Therapeutic Potential and Pharmacological Activities of *Atractylodes lancea* (Thunb.) DC.

Running Title: Pharmacology of *Atractylodes lancea* (Thunb) DC**.**

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Abstract

The rhizome of *Atractylodes lancea* (Thunb.) DC. (AL) is extensively used in Chinese, Thai, and Japanese traditional medicines as crude extracts/decoctions or a component in various herbal formulations. Various pharmacological activities of AL and its major constituents have been demonstrated *in vitro*, *ex vivo*, and in animal models. Results from the toxicity studies in animal models suggest safety profile of AL and its active constituents. Despite extensive use with positive impression in many diseases, there has not been a clinical study that can conclusively support its efficacy and safety profile in human. This review comprehensively summarizes current information on the pharmacological activities of AL and their active constituents including anticancer, anti-inflammatory, antimicrobial and antipyretic activities, as well as activities on central nervous, cardiovascular, and gastrointestinal systems.

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1. Introduction

According to the World Health Organization (WHO) report in 2011 [1], traditional medicine addresses up to two-third of the world's population's primary health care needs. One major component of traditional medicine is the use of herbal medicine. A common issue of herbal medicine is the limitation of information on their pharmacological activities and their constituents. Traditionally, the use of herbal medicine was based on empirical treatment and then passed on from generation to generation. In the past 20 years, there were more studies on pharmacological activities and the constituents of many herbal medicines, but the information is often published in local journals and is not extensively disseminated. The limited access to these information prevented many herbal medicines from being developed to their full potential.

The rhizome of *Atractylodes lancea (Thunb.) DC.* (AL) has been used widely in many countries for various indications. This compound is called "Cangzhu" in China, "Khod-Kha-Mao" in Thailand, and "So-jutsu" in Japan. In Chinese traditional medicine, this rhizome is used extensively for the treatment of several diseases such as rheumatic diseases, digestive disorders, night blindness, and influenza. These traditional uses are explained by the compound's ability to eliminate dampness, strengthen the spleen, expel wind-cold from the superficial parts of the body, and clear away the common cold [2]. In Thai traditional medicine, the dried rhizome of AL has been used to treat fever and the common cold [3]. Moreover, it has also been used as a component in Thai traditional medicine in order to relieve gastrointestinal symptoms including dyspepsia, flatulence, nausea, and noninfectious diarrhea. In Japan, the rhizome of AL is a component in several Kampo medicines, *e.g*., Juzen-taiho-to [4] and Saireito [5,6].

History of extensive use of this herb in mankind has facilitated the development of this herb to its full therapeutic potential. This has brought about this review article, whose purpose is to aid the readers in gaining a better understanding of the potential and toxicity of this medicinal plant and to contribute to appropriate decision-making in further development of AL. This review article will focus on the pharmacological activities of the crude extract of AL rhizome including its major constituents: β-eudesmol, hinesol, atractylone and atractylodin [7-9].

2. The pharmacological activities of *Atractylodes lancea* (Thunb.) DC.

2.1 Anticancer activities

Several conventional anticancer drugs being used in patients with cancers are derived from plants. These include Vinblastine, Vincristine, Etoposide, Teniposide, Paclitaxel, Vinorelbine, Docetaxel, Topotecan, and Irinotecan, all of which have been approved by the US Food and Drug Administration [10]. Moreover, there are several herbal medicines of which their promising anticancer activities were demonstrated in laboratory experiments and clinical trials [11]. Recently, it appears that the rhizome of AL is a promising candidate herbal plant for further development as anticancer drugs, particularly as an alternative treatment in patients with cholangiocarcionma (CCA), the cancer of bile duct.

The anticancer activities of AL particularly anti-CCA have been demonstrated in several studies both *in vitro* and *in vivo*. Of a total of 28 plants and 5 herbal formulations used in Thai traditional medicine investigated for their cytotoxic activities, the crude ethanolic extract of AL rhizome was shown to exhibit the most potent and selective

activity against CCA cell line (CL-6) with IC_{50} (concentration which inhibits cell growth by 50%) of 24.09±3.40 (mean±SD) µg/ml and SI (selectivity index) of 8.6 [12]. Results of the *in vitro* screening of tumoricidal properties of international medicinal herbs conducted in the United States also confirmed the anticancer activity of AL in murine neuroblastoma cells originally derived from a spontaneous malignant tumor with moderate to strong activity with LC_{50} (50% lethal concentration, the concentration which causes 50% cell death) of 0.704 mg/ml [13]. These two studies have caught researchers' attentions to further investigate the anticancer property of AL. Based on calcein-AM and Hoechst 33342 assays, the cytotoxic activity of the ethanolic extract of AL against CL-6 was found to be more potent and more selective than the standard anticancer 5-fluorouracil (5-FU) [14]. Additionally, AL also exhibited significant inhibitory effects on clonogenic survival, tube formation, and invasion of CL-6 cells through a basement membrane model in a dose-dependent manner. However, this compound did not significantly exhibit antioxidative activity determined by the radical-scarvenging activity of 2,2-diphenyl-1-picrylhydrazyl radical (DPPH). With regards to antitumoric property of AL in animal models, the ethanolic extract at the concentrations of 1,000, 3,000, and 5,000 mg/kg body weight significantly inhibited tumor growth in CCA-xenografted nude mice [15]. The tumor size of AL-treated group was reduced to about 10% of that in the control group on day 40 after treatment (mean±SD: tumor volumes: 550±13 and 20,661±126 mm^3 for AL-treated and control group, respectively). At the highest dose of 5,000 mg/kg body weight, AL significantly inhibited lung metastasis by about 95%, while in the control group lung metastasis accounted for about 90% of total lung mass. All dose levels provided about 2-fold prolongation of the survival time of mice compared with the control group (mean±SD: 83.3±0.88 and 40.0±0.57 days in AL-treated and control group, respectively).

Lines of evidence have suggested that either anti-angiogenic or apoptotic-related activity or both, might at least in part contribute to cytotoxic activity of AL. Tsuneki *et al*. [16] investigated the anti-angiogenic activity of β-eudesmol, the main constituent of AL, both *in vitro* and *in vivo*. The proliferation of various endothelial cells including porcine brain microvascular endothelial cells (PBMEC) derived from cerebral microvessel, human dermal microvascular endothelial cells (HDMEC) derived from peripheral microvessels, and human umbilical vein endothelial cells (HUVEC) derived from peripheral veins, were markedly inhibited by β-eudesmol at concentrations ranging from 50 to 100 μM. Moreover, β-eudesmol also showed a broad spectrum of anti-angiogenic effects not only on blockade of the phosphorylation of extracellular signal-related kinase (ERK) 1/2 induced by basic fibroblast growth factor (bFGF) or vascular endothelial growth factor (VEGF), but also on prevention of endothelial tube formation and inhibition of cell migration stimulated by bFGF. In animal model, β-eudesmol significantly inhibited angiogenesis of subcutaneously implanted Matrigel plugs in mice and adjuvant-induced granuloma in mice [16]. These results were consistent with the observations by Ma *et al*. [17], showing an inhibitory effect of β-eudesmol (50-100 μM) in HUVEC induced by VEGF and bFGF. Apart from HUVEC, Hela (human cervical cells), the proliferation of SGC-7901 (human gastric cancer cells), and BEL-7402 (human liver cancer cells) were also inhibited by β-eudesmol (10-100 μM) in a time- and dose-dependent manner. Furthermore, β-eudesmol (2.5-5 mg/kg) significantly inhibited tumor growth in mice implanted with H_{22} and S_{180} tumor cells and also obviously inhibited vascular index (calculated by carmine content in the tumor tissues divided by tumor tissue weight) [17]. Recently, Zhao *et al.* [18] demonstrated that AL extract inhibited the growth of human gastric cancer cells in a dose- and time-dependent manner, and proposed that the cytotoxic mechanism of AL was related to apoptosis and cell cycle arrest through

mitochondria-dependent and death receptor-dependent apoptotic pathways. Further investigation should be focused on the mechanism of action of anticancer property of AL in CCA, identification of its active constituents, as well as confirmation of its clinical efficacy and safety in CCA patients.

2.2 Pharmacological activities on nervous system

Although neither serious adverse effect on central nervous system (CNS) nor any morbidity has been reported in human so far, the use of AL in human should be with caution in patients with nervous problems due to its various effects on nervous system. The pharmacological activity of the rhizome extract of AL on central nervous system has been demonstrated in various animal models with regards to its effects on general behavior and spontaneous movement, anti-electroshock convulsion, and potentiation of hypnotic action of hexobarbital sodium [19]. AL extract at the highest dose of 5,000 mg/kg body weight significantly interfered with muscle relaxation in mice similar to that produced by the reference drug diazepam (4 mg/kg body weight) [15]. The acetone extract of AL rhizome also showed an anti-anoxic effect in potassium cyanide (KCN)-induced anoxia in mice [20]. Nine out of ten (90%) mice treated with the AL extract at the dose of 1,500 mg/kg body weight survived, while none in the control group survived (0/10: 0%). The anti-anoxic action of AL rhizome extract was shown to be due mainly to its active constituent β-eudesmol. Six out of ten mice (60%) treated with β-eudesmol at the dose of 300 mg/kg body weight survived, whereas none in control group survived (0/10: 0%).

The effect on post-synaptic neuromuscular junction (NMJ) of β-eudesmol was shown to be primarily through the blockage of nicotinic acetylcholine receptors (nAChR) *via* accelerated desensitization [21-23]. The potentiating effect of β-eudesmol on NMJ

was greater in diabetic than in normal muscles [24,25]. β-eudesmol has been proposed as a promising compound for potentiating neuronal function. It was shown to induce neurite outgrowth from rat pheochromocytoma cells (PC-12) *via* mitogen-activated protein kinase (MAPK) activation [26].

2.3 Pharmacological activities on cardiovascular system

AL extract at the dose levels of 1,000, 3,000, and 5,000 mg/kg body weight significantly reduced the heart rate of rats, but only the highest dose (5,000 mg/kg body weight) significantly decreased both systolic and diastolic blood pressure [15]. However, the mechanism of the anti-hypertensive effect of AL is still unknown. The anti-platelet activity of AL has been demonstrated in collagen-induced platelet aggregation model [27]. Since it did not inhibit adrenaline/ADP- or adrenaline/5-HT-induced platelet aggregation, its mechanism of action has been thought to be *via* suppression of collagen-induced signal pathway, the upstream of the release of thromboxane A2 (TXA2) from platelets. Altogether, results suggest that care should be taken when using AL extract or its active constituents in patients with platelet disorders or coagulopathy.

2.4 Pharmacological activities on gastrointestinal system

The pharmacological effects of AL and its constituents on gastrointestinal system support their clinical use for alleviation of digestive symptoms in traditional medicine. AL extract has been shown to delay gastric emptying and stimulate small intestinal motility. The mechanisms of its action on these activities could be through either the inhibition of both dopamine D2 and 5-HT3 receptors [28], or activation of vagal tone and inhibition of corticotropin-releasing factor (CRF) [29]. The main activity was shown to be due to the atractylodin component [30].

AL extract at the dose levels of 1,000, 3,000, and 5,000 mg/kg body weight produced an anti-ulcer effect at similar potency as the reference drug omeprazole given at a dose of 20 mg/kg body weight [15]. Results from a previous study in pylorus-ligated rats suggest that the mechanism of action of AL extract on anti-ulcer activity might be mediated through inhibition of gastric secretion and reduction of effects on histamine-induced ulceration and stress-induced ulceration [31]. β-eudesmol is thought to be an active compound which exerts inhibitory effect on gastric secretion stimulated by histamine. The compound could prevent gastric ulceration as effectively as cimetidine at the same dose level (10 mg/kg body weight) [32]. Apart from β-eudesmol, the anti-ulcer activity of AL was also shown with hinesol, another main constituent in AL extract at the dose of 100 mg/kg body weight. Further investigation should be performed to elucidate the mechanisms of action of AL and its constituents on gastrointestinal system.

2.5 Other pharmacological activities

The anti-inflammatory activity of AL might be due to the contribution of several of its active constituents through various mechanisms. The lipophilic extract from AL rhizome exhibited potent inhibitory effect against 5-lipoxygenase (5-LOX) and cyclooxygenase-1 (COX-1) with IC_{50} of 2.9 and 30.5 µg/ml, respectively [33]. Isolated compound that exhibited potent inhibitory activities against both enzymes was shown to be atractylochromene (IC_{50} for 5-LOX and COX-1 = 0.6 and 3.3 µM, respectively). Despite relatively low potency on COX-1 (IC_{50} = 64.3 µM), quinone, another isolated compound, showed a selective inhibitory activity against 5-LOX (IC_{50} = 0.2 µM). Atractylone also exhibited inhibitory effects against 5-LOX but with potency about 100-fold lower than quinone (IC_{50} = 25.1 µM). The study conducted by Seo *et al*. [34] demonstrated that the anti-inflammatory effect of β-eudesmol was *via* regulation of interleukin (IL-6) production and expression through regulation of the p38 MAPK and

nuclear factor (NF)-κB. In addition, it also suppressed receptor-interacting protein 2 (RIP2)/caspase-1 activation induced by phorbol 12-myristate 13-acetate calcium ionophore A23187 (PMACI).

The antimicrobial activity of AL against various micro-organisms has been demonstrated in various studies including *Staphylococcus aureus* [35], *Escherichia coli* [35,36], *Saccharomyces cerevisiae*, and *Candida albicans* [36]. Moreover, the growth of some fungi species, such as *Rhodotorula glutinis* and *Saprolegnia*, was also inhibited by the volatile oil extract of AL. The activity on *Rhizopus* and *Absidia* was however, relatively weak [37].

Although AL extract did not produce any significant central or peripheral analgesic effects, it was shown to produce an antipyretic effect at a dose of 5,000 mg/kg body weight in the rat model [15]. This antipyretic activity supports its use for relieve fever and cold as indicated in Thai traditional medicine.

3. Safety profiles of *Atractylodes lancea* (Thunb.) DC.

AL rhizome showed safety profiles in various animal models. Following administration of AL extract at the high dose level of 5,000 mg/kg body weight in rats and mice, no significant toxicity except stomach irritation and general CNS depressant signs (reduced alertness and locomotion and diminished response to touch and balance) was observed [15]. Results from the acute and subacute toxicity tests both in rats and mice indicated safety profiles of AL in a broad range of dose levels (1,000-5,000 mg/kg body weight).

Several clinical studies of AL have been conducted in patients with different diseases/symptoms using AL in the forms of various formulations [4,38-41]; however, there has been no clinical study conducted using AL extract or its major constituents alone. This thus signifies the needs for further investigations in clinical trials to prove their clinical efficacy and safety profiles in humans. Despite the lack of clinical studies to directly support its safety in human, available information has indicated no serious adverse event when they were administered in humans. Ayurved Siriraj herbal recipe Chantaleela which consists of 60.6 mg AL in each tablet (250 mg/tablet) was administered to healthy male and female volunteers at the dose of 545.4 mg of AL/day for 1 day (divided into 3 doses, administered every 8 hours). No adverse event was observed in any subject for 10 days follow-up [42]. Moreover, observational study conducted in China showed a safety profile of “Fufang Cangzhu Tang”, a Chinese herbal formula which contains 15 g Atractylodes rhizome decocted into 300 ml of liquor and separately administered orally twice a day for 8 weeks in 32 senile patients with obesity or overweight complicated with impaired glucose tolerance [43].

4. Conclusion

AL rhizome has been shown to exhibit various pharmacological activities including anticancer activities, activities on nervous and gastrointestinal systems, as well as anti-hypertensive, anti-platelet, anti-ulcer, anti-inflammatory, antimicrobial, and antipyretic activities. Despite extensive use with positive impression, there has not been a clinical study that can conclusively support its efficacy and safety profile. Further investigations should focus on the application of AL in patients with different diseases/symptoms. In

addition, more investigation is required to identify the specific mechanisms of certain pharmacological activities, including anticancer activities of AL, and its active constituents.

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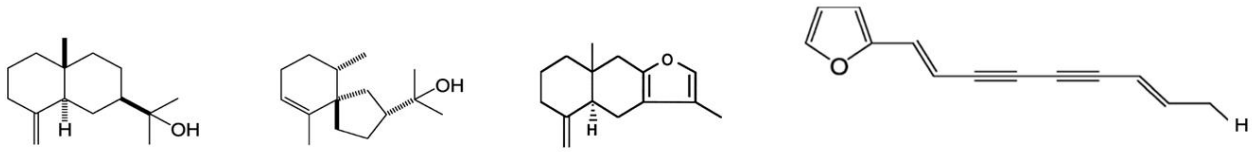
363 Figure 1.The chemical structures of major components of *Atractylodes lancea* (Thunb.)

364 DC.



β-eudesmol Hinesol Atractylone Atractylodin

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Table 1. The pharmacological activities of *Atractylodes lancea* (Thunb.) DC. and its compounds

Pharmacological activity	Model		Active ingredient	Mechanism of action	Reference
Anti-tumour activities					
Cytotoxic activity	In vitro	50% Ethanol extract 50 µg/ml			[12]
	In vitro	50% Ethanol extract 50 µg/ml			[14]
	In vitro	Petroleum ether fraction, ethyl acetate fraction, n-butanol fraction, and water fraction of AL 0.0625-1 mg/ml		- Induction of cell apoptosis via the mitochondrial pathway	[18]
	In vitro	100% Ethanol extract 5 mg/ml			[13]
	In vitro		Prenylated		[44]

			dihydrobenzofuran derivative		
Anticancer activity	Mice	50% Ethanol extract 1,000-5,000 mg/kg			[15]
Anti-angiogenic activity	In vitro	β-eudesmol 50 and 100 μM	β-eudesmol	- Inhibition of the endothelial cell proliferation - Suppression of DNA synthesis - Inhibition of endothelial cell migration - Inhibition of tube formation by endothelial cells - Blockage of bFGF- and VEGF-induced ERK1/2 activation (only at the concentration of 100 uM) - Inhibition of phosphorylation of CREB induced by VEGF in the growth factor signaling pathway	[16]

	Mice	β-eudesmol 0.90 µmol/kg	β-eudesmol		[16]
	In vitro	β-eudesmol 50 and 100 µM	β-eudesmol	- Inhibition of the growth factor signaling pathway by depressing activation of ERK-MAPK - Suppression of CREB activation in growth factor signaling pathway	[17]
	Mice	β-eudesmol 2.5-5 mg/kg	β-eudesmol		[17]
	In vitro	50% Ethanol extract 25-100 µg/ml			[14]
Anti-clonogenic activity	In vitro	50% Ethanol extract 12.5-50 µg/ml			[14]
Inhibitory activity on cell invasion	In vitro	50% Ethanol extract 12.5-150 µg/ml			[14]
Pharmacological activities on nervous system					

NMJ blocking activity	Ex vivo	β-eudesmol 200 µM	β-eudesmol	- Blockade of nicotinic ACh receptors by accelerating the desensitization of the nicotinic ACh receptor	[21]
	Ex vivo	β-eudesmol 20 µM	β-eudesmol	- Blockade of closed state of nicotinic ACh receptors by accelerating the desensitization of the nicotinic ACh receptor	[23]
	Ex vivo	β-eudesmol 20 µM	β-eudesmol	- Depression of the regenerative release of ACh during repetitive stimulation	[22]
	Ex vivo	β-eudesmol 80 µM	β-eudesmol		[25]
CNS activity on neuronal differentiation	In vitro	β-eudesmol 100 and 150 µM	β-eudesmol	- Induction of neurite outgrowth mediated by MAPK activation	[26]
Anti-anoxic activity	Mice	β-eudesmol 300 mg/kg	β-eudesmol		[20]

Motor coordination impairment	Mice	50% Ethanol extract 5,000 mg/kg		[15]
CNS depressant activity	Mice	Benzene extract 200-1,000 mg/kg		[19]
Pharmacological activities on cardiovascular system				
Anti-hypertensive activity	Rats	50% Ethanol extract 5,000 mg/kg		[15]
Anti-platelet activity	In vitro	Crude extract 30-1,000 µg/ml	- Inhibition of collagen-induced signal pathway, which is upstream of the release of TXA2 from platelets	[27]
Pharmacological activities on gastrointestinal system				
Anti-ulcer activity	Rats	50% Ethanol extract 1,000-5,000 mg/kg		[15]

	Rats	Benzene extract 500 mg/kg			[19]
	Rats	50% Methanol extract 200 mg/kg		- Inhibition of gastric secretion by histamine H2-receptor blocking	[31]
	Rats	β-eudesmol 50 mg/kg	β-eudesmol	- Inhibition of gastric secretion by histamine H2-receptor blocking	[32]
	Rats	Hinesol 100 mg/kg	Hinesol	- Inhibit gastric secretion by unknown mechanism	[32]
Improvement of the delayed gastric emptying	Rats	Ethanol extract 30-120 mg/kg		- Inhibition of the CRF release - Activation of vagal pathway - Involvement in the release of gastrointestinal hormones such as motilin, gastrin and somatostatin	[29]

	Rats	Water extract 250 mg/kg and Atractylodin and its derivatives 0.1-0.3 mg/kg	Atractylodin and its derivatives		[30]
Intestinal motility stimulation	Mice	Water extract 500-1,000 mg/kg and β-eudesmol 50-100 mg/kg	β-eudesmol	- Inhibition of the dopamine D2 receptor and the 5-HT3 receptor	[28]
Other pharmacological activities					
Anti-inflammatory activity	Rats	50% Ethanol extract 5,000 mg/kg			[15]
	In vitro	β-eudesmol 2, 20 μM	β-eudesmol	- Regulation of IL-6 through regulation of the p38 MAPK and NF-κB - Suppression of RIP2 expression and caspase-1 activation	[34]
	In vitro		Atractylochromene, Quinone, Atractylon	Inhibition against 5-LOX and COX-1	[33]

	Mice	Atractylenolide I 300 mg/kg	Atractylenolide I	[45]
Antipyretic activity	Rats	50% Ethanol extract 5,000 mg/kg		[15]
Antimicrobial activity - against E. coli, S. cerevisiae, and C. albicans	In vitro	95% Ethanol extract 200 mg/ml		[36]
- against E. coli, S. aureus	In vitro		Atractylodin derivatives	[35]
- against Rhodotorulaglutinis and Saprolegnia	In vitro			[37]

AL, *Atractylodes lancea*; bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; ERK, extracellular signal-regulated kinase; CREB, cyclic adenosine monophosphate (cAMP) response element binding protein; NMJ, neuromuscular junction; ACh, acetylcholine; TXA2, thromboxane A2; CRF,

Corticotropin-releasing factor; IL, interleukin; MAPK, mitogen-activated protein kinase; NK-κB, nuclear factor-κB; RIP2, receptor-interacting protein 2; LOX, lipoxygenase; COX, cyclo-oxygenase.