

Review

Overview of commonly used Chinese herbs

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There are several Chinese herbs used as food supplement or as an alternative medicine. *Fructus lycii*, *Panax ginseng*, *Cervi cornu pantotrichum*, *Herba epimedii* and *Angelica sinensis* are among the most commonly prescribed. All of them have been claimed for various indications which are mainly due to their variety of active ingredients or chemical compositions. Even though Chinese herbs have been used and claimed for their efficacy for decades, some toxicity has been found, thus the need to be cautious. In this review, we describe the most common indications of *F. lycii*, *P. ginseng*, *C. cornu pantotrichum*, *H. epimedii* and *A. sinensis* and also report their toxicity, if any have been found.

Key word: Chinese herbs, *Fructus lycii*, *Panax ginseng*, *Cervi cornu pantotrichum*, *Herba epimedii*, *Angelica sinensis*

INTRODUCTION

Traditional medicine involving Chinese herbs is currently gaining a lot of attention due to its quite promising effect, as well as its better clearance (Schulz, 2006), resulting in less accumulation and lower toxicity. Since several active compounds have been found in some herbs, certain herbal medicine products can possess many biological activities. The use of Chinese herbs not only depends on its active ingredients and clinical results, but also on people's belief. Many Chinese herbs have become very popular and have been used as alternative medicine for certain diseases, such as cancer, because of their effectiveness and lower adverse reactions compared to modern medicine (Schulz, 2006; Yi et al., 2010). Even though many herbs have been recognized for their efficacy, some toxicity can be found, especially with their impurities. Quality control of active ingredients and impurities are necessary for herbal medicine in order to obtain the optimum action. Some of the commonly used

Chinese herbs will now be described in detail.

FRUCTUS LYCII

Fructus lycii, also called gouqizi or Chinese wolfberry in Chinese pharmacopeia, has been used for thousands of years as traditional Chinese herbal medicine. The standard species of this fruit are *Lycium barbarum* L. and *L. chinense* mill. belonging to the Solanaceae family (Chen and Chen, 2004). *F. lycii* is an oblong, orange to dark red berry and possesses a bitter to sweet taste (Wu, 2005).

Traditional and current uses

In Chinese pharmacopeia, *F. lycii* is one of the ingredients in Chinese medicine formula. It is used for nourishing the blood in the liver and kidney, and helping to re-balance 'Yin' and 'Yan' in the body. The ancient Chinese subscribe to a concept called Yin Yang which is a belief that there exist two complementary forces in the universe. One is Yang which represents everything

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positive or masculine and the other is Yin which is characterized as negative or feminine. One is not better than the other. Instead they are both necessary and a balance of both is highly desirable (Fong, 2010). *F. lycii* has been used in Chinese medicine for treating dizziness, diminished visual acuity, dryness or tearing from exposure to wind, soreness and weakness of the lower back and knees, nocturnal emission, night sweating, blurry vision, tinnitus and impotence (Chen and Chen, 2004; Wu, 2005). It also possesses antioxidant, anti-aging, anti-tumor, immune-stimulatory, hypoglycemic, hypolipidemic, hepatoprotective and cytoprotective activity (Potterat, 2009).

Sources and chemical composition

There are various components found in *F. lycii* such as polysaccharides, which are the major constituents in this fruit, carotenoids and flavonoids. *L. barbarum* polysaccharides (LBP) consist of a complex mixture of highly branched and only partly characterized polysaccharides and proteoglycans. Luo et al. (2001) tested the anti-fatigue dose of LBP in mice and found that 10 mg/kg/day was the best amount for remarkable adaptability to exercise load, enhanced resistance and accelerated elimination of fatigue. A second major substance is carotenoid, whose expression increases during the ripening process. Zeaxanthin dipalmitate is the predominant constituent from this compound group. In addition, β -cryptoxanthin palmitate, zeaxanthin monopalmitate, and small amounts of free zeaxanthin and β -carotene are also present. This fruit contains some vitamins such as riboflavin, thiamin and ascorbic acid. Flavonoids, such as aglycones myricetin, quercetin and kaempferol, are other important classes of compounds in this fruit. Essential oil and fatty acids are also found in this fruit. Hexadecanoic acid, linoleic acid, β -elemene, myristic acid and ethyl hexadecanoate have been identified as the main constituents. *F. lycii* also contains free amino acids with proline as the major constituent, taurine, γ -aminobutyric acid and betaine (trimethylglycine). Some miscellaneous compounds such as β -sitosterol and its glucoside daucosterol, scopoletin, p-coumaric acid, the dopamine derivative lyciumide A and L-monomethyl succinate are also found in this fruit (Bensky et al., 2004; Chen and Chen, 2004; Potterat, 2009).

Pharmacological and toxicological effects

Antioxidation

The antioxidant activity of *F. lycii* has been investigated in various *in vitro* and *in vivo* studies. The components that show antioxidant activity are the polysaccharides and

flavonoids. Both compounds show three types of antioxidant activities: Radical-scavenging activity, reducing capacity and metal chelating activity (Le et al., 2007; Li and Zhou, 2007a, b). Qian et al. (2004) studied the effect of flavonoids in the polar extract of *L. chinense* where the extract exhibited free radical scavenging activity (Qian, 2004). LBP has been observed to decrease DNA damage in peripheral lymphocytes in non-insulin dependent diabetes mellitus rats via a decrease in oxidative stress. Therefore, LBP can control blood glucose and modulate glucose metabolism (Wu et al., 2006). In addition, LBP has been shown to increase glycogen level and antioxidant enzyme activities, and decrease malondialdehyde (MDA) level and creatine kinase activities in rats undergoing an exhaustive exercise program. This demonstrates that LBP administration can significantly decrease the oxidative stress induced by exhaustive exercise (Niu et al., 2008).

In aged mice, oral administration of LBP over a period of 30 days significantly restored marker enzyme (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px)) activity in aged mice compared to control (Li et al., 2007a). The extract of *L. barbarum* has been demonstrated to significantly reduce blood glucose levels and serum total cholesterol (TC) and triglyceride (TG) concentrations. In addition, the extract could increase high density lipoprotein cholesterol (HDL-c) levels. The results suggested that LBP containing several monosaccharides and 17 amino acids were major bioactive constituents of hypoglycemic effect. Polysaccharides and vitamin antioxidants could be the possible active inducers of the hypolipidemic effect (Luo et al., 2004). Amagase et al. (2009) investigated the effects of *L. barbarum* in a 30-day randomized, double-blind, placebo-controlled clinical study. *L. barbarum* increased antioxidant efficacies in humans by stimulating endogenous factors. They suggested that long-term use of *L. barbarum* might help prevent or reduce free radical-related conditions (Amagase et al., 2009).

Hepatoprotective effects

The study of Kim et al. (1997) found that a chloroform/methanol extract of the fruit contained two cerebrosides showing significant protection against carbon tetrachloride (CCl₄)-induced injury in primary cultured rat hepatocytes. However, the mechanism of action was not determined (Kim et al., 1997a). Ha et al. (2005) studied the protective effects of *L. chinense* fruit on carbon tetrachloride-induced hepatotoxicity in rats. Pretreatment with the fruit before the injection of carbon tetrachloride significantly reduced the elevation of serum liver enzyme levels [alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP)]. The mechanism of action was free radical scavenging, which could act against pathological alterations

caused by the administration of carbon tetrachloride (Ha et al., 2005). In 2010, the mechanism of the hepatoprotective effect of *L. chinense* Miller fruits was investigated in primary human liver cell culture. The results showed that Lycium alcoholic extract protected liver cells against hydrogen peroxide-induced liver cell damage. The underlying mechanism appeared to involve antioxidative properties and a decrease in the expression of CYP2E1 (Pan et al., 2010).

Zeaxanthin and zeaxanthin dipalmitate have been demonstrated to display anti-hepatotoxic activity by reducing hepatic fibrosis induced by bile duct ligation/scission in rats at a dose of 25 mg/kg through antioxidative activity (Kim et al., 1997b). Furthermore, the three pyrrole derivatives of the ethyl acetate fraction of the fruit have also shown hepatoprotective effects comparable to silybin during carbon tetrachloride-induced toxicity in rat hepatocytes (Chin et al., 2003).

Immune modulation

The polysaccharide–protein complex from LBP are the bioactive components in immune modulation; whereas, carotenoids and flavonoids have not shown any involvement in this process (Chang and So, 2007). Previous studies have demonstrated that LBP can enhance immune function and induce lymphocyte proliferation and cytokine production (Gan, 2003; Gan, 2004). Gan et al. (2003) studied the effects of LBP on the expression of interleukin-2 (IL-2) and tumor necrosis factor- α in human peripheral blood mononuclear cells. After LBP addition to the primary cell culture, LBP increased the expression of IL-2 and tumor necrosis factor- α at both mRNA and protein levels in a dose-dependent manner (Gan, 2003). Gan *et al.* (2004) investigated the effect of LBP on the immune system of S180-bearing mice and observed that LBP could significantly inhibit the growth of transplantable sarcoma S180 and increase macrophage phagocytosis, spleen lymphocyte proliferation, cytotoxic T-lymphocyte (CTL) activity and IL-2 mRNA expression, but these effects were not dose-dependent (Gan, 2004).

Antitumor activity

If LBP can increase IL-2 and tumor necrosis factor- α level, two cytokines that can inhibit tumor growth, LBP might also contribute to antitumor activity. As the study of Gan et al. (2004) showed, LBP could significantly inhibit the growth of transplantable sarcoma S180 in S180-bearing mice (Gan, 2004). Zhang et al. (2005) studied the effect of LBP on the proliferation rate, cell cycle distribution and apoptosis in the human hepatoma QGY7703 cell line. LBP displayed an inhibitory effect on

QGY7703 cell growth with cycle arrest in the S phase and apoptosis induction (Zhang et al., 2005b). In addition, LBP inhibited proliferation and stimulated p53-mediated apoptosis in rat and human hepatocellular carcinoma cells (Chao et al., 2006). In 2009, Li et al. studied the effect of *L. barbarum* on the human breast cancer cell line MCF-7. The results showed that an aqueous extract was shown to inhibit the growth of the estrogen receptor-positive human breast cancer cell line MCF-7 by altering estradiol cellular metabolism (Li et al., 2009).

Neuroprotective effects

There are few studies on this field and the data are mainly *in vitro* studies by the same authors. Pretreatment with an aqueous extract of *L. barbarum* has been demonstrated to significantly reduce the release of lactate dehydrogenase (LDH), an enzyme that catalyzes the conversion of lactate to pyruvate which is an important step in energy production in cells, during Abeta peptide-induced toxicity in a primary neuron cell line. Moreover, it has been shown to attenuate Abeta peptide-activated caspase 3-like activity and elicit a typical dose-dependent neuroprotective effect. The underlying mechanism appears to involve inhibition of the A β -triggered c-Jun N-terminal kinase (JNK) signaling pathway (Yu et al., 2005) which is a member of mitogen-activated protein kinase family participating in many of the signaling pathways associated with stress (Kwon et al., 2011). There are many studies indicating that oxidative stress can induce cell damage and has been implicated in a variety of neurodegenerative disorders (Behl, 1999; Olanow, 1993). The extract from *L. barbarum* protected against DTT-induced toxicity in neurons via attenuated DTT-induced PERK phosphorylation that increased with age (Yu et al., 2007). The mechanisms of the cytoprotective effects were independent of the antioxidative effects (Yu et al., 2006). Furthermore, pretreatment of LBP protected neurons effectively against A β -induced apoptosis by reducing the activity of both caspase-2 and -3. LBP can also inhibit phosphorylation of double-stranded RNA-dependent protein kinase (PKR). Oral administration of *L. barbarum* in Sprague-Dawley rats significantly reduced the loss of retinal ganglion cells in the retina, although elevated intraocular pressure was not significantly altered. This was the first *in vivo* report showing the therapeutic function of *L. barbarum* against neurodegeneration in the retina of a rat ocular hypertension model (Chan et al., 2007).

Treating male infertility

L. barbarum fruits have been used as a traditional remedy for male infertility in China. There are currently few studies on the fertility-facilitating effects of *F. lycii*.

Polysaccharides are the most important functional constituent of *F. lycii*. There was a study that showed *Fructus lycii* polysaccharides inhibiting time- and hyperthermia-induced structural damage in murine seminiferous epithelium and delaying apoptosis in this system (Wang et al., 2002). The major cause of structural degradation and apoptosis in hyperthermic testes is oxidative stress. *F. lycii* polysaccharides were shown to protect against this testicular degeneration via an antioxidant effect (Wang et al., 2002). LBP provided a protective effect against the testicular tissue damage induced by heat-exposure and chemical (hydrogen peroxide).

LBP has also been demonstrated to increase testis and epididymis weights, improve SOD activity, and raise sexual hormone levels in damaged rat testes. In addition, LBP has been shown to improve reproductive function in hemicastrated male rats, increase sexual hormone level, raise accessory sexual organ weights, and improve sperm quantity and quality (Luo et al., 2006).

Product availability and quality control

There are two related species of this fruit, *L. barbarum* L. and *L. chinense* Mill. *L. barbarum* L. is a deciduous shrub one to three meters high and widely distributed in warm regions of the world, particularly in the Mediterranean area, southwest and central Asia. It is also cultivated in North America and Australia. *L. chinense* is smaller than *L. barbarum* L. and mainly distributed in East Asia, and grown particularly in South China, Korea and Japan. However, the fruits of the *Lycium* species possess a highly similar anatomy and tissue structure. The chemical components of fruits from both species appear similar (Potterat, 2009).

The differences in composition and properties among different *F. lycii* from different geographic region, due to soil and climate, are observed historically, which lead to the differences in their functions (Lu et al., 2008). In order to discriminate *F. lycii* from different geographic regions, several analytical methods have been applied to detect a few active components such as high performance liquid chromatography (HPLC) fingerprint, thin layer chromatography (TLC) and colorimeter. However, since there are many active components and being that it is inappropriate to select only several specific components as essential criteria (Lu et al., 2008), two-dimensional near-infrared correlation spectroscopy has been used to successfully control the quality of *F. lycii* without losing the original natural instinct and compatibility of traditional Chinese herbal medicine (Hua et al., 2003; Lu et al., 2008). Moreover, the polysaccharides of *L. barbarum*, the major component in this fruit, were also analyzed by preparative high performance size exclusion chromatography (HPSEC). After protein hydrolysis, two major fractions were obtained with a molecular weight of 79250

and 24470 amu, respectively (Wang et al., 2009a).

Reported toxicity

The median lethal dose (LD₅₀) of a water extract of *F. lycii* has been reported as 8.32 g/kg by subcutaneous application in mice (Chang et al., 2001). Acute overdose of *F. lycii* is characterized by tremor, dyspnea, tearing, gastrointestinal disturbances, and dermal redness and itching (Chen and Chen, 2004).

PANAX GINSENG

P. ginseng L. is a perennial herb that grows in the mountainous forests of eastern Asia, the United States and Canada. The use of this herb in Chinese traditional medicine stems from the "doctrine of signature" concept, because the root of the ginseng looks like human and is therefore used to treat all male diseases.

Traditional and current uses

Ginseng is used as a tonic to invigorate a human's physical, mental and sexual capability. According to traditional Chinese medicine philosophy, predomination of yin generates cold and obstructs yang-qi, clinically leading to cold symptoms such as chills, dispiritedness, pale complexion, cold limbs, loose stool, clear urine, whitish tongue coating, deep and slow pulse; while predomination of yang leads to heat, so usual clinical manifestation is fever, accompanied by profuse sweating, thirst, reddish complexion, reddish tongue with yellowish coating, full and large or rapid pulse; or accompanied by pathogenic heat disturbing the interior with the symptoms of dysphoria, insomnia, mania, dry feces and scanty brownish urine (Guilin Sino-Western, 2003). Because of that concept, two types of ginsengs have been used in opposite effect. *P. ginseng* (Korean ginseng) is a "hot" or "yang" tonic used to treat "cold" diseases, whereas *P. quinquefolium* (American ginseng) is "cool" or "yin" and is used to treat "hot" symptoms, such as stress, insomnia, palpitations and headache. It is also said to possess anti-stress activity (also means an "adaptogen") (Awang, 1998), improve glycemic control, stimulate immune functions, treat toxic hepatitis, improve athletic performance, enhance longevity, and relieve symptoms associated with cancer, aging and senility such as asthenia, atherosclerosis, blood and bleeding disorders. Ginseng is also widely used as an aphrodisiac.

Sources and chemical composition

The term "ginseng" can refer to the species of the genus

Panax (Korean, Chinese, Japanese or American ginseng), as well as to *Eleutherococcus senticosus* (Siberian or Russian ginseng). The distinction between the species is important because there are many differences in habitual and harvest characteristics in addition to chemical compositions that can cause different therapeutic and toxic effects. Ginseng and ginsenoside (termed saponin) have been identified as active ingredients of ginseng (Hu et al., 2008; Rhim et al., 2002). In this review, the term “ginseng” will be used to refer to *P. ginseng* (also called Korean ginseng or Chinese ginseng), while “Japanese ginseng” and “American ginseng” will be used to refer to *P. pseudoginseng* and *P. quinquefolius*, respectively. Others are less important than these three species and will not be included in the scope of this review.

Pharmacological and toxicological effects

Endocrine effects

Ginseng has been used in various types of endocrine disorders, especially in diabetes mellitus, because of its hypoglycemic effects by possibly accelerating hepatic lipogenesis and increasing glycogen synthesis and storage (Oshima et al., 1985; Yokozawa et al., 1975). In a small human study of 36 newly diagnosed type II diabetes patients, ginseng at a dose of 200 mg daily was shown to have a statistically significant benefit on glycosylated hemoglobin compared to 100 mg of ginseng or placebo daily after 8 weeks of therapy (6 versus 6.5% for the 200 mg ginseng extract powder and 100 mg ginseng extract powder or placebo group, respectively). Patients who received 100 mg of ginseng had a smaller mean fasting blood glucose level than those who took 200 mg of ginseng or placebo; the mean fasting blood glucose was 7.7 mmol/L for the 100 mg ginseng extract powder group, 7.4 mmol/L for the 200 mg ginseng extract powder group, and 8.3 mmol/L for the placebo group at the end of the study (Sotaniemi et al., 1995).

Neurological effects

Ginseng products that are available on the market have been reported to have stimulatory effects on the central nervous system (CNS) in both animal models and humans (Siegel, 1979; Takagi et al., 1972). Ginsenoside Rg1 inhibits neuronal apoptosis *in vitro* while ginsenoside Rb1 reverses short-term memory loss in rats (Awang, 1998; Li et al., 1997; Takagi et al., 1972). It is believed that ginseng may play an important role in the treatment modality of human dementia. Wesnes and colleagues studied the memory-enhancing effect of either ginseng or *Ginkgo biloba* in healthy middle-aged volunteers and found that administration of either agent resulted in a

small but statistically significant improvement in the index of memory quality as compared to placebo (Wesnes et al., 2000). Attention-deficit hyperactivity disorder (ADHD) patients may partly benefit from ginseng products due to data from the study of Lyon and colleagues. This was a pilot study to evaluate the effects of a combination product containing both American ginseng and ginkgo for the treatment of ADHD. The investigators reported improvement in 31 to 67% of the subjects depending on the type of outcome measured. However, no placebo group was included so it is difficult to ascertain if the effect was caused by the herbal treatment or not (Lyon et al., 2001).

Cardiovascular effects

In animal models, ginsenoside Rb1 decreases blood pressure by relaxing vascular smooth muscle (Kaku et al., 1975). Administration of ginseng at a dose of 4.5 g/day was studied in a small number of human subjects, which demonstrated its hypotensive effect in two patients from a total of 26 subjects (7.7%) (Han et al., 1998). An *in vitro* study using a crude extract of *Ginseng saponins* showed the relaxation effect on rabbit corpus carnosum smooth muscle, suggesting that some components of ginseng may be a nitric oxide donor (Kim et al., 1998). This finding might provide scientific evidence for traditional claims that ginseng enhances sexual potency, and supports results of another study that showed increased penile rigidity and girth compared to placebo or trazodone in patients with erectile dysfunction (Choi et al., 1995).

Yamamoto and colleagues used the ginseng powder in their pilot clinical study to demonstrate the effects of ginseng on human lipid profiles. Red ginseng powder was shown to decrease triglyceride concentration as well as increase high-density lipoprotein (HDL)-cholesterol concentration ($p < 0.05$ compared with baseline for both triglyceride and HDL levels) (Yamamoto et al., 1983). In another study, ginseng also showed antiplatelet activity by regulating the levels of cyclic guanosine monophosphate (cGMP) and thromboxane A₂ (Park et al., 1995).

Product availability and quality control

Two commercial forms of ginseng are available. “White” ginseng consists of dried root and “red” ginseng is prepared by fresh, unpeeled root steaming before drying. White and red ginseng contain different amount of active ingredient. Red ginseng contains 2.5 times higher concentration of protopanaxadiol class ginsenosides, the more cytotoxic and efficient cellular uptake on breast cancer cell line, than white ginseng while protopanaxatriol class ginsenosides, the less active compound, were only

present in white ginseng (Lee et al., 2011). The greater cellular uptake of protopanaxadiol class ginsenosides resulted in more substantial antiproliferative activity in human breast cancer cells. Many formulations of ginseng are available including tablets, capsules, soft capsules, powders, tinctures, teas, candy, fresh or dry slices, and whole fresh or dry root. There are also a variety of products that claim to contain ginseng such as cigarettes, toothpastes, cosmetics, soaps, beverages, gum and coffee. These products have varying amounts of ginseng, quality of formulation, price and shelf-life. In general, tinctures are more expensive but last for years while powder capsules are cheaper but have a short shelf-life of only one year. The most important aspect of the quality control process of these ginseng products is based on standardization of the ginsenosides, the purported active ingredients. The amount of ginsenosides in ginseng products, available on the market worldwide, varies widely among brands and often differs from the content stated on the label or lacks consistency between batches. Ginseng commonly can be taken as pure compound (*P. ginseng* from Now Foods® (Bloomington, IL, USA), contained 1.04 g of *P. ginseng*/capsule) or combination with other components such as Ginseng Power Max from Action Labs® (Anaheim, CA, USA) contained red Chinese ginseng 350 mg, Korean ginseng 350 mg, *Peruvian Maca* (*Lepidium* spp.) 175 mg, Eleuthero (*E. senticosus*) 150 mg, American ginseng 150 mg and *Rhodiola* (*Rhodiola rosea*) 50 mg. There are other types of ginseng on the market including Siberian, Brazilian and Indian ginseng as intentional or unintentional adulterant to ginseng herbal products. These are not of the genus *Panax* and do not contain ginsenosides.

For quality assessment, ginsenosides need to be determined. Ginsenosides can be simply classified as neutral and acidic saponins. Major neutral saponins are ginsenosides Rg1, Re, Rf, Rb1, Rb2, Rc, and Rd; the acidic ginsenosides include four malonyl derivatives of the ginsenosides Rb1, Rb2, Rc, and Rd and ginsenoside R0 (Yamaguchi et al., 1988). Numerous analytical techniques, including TLC, gas chromatography (GC), HPLC coupled with ultraviolet detection (HPLC-UV), evaporative light scattering detection (HPLC-ELSD), or MS (LC-MS), capillary electrophoresis (CE), near infrared spectroscopy (NIR), and enzyme immunoassay (EIA) have been used to quantitate ginsenosides (Fuzzati, 2004). Of these techniques, HPLC-UV is the most frequently used and considered a valuable tool for the quality assessment of ginseng products (Kim et al., 2007).

Reported toxicity

The term “ginseng abuse syndrome” (GAS) was coined from the result of Siegel's study that included 133

persons who had been using ginseng products for at least a month. Most subjects experienced CNS arousal and excitation at an average dose of 3 g of ginseng root. Fourteen people experienced GAS, which was composed of hypertension, nervousness, sleeplessness, morning diarrhea, and skin eruptions. Five of the 14 subjects also had edema while 4 reported depersonalization and confusion at a dose of 15 g, and depression at a dose greater than 15 g. The CNS effects appeared to be dose-dependent (Siegel, 1979) and most users reported that dosing titration was required to minimize nervousness and tremor. There are several case reports that show some adverse reactions from ginseng products on other organ systems such as hypertension, Steven-Johnson syndrome, mastalgia, abnormal vaginal bleeding, and masculinization of the fetus in mothers using ginseng products while pregnant.

CERVI CORNU PANTOTRICHUM

C. cornu pantotrichum or Lurong is pilose deer antler, which is the one of most popular components of traditional Chinese herbal medicine. Young pilose antlers of the male *C. nippon* Temminck or *C. elaphus* Linnaeus (Family Cervidae), which are the standard species, are used. The horn is cut into slices or ground into powder for use. There are three other products derived from deer velvet and antlers: deer antler (*C. cornu*), deer antler glue (*C. cornu colla*) and degelatinated deer antler powder (*C. cornu degelatinatum*). Even though the four products have the same source, their therapeutic functions are different (Bensky et al., 2004; Liu et al., 2010; Wu, 2005). It has been used for thousands of years in treating neurosis, enriching vital energy, nursing the blood, strengthening the kidney and prolonging life (Won, 1994).

Traditional and current uses

In Chinese medicine formula, *Cervi cornu pantotrichum* is used to treat kidney ‘yang’ deficiency with impotence, infertility, anemia due to blood and kidney ‘yin’ deficiency, strengthen the tendon and bones, and heal chronic Yin sore and boils (Bensky et al., 2004; Chen and Chen, 2004). It is currently used in the effective remedy for erectile dysfunction, acute and chronic arthritis, osteoporosis, and fracture in animal model or human clinical trials (Chen and Lin, 2008; Ghosh et al., 2001; Kim et al., 2008; Low and Tan, 2007; Wang et al., 2007d).

Sources and chemical composition

There are two different species of deer used for their velvet in China: the sika deer (*C. nippon*) and red deer

(*C. elaphus*). Velvet from the sika deer is known in Chinese as either plum blossom deer velvet or simply blossom deer velvet, which is a yellow-haired velvet covering the young antlers. Velvet from red deer is known as horse deer velvet, which is a greenish blue color. The therapeutic action of the two species is similar. However, deer velvet is collected from deers all over the world at present, including North America, Europe, Australia and New Zealand (Bensky et al., 2004).

C. cornu pantotrichum is the deer antler velvet that is collected from the early stage of antler growth and is formed from cartilage that later rapidly converts to bone, after which all blood supply is lost. Antlers are deciduous every spring in male deer while new antlers grow on the base of the previous year's antlers. The antlers are removed safely by surgery after the new antlers have grown for 55 to 60 days (Bensky et al., 2004).

Of all the products derived from deer velvet and antlers, *C. cornu pantotrichum* has the strongest therapeutic effect (Bensky et al., 2004). All the products have similar components but their therapeutic functions are different. In *C. cornu pantotrichum*, the following can be found: proteins, amino acids, nine kinds of fatty acids including oleic acid, linoleic acid, linolenic acid, ten kinds of phospholipids, endocrine hormones and polysaccharides. Furthermore, inorganic elements such as Ca, Na, Zn, Fe, Mg and Si have also been found (Liu et al., 2010). There are additional chemical compounds found in *C. cornu pantotrichum* such as pantocrine, lysophosphatidylcholine, ganglioside, putrescine, spermidine, spermine, growth factors, chondroitin sulfate, androgen, estradiol, estrone, ceramide, lecithin, cephalin and sphingomyelin (Chen and Chen, 2004; Lee et al., 2004).

In addition, the velvet and antlers have a high content of keratin. It has been demonstrated from the protein analysis of velvet antlers that keratin may be used as an index of standardization of velvet antler components because keratin is common to each specific species (Won, 1994).

Pharmacological and toxicological effects

Anti-narcotic

Oral administration of water extract of velvet antler from *C. elaphus* prior to morphine treatment can develop morphine-induced conditioned place preference and postsynaptic dopamine (DA) receptor super-sensitivity in mice. These results suggested that velvet antler recovered the dysfunction in the dopaminergic system produced by morphine (Kim and Lim, 1999). The repeated administration of water extract of velvet antler can also inhibit analgesic tolerance, physical dependence, and reverse tolerance caused by the repeated administration of morphine. However, a single

administration of the extract does not inhibit morphine-induced analgesia and morphine-induced hyperactivity (Kim et al., 1999).

Bone proliferation and growth

A number of growth factors has been identified in deer antler extract, including bone morphogenetic proteins that induce the formation of bone and cartilage (Feng et al., 1995; Feng et al., 1997) and fibroblast growth factors that affect the multiple-step progress of osteoblast differentiation and mineralization (Sim et al., 2001). In 2005, there was a study that found that deer antler aqua-acupuncture (DAA) possessed anti-bone resorption activity in adjuvant-induced arthritic rats (Kim et al., 2005). When cervus and cucumis polypeptides were injected into the radius fracture of rabbits at different concentrations, the expression level of vascular endothelial growth factor in the high dose group was higher than that in the low dose group. In addition, fractures in the high dose group had all completely healed and the bone was of higher strength compared to the low dose and control groups (Wang et al., 2007d). In addition, chloroform extract of deer antler also inhibited osteoclast differentiation in mouse bone marrow cultures stimulated by receptor activator of NF- κ B ligand and macrophage-colony stimulating factor. The extract suppressed the activation of extracellular signal-regulated kinase, protein kinase B and inhibitor of kappa B in osteoclast precursor cells (Li et al., 2007b). These results were consistent with the study of Kim et al. (2005). Chen et al. (2008) reported that the pilose antler polypeptides also improved proliferation of rat chondrocytes *in vitro* (Chen and Lin, 2008). After induction of avascular necrosis of the femoral head by corticosteroids in rats, oral administration of water extract of deer antler reduced the degree of necrosis. The extract also promoted osteoblastic proliferation through regulating cell cycle progression (Shi et al., 2010).

Anti-arthritis

C. cornu pantotrichum has been shown to exert an inhibitory effect on the production of IL-1 β and tumor necrosis factor- α (TNF- α) from macrophages in mice that have been stimulated with bacterial lipopolysaccharides. In the *in vitro* study, it also strongly inhibited T-cell activation, including blastogenesis and cytokine production, stimulated by antigens. The function of B-cells is important in the severity and length of arthritis and therefore, the effect of the extract on B-cells function was examined. The results showed that intraperitoneal injection of the extract inhibited antibody production in rats (Kim et al., 2003). In 2004, Kim et al. reported that the *C. cornu pantotrichum* from *C. korean* TEMMINCK

var. *mantchuricus* Swinhoe (Nokyong in Korean) suppressed the development of arthritis, consistent with the results from the previous study (Kim et al., 2004). Moreover, when the extract treatment and the initial or booster immunization started, the progression of arthritis and the immune response to collagen were inhibited (Kang et al., 2006). The inhibitory effect of the extract on arthritis correlated with the effects of transforming growth factor- β (TGF- β), which has potent immunosuppressive effects of cytokine. The results suggested that the extract and TGF- β 3 exerted inhibitory effects on the development of an induced arthritic condition in a similar pattern in rats. The extract has also been shown to control inflammatory proteins and protect cartilage (Kim et al., 2008).

Product availability and quality control

In Chinese pharmacopeia, the quality criteria for *C. cornu pantotrichum* from sika deer include a thick, round appearance with a full end part as well as a reddish brown surface with soft, yellowish red hairs. Good quality *C. cornu pantotrichum* from red deer consists of full and lightweight antler, with grayish black or grayish yellow hairs. Beside *C. cornu pantotrichum* from sika and red deer, deer velvet is collected from deers in many countries as afore-described. Because of the high price of this medicine, many counterfeit versions are found on the market. The adulterants include slices of old deer antlers that have been artificially coated with fine hairs. These fakes are usually easy to recognize (Bensky et al., 2004).

For chemical composition, *C. cornu pantotrichum* contains proteins, amino acids, 9 kinds of fatty acids include oleic acid, linoleic acid, linolenic acid, 10 kinds of phospholipids, endocrine, and polysaccharide which are considered as active ingredients (Wang et al., 2007b; Yan et al., 2004).

Reported toxicity

The median lethal dose (LD₅₀) of pantocrine, a liquid alcoholic extract from antlers in the velvet of the deer cervus, in mice has been reported as 34 ml/kg via intravenous injection, 104 ml/kg via intraperitoneal injection, 114 ml/kg via subcutaneous injection, 97.8 ml/kg via intramuscular injection and 117 ml/kg via oral ingestion. Overdose symptoms of *C. cornu pantotrichum* are characterized by tremor, dyspnea, tearing, gastrointestinal disturbances, dermal redness and itching (Chen and Chen, 2004).

HERBA EPIMEDII

Herba epimedii or Yin yang huo in Chinese pharmacopeia

is one of the most popular components of traditional Chinese herbal medicine. It is made from the aerial parts of *Epimedium* L. (Berberidaceae) including the herbs multiple species: *Epimedium brevicornum* Maxim., *E. sagittatum* Maxim., *E. pubescens* Maxim., *E. wushanense* T. S. Ying and *E. koreanum* Nakai (Bensky et al., 2004; Wu, 2005). They have been commonly used in the treatment of cardiovascular diseases and other chronic illnesses (infertility, amnesia and asthenia, impotence and senile functional diseases) in China for over 2,000 years (Meng, 2005).

Traditional and current uses

In Chinese medicine formula, *H. epimedii* is the herb used to reinforce the kidney 'yang', strengthen the tendon and bones and expel wind-dampness (Bensky et al., 2004; Chen and Chen, 2004). It is widely used in the effective remedy for cardiovascular diseases, osteoporosis and for improving sexual and neurological functions (Sze et al., 2010).

Sources and chemical composition

H. epimedii is also grown as a herb for various medicinal purposes in Japan, Korea and the Mediterranean region (Zhang et al., 2008c). In China, it is mainly produced in the provinces of Shanxi, Sichuan, Hubei, Shanxi and Guangxi. This herb is collected in the spring and autumn, then dried in sunlight and sliced and used unprepared or stir-baked with sheep fat (Wu, 2005). There are several compounds in this plant including lignans, flavonoids, flavonol glycosides, terpene glycosides and phenolic carboxylic acids (Guo et al., Ito et al., 1988; Li et al., 1995a, 1995b, 1996; Matsushita et al., 1990; Mizuno et al., 1987; Wang et al., 2007a). The major effective medicinal compounds are the flavonoids and more than 60 kinds have been identified. The major constituents of flavonoids are epimedin A, B, C and icariin, which possess important pharmacological activities (Zhang et al., 2008c). Epimedin A, B, C and icariin are usually used as the marker compounds for evaluating *H. epimedii* by HPLC and capillary zone electrophoresis (Zhang et al., 2008a). In addition, icariin has been used to monitor the quality of this herb as defined by the Committee of China Pharmacopoeia (Committee of China Pharmacopoeia, 2005).

Pharmacological and toxicological effects

Antioxidation

H. epimedii contains antioxidant constituents such as total flavonoids, icariin, polysaccharides and vitamin C.

These compounds exert antioxidant activity in different organs. The total flavonoids of this herb contribute to anti-inflammatory effects, which are believed to be related to their antioxidant activities. They also inhibit prostaglandin E and malondialdehyde, the metabolic product of lipid peroxidation, and enhance the activity of free-radical scavenging enzyme (Sze et al., 2010). Icariin has been reported to protect against oxidative-induced hemolysis (Liu et al., 2004). Icariin protected against oxidative damage of DNA in a concentration-dependent manner, as demonstrated by measuring the formation of carbonyl compounds that can react with thiobarbituric acid (TBA) to form thiobarbituric acid reactive substances (TBARS) (Zhao et al., 2007). The possible mechanism of antioxidative activity of icariin might be the stabilization function derived from intramolecular hydrogen bonds when the hydrogen atom in the –OH group of *icariin* is subtracted by a radical (Zai-Qun, 2006). Meanwhile, the antioxidative activity of polysaccharides has been shown to be due to an increase in the activities of key intracellular antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase. In addition, vitamin C found in *H. epimedii* can contribute to the antioxidant properties of *H. epimedii* (Sze et al., 2010).

Estrogen-like activity

H. epimedii has been applied as a tonic for the reproductive system such as increasing libido, treating impotence and infertility (Bensky et al., 2004). It also has been used for estrogen hormone replacement therapy (Zhang et al., 2005a). Icariin, icaritin and desmethylicaritin, the flavonoids of *H. epimedii*, were investigated for their estrogen-like activities using the modified MCF-7 cell proliferation assay. The results showed that only icaritin and desmethylicaritin possessed estrogen-like activities and that the activities were mediated by the estrogen receptor (Wang, 2004; Wang and Lou, 2004). However, icariin can be metabolized to icaritin and desmethylicaritin by human intestinal bacteria *in vitro*. All preparations of *H. epimedii* are taken orally; therefore, inactive icariin first metabolizes to estrogenic icaritin and desmethylicaritin *in vivo* and then generates effects as selective estrogen receptor modulators to exert pharmacological activities (Ye and Lou, 2005). However, minor bioactive flavonoid aglycones such as apigenin, kaempferol, luteolin and quercetin have been found to significantly exert estrogenic effects whereas the major flavonoids, icariin and epimedin A, B, C, do not increase estrogenic activity (Shen et al., 2007). The ethanol extract of *H. epimedii* was investigated for estrogenic activity, which partially demonstrated it (Zhang et al., 2005a). In addition, the polyphenolic extract of the leaves of *E. brevicornum* was found to exhibit significant estrogenic activity in a recombinant yeast cell assay and the Ishikawa Var-I assay (Denaeyer et al., 2005). In

another *in vivo* study, the ethanolic *E. brevicornum* extracts increased estrogen receptor α activity in rat after oral administration (Yap et al., 2007). Among the major *Epimedium* species, specimens of *E. koreanum*, *E. pubescens* and *E. brevicornum* have exhibited high estrogen receptor α and β activities (Shen et al., 2007).

Osteoprotective effect

H. epimedii has been one of the most frequently used herbs in formulas to be prescribed for the treatment of osteoporosis for a long time in China. There are various studies about the effect of this herb on the process of bone metabolism and bone formation in Chinese language journals. Results show that *H. epimedii* stimulates osteoblastic proliferation, inhibits osteoclastic resorption and increases mineral content (Wong and Rabie, 2006). Meng (2005) studied the effects of *H. epimedii* in an osteoblast model. The ethanolic extract and N-butanol extract of *H. epimedii* promoted the proliferative activity of osteoblasts, with icariin eliciting the most significant effect on osteoblast proliferation (Meng, 2005). An *in vivo* study demonstrated that the extract of *H. epimedii* prevented ovariectomized-induced bone loss by increasing bone turnover rate and restoring the loss of trabecular bone architecture in ovariectomized rats. In addition, *in vitro* data showed that the mechanisms were mediated by its direct action of stimulating osteoblast activities and inhibiting osteoclastogenesis (Xie et al., 2005).

Icariin has been investigated for its antiosteoporotic activity in an ovariectomized rat model of osteoporosis where it was shown to effectively prevent bone loss due to estrogen deficiency (Nian et al., 2009). The mechanism of icariin enhancing bone formation is mediated via the induction of bone morphogenetic protein-2 and nitric oxide synthesis. It also regulates transcription factor gene expression for bone formation such as the *Cbfa1/ Runx2*, *OPG* and *RANKL* genes (Hsieh et al., 2010). Icaritin, the metabolite of icariin, can enhance the differentiation and proliferation of osteoblasts, facilitate matrix calcification, as well as inhibit osteoclastic differentiation and activity. Interestingly, the effects of icaritin are more potent than icariin (Huang et al., 2007). Total flavonoids of *H. epimedii* have also been reported to promote the differentiation of primary rat osteoblasts by increasing alkaline phosphatase activity (Zhang et al., 2008a). In human mesenchymal stem cells, the flavonoids of *H. epimedii* were reported to promote osteogenesis, facilitate the process of matrix calcification and inhibit osteoclastic differentiation (Zhang et al., 2009). The flavonoids of *H. epimedii* can enhance the mRNA expression of *BMP-2*, *BMP-4*, *Runx2*, *betacatenin* and *cyclin D1*, regulators in the *BMP* and *Wnt/catenin* signaling pathways (Zhang et al., 2010). Zhang et al.

(2008) investigated the effect of epimedium-derived flavonoids (EPF) on both skeletal and nonskeletal factors related to hip fracture risk in late postmenopausal women in a 24-month randomized, double-blind and placebo-controlled trial. The results showed that EPF had beneficial effects on both skeletal and non-skeletal factors related to hip fracture risk in late postmenopausal women by significantly increased muscle force coefficient of lower limb and dynamic balance coefficient after 24 months of EPF administration (Zhang et al., 2008b).

Treatment of erectile dysfunction

H. epimedii has been used in sexual disorders such as impotence, lack of sexual desire, incomplete erection, premature ejaculation, spermatorrhea, low sperm count, soreness and weakness of the lower back and knees, and infertility (Chen and Chen, 2004). This herb contains a phosphodiesterase type 5 (PDE5) inhibitory compound, icariin, which has the same target as sildenafil (Lin et al., 2003). The PDE5 inhibitory effects of icariin have been reported to be greater than those of zaprinast. In addition, icariin can enhance cGMP levels in cavernous smooth muscle cells treated with sodium nitroprusside (Ning et al., 2006). The effect of icariin on erectile function was investigated by using castrated rats in an *in vivo* study. Oral administration of icariin for 4 weeks improved erectile function of castrated rats, which correlated with an increased percentage of smooth muscle in trabecular tissue, and the mRNA and protein expression of nitric oxide synthase, but had no influence on serum testosterone levels (Liu et al., 2005). Intracavernous administration of *E. brevicornum* extract enhanced penile erection in rats, with nitric oxide activity considered to be the mechanism (Chen and Chiu, 2006). Moreover, the extract affects sympathetic modulatory activities of the heart but do not increase the sympathetic control of the cardiovascular system or blood pressure (Han et al., 2007). Makarova et al. (2007) studied the effect of lipid-based suspension of *E. koreanum* Nakai extract on sexual behavior in rats and found that the extract improved erectile function of aged rats (Makarova et al., 2007). PDE5 inhibitory effects of icariin can also be implicated in the therapeutic activity of cardiovascular diseases, pulmonary hypertension, female sexual dysfunction, premature ejaculation, stroke, leukemia and renal failure (Rahimi et al., 2010).

Antidepressant

There are few studies on this field and the data are from the same authors. The behavioral and neuro-endocrinological effects of icariin were studied in rats by using the forced swimming test and the tail suspension test. After oral administration for 21 consecutive days,

icariin possessed potent antidepressant-like properties that were mediated by a decrease in brain monoamine oxidase (MAO) A and B activities, as well as serum corticotropin-releasing factor (CRF) levels (Pan et al., 2005). In 2007, the effects of icariin on a chronic mild stress (CMS) model of depression in male Wistar rats were studied. Icariin exhibited potent antidepressant-like activities and was found to improve the abnormalities in the hypothalamic–pituitary–adrenal axis functions (Pan et al., 2007). Icariin can also target the interaction of the limbic-hypothalamic-pituitary-adrenal (LHPA) stress circuit and serotonergic function in CMS rats (Pan et al., 2010).

Anticancer

There are a few *in vitro* studies on this field. The aqueous extract of *E. sagittatum* showed strong anti-angiogenic activity both in chick embryo chorioallantoic membrane and bovine aortic endothelial cell models, useful in suppressing tumor growth (Wang, 2004). Icariside II, the flavonoid glycoside in *E. koreanum*, decreases the protein level of Hypoxia-inducible factor-1 (HIF-1 α) and leads to suppression of hypoxia-induced responses such as angiogenesis, glucose metabolism and metastasis in human osteosarcoma (HOS) cells. Icariside II can potentially treat cancers that involve overexpression of HIF-1 α which is normally found in ovarian, breast or colon cancer (Choi et al., 2008). Moreover, icariin was investigated for its anticancer effect on a human gastric cancer cell line and the results showed that icariin suppressed tumor cell invasion and migration via the Rac1-dependent VASP pathway and may be a potential anti-cancer drug (Wang et al., 2010).

Immunological effects

H. epimedii has been studied for its immunostimulating effects in mice. Polysaccharides, flavonoids and icariin of *H. epimedii* have been found to enhance the immune response in mice after oral administration of sheep red blood cells. They increased T-cell proliferation and phagocytic activity of macrophages (Xiao et al., 1993). The aqueous extract of *H. epimedii* was effective on Th1 and Th2 cells, as exhibited by the enhancement of IgG1, IgG2a and IgM levels, and cytokines in mice after immunization with ovalbumin (Kim et al., 2001).

Cardiovascular effects

Icariin from *H. epimedii* inhibits H₂O₂-induced nitric oxide (NO) decrease by inhibiting NO degradation. Nitric oxide from endothelial cells possesses antioxidant and anti-apoptosis activity. Therefore, icariin may be useful in

preventing endothelial cell damage induced by reactive oxygen species (Wang and Huang, 2005). In addition, icariin can enhance the expression of eNOS gene and up-regulate the production of NO (Xu and Huang, 2007). The *H. epimedii* extract has also been reported to inhibit the activity of S-adenosyl-L-homocysteine hydrolase, an enzyme that converts methionine to homocysteine and causes various diseases such as cardiovascular disease (Zhang et al., 2005c).

Neurological effects

Icariin has protective effects against oxygen and glucose deprivation (OGD)-induced neuron injury. This might be related to its antiapoptotic effect, antioxidative stress and the stabilization of intracellular calcium concentration (Li et al., 2005). The mechanism underlying this neurological protective effect involves the enhanced expression of Sirtuin type 1 (SIRT1), a member of a highly conserved gene family that increases DNA stability and prolonged survival in yeast and higher organisms, as well as mammals. In addition, the mechanism is partially involved with the activation of the mitogen activated protein kinase (MAPK/P38) pathway (Wang et al., 2009b). Icariin can protect against brain dysfunction induced by lipopolysaccharide in rats, and improve spatial learning and memory abilities by decreasing expressions of TNF- α , IL-1 and COX-2 in the hippocampus (Guo et al., 2010). Icariin can also reduce the degeneration of cortical neurons induced by LPS-activated microglia by blocking the TAK1/IKK/NF- κ B and JNK/p38 MAPK pathways (Zeng et al., 2010a). In an Alzheimer's disease model, icariin was shown to improve memory loss after chronic D-galactose administration in rats as preferred as aging and age-associated neurodegeneration model (Li et al., 2010). Moreover, icariin also exhibits a significant neuroprotective effect on neurons affected by β -amyloid proteins by inhibiting tau protein hyperphosphorylation (Zeng et al., 2010b).

Product availability and quality control

Many *Epimedium* species are used in Chinese medicine (Quan et al., 2010). They can vary in their icariin and flavonoid contents according to the species, harvest season, storage, geographical origin or other growing conditions (Zhang et al., 2008c). However, the quality of medicinal preparations is not assured because raw and processed materials can be mixed from different species (Sheng et al., 2008). Based on the standard criteria by the Chinese Pharmacopoeia (2005), flavonoid content as determined by UV is required to be more than 5.0% and icariin content (determined by HPLC) more than 0.5% (Committee of China Pharmacopoeia, 2005). *Epimedium* herbs can be stored long term because there is no

significant difference in icariin content between freshly prepared samples and those stored (Quan et al., 2010; Sheng et al., 2008). In Chinese pharmacopoeia, the quality criteria of *H. epimedii* consist of many leaves and only a few stalks. The leaves should be yellowish green and unfragmented (Bensky et al., 2004).

Reported toxicity

The median lethal dose (LD₅₀) of *H. epimedii* extract in mice has been reported as 36 g/kg via intraperitoneal injection. Overdose symptoms of *H. epimedii* are characterized by dilation of pupils, increased physical movement, mild spasms and cramps. Respiratory depression can be found in severe cases (Chen and Chen, 2004). However, no toxicity has been found via oral administration in mice (Kim et al., 2001).

ANGELICA SINENSIS (DONG QUAI)

A. sinensis (Dong quai) is a fragrant, perennial herb commonly found in China, Japan and Korea, and has various names including Chinese Angelica, dang gui (Chinese), toki (Japanese), tanggwi (Korean), and kinesisk kvan (Danish). Dong quai is a member of the Umbelliferae family, which produces white flowers that bloom in umbrella-like clusters. In traditional Chinese medicine, Dong quai is used as dried root for treating several disorders. Its flavor is a combination of bitter, sweet and pungent tastes. Its overall effect is warming in nature and is suitable for strengthening heart, lung and liver meridians, as well as lubricating the bowel. Dong quai is considered a blood tonic and has been used by generations of women for health concerns such as menstrual pain, menstrual cycle regulation, and peri- and post-menopausal symptoms.

Traditional and current uses

According to traditional Chinese medicine, Dong quai possesses sweet, acrid, warm, and pungent properties and enters the heart, liver and spleen channels. These properties make dong quai the most appropriate herb for harmonizing the blood. It has been used as a blood tonic to invigorate blood circulation and treat heart and liver blood deficiencies including anemia, pale complexions, brittle nails, dry hair, dizziness, blurred vision, palpitation and abdominal pain related to blood deficiency, and coolness.

The combination of dong quai with other herbs, such as astragal roots, is useful in various blood disorders. Dong quai has also been used in gastrointestinal disorders to moisten or lubricate the bowel for unblocking. For female health, Dong quai plays several important roles especially

in the postpartum period, menstrual disorders, amenorrhea, menopausal symptoms and even during pregnancy if used with caution. Dong quai is also used as an aphrodisiac to enhance sexual performance.

Sources and chemical composition

Dong quai grows at high altitudes in the cold damp mountains of China, Korea and Japan. The yellowish-brown thick-branched roots of Dong quai are the parts used as medicinal herb. Dong quai root contains 0.4 to 0.7% volatile oil, the key components of which are ligustilide, n-butylidenephthalide, n-butylphthalide, ferulic acid, nicotinic acid and succinic acid (Zhu, 1987). Significant amounts of vitamin A and carotenoids (0.675%), vitamin B12 (0.25 to 0.40 mcg/100 g), vitamin E, ascorbic acid, folic acid, biotin, various phytosterols (e.g., beta-sitosterol), calcium, magnesium and other essential macrominerals are also found in Dong quai roots (Zhu, 1987).

Other constituents of this medicinal herb include N-valerophenone-O-carboxylic acid, delta-2,4-dihydrophthalic anhydride, uracil, adenine, carvacrol, safrole, isosafrole, sesquiterpenes, beta-cadinene, n-dodecanol, n-tetradecanol, palmitic acid, angelic acid, myristic acid, sucrose (40%) and a polysaccharide with a molecular weight of approximately 3,000 (Zhu, 1987).

Natural coumarin derivatives have been attributed to dong quai, but reports differ regarding which ones are really present. The coumarin derivatives include angelol, angelicone, bergapten, oxypeucedanin, osthole, psoralen and 7-desmethyloberosin (Zhu, 1987).

Pharmacological and toxicological effects

Dong quai has various clinical implications due to its varied pharmacologically active constituents.

Cardiovascular effects

Dong quai has demonstrated quinidine-like activity on the heart. It can prolong the refractory period, lower blood pressure, and correct experimental atrial fibrillation induced by atropine, pituitrin, strophanthin, acetylcholine or electrical stimulation. Dong quai can dilate the coronary vessels, increase coronary flow, and reduce respiratory rate. An animal study using a water-based extract of Dong quai demonstrated a marked protective effect against myocardial dysfunction and myocardial injury induced by ischemia. A histological study has also demonstrated that a preparation of Dong quai and ligusticum significantly protected human umbilical vein endothelial cells against hydrogen peroxide damage, primarily by inhibiting reactive oxygen species formation

and promoting endothelial nitric oxide synthase (eNOS) expression (Hou et al., 2004).

Coumarins and coumarin derivatives, natural anticoagulants in *Angelica* spp., have been associated with both the bioactivity and toxicity of the plants; however, dong quai (*A. sinensis*) contains a lower coumarin content compared to other closely related species. Ferulic acid, one of the constituents of Dong quai, can inhibit the polymerization of platelets in blood circulation. It retards the platelet release of 5-hydroxytryptamine (5-HT) and adenosine diphosphate (ADP) (Zhu, 1987). Both ferulic acid and an aqueous extract of Dong quai have been found to inhibit platelet aggregation and serotonin release. These might be the mechanisms underlying the cardio-protective activity aforementioned.

Immune support and hematopoiesis

Lymphocyte proliferation assays indicate dong quai consistently exerts an immunostimulatory effect (Wilasrusmee et al., 2002a, b). A high molecular weight polysaccharide found in Dong quai has demonstrated immunostimulating activity and a blood tonifying effect by inducing hematopoiesis in the bone marrow. This is accomplished, in part, by either direct or indirect stimulation of macrophages, fibroblasts, erythrocytes, granulocytes and lymphocytes, and can induce an increased secretion of human growth factors from muscle tissue. Hematopoiesis is further supported by the presence of significant amounts of vitamin B12, folic acid and biotin in Dong quai.

Nephroprotective effects

A herbal preparation of Dong quai has long been used in China to treat nephrotic syndrome, as it has been thought to elicit antifibrotic effects. In a rat model study, chronic nephritic rats induced by puromycin were treated with either a Dong quai and other herb (*Astragalus*) mixture (3 ml/day) or enalapril (10 mg/kg). The normal control group received saline and another group received puromycin but no treatment. After 12 weeks, the untreated rats showed marked renal fibrosis. However, Dong quai significantly retarded the progression of renal fibrosis and deterioration of renal histological damage, with effects comparable to those induced by enalapril (Wang et al., 2004).

Antispasmodic activity

Ligustilide, butylidenephthalide and butylphthalide have been found to have antispasmodic activity against rat uterine contractions and in other smooth muscle systems. The components are characterized as non-specific

antispasmodics with the mechanism involved different from that used by papaverine, an opium alkaloid used primarily in the treatment of visceral spasm, vasospasm (Ko, 1980).

Gynecological effects

Administration of Dong quai is associated with both stimulating and relaxing effects on the uterine smooth muscle because there are two general components of Dong quai that affect uterine smooth muscle in opposite ways. The antispasmodic component of the herb is attributed to the volatile oils, such as ligustilide, butylidenephthalide and butylphthalide. As a balance, the uterine stimulating aspect is caused by the water and alcohol extract, nonvolatile constituents of the herb (Zhu, 1987). A small clinical study showed that when the uterus is in a relaxation state, Dong quai can induce contraction, while when it is in a contraction state, Dong quai promotes relaxation. Animal experiments *in vivo* have demonstrated increased excitability of the uterus, where the contractive rhythm of uterine smooth muscle changed from fast, weak and irregular to slower, stronger and more coordinated, depending on the uterine tone. This is believed to be the pharmacological basis for using dong quai during dysmenorrhea, which is not related to its estrogenic activity (Hirata et al., 1997).

One of the most common applications for Dong quai is for relieving vasomotor symptoms associated with the menopause. Such symptoms include hot flushes, skin flushing, perspiration and chills. The mechanism of action, however, is still unclear. In a randomized, double-blind, placebo-controlled clinical trial, 71 postmenopausal women received either Dong quai root (4.5 g) or placebo daily for 24 weeks (Hirata et al., 1997). There were no differences in vasomotor symptoms between the two groups and there appeared to be no estrogen-like effects on vaginal epithelial tissue. However, this lack of effect could be attributed to using Dong quai alone since traditional Chinese practitioners never prescribe it alone, but rather in combination with several other herbs. The researchers chose to study Dong quai alone because many women in the United States who take it to relieve menopausal symptoms purchase the herb over-the-counter as a single entity. Women should be discouraged from using Dong quai alone for relieving menopausal complaints. A herbal mixture containing *A. sinensis* root, *Paeonia lactiflora* root, *Ligusticum* rhizome, *Atractylodes* rhizome, *Alismatis* rhizome and *Sclerotium poria* has been reported to reduce menopausal disturbances, including vasomotor symptoms by 70% (Hirata et al., 1997).

Product availability and quality control

Dong quai is available in several forms, and dosages

vary accordingly. Typical oral dosages are as follows: dried root, 3 to 15 g daily by decoction; powdered root, 1 to 2 g 3 times daily; tea, 1 cup 1 to 3 times daily (1 g per cup); tincture (1:2), 4 to 8 ml (1 to 2 teaspoonful) per day; and capsules/tablets, 500 mg 1 to 6 times daily.

HPLC has been used to analyze chemical constituents of *A. sinensis*. By comparing the retention times, UV spectra, mass spectra and molecular weights of detected compounds with those published in literature, 15 constituents of *A. sinensis* could be tentatively identified and used for assessment of its quality (Wang et al., 2007c).

Reported toxicity

Dong quai has very low toxicity. The LD50 of a concentrated (8:1 to 16:1) Dong quai extract in mice is at 100 g/kg body weight. Intravenous administration of the essential oil to animals at doses of 1 ml/kg can cause a drop in blood pressure and depression of respiration. Overdose of Dong quai is characterized by fatigue, drowsiness, itching, dyspepsia and abdominal pain. Long-term ingestion at a dosage of 6 g/kg displays no abnormalities in physical activities, food intake body weight, urine examination or hematological examinations.

There is a case report of a man who developed gynecomastia after taking Dong quai capsules daily for approximately one month (Goh and Loh, 2001). The patient discontinued the "Dong quai" pills and his gynecomastia regressed completely when examined three months later. It is important to note that the pills in question were not properly analyzed to confirm or refute the purity of the product. Consequently, the authors could not rule out presence of a pharmacologically active contaminant that may have contributed to the patient's condition (Kiong, 2001).

Although no reported side effects have occurred with the use of authentic dong quai, various sources continue to warn of potential photosensitivity reactions due to the presence of psoralen and bergapten. Both psoralen and bergapten are furanocoumarins widely studied for their photosensitizing properties. Other related species of *Angelica* (e.g., *A. gigas*, *A. dahurica* and *A. pubescens*) pose a greater risk than Dong quai due to their higher furanocoumarin content. Dong quai is contraindicated in pregnancy, particularly in the first trimester, due to potential uterine stimulant and relaxant effects.

Pharmacokinetic properties and drug interactions

Data from an *in vitro* study has demonstrated the inducing property of Dong quai on the cytochrome P450 isoenzyme system, but report of a pharmacokinetic interaction between Dong quai and warfarin in an animal model does not support this interaction. Single subcutaneous doses of warfarin (2 mg/kg) were administered

with or without oral Dong quai extract (2 g/kg, twice daily for three days). The Dong quai treatment did not affect prothrombin time on its own, but significantly lowered the value three days after co-administration with warfarin. No significant variation in the pharmacokinetic parameters of warfarin after Dong quai treatment was found for either single-dose administration or steady-state concentrations of warfarin (Heck et al., 2000).

In a case report, a 46-year-old woman who had been taking 5 mg/day warfarin for nearly two years and had an international normalized ratio (INR) stabilized at 2 to 3 experienced an increase in her INR to 4.9 over the course of approximately two months. Changes in medication regimen, diet, alcohol consumption or other lifestyle factors that may have affected the INR were ruled out. However, the patient stated that for the previous four weeks she had been taking Dong quai for perimenopausal symptoms as recommended by a herbalist and had forgotten to mention this earlier. The dosage was one 565-mg tablet once to twice daily. The patient was instructed to discontinue Dong quai, and within four weeks her INR returned to the therapeutic range of 2.48. In view of this information, caution is advised for patients receiving chronic treatment with warfarin. Dong quai may potentiate the therapeutic and adverse effects associated with antiplatelet medications.

CONCLUSION

Chinese herbal medicine is widely used worldwide. Both beneficial activities and toxicities have been reported, and their uses should therefore be carefully considered. Because of their well-known benefits, combination of several herbal medicines has been registered as food supplements in many countries.

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