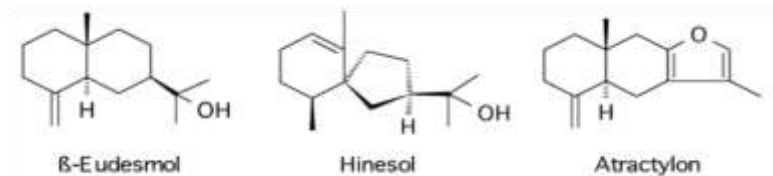


Figure 2. Chemical structures of the major constituents of *Atractylodes lancea* (Thunb.) DC. (State Administration of Traditional Chinese Medicine, 1995-6).

inoculated with the parasites alone (Araujo et al., 1998; Araujo et al., 1999).

Curcumin regulated the expression and activity of matrix metalloproteinases-9, and metalloproteinases-2 during preventing and healing of indomethacin-induced gastric ulcer (Swarnakar et al., 2005). Report of a subsequent Phase III clinical trial in patients with ulcerative colitis confirmed the ant-ulcer property of curcumin (Lahiff and Moss, 2011).

The potential roles in cholangiocarcinoma and other types of cancer

For cancer chemoprevention, several studies demonstrated that the CUR extract and curcumin prevented the occurrence and progression of several types of cancer (colon, lung, breast, liver, stomach, esophagus, skin, lymphomas, and leukemia) induced by various carcinogens in rodent models (Surh, 2003; Aggarwal et al., 2006; Lin, 2007). Significant reduction of inflammation, free radical generation and carcinogenesis was shown (Goel et al., 2008; Kunnumakkara et al., 2008).

For anti-CCA activities, curcumin reduced the aggregation of inflammatory cells surrounding the hepatic bile ducts in hamsters with opisthorchiasis at an early stage (Boonjaraspinyo et al., 2009). This was proposed to be related with a reduction in the risk of CCA. Furthermore, curcumin was shown to suppress the activation of transcription factors such as NF- κ B, signal transducer and activator of transcription (STAT-3), and activator protein (AP-1) (Aggarwal et al., 2006). The modulation of the NF- κ B expression by curcumin has been linked with oxidant-generating gene (inducible nitric oxide synthase; iNOS), anti-oxidant gene (extracellular superoxide dismutase; SOD3), nitrate DNA damage, cell proliferation inhibition, and periductal fibrosis reduction, resulting in a marked reduction of the virulence of OV in infected hamsters (Pinlaor et al., 2009, 2010). In addition, curcumin showed antiproliferative and apoptotic effects through activation of multiple cell signaling pathways in human CCA cell lines (Prakobwong et al., 2011a). Curcumin also exhibited an anticarcinogenic potential via suppression of pro-inflammatory pathways (through NF- κ B) involved in multiple steps of carcinogenesis through

CCA-hamster (Prakobwong et al., 2011b).

The anti-CCA activity of ethanolic extract (50%) of CUR was subsequently confirmed in human CCA cell line and CCA cell-xenografted nude mouse model (Plengsuriyakarn et al., 2012a,b). High dose of CUR significantly reduced tumor volume (by 40.5%), inhibited lung metastasis (by 60%) and prolonged survival time (by 160.8%) compared with control.

Atractylodes lancea (Thunb) DC

The dried rhizome of *Atractylodes lancea* (Thunb.) DC. (AL: “Khod-Kha-Mao” or “Cang Zhu”) in the family Compositae, is a common medicinal plant used in Thai and Chinese traditional medicine for treatment of rheumatic disease, digestive disorders, night blindness, and influenza (Xiao, 2002). It is spicy or pungent, bitter, warm, and aromatic. This plant acts on expelling the wind-cold from the superficial parts of the body, as well as the cold-dampness, and excessive fluids in spleen and stomach. It is therefore indicated for the diseases caused by dampness.

Chemical composition

The major constituents in the essential oils from the rhizome of AL are β -eudesmol, hinesol, and atractylon (Figure 2). Other minor constituents including atractylodin, atractylodinol, acetylactylodinol, and atractylenolide I-III are also reported (Zhang et al., 2011).

Biological and pharmacological activities

The rhizome extract of AL exhibited antihypertensive (at all dose levels), anti-ulcer (at all dose levels), anti-inflammatory (at high dose), and antipyretic (at high dose) activities (Plengsuriyakarn et al., 2012a). The observed significant anti-ulcer activity (96-98%) of AL confirms its used to improve stomach damage through its anti-ulcer (Kubo et al., 1983) and inhibitory activities on gastric secretion (Nogami et al., 1986). This anti-ulcer activity was more potent than the reference drug, omeprazole, given at the dose of 20 mg/kg body weight.

Table 3. Chemical structures of active constituents isolated from each components of PPF.

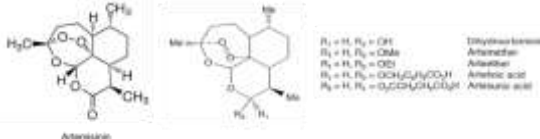
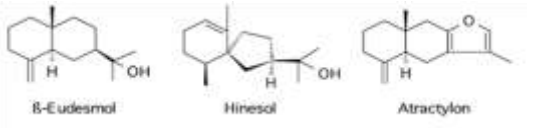
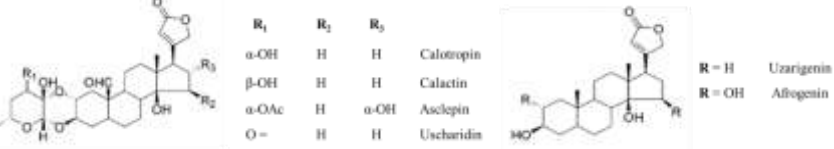
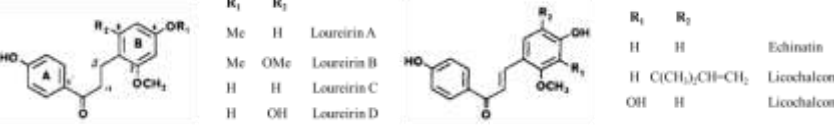
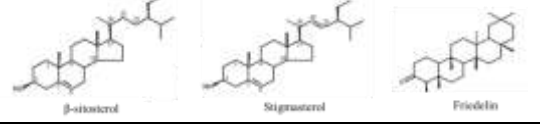
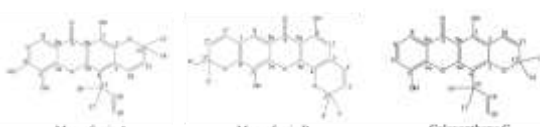
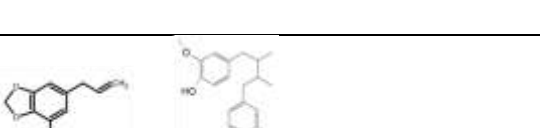
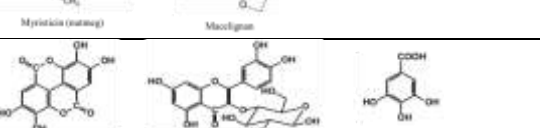
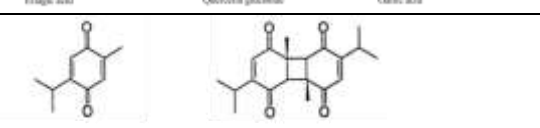
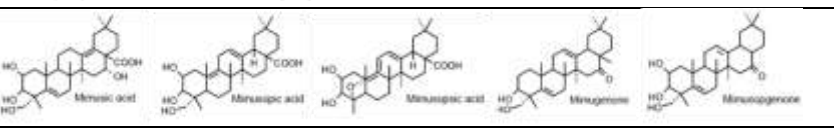
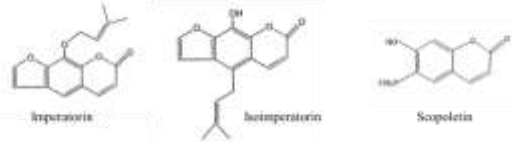

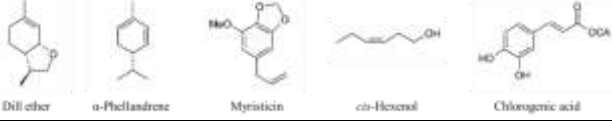

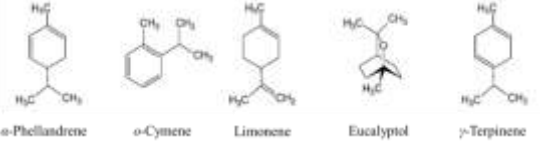
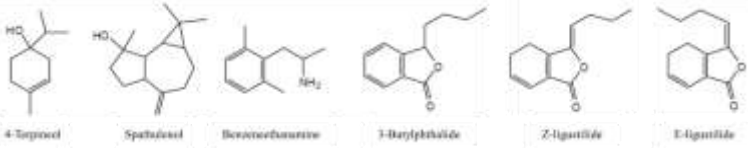

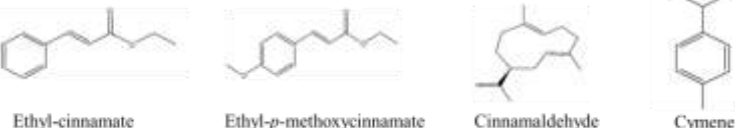
Medicinal plants	Major chemical constituent (s)
<i>A. annua</i> Linn. (Balint, 2001)	 <p> $R_1 = H, R_2 = OH$ $R_1 = H, R_2 = OMe$ $R_1 = H, R_2 = OEt$ $R_1 = H, R_2 = OCH_2CH_2CO_2H$ $R_1 = H, R_2 = O_2CCH_2CH_2CO_2H$ </p> <p> Tiliroside Anarsin Anarsin Anarsin Anarsin Anarsin </p>
<i>A. lancea</i> (Thunb.) DC. (State Administration of Traditional Chinese Medicine, 1995-6)	 <p>B-Eudesmol Hinesol Atractylon</p>
<i>A. curassavica</i> Linn. (Roy et al., 2005)	 <p> R_1 R_2 R_3 $\alpha-OH$ H H Calotropin $\beta-OH$ H H Calactin $\alpha-OAc$ H $\alpha-OH$ Asclepin $O =$ H H Uscharidin </p> <p> $R = H$ Uzargenin $R = OH$ Aflogenin </p>
<i>D. loureiri</i> Gagnep. (Meksuriyen and Cordell, 1988)	 <p> R_1 R_2 Me H Loureirin A Me OMe Loureirin B H H Loureirin C H OH Loureirin D </p> <p> R_1 R_2 H H Echinatin H $C(CH_3)_2CH=CH_2$ Licochalcone A OH H Licochalcone B </p>
<i>M. siamensis</i> Kosterm. (Subhadhirasakul and Pechpongs, 2005)	 <p>β-sitosterol Stigmasterol Fiedlin</p>
<i>M. ferrea</i> Linn. (Teh et al., 2011)	 <p>Mesaferin A Mesaferin B Calosanthone C</p>
<i>M. fragrans</i> Houltt. (Anggakusuma et al., 2010)	 <p>Myristicin (natural) Myristigon</p>
<i>S. aromaticum</i> (L.) Merr. & L.M. Perry (Atawodi et al., 2011)	 <p>Ellagic acid Quercetin glucoside Gallic acid</p>
<i>N. sativa</i> Linn. (Banerjee et al., 2010)	 <p>Thymoquinone Dithymoquinone</p>
<i>M. elengi</i> Linn. (Sahua et al., 2001)	 <p>Mursic acid Mursic acid Mursic acid Mursigenin Mursigenin</p>
Medicinal plants	Major chemical constituent (s)

Table 3. cont.

<i>A. dahurica</i> Benth. (Baek et al., 2010)	 <p>Isupatorin Isoperatorin Scopoletin</p>
<i>A. sinensis</i> (Oliv.) Diels. (Chao and Lin, 2011)	 <p>Ferulic acid Z-ligustilide E-butylidenephthalide Z-ligustilide dimer E-232</p>
<i>A. graveolens</i> Linn. (Bonnländer and Winterhalter, 2000)	 <p>Dill ether α-Phellandrene Myristicin cis-Hexenol Chlorogenic acid</p>
<i>C. cyminum</i> Linn. (Hajlaoui et al., 2010)	 <p>Cuminaldehyde o-Cymene</p>
<i>F. vulgare</i> Mill. var. dulce Alef (Shahat et al., 2011)	 <p>α-Phellandrene o-Cymene Limonene Eucalyptol γ-Terpinene</p>
<i>L. sinense</i> (Oliv.) cv. Chuanxiong (Tang et al., 2010)	 <p>4-Terpenol Spathulol Bornanibutanone 3-Barylphthalide Z-ligustilide E-ligustilide</p>
<i>A. testaceum</i> Ridl. (Sirata et al., 2001)	 <p>β-Pinene 1,8-Cineole</p>
<i>K. galanga</i> Linn. (Umar et al., 2011)	 <p>Ethyl-cinnamate Ethyl-p-methoxycinnamate Cinnamaldehyde Cymene</p>

The compound 2-[(2'E)-3',7'-dimethyl-2',6'-octadienyl]-4-methoxy-6-methyl phenol isolated from the rhizome of AL showed potent inhibitory effects on 5-LOX and COX-1 (Resch et al., 2001).

AL and its derivatives which contain α- and β-unsaturated carbonyl fragment, were found to be active against *Escherichia coli* and *Staphylococcus aureus* (Chen et al., 2012). The volatile oil from AL showed

strong antimicrobial activity against *Rhodotorula glutinis* and *Saprolegnia* (Wang et al., 2009).

The potential roles in cholangiocarcinoma and other types of cancer

Using MMT cytotoxic assay, Mahavorasirikul et al. (2011) demonstrated the promising cytotoxic activities of the

ethanolic extract (50%) of AL against CL-6 (CCA cell line), HepG2 (hepatocarcinoma cell line), and Hep2 (esophagus cancer) cells with high selectivity index comparing with the standard drug, 5-FU. In addition, the cytotoxic and inhibitory activities on cell invasion and tube formation were also demonstrated (Plengsuriyakarn et al., 2012b). The anti-CCA activity of the ethanolic extract (50%) of AL was investigated in human CCA xenografted-mouse model and results showed a significant reduction of tumor mass (by 97.3% of tumor volume), prolongation of survival time (by 208.5%), and inhibition of lung metastasis (by 95% of the total lung mass) compared with untreated control. It also showed virtually no toxicity with only minimal CNS effects on locomotor activity at the maximum dose of 5,000 mg/kg body weight (Plengsuriyakarn et al., 2012a).

Apart from CCA, AL also exhibited anticancer activities against melanoma, colon cancer, Dalton's lymphoma ascites (DLA), and Ehrlich ascites carcinoma (EAC) (Duan et al., 2008; Yan et al., 2010). β -eudesmol was found to significantly inhibit angiogenesis through the blockade of the ERK signaling pathway (Tsuneki et al., 2005).

Prasa-Prao-Yhai formulation

Pra-Sa-Prao-Yhai formulation (PPF) is the Thai traditional medicine which has been used for the treatment of fever in children (Chayamarit, 1995). This remedy consists of a mixture of various parts from 18 medicinal plants as summarized in Table 1. The roots and rhizomes of *Ligusticum* species, and *A. dahurica* Benth. have been used in the traditional Chinese medicine as an antipyretic and analgesic to treat colds, headaches, and toothaches (The Pharmacopoeia Commission of PRC, 2005).

Chemical composition

The chemical constituents of all of the 18 herbal components of PPF are shown in Table 3):

Biological and pharmacological activities

PPF and some of the isolated chemical constituents have been shown to possess various pharmacological activities in different *in vitro* and *in vivo* models. Apart from AL, anti-inflammatory activities were also demonstrated with *A. sinensis* (Han and Guo, 2012), *A. dahurica* Benth. (Lee et al., 2011), *M. elengi* Linn. (Purnima et al., 2010), *N. sativa* (Padhye et al., 2008), *S. aromaticum* (L.) (Tanko et al., 2008), *K. galangal* (Sulaiman et al., 2008), *D. loureiri* Gagnep (Likhitwitayawuid et al., 2002), *M. ferrea* Linn. (Ambasta, 1992), and *M. fragrans* Houtt. (Ozaki et al., 1989). The anti-inflammatory action of *M. fragrans* Houtt. (nutmeg) was shown to be due to the myristicin that it contains

(Ozaki et al., 1989). Anti-inflammatory effect of thymoquinone from the seed of *N. sativa* was shown to be a potent inhibitor of eicosanoid production, namely thromboxane B2 and leukotrienes B4, by inhibiting both COX-1, COX-2, and LOX-5 enzymes (Houghton et al., 1995). The ethanol fraction of *A. sinensis* (Oliv.) Diels and *A. dahurica* showed an anti-inflammatory effect through suppression of NF- κ B-dependent activity (Lee et al., 2011). Flavonoids and stilbenoids isolated from the stem wood of *D. loureiri* exhibited COX-1, and COX-2 inhibitory activities (Likhitwitayawuid et al., 2002). The anti-inflammatory activity by protection against dexamethasone-induced disorders was reported in the roots of *A. dahurica* Benth. (Song et al., 2005). Besides its potent anti-oxidant effect (Piao et al., 2004), the anti-inflammatory mechanisms of byakangelicin, the active component of *A. dahurica* Benth involve the inhibitory effect against compound 48/80-induced histamine release (Kimura and Okuda, 1997), tumour necrosis factor- α , and PGE2, through inhibition of COX-2 (Kang et al., 2007).

Previous studies demonstrated the analgesic activity of various components of PPF. These include *M. ferrea* Linn. (Hassan et al., 2007), *N. sativa* Linn. (Padhye et al., 2008), *M. elengi* Linn. (Purnima et al., 2010), *K. galangal* (Sulaiman et al., 2008), *A. dahurica* Benth. (Kang et al., 2008), *M. fragrans* Houtt. (Sonavane et al., 2001), *L. sinense* (Gao and Xu, 2010), and *S. aromaticum* (Tanko et al., 2008). The analgesic activity of PPF was found to be centrally acting. The antinociceptive effects of *N. sativa* oil and the active compound thymoquinone were through indirect activation of the superspinal μ 1 and kappa opioid receptors (Khanna et al., 1993; Abdel-Fattah et al., 2000). Promising antipyretic activity was observed with *A. dahurica* Benth. (Li et al., 1991). The seeds of *N. sativa* also exhibited an antihypertensive property (Padhye et al., 2008).

The potential roles in cholangiocarcinoma and other types of cancer

The cytotoxic activity of the ethanolic extract (50%) of PPF against the CCA cell, CL-6 was investigated using MTT, calcein-AM, and Hoechst assays (Plengsuriyakarn et al., 2012b). The cytotoxic activity against CL-6 was attributed to the activities of the two components of PPF: *M. elengi* Linn. (flower) (IC_{50} = 48.53 μ g/ml), and *K. galangal* ("Proh hom" in Thai; leaf) (IC_{50} = 37.36 μ g/ml) (Mahavorasirikul et al., 2010). In addition, dihydroartimisinin, one of the derivatives of *A. annua* Linn. was also shown to exhibit potent cytotoxic activity against CL-6 and Hep-G2 cell lines, with IC_{50} values of 75 and 29 μ M, respectively (Chaijaroenkul et al., 2011). Moderate anti-CCA activity of PPF was demonstrated in xenografted mouse model, of which the tumor volume was reduced by 21.2%, and the survival time was prolon-

ged by 174% compared with the untreated group. Inhibition of lung metastasis occurred on average 60% of total lung mass (Plengsuriyakarn et al., 2012a).

Other medicinal plants

Apart from ZO, AL, CUR, and PPF, several plants and isolated compounds have been reported for their potential roles in CCA. These include *Thunbergia laurifolia* Linn., *Garcinia hanburyi* Hook.f., *Kaemperia parviflora* Wall. Ex Baker, sho-saiko-to, tannic acid, triptolide, and cepharanthine (Yano et al., 1994; Tengchaisri et al., 1998; Marienfeld et al., 2003; Leardkamolkarn et al., 2009; Hahnvajanawong et al., 2010; Seubwai et al., 2010; Wonkchalee et al., 2012).

Thunbergia laurifolia Linn. (family Acanthaceae), commonly known in Thailand as “Rang Chuet”, is used as an antipyretic and detoxifying (as an antidote for poisons) activities (Kanchanapoom et al., 2002). Its leaf was shown to exhibit anti-oxidant (Oonsivilai et al., 2001) and anticancer properties in leukemia cells *via* induction of cell-cycle arrest (Ruela-de-Sousa RR, 2010). The anti-oxidant, anti-inflammatory and anti-CCA properties of *T. laurifolia* were demonstrated in Syrian hamsters infected with the human liver fluke *O. viverrini*. (Wonkchalee et al., 2012).

Garcinia hanburyi Hook.f. (family Guttiferae), known in Thai as “Rong” is used as a purgative and for treatment of infected wounds (Saralamp et al., 1996). The gambogic acid, derived from the gamboges resin of *G. hanburyi* has been shown to induce apoptosis in human gastric carcinoma cells (Zhao et al., 2004). For anti-CCA property, four fractions of xanthones isolated from *G. hanburyi* were shown to inhibit proliferation and induction of apoptosis in CCA cell lines by down-regulating Bcl-2 protein and up-regulating Bax and AIF protein, and activating caspase-9 and -3 and DNA fragmentation (Hahnvajanawong et al., 2010).

Kaemperia parviflora Wall. Ex Baker (family Zingiberaceae), known in Thai as “Krachaidum”, is used to enhance sexual ability, relieve of pain, and alleviate abdominal discomfort (Churdboonchart, 2000). Its major constituents are polyphenolic flavonoids (Sutthanut et al., 2007) which possess several pharmacological activities including anti-inflammatory, antibacterial, antimutagenic, anti-oxidant, and antithrombotic effects (Bors and Saran, 1987; Fotsis et al., 1997; Robak et al., 1988). The flavonoids component in *K. parviflora* Wall. Ex Baker extracts was shown to exhibit anticancer activity against chronic-parasitic and non-parasitic types of CCA cells, with potent anti-invasion effect, apoptosis induction with subsequent induction of irreversible cell death program (Leardkamolkarn et al., 2009). Its extract and isolated constituents caused apoptotic nuclei in CCA cell lines. In addition, they significantly increased caspase-3 activity, which signaling and subsequent promoting apoptotic cell death in a common pathway of cytotoxic drug exposure.

Sho-saiko-to, the formulation of 7 medicinal plants, *i.e.*, *Bupleuri radix*, *Pinelliae tuber*, *Scutellariae radix*, *Zizyphi fructus*, *Ginseng radix*, *Glycyrrhizae radix*, and *Zingiberis rhizoma*, is a herbal supplement to enhance liver health both promoting liver regeneration and preventing liver injury in Japan (Shimizu, 2000). It is widely used in Japan in patients with chronic hepatitis and cirrhosis; it plays a chemopreventive role in the development of hepatocellular carcinoma in cirrhotic patients (Shimizu, 2000). For CCA, sho-saiko-to formulation exerts its inhibitory effect on CCA cell proliferation in an *in vitro* model. It induced apoptosis and cell cycle arrest in the early period of the exposure and also induced cell cycle arrest at the G₀/G₁ phase in the late period of the exposure (Yano et al., 1994).

Tripterygium wilfordii (family Celastraceae), is a climbing vine used in traditional Chinese medicine for treatment of fever, chill, edema and carbuncle (Bao and Dai, 2011). Recently, *T. wilfordii* has been investigated for its clinical application for treatment of rheumatoid arthritis, chronic hepatitis, chronic nephritis, ankylosing spondylitis, polycystic kidney disease, and several skin disorders (Zhen et al., 1995). Its major constituent is triptolide which showed *in vitro* and *in vivo* activities against models of polycystic kidney disease and pancreatic cancer (Leuenroth et al., 2007). Several lines of evidence support the anti-CCA activity of triptolide. Tengchaisri et al. (1998) demonstrated the effective inhibition on tumor growth in hamsters against CCA both *in vitro* and *in vivo*. The combination triptolide and TRAIL enhanced cytotoxic and apoptotic activities in resistant cell lines through activation of caspase-8 and down-regulation of anti-apoptotic factors (Mcl-1 and cFLIP (Panichakul et al., 2006; Clawson et al., 2010). In addition, the combination also decreased cell viability through increasing of Annexin-V, PARP cleavage and caspase-3 activity and decreasing of XIAP expression in dose-dependent manner (Panichakul et al., 2006; Clawson et al., 2010).

Tannic acid is a plant-derived polyphenol compounds widely found in food and broadly applied to various industrial food additives (Chung et al., 1998). It promotes chemopreventive activity on skin tumor in hairless mice by ≤70% (Gali-Muhtasib et al., 2000). Furthermore, it induced apoptosis in human oral squamous cell carcinoma and salivary gland cancer cell lines (Yang et al., 2000). The anti-CCA activity of tannic acid was demonstrated both *in vitro* and *in vivo*. Marienfeld et al. (2003) reported that tannic acid inhibited proliferation of malignant human cholangiocytes *in vitro* and reduced the growth rate of Mz-ChA-1 CCA xenografts in athymic BALB/c mice following the administration of water containing 0.05% tannic acid. In addition, it was also demonstrated to produce synergistic effect on the cytotoxic activity of conventional chemotherapeutic drugs in human CCA through the modulation of drug efflux pathways (Naus et al., 2007).

Cepharanthin, a biscochlorine alkaloid extracted from the roots of *Stephania cepharantha* Hayata, is widely used in Japan for treatment of acute and chronic diseases (Kimoto et al., 1997). It is known to possess anti-inflammatory, anti-allergic, and immunomodulatory activities and hence is used for chemoprevention and treatment of many diseases. Furthermore, cepharanthin produced anticancer activities in various cell types through cell cycle arrest, cell proliferation inhibition, pro-apoptotic actions, as well as cell invasion inhibition (Bun et al., 2009).

Its cytotoxic activity against human CCA cell line and inoculated-mice was also demonstrated to be through activation of apoptosis as a result of inhibition of NF- κ B activation (Seubwai et al., 2010). Cepharanthin induced apoptosis in CCA cells via activation of caspase-3 and caspase-9, inhibition of nuclear translocations of NF- κ B (p50, p52, and p65), and suppression of tumor growth in CCA-inoculated mice, as well as reduction of tumor growth of patient tissues as determined by histo-culture drug response assay (Seubwai et al., 2010).

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