Chemical Information Review Document

for

Dong quai
[CAS Nos. 308068-61-3 (root) and 299184-76-2 (extract)]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

September 2008

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Abstract

Dong quai has been used for thousands of years in traditional Chinese, Korean, and Japanese medicine. Dong quai is marketed in the United States as a dietary supplement. It has been used to treat a variety of ailments including, dehydration, lumbago, hypertonia, nervous disorders, menopausal symptoms, neuralgia, angina, insomnia, and arthritis. Overall, human studies suggest that there is little evidence to support the use of Dong quai for any condition. Numerous side effects have been reported in clinical studies (e.g., headaches, abnormal heart rhythms, blood pressure abnormalities) and studies suggest that Dong quai may interfere or exacerbate effects produced by numerous drugs and herbs. Acute toxicity studies indicate that administration of Dong quai produced no effects at a dose up to 5000 mg/kg; similar results were observed in subchronic studies. Dong quai extracts have been reported to have synergistic effects with various chemicals and have antiproliferative and proapoptotic activities in cancer cells. No effect on fertility was observed after administration of Dong quai extract. Numerous studies have shown that Dong quai and its constituents have anticarcinogenic effects. While some studies indicated that Dong quai produces estrogen-like effects, other studies indicated minimal interaction with the endocrine system or suggested that the effects may not occur through interaction with estrogen receptors. One study showed that ethanol extracts of Dong quai had anti-estrogenic and anti-androgenic activity. Additional activities associated with Dong quai extracts and its constituents include modulation of enzyme activity, cellular proliferation, and gene expression; anxiolytic activity; insecticidal and antifungal activity; nephroprotective; gastric protective; pulmonary system protective; immunomodulatory effects; and antioxidant activity.

Executive Summary

Basis for Nomination

Dong quai (*Angelica sinensis* [*A. sinensis*] root or root oil) was nominated for toxicological characterization by a private individual because of its widespread use in dietary supplements, lack of adequate toxicological data, and concern regarding potential adverse effects, particularly for women of child-bearing age. It is a common ingredient used in traditional Chinese medicines for dietary supplement and has numerous applications including treatment of menstrual and menopausal symptoms, predominantly in Western medicine.

Nontoxicological Data

Dong quai, a perennial herb from Gansu and Shanxi provinces of China, grows in cold, damp, high-forested mountain terrain and in rich, deep sandy soil. It also is found in the United Kingdom, Lapland, and Iceland. Dong quai has been used for thousands of years in traditional Chinese, Korean, and Japanese medicine and is usually combined with other herbs. It has been used to treat a variety of ailments including, dehydration, lumbago, hypertonia, nervous disorders, menopausal symptoms, neuralgia, angina, insomnia, and arthritis. Constituents of Dong quai, typically identified using gas chromatography-mass spectrometry or high-performance liquid chromatography techniques, include alkyl phthalides, furanocoumarin, coumarins, terpenes, phytosterols, organic acids, and an immune-stimulating polysaccharide. Dong quai is commercially available in a variety of forms (e.g., capsules, tablets, tinctures) via the Internet, natural food stores, drug stores, chemical companies, and other retail stores. It is available solely and in a mixture with other herbs, vitamins, and minerals. Dong quai is marketed in the United States as a dietary supplement. It is typically processed by soaking, steaming, boiling, or frying *A. sinensis* in a variety of solvents (e.g., Chinese wine). Fumigation also may be used to process *A. sinensis* roots. The method of processing affects the composition of the *A. sinensis* extract. In addition to dietary supplements, exposure to Dong quai may occur through use of cosmetics or consumer products. According to 21CFR182.10, Angelica, Angelica root, and Angelica seed are generally recognized as safe for their intended use, within the meaning of Section 409 of the Food, Drug, and Cosmetic Act.

Human Data

Many human studies evaluating the beneficial effects of Dong quai have been conducted to date; many focused on the alleviation of menopausal symptoms. Overall, studies suggest that there is little evidence to support the use of Dong quai for any condition, including menopausal symptoms, kidney diseases, and coronary artery disease. Reported adverse effects include headaches, sedation/drowsiness, insomnia, fever/sweating/hot flashes, abnormal heart rhythms, blood pressure abnormalities, wheezing/asthma, worsened premenstrual symptoms, nephrosis, skin rash, gastrointestinal upset, acute onset of hypertension, and increased international normalized ratio. Dong quai may exacerbate effects produced by anticoagulant or antiplatelet drugs and herbs. Dong quai also may modulate effects of drugs that cause photosensitivity or affect heart rhythm. Numerous contraindications to Dong quai consumption have been noted. The constituents/analogues indirubin and meisoindigo in the Danggui Luhui Wang formula were reported to induce remission in patients with chronic phase chronic meylogenous leukemia.

Toxicological Data

No initiation/promotion, genotoxicity, or immunotoxicity studies were available for Dong quai. Additionally, data regarding chronic exposure, carcinogenicity, cogenotoxicity, and antigenotoxicity were not found for Dong quai or its constituents.

<u>Chemical Disposition, Metabolism, and Toxicokinetics</u>

The plasma concentration-time curve of ferulic acid, after oral administration of *Radix A. sinensis* and *Cortex Cinnamomi* to mice, conformed to a one-compartment model. Intragastric administration of *Radix A. sinensis* to rats resulted in peak plasma ferulic acid concentrations 5 minutes after treatment. In rats

exposed to a mixture of *Radix astragli* and *Radix A. sinensis*, ferulic acid was rapidly absorbed and eliminated. In rabbits given danggui oral solution (DOS), 32 components were common in plasma samples and DOS. Rabbit studies also showed that >40 components were absorbed after oral administration.

Studies with ligustilide showed that absorption after oral administration and intraperitoneal injection was rapid. The diffusion rate of ligustilide from blood to tissues was moderate, while the elimination rate was time- and dose-dependent. The wide distribution of ligustilide in tissues suggested that it could cross the blood-brain barrier. *In vitro* studies indicated that metabolism occurred only in the presence of an NADPH-regenerating system. Oral administration of *dl*-3-*n*-butylphthalide to rats showed that a majority of the applied dose was excreted in 24 hours.

Acute Toxicity

The LD_{50} values for Dong quai in mice was reported to be 100 g/kg (root extract) and 38 and 50 mL/kg (dried root; ethanol-water extract). The LD_{50} values for ferulic acid and 3-butylidenephthalide were reported to be >857 mg/kg. Acute toxicity studies indicate that administration of Dong quai produced no effects at a dose up to 5000 mg/kg. Intraperitoneal and intravenous (i.v.) injection of ferulic acid into mice caused behavioral changes and pleural thickening (i.v. only).

Short-term and Subchronic Exposure

A short abstract reported that daily oral administration of an alcoholic extract of *A. sinensis* for 3 months caused no significant changes in body or tissue weights or evaluated hematological and histopathological endpoints.

Synergistic/Antagonistic Effects

Dong quai has been reported to have many synergistic effects with various chemicals. For example, *A. sinensis* was observed to have a protective role on cartilage tissue and in the proliferation and differentiation of neural stem cells from hypoxic embryonic rats. *A. sinensis* alleviated bleomycin-induced pulmonary fibrosis in Sprague-Dawley rats. The ethanol extract of *Angelicae Radix* significantly inhibited the interferon-γ and tumor necrosis factor-α mediated cytotoxicity of rat thyroid cells. A low molecular weight fraction of an aqueous extract of *A. sinensis* had a protective effect in mice against lethal endotoxemia and sepsis.

In mice, polysaccharides from *A. sinensis* had a protective effect on bone marrow and gastrointestinal tissues against the cytotoxicity of cyclophosphamide, while sodium ferulate improved acetaminophen-induced liver toxicity, inhibited serum alanine aminotransferase activity, prevented depletion of liver glycogen and glutathione, increased liver homogenate and microsomal gluathione S-transferase activities, and reduced malondialdehyde content, mitochondria, and liver microsomal membrane fluidity. Ferulic acid inhibited cytochrome c-induced apoptosis in bovine hearts.

Cytotoxicity

Studies have shown that constituents of *Angelicae Sinensis Radix* were cytotoxic against mouse lymphocytic leukemia (L1210 cell line), human leukemia (K562 cell line), malignant glioblastoma multiforme cells, and mouse maloncytes. Studies also showed that Dong quai had cytotoxic effects against cancer cells. Overall, *A. sinensis* extracts produced antiproliferative and proapoptotic effects in numerous human and rodent cancer cell lines and types.

Reproductive and Teratological Effects

Subcutaneous injection of mice with an aqueous extract of *A. sinensis* had no effect on fertility. When Dong quai was administered to rats as part of a formulation (composed of six crude drugs including *A.*

Radix), increased placental blood flow and fetal body weight was observed. Development of small-for-date baby was decreased by administration of the formulation.

Initiation/Promotion Studies

No data were available for Dong quai. Topical application of ferulic acid to female mice, initiated with 7,12-dimethylbenz[*a*]-anthracene (DMBA) and promoted with 12-*O*-tetradecanoylphorbol-13-acetate (TPA), inhibited the number of TPA-induced tumors per mouse. However, ferulic acid had no effect when skin tumors were initiated in mice using DMBA followed by promotion with TPA.

Anticarcinogenicity

Numerous studies have shown that Dong quai and its constituents have anticarcinogenic effects. For example, when *Angelica radix* was administered to mice before and after transplantation of Ehrlich tumors, high survival and cure rates were reported. Polysaccharides isolated from *A. sinensis*, ferulic acid, arabinoglucan, *n*-butylidenephthalide, and 3-*n*-butylphthalide also exhibited anticarcinogenicty effects on human and rodent cancers *in vitro* and *in vivo*.

Genotoxicity

No data were available for Dong quai. Ferulic acid was negative for mutagenicity in *Salmonella typhimurium* in the presence and absence of metabolic activation.

Immunotoxicity

No data were available for Dong quai. When bergapten was orally administered to guinea pigs, an association between serum concentration and the phototoxicity (mainly in the epidermis) was observed.

Other Data

There are conflicting results in the literature on the effects of Dong quai in the endocrine system. While some studies indicated that Dong quai produces estrogen-like effects (e.g., increased MCF-7 cellular proliferation and affinity for estrogen receptors), other studies indicated minimal endocrine activity or suggested that the effects may not occur through interaction with the estrogen receptor. A study showed that ethanol extracts of Dong quai had anti-estrogenic and -androgenic activity.

Overall, studies with enzymes showed that extracts of *A. sinensis* can modify the activity of a variety of enzymes, including metabolic enzymes. Male rats gavaged with aqueous and ethanol extracts of Dong quai had increased liver microsome protein content and decreased cytochrome P450 levels. Results also showed that aqueous and ethanol extracts of Dong quai differentially modulated cytochrome P450 isoform activities. *In vivo* studies with *A. sinensis* polysaccharides (ASP) showed that ASP increased P450 levels and activities of additional metabolic enzymes (e.g., NAPH-cytochrome C reductase).

There are conflicting results on the effects of *A. sinensis* extracts on cellular proliferation and apoptosis. While some studies showed that *A. sinensis* extracts possess anti-proliferative and pro-apoptotic activities in vascular smooth muscle cells and rat T6 cells, others reported that *Angelica* extracts induced proliferation in murine bone marrow mononuclear and gastric epithelial cells. Dong quai also induced differentiation of mesanchymal stem cells and migration of gastric epithelial cells.

A. sinensis and Dong quai and its components modulate the expression of a variety of genes, which were proposed to play an integral role in the observed effects of Dong quai (e.g., neuroprotective effects). Additional activities ascribed to *Angelica* extracts and its active constituents include anxiolytic, insecticidal, and antifungal activity; nephroprotective, gastric protective, and pulmonary system protective effects; immunomodulatory effects; and antioxidant activity.

Structure-Activity Relationships

No data were directly applicable. A discussion of the activity of some constituents is provided in Appendix C.

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Chemical Information Review Document for Dong quai [CAS Nos. 308068-61-3 (root) and 299184-76-2 (extract)]

Tables:

1.0 Basis for Nomination

Dong quai (*Angelica sinensis* [*A. sinensis*] root or root oil) was nominated for toxicological characterization by a private individual because of its widespread use in dietary supplements, lack of adequate toxicological data, and concern regarding potential adverse effects, particularly for women of child-bearing age. It is a common ingredient used in traditional Chinese medicines (TCMs) for dietary supplement and has numerous applications including treatment of menstrual and menopausal symptoms, predominantly in Western medicine.

2.0 Introduction

Dong quai (Dang gui), a perennial herb from Gansu and Shanxi provinces of China, grows in cold, damp, high-forested mountain terrain and in rich, deep sandy soil. It also is commonly found in riverbanks and damp meadows and in countries such as the United Kingdom, Lapland, and Iceland. It is widely cultivated and blooms in the summer with compound white umbels. The main root is short (approximately 15-25 cm long) with additional roots branching off it. The outer surface of the root is brown with irregular wrinkles and yellow flesh (R'vival, undated; HolisticOnLine, 2000).

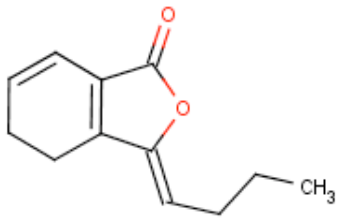
Compounds in Dong quai include alkyl phthalides (ligustilides, angelicide, and butylphthalide), furanocoumarin (archangelicin, bergapten, and imperatorin), coumarins (angelol G and angelicone), terpenes (cadinene and carvacrol), phytosterols (beta-sitosterol and stigmasterol), organic acids (ferulic, succinic, and myristic), and an immunostimulating polysaccharide (Bhatti et al., 2004). See Appendix C for more details about these compounds.

Dong quai
[308068-61-3 (root) and 299184-76-2 (extract)]

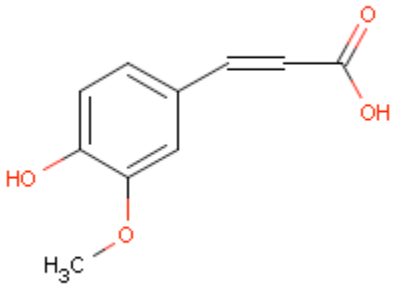
Source: MDidea Extracts Professional (2008)

Major Constituents

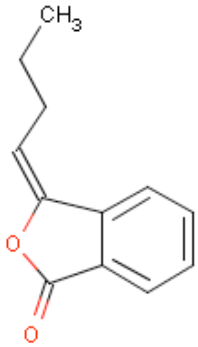
Ligustilide
[4431-01-0]



Ferulic Acid
[1135-24-6]



3-Butylidenephthalide
[551-08-6]



2.1 Chemical Identification and Analysis

Identification

Ligustilide ($C_{12}H_{14}O_2$; mol. wt. = 190.24) is also called:

1(3H)-Isobenzofuranone, 3-butylidene-4,5-dihydro-

PubChem CID: 158018
InChI: InChI=1/C12H14O2/c1-2-3-8-11-9-6-4-5-7-10(9)12(13)14-11/h5,7-8H,2-4,6H2,1H3/b11-8-
Smiles: C1(O\C(C=2CCC=CC12)=C/CCC)=O

Ferulic acid ($C_{10}H_{10}O_4$; mol. wt. = 194.18) is also called:

2-Propenoic acid, 3-(4-hydroxy-3-methoxyphenyl)-
3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid
3-(4-Hydroxy-3-methoxyphenyl)acrylic acid
3-Methoxy-4-hydroxycinnamic acid
4-Hydroxy-3-methoxy cinnamic acid
Cinnamic acid, 4-hydroxy-3-methoxy- (8CI)
Coniferic acid

PubChem CID: 709
InChI: InChI=1/C10H10O4/c1-14-9-6-7(2-4-8(9)11)3-5-10(12)13/h2-6,11H,1H3,(H,12,13)
Smiles: c1cc(\C=C/C(O)=O)cc(c1O)OC

3-Butylidenephthalide ($C_{12}H_{12}O_2$; mol. wt. = 188.23) is also called:

1(3H)-Isobenzofuranone, 3-butylidene-
3-Butylidene phthalide
3-Butylidene-1(3H)-isobenzofuranone
n-Butylidene phthalide
AI3-37306
Butylidenephthalide
BdPh
Butylidene phthalide
EINECS 208-991-3

FEMA No. 3333
Ligusticum lactone
NSC 325307
Phthalide, 3-butylidene-

PubChem CID: 642376 (3Z)-, 5352899 (3E)-
InChI: InChI=1/C12H12O2/c1-2-3-8-11-9-6-4-5-7-10(9)12(13)14-11/h4-8H,2-3H2,1H3/b11-8+
Smiles: c\12c(C(=O)OC1=C/CCC)cccc2

Sources: ChemIDplus (undated—a-c); PubChem (undated—a-c)

Analysis

Gas chromatography-mass spectrometry (GC-MS) has been used in a variety of applications for the identification of components of TCMs, including Dong quai. GC-MS has been shown to identify components in the essential oils of the main root and root fiber of Dong quai (L.-F. Huang et al., 2004 [PMID:14658022]). Essential oils of *A. sinensis* analyzed by GC-MS with chemometric resolution identified 76 of 91 constituents. These constituents amounted to 91.36% of the total content with ligustilide, butylidene phthalide, 2-methoxy-4-vinylphenol, carvacrol, allo-ocimene, 2,6,6-trimethylbicyclo-[3,1,1]hept-2-ene as the main constituents of *A. sinensis* root (M. Wu et al., 2005). Ligustilide was extracted from *A. sinensis* and *Ligusticum chuanxiong* by water at 150 °C and 40 bar, concentrated by headspace solid-phase microextraction and analyzed by GC-MS (C. Deng et al, 2005 [PMID:16117002]). Volatile oils from Japanese and North Korean varieties of *A. sinensis* (Oliv.) obtained by steam distillation of fresh leaves and whole flowers and analyzed by GC and GC-MS detected approximately 50 compounds including (*Z*)-ligustilide in Japanese leaf, flower oils and in oils of North Korean variety (11.9, 33.6, and 13.6%, respectively) (Dung et al., 1996). Rapid analysis of (*Z*)-ligustilide in rabbit plasma after oral administration of the essential oil of Dong quai also was possible using headspace single-drop microextraction followed by GC-MS (Dong et al., 2007 [PMID:17623474]). Volatile components in dry root samples of *A. sinensis* and *A. pubescens* (Duohuo) determined by headspace solid-phase microextraction GC-MS method identified 36 and 87 compounds in *A. sinensis* and *A. pubescens* roots, respectively (G. Song et al., 2004).

High-performance liquid chromatography (HPLC) also has been widely used in the evaluation of the components of Dong quai. HPLC with ultraviolet detection analyzed ligustilide and ferulic acid content in different extracts of *A. sinenses* (J.-C. Song et al., 2007). S. Wang et al. (2007) showed that HPLC, coupled with discriminant analysis, could differentiate *A. Sinensis* (Oliv.) Diels from different geographic regions based on development of a chromatographic fingerprint. HPLC with pulsed amperometric detection combined with atmospheric pressure chemical ionization (APCI) and electrospray ionization mass spectrometry identified 15 constituents (such as (*Z*)-ligustilide, (*Z*)-butylidinephthalide, polysaccharides, and ferulic acid) of *A. sinensis* (Y.-L. Wang, et al., 2007 [PMID:17623360]). Using HPLC, the average content of (*Z*)-ligustilide in Szechwan Lovage Rhizome herb, was determined to be 7.40 ± 3.54 mg/g (S.-Q. Cheng et al., 2006 [PMID:17048579]). Using HPLC-electrospray ionization-mass spectrometry, 16 compounds, including phthalides, were identified in the rhizome of *A. sinensis* (Lin et al., 1998).

The pharmacokinetics of five main bioactive components of Daggui Buxue Tang extract in rat plasma was studied using liquid chromatography-mass spectrometry (LC-MS) (Wen et al., 2008 [PMID:18346946]). Additionally, the pharmacokinetics of ligustilide have been studied in rats using GC-MS (Y. Shi et al., 2006 [PMID:16583458]). In rabbit plasma, rapid screening and analysis of various absorbed bioactive components and metabolites of Dangguibuxue decocotion was performed using liquid chromatography/diode array detection mass spectrometry (LC/DAD-MS) with the metabolic fingerprinting technique; 46 components were found absorbed (P. Wang et al., 2007 [PMID:17154345]). In a separate study, the same technique was used with atmospheric pressure chemical ionization mass spectrometry in negative mode (LC-DAD-APCI-MS); >32 constituents were found absorbed (Y.-L. Wang et al., 2005 [PMID:16132135]). The absorption of *A. sinensis* in rabbit plasma has also been evaluated with HPLC-DAD-MS and multicomponent spectral correlative chromatography; >40 ingredients were found absorbed into rabbit body (Y.-L. Wang et al., 2006).

Ferulic acid extracted from two types of *A. sinensis* and analyzed by HPLC reported 100% recovery with 3.19% relative standard deviation (Ma and Ding, 2006). Ferulic acid extracted from the roots of *A. sinensis* with supercritical CO_2 showed maximum content of 0.35-0.37% ferulic acid; conventional percolation methods showed higher amounts (0.61-0.85%) of ferulic acid (Sun et al., 2006 [PMID:16753921]).

Another method of analyzing radix *A. sinensis* is by powder X-ray diffraction Fourier fingerprinting pattern method (S. Wang et al., 2003 [PMID:14768388]).

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
	Ligustilide	
Physical State	not available	
Odor	not available	
Boiling Point (°C)	377 ± 11.0 @760 mm Hg (calculated)	Registry (2006)
Melting Point (°C)	not available	
Flash Point (°C)	158.6 ± 16.7 (calculated)	Registry (2006)
Vapor Pressure (mm Hg)	6.55 x10^{-6} (calculated)	Registry (2006)
Specific Gravity	1.10 ± 0.1 g/cm^3 (calculated)	Registry (2006)
Water Solubility	not available	
Octanol-water partition coefficient (log K_{OW})	not available	
Bioconcentration Factor	58.07 (pH1-10) @ 25°C (calculated)	Registry (2006)
Log P	2.624 ± 0.433 @ 25°C (calculated)	Registry (2006)
	Ferulic acid	
Physical State	not available	
Odor	not available	
Boiling Point (°C)	not available	
Melting Point (°C)	not available	
Flash Point (°C)	not available	
Vapor Pressure (mm Hg)	2.69×10^{-6} @ 25 °C (estimated)	ChemIDplus (undated-b)
Specific Gravity	not available	
Water Solubility (mg/L)	5970 @ 25 °C (estimated)	ChemIDplus (undated-b)
Octanol-water partition coefficient (log K_{OW})	1.51	ChemIDplus (undated-b)

Note: Data for 3-butylidenephthalide were not available.

Dong quai has a distinctive sweet, pungent aroma (Herb Database, undated). Many alkylphthalides and their dimers have been identified as components of Dong quai extract. (*Z*)-Ligustilide, which represents about 60% of the total phthalide content, is unstable, changing to other phthalides through oxidation, dimerization, and other chemical reactions. An epoxide is one of the oxidation products (Lin et al., 1998).

2.3 Commercial Availability

Dong quai (root, extracts, tinctures, capsules, teas) is commercially available via the Internet (e.g., Amazon.com, HerbWise, Viable Herbal Solutions, Allegro Medical Supplies, iHerb), natural food stores, drug stores, and other retail stores. Chemical companies (e.g., Chromadex, Inc., California and Spectrum Chemicals and Laboratory Products Inc., California) supply Dong quai root and root powder as listed in their catalogs (ChemExper, 2008). It also is found in nutritional supplements marketed by companies such as the Bayer Corporation and American Home Products (Chain Drug Review, 1999).

Dong quai is marketed in the US as a dietary supplement (Want et al., 2005). It is available solely and in a mixture with other herbs, vitamins, and minerals (e.g., Dong QuaiSingle Herb Capsules, Dong QuaiStandardized Extract Tablets, Avlimil, Phyto Estrogen Power, Menopausal Formula, and Menstrual-Ease) (Bhatti et al., 2004). It also is sold with brand names such as GNC Herbal Plus Fingerprinted Dong quai 500 mg and GNC Natures Fingerprint Dong quai 550 mg. The Dietary Supplements Labels Database (2007), managed by the US National Library of Medicine, shows that approximately 40 brand names contain "Dong quai" as one of their ingredients (e.g., Rainbow Light PMS Relief, Natures Sunshine Flash Ease Tablets, Natural Balance Ladies Choice, Planetary Formulas CholestGar, and Veglife Herbal Estrogen).

3.0 Production Processes

Processing of *A. sinensis* includes soaking, steaming, boiling, or frying in Chinese wine, rice vinegar, juice of ginger or other herbs; or fried with rice, earth, or urine of children. The method of processing affects the concentration of constituents (volatile oils, saccharide and ferulic acid) of *A. sinensis* (Yu, 2006).

Fresh roots of *A. sinensis* (Oliv.) Diels samples (A, B, and C) were collected and processed (based on 2002 Good Agricultural Practice Guidelines in China) by fumigating with fumes from burning wheat stems, broad bean stems, and wood, respectively. Samples D and E were dried in shade and sunlight, respectively. Constituents of the processed samples were then analyzed by UV/VIS spectrophotometry (for polysaccharides), HPLC (for (*Z*)-ligustilide and free and total ferulic acid), and Fourier-transform infrared spectra. Results showed that the fumigation process from burning wheat stems (Sample A) yielded the highest levels of ligustilide, free ferulic acid, and total ferulic acid; the level of polysaccharides also were relatively higher in content. The authors concluded that that the fumigation with wheat stems can be considered the most suitable for processing (G.H. Lu et al., 2006 abstr.).

In vitro culture before planting described a suspension culture of embryogenic callus taken from embryos of *A. sinensis*, shaken at 100 rpm and 0.3% agar added to produce somatic and germinating embryos. Forty percent of germinating embryos survived after culturing on filter

paper wetted with Murashige and Skoog basal medium in 3% sucrose and then planted in the soil successfully (Tsay and Huang, 1998). A tissue culture method for *in vitro* propagation via embryogenesis and organogenesis of some Chinese herbs including *A. sinensis* and other medicinal plants also was reviewed by Nalawade and Tsay (2004).

A. sinensis are sliced (1.7-2.7 mm thick), air or oven dried at <45 °C, mixed with yellow wine, and fried at ≤50 °C until dark brown. The extracted pieces were then made into granules by decocting in water to obtain a concentrated extract, mixed with an adjuvant, granulated, dried, and graded. Ferulic acid and ligustilide content in the extracted pieces were found to be not less than 0.05 % and 0.08 %, respectively (Y. Zhang et al., 2008 pat.).

[Note: Hsu and Fu (2004) noted that some herbal extracts exhibited detectable levels of endotoxin (>1 ng/mL). The authors indicate that the levels are greater than those necessary for cytokine production. Therefore, endotoxin contamination should be assessed in herbal extracts.]

4.0 Production and Import Volumes

A 1996 Whole Foods survey of health food stores (100/9,000 stores responded) showed Dong quai ranked 17th in herbal supplement sales volume (American Botanical Council, 1999).

5.0 Uses

Dong quai has been used for thousands of years in traditional Chinese, Korean, and Japanese medicine and is usually combined with other herbs. The powdered root of *A. sinensis* can be used in capsules, tablets, tinctures, or as tea (HolisticOnLine, 2000). It is purported to curtail excess antibody production, reduce food allergies, and lessen inflammatory reactions. It has been shown to suppress high TH2 cytokine profile in individuals with CFIDS, AIDS, and chronic candidiasis (Anonymous, 1998 [PMID:11366544]).

In China, Dong quai has been used to treat a variety of ailments. It has been used to treat blood deficiency and blood stagnation (in Si Wu Tang mixture) and spleen deficiency and liver Qi stasis (in Xia Yao San mixture) (Belford-Courtney, 1994; Memorial Sloan-Kettering Cancer Center, 2007; Zhu, 1987 [PubMed:3425569]). It also has been used to treat dehydration, lumbago, hypertonia, and nervous disorders in folk medicine (WHO, 2004). Dong quai has been used in injection into acupuncture points, for painful injury, neuralgia, angina, and arthritis. Angelica root in chicken soup is used after childbirth (Herb Database, undated). Dong quai has been referred to as the "female ginseng" and serves as an all-purpose women's herb (Memorial Sloan-Kettering Cancer Center, 2007). It is used to regain normal menstrual cycles after taking birth control pills and relief from hot flashes during menopause. It can be used as a mild laxative, for insomnia, and to stabilize blood pressure in both men and women (Raintree Nutrition, 1996). Dong quai combined with other herbs has been proposed to be used for the treatment of obesity (Fujimoto, 2001 pat.). *A. sinensis* oil containing ≥60-99% ligustilide also has been proposed to treat and prevent diseases caused by endotoxin and to control inflammation factors induced by endotoxin (Teng et al., 2006 pat.). Dong quai also has been included in specialty bath and body products (Grossman, 1999).

6.0 Environmental Occurrence and Persistence

No relevant data were available.

7.0 Human Exposure

Exposure from Herbal Dietary Supplements and Traditional Medicines

In the 2000 edition of the *Pharmacopoeia of the People's Republic of China*, more than 80 formulas include *A. sinensis* root. The Japanese *Pharmacopoeia* includes 56 formulations with *A. sinensis* root (Deng, 2005 diss.). Many single- and multi-ingredient products containing powdered or dried root slices, Dong quai root fluid extracts, tinctures, decoctions, and its essential oil as well as dried leaf preparations are available as dietary supplements.

The recommended dosage of Dong quai depends upon the manufacturer and can be highly variable. Dong quai dosages in dietary supplements, as shown in the Dietary Supplements Labels Database (2007), range from 10 to 550 mg/day. Additional recommended dosages include 3 to 3.6 g powdered herb/day, 0.75 to 30 g crude Dong quai root/day, and 4.5 to 9.0 g crude drug/day (MedFacts Natural Products Professional Database, undated; University of Maryland Medical Center, 2008; WHO, 2004). According to HighBeam Encyclopedia (2004), oral dosages of additional forms of Dong quai are:

- Dried root: 3-15 g daily by decoction
- Powdered root: 1-2g 3 x/day
- Tea: 1 cup 1-3 x/day (1 g/cup)
- Tincture (1:2): 4-8 mL (1-2 tsp)/day.

It has been suggested that long-term use of Dong quai products should be avoided due to the content of safrole in the essential oil of Dong quai (Natural Standard Research Collaboration, 2008).

Exposure from Cosmetics

The Skin Deep Cosmetic Safety Database lists 19 cosmetic products that contain Dong quai root extract. Sunscreen products with Dong quai typically limit content to less than one percent (Natural Standard Research Collaboration, 2008). Other substances in multi-ingredient formulations may influence dermal absorption of Dong quai constituents such as ferulic acid (Wei et al., 2000 [PMID:12205970]).

Exposure to Constituents in Common with Other Herbal Dietary Supplements, Foods, and Cosmetics

Several constituents present in Dong quai have been found in other dietary supplements and foods. Phthalides have been found in other *Angelica* species (e.g., *A. gigas*), *Ligusticum chuanxiong* (or *wallichi*), and *Levesticum officinale* (lovage) (Blumenthal, 1998; Dr. Duke's Phytochemical and Ethnobotanical Databases, 2008). Ligustilide was reported at 5000 ppm in the essential oil of celery. Dr. Duke's Phytochemical and Ethnobotanical Databases (2008) indicated that ferulic acid has been found in garlic bulbs, potatoes, spinach and cabbage leaves, citrus fruits, peanuts, and corn.

Several fruits, vegetables, and cold-pressed oils from citrus fruits contain furocoumarins (e.g., 5-[bergapten] and 8-methoxypsoralens), which may be used as food and cosmetic ingredients. Furocoumarins, when combined with ultraviolet radiation, may be phototoxic, cytotoxic, and mutagenic. Bergapten was found in citrus fruits, parsnips (3800 ppm), carrots (0.3 ppm), and

celery. The Senate Commission on Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft reviewed these two furocoumarins for safety and stated that typical amounts of processed foods that have been correctly stored present no significant risk for phototoxicity (DFG SKLM, 2004). EMEA (2007) concluded that there were no additional risks associated with furocoumarin ingestion at up to 15 µg/day from *A. archangelica* and other *Angelica* species when total furocoumarin exposure was as much as 1.5 mg/day. However, use in children and pregnant women was contraindicated. Additionally, if dietary supplement use would lead to a furocoumarins exposure of more than 1.5 mg/day, the Agency stated that a detailed risk benefit assessment was necessary.

Contamination by Lead or Pesticides

Herbs for traditional Chinese medicine grown in China may be harvested from soils contaminated with heavy metals, which may lead to contamination by lead or pesticides. Lead concentrations were determined in purchased preparations of *A. sinensis radix* and a combination drug Shy-Wuh-Tang with *A. sinensis*. *A. sinensis radix* with 19.42 ± 0.01 µg Pb/kg had the lowest concentration while Shy-Wuh-Tang had the highest (322.31 ± 0.30 µg Pb/kg). A study of lead concentrations in breast milk of women who took Chinese herbal medicines found significantly higher lead concentrations in the consumption group than in the control group. Intakes by two infants were estimated to have exceeded a provisional tolerable daily intake of 3.57 µg Pb/kg bw/day. The authors concluded that herbal consumption increased lead levels in breast milk and in nursing infants (L.C. Chien et al., 2006 [PMID:16398988]).

8.0 Regulatory Status

In 21CFR182.10, Angelica, Angelica root, and Angelica seed [Angelica archangelica L. or other spp. of Angelica.] are listed as spices and other natural seasonings and flavorings that are generally recognized as safe for their intended use, within the meaning of Section 409 of the Federal Food, Drug, and Cosmetic Act (U.S. FDA, 2003).

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

Clinical Trials

Many human studies of the beneficial effects of Dong quai are available; a few are reviewed here. No attempt was made to retrieve all studies to identify side effects. The Natural Standard Monograph stated that little human evidence supports the use of Dong quai for any condition, including menopausal symptoms, kidney diseases, and coronary artery disease (Natural Standard Research Collaboration, 2008). Human efficacy studies for treatment of menstrual disorders were reviewed by WHO (2004). Most clinical studies have been poorly designed, reported insignificant results, and/or used multi-ingredient formulations. Other clinical studies and pharmacological activities of *A. sinensis* and some of its active principles, including polysaccharides, ferulic acid, and ligustilide were reviewed by Deng (2005 diss.).

A double-blind, randomized, placebo-controlled six-month clinical trial of Dong quai was conducted with 71 postmenopausal women (61 completed the study). No statistically significant differences between the treated and placebo groups were observed in any of the measures

evaluated (e.g., endometrial thickness and number of vasomotor flushes ["hot flashes"]). Frequencies of burping, gas, and headache were similar in both groups (Hirata et al., 1997 [PMID:9418683]).

A double-blind, randomized, placebo-controlled study of *A. sinensis* used alone to treat hot flashes in men with prostate cancer who have been deprived of androgen for at least one month is being conducted by Lawson Health Research Institute at the Urology Clinic and Prostate Centre, St. Joseph's Health Care London (Ontario, Canada). [Noted: The trial has an estimated completion date of July 2008 (ClinicalTrials.gov, 2008 [Identifier NCT00199485]). No interim publications were identified.]

Studies also have been conducted with herbal preparations that contain *A. sinensis*. In a one-year randomized, double-blind, placebo-controlled U.S. clinical trial Dong quai, in a multibotanical preparation, was shown to have no effect on vaginal epithelium, endometrium, or reproductive hormones (Reed et al., 2008 [PMID:18257142]). Comparatively, a randomized, double-blind, multiple-dose escalation study of Danggui Buxue Tang (*Radix Angelicae* and *Radix Astragali*) (DBT) showed that DBT was better than placebo in controlling vasomotor symptoms of postmenopausal Chinese women (Haines et al., 2007 abstr.; ClinicalTrials.gov, 2008 [Identifier NCT00420576]). Additionally, two different herbal preparations containing *A. sinensis* were reported to be effective for the treatment of menopausal symptoms in 12-week, placebo-controlled trials (Huntley and Ernst, 2003; Kupfersztain et al., 2003 [PMID:14664413]).

ClinicalTrials.gov (2008 [Identifier NCT00421564]) further identified a clinical trial that evaluated the effect of DBT on menopausal symptoms of hot flushes and sweating.

Adverse Effects

Case Reports

After a 32-year-old woman ingested two servings of a Chinese soup containing Malaysian Dong quai, she suffered an acute onset of hypertension accompanied by headache, weakness, light headedness, and vomiting. Her condition returned to normal within 12 hours. Her breast-fed infant was hypertensive the next day; his pressure returned to normal after 48 hours while breast-feeding was withheld. The Malaysian preparation was judged to be "true dong quai" and showed no analytic differences with other purchased Dong quai products (Nambiar et al., 1999 lett.).

A 46-year-old African-American woman, taking warfarin, showed a increased prothrombin time and international normalized ratio, which is a measure of time needed for blood to clot, after use of Dong quai at daily doses of one to two 565-mg tablets per day for four weeks. Levels returned to the acceptable range one month after cessation of Dong quai (Page and Lawrence, 1999 [PMID:10417036]).

A case report of a Singapore man who developed gynecomastia after taking Dong quai pills may have been due to adulteration with synthetic estrogen (EBSCO Publishing, 2004; Goh and Loh, 2001 [PMID:11405562]).

Side Effects

No reliable studies of adverse effects from chronic exposure to Dong quai are available. However, the Natural Standard Monograph (Natural Standard Research Collaboration, 2008) listed the following as side effects reported in well-designed studies:

headache	abnormal heart rhythms	reduced menstrual flow
light headedness/dizziness	blood pressure	nephrosis
sedation/drowsiness	abnormalities	skin rash
insomnia	wheezing/asthma	upset stomach
irritability	laxative effects/diarrhea	nausea and vomiting
fever/sweating/hot flashes	worsened premenstrual	burping or bloating
weakness	symptoms	loss of appetite

Immunotoxicity

Few studies or case reports were found regarding dermal sensitivity to Dong quai. *Radix Angelicae Pubescentis* was frequently positive in patch tests among 30 patients with dermatitis who used TCM. *Radix Angelicae Dahuricae* had low allergenicity (H.H. Chen et al., 2003 [PMID:14641114]). A case study showed that Dong quai extract produced an early asthmatic response in bronchoprovocation tests but no specific immunoglobulin E binding. The extract released a greater amount of histamine from basophils of the patient than from those of a healthy control, which may have led to the bronchoconstriction in the patient (S.K. Lee et al., 2001 [PMID:11345295]). [The *Angelica radix* used may have been the Korean species.] Dong quai constituents, bergapten and psoralens, may induce dermal photosensitivity responses (Graedon and Graedon, 1999).

Human Drug Interactions

Dong quai may exacerbate effects produced by anticoagulant (blood-thinning) or antiplatelet (antithrombotic) drugs and herbs such as Coumadin® (warfarin), heparin, aspirin, ibuprofen (e.g., Advil®), naproxen (e.g., Aleve®), celecoxib (Celebrex®), Clopidogrel hydrogen sulfate (Plavix®), Ticlopidine (e.g., Ticlid®), Pentoxifylline (e.g., Trental®), Ginkgo, Ginseng, Licorice, and Chamomile (Bhatti et al., 2004; EBSCO Publishing, 2004; St. Luke's Regional Medical Center, 2000). Other dietary supplements with documented potential interactions with warfarin (e.g., danshen, devil's claw, green tea, vitamin E, and coenzyme Q10; [Heck et al., 2000 [PMID:10902065]; S.-M. Huang, 2005]) might also increase bleeding risk when taken with Dong quai.

Dong quai may potentiate effects of other drugs that cause photosensitivity such as tretinoin (Retin-A®, Renova®) and some types of antidepressants (e.g., serotonin reuptake inhibitors, antineoplastic, antibiotic, and antipsychotic drugs; the dietary supplement St. John's wort); and products containing capsacain (e.g., Zostrix®). Drugs that affect heart rhythm such as digoxin; β-blockers (e.g., metoprolol [Lopressor®, Toprol®]); calcium-channel blockers (e.g., nifepidine [Procardia®]); or other anti-arrhythmic drugs also may be potentiated by Dong quai. Dong quai interaction with estrogenic drugs used for birth control or hormone replacement and selective estrogen receptor (ER) modulators is unknown (Natural Standard Research Collaboration, 2008).

Contraindications

Dong quai is not recommended for

- Pregnant or nursing mothers
- Women who have had breast cancer
- Children or patients with diarrhea
- Patients with hemorrhagic diseases or hypermenorrhea
- Patients with gastroesophageal reflux
- Persons who have prolonged exposure to sunlight or to artificial ultraviolet light
- Patients with diabetes or glucose intolerance
- Persons with known allergic sensitivity to plants in the Apiaceae/Umbelliferae family ()

(Graedon and Graedon, 1999; Lau et al., 2005 [PMID:16278617]; Natural Standard Research Collaboration, 2008; Tilgner, 1999; WHO, 2004).

It is not clear whether Dong quai use would be unsafe in persons with other hormone-sensitive conditions (Natural Standard Research Collaboration, 2008).

Anticarcinogenicity

The constituents/analogues indirubin and meisoindigo in the Danggui Luhui Wang formula were reported to induce hematologic remission in patients with chronic phase chronic meylogenous leukemia (Xiao and Hao, 2006).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Details of the following studies are presented in **Table 1**.

A. Sinensis Alone or in a Binary Mixture (Detection of Ferulic Acid)

When a combination of *Radix A. sinensis* and *Cortex Cinnamomi* was orally administered to mice, the plasma concentration-time curve of ferulic acid (one-compartmental model) resulted in a relative bioavailability of 226.75% (Z.Y. Yang et al., 2006 [PMID:17048653]). After oral (intragastric) administration of *Radix A. sinensis* (dose not provided) to rats, peak ferulic acid concentrations in plasma were observed at 5 minutes after treatment; half-life was ~89 minutes. The values of normalized AUC_{180} (area under plasma-concentration time curve from 0 to 180 minutes) and c_{max} (peak concentration) by dose of ferulic acid were ~4376 ng·min/mL and 109 ng/mL, respectively (X.D. Liu et al., 2003). In rats fed DBT, ferulic acid was rapidly absorbed and eliminated. [Noted: Comparisons were made with four other components (calycosin-7-*O*-β-D-glucoside, ononin, astragaloside I, and stragaloside IV)] (Wen et al., 2008 [PMID:18346946]).

In a rabbit given danggui oral solution (DOS) (50 g/kg), 32 components found common in both plasma samples and DOS were absorbed into the body. Ten other peaks were found only in the plasma samples—possible metabolites of the chemicals in the DOS (Y.L. Wang et al., 2005 [PMID:16132135]). In a follow-up study using a multicomponent spectral correlative chromatography algorithm, >40 chemical ingredients were found absorbed into the rabbit body [data, similar to 2005 study, not presented in table] (Y.L. Wang et al., 2006). In another similar study, 46 components in an oral solution of Dangguibuxue decoction, composed of huangqi (*Radix astragali*) and danggui (*Radix A. sinensis*) (5:1 m/m), were found absorbed into the rabbit body (P. Wang et al., 2007 [PMID:17154345]).

Ligustilide

When rats were orally administered ligustilide (20 mg/kg), absorption of ligustilide was rapid; peak concentration was reached at ~40 minutes. The diffusion rate of ligustilide from blood to tissues was moderate (distribution volume, ~2.2 L/kg), while the elimination rate was variable: rapid elimination was seen from 0.65 to 3 hours, while a slightly slower elimination was seen from 3 to 12 hours. The wide distribution of ligustilide in tissues suggested that it could cross the blood-brain barrier (Y. Shi et al., 2006 [PMID:16583458]).

In another study, the rapid absorption of ligustilide (500 mg/kg) via the oral route was observed. Bioavailability was 2.6% and plasma concentration decreased in a multiphase manner. Similarly, when administered via intraperitoneal (i.p.) injection, ligustilide (26 or 52 mg/kg) was rapidly absorbed (see T_{max}) and eliminated ($t_{1/2}$); pharmacokinetic parameters were found to be dose-dependent. Intravenous administration of ligustilide to rats resulted in widespread distribution in the body (V_d) and rapid elimination ($t_{1/2}$) from plasma; elimination and clearance were significantly faster as the Chuanxiong extract than as the pure form. Bioavailability was ~46% for the i.p. route with the Chuanxiong extract (compared to the pure form) and 52% and 98% via the i.p. route with the low and high doses, respectively. Additionally, 15 metabolites were found; of these, seven were identified (including butylidenephthalide). Metabolism occurred *in vitro* in rat intestinal S9 fractions or microsomes only in the presence of an NADPH-regenerating system (R. Yan et al., 2008 [PMID:18039808]). [The authors proposed metabolic pathways of ligustilide in the rat; see Figure 4 in publication.]

dl-3-*n*-Butylphthalide (NBP)

When rats were orally administered ^{3}H-NBP (dose not provided), ~74% of the applied dose was excreted in the urine and feces at 24 hours and 2.53% at 72 hours, indicating no accumulation of NBP. Two metabolites were detected: MI in the brain, and MI and MII in the urine. Because the ratio of radioactive MI to NBP was 1:1 in the brain at 1 hour after dosing, MI and MII were proposed as the main *in vivo* metabolites of NBP and MI an active metabolite (C.H. Wang et al., 1997 [PMID:11596286]).

Table 1. Chemical Disposition, Metabolism, and Toxicokinetics of Dong Quai and Its Constituents

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***A. Sinensis* Alone or in a Binary Mixture**				
Mice, strain, age, number, and sex n.p.	combination of *Radix A. sinensis* and *Cortex Cinnamomi*	oral; dose n.p., duration n.p., observation period n.p.	Plasma concentration-time curve of ferulic acid (one-compartmental model) resulted in a relative bioavailability of 226.75%, an increase in that of ferulic acid.	Z.Y. Yang et al. (2006) [PMID:17048653]
Rats, strain, age, number, and sex n.p.		oral (intragastric); dose n.p.; duration n.p.; observed for up to 180 min	Peak ferulic acid concentrations in plasma were observed at 5 min after treatment; half-life was ~89 min. AUC_{180} = ~4376 ng·min/mL c_{max} = 109 ng/mL	X.D. Liu et al. (2003)
Rats, Sprague-Dawley, age n.p., 6/group, sex n.p.	Danggui Buxue Tang (DBT), made of *Radix Astragli* and *Radix Angelica Sinensis* (5:1 w/w)	oral; 13.5 mL/kg, sacrificed at 0.08, 0.16, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 18, or 24 hr and blood collected	Ferulic acid concentrations were fitted to a one-compartment model. T_{max} = 0.43 hr C_{max} = 0.049 µg/mL $t_{1/2}$ = 0.5 hr CL = 546.4 mL/kg·h $AUC_{0-\infty}$ = 0.065 µg/hr·mL MRT = 1.26 hr	Wen et al. (2008) [PMID:18346946]
Rabbit, strain and age n.p., 1, sex n.p.	*A. sinensis* (danggui oral solution [DOS])	oral; 50 g/kg; blood collected at 0, 15, 40 min, 1, 1.5, 2, and 3 hr	In DOS and plasma samples, 32 peaks were common; these were absorbed into the rabbit's body. Compounds identified were senkyunolides I and H, *Z*-6,7-epoxyligustilide, 3-butylidene-7-hydroxyphthalide, *Z*-ligustilide, *Z*-butylidenephthalide, dimers of ligustilide, falcarindiol, linolenic acid, and linoleic acid. In the plasma sample, 10 peaks were found. These are possible metabolites of the chemicals in the DOS. Y.L. Wang et al. (2006) later found >40 absorbed components using their analytical technique with MSCC.	Y.L. Wang et al. (2005) [PMID:16132135]

Table 1. Chemical Disposition, Metabolism, and Toxicokinetics of Dong Quai and Its Constituents (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rabbit, strain and age n.p., 1, sex n.p.	oral solution of Dangguibuxue decoction (ODD)	oral; 50 g/kg; blood collected at 0, 20, 40 min, 1, 1.5, 2, 3, and 4 hr	In the ODD and plasma samples, 46 peaks were common; these were absorbed into the rabbit's body. Compounded identified were calycosin-7-*O*-β-D-glycoside, (6a*R*,11a*R*)-3-hydroxy-9,10-dimethoxypterocarpan-3-*O*-β-D-glycoside, ononin, *L*-3-hydroxy-9,10-dimethoxypterocarpan, formononetin, (3*R*)-7,2'-dihydroxy-3',4'-dimethoxyisoflavan, sedanenolide, *E*-ligustilide, *Z*-ligustilide, *Z*-butylidenephthalide, and astragaloside IV. In the ODD, 21 peaks were found. These are possible metabolites of the components in the ODD.	P. Wang et al. (2007) [PMID:17154345]
Ligustilide				
Rats, Sprague-Dawley, age n.p., 5/dose group, M and F	ligustilide, purity n.p.	oral; 20 mg/kg; observed for up to 12 hr (last blood collection) Group 1 rats (blood studies): samples collected at 0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12 hr after administration. Group 2 rats (tissue studies): heart, liver, spleen, lung, kidney, cerebrum, and cerebellum collected at 1.2 hr.	Pharmacokinetics: K_a = 3.5±0.6/hr V/F(c) = 2.21±0.04 L/kg T_{max} = 0.65±0.01 hr AUC = 34 6±μg·hr/mL C_{max} = 1.5±0.2 μg/mL CL_s = 0.90±0.15 L/hr Tissue distribution (in descending order): affected organs: cerebellum > cerebrum > heart elimination organs: spleen > kidney > liver ≈ lung Results suggested that ligustilide crosses blood-brain barrier and enters extracellular fluids of the brain, particularly that of the cerebellum.	Y. Shi et al. (2006) [PMID:16583458]

Table 1. Chemical Disposition, Metabolism, and Toxicokinetics of Dong Quai and Its Constituents (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rats, Sprague-Dawley, age n.p., 5M/dose group	ligustilide as a "purified" form, in Chuanxiong extract, or formulated in saline	i.v.; 15.6 mg/kg of "purified" form or 14.9 mg/kg in Chuanxiong extract in Pharmatek formulation-6 into femoral vein via catheter p.o.; 100, 360, or 500 mg/kg in saline i.p.; 26 or 52 mg/kg in saline Blood samples were collected at intervals over a 48-hr period.	<u>i.v. administration</u>: 15.6 mg/kg 14.9 mg/kg C_{max} (mg/L) 13.19±0.84 6.93±0.60[a] $t_{1/2}$ (hr) 0.31±0.12 0.22±0.07 $AUC_{0-\mu}$ (mg/L) 1.81±0.24 0.79±0.10[a] V_d/F (L/kg) 3.76±1.23 5.62±1.19 CL/F (L/hr/kg) 9.14±1.27 20.35±3.05[a] MRT (hr) 0.30±0.07 0.19±0.03 <u>i.p. administration</u>: 26 mg/kg 52 mg/kg T_{max} (hr) 0.05±0.02 0.08±0.01 C_{max} (mg/L) 7.48±1.10[a] 20.75±2.55[b] $t_{1/2}$ (hr) 0.36±0.05 0.44±0.08[b] $AUC_{0-\mu}$ (mg/L) 0.93±0.07[a] 1.77±0.23[b] V_d/F (L/kg) 6.54±1.56 6.32±1.81 CL/F (L/hr/kg) 16.90±1.21[a] 9.26±1.04[b] MRT (hr) 0.30±0.05 0.41±0.03 <u>p.o. administration</u>: 500 mg/kg T_{max} (hr) 0.36±0.19 C_{max} (mg/L) 0.66±0.23[a] $t_{1/2}$ (hr) 3.43±1.01[a] $AUC_{0-\mu}$ (mg/L) 0.047±0.012[a] V_d/F (L/kg) 1641.9±121.6[a] CL/F (L/hr/kg) 411.1±145.7[a] MRT (hr) 5.14±1.56[a] Plasma concentrations decreased in a multiphase manner. ********** [a]significantly different compared with 15.6 mg/kg i.v. [b]significantly different compared with 26 mg/kg i.p. <u>Potential metabolites</u>: 15 peaks were found *in vivo*; 8 peaks were found *in vitro* (only in NADPH-regenerating system, +S9); 7 identified: butylidenephthalide, senkyunolide I, senkyunolide H, 3-hydroxybutylphthalide [all clearly characterized], 11-hydroxyligustilide, two isomers of hydroxyligustilide glutathione conjugate	Yan et al. (2008) [PMID:18039808]

Table 1. Chemical Disposition, Metabolism, and Toxicokinetics of Dong Quai and Its Constituents (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
***dl*-3-*n*-Butylphthalide**				
Rats, strain, age, number, and sex n.p.	^{3}H-*dl*-3-*n*-butylphthalide, purity n.p.	oral (intragastric); dose and duration n.p.; observed up to 72 hr	Within 24 hr, 73.7% of total radioactivity was excreted in urine and feces. Within 72 hr, 2.53% of the dose was excreted in urine and feces. These results indicated no accumulation *in vivo*. Metabolite MI was detected in the brain, and MI and MII were found in urine. At 1 hr after dosing, radioactive MI:prototype drug was 1:1 in the brain.	C.H. Wang et al. (1997) [PMID:11596286]

Abbreviations: F = female(s); hr = hour(s); M = male(s); min = minute(s); MSCC = multicomponent spectral correlative chromatography; n.p. = not provided

9.1.3 Acute Exposure

Acute toxicity values for Dong quai and some constituents are presented in **Table 2**.

Table 2. Acute Toxicity Values for Dong quai and Its Constituents

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
A. Sinensis (Oliv.) Diels			
root extract			
i.v.	mouse (sex and strain n.p.)	LD_{50} = ~100 g/kg	Mei et al. (1991); RTECS (2006)
dried root; ethanol-water (1:1) extract			
oral	mouse, male, strain n.p.	LD_{50} = 50.0 mL/kg	Yang and Chen (1992)
i.p.	mouse, mail, strain n.p.	LD_{50} = 38.0 mL/kg	Yang and Chen (1992)
Ferulic acid [1135-24-6]			
i.v.	mouse (sex and strain n.p.)	LD_{50} = 857 mg/kg	ChemIDplus (undated-b)
i.p.	mouse (sex and strain n.p.)	LD > 350 mg/kg*	ChemIDplus (undated-b)
3-Butylidenephthalide [551-08-6]			
oral	rat (sex and strain n.p.)	LD_{50} = 1850 mg/kg	ChemIDplus (undated-c)
dermal	rabbit (sex and strain n.p.)	LD_{50} >5000 mg/kg	ChemIDplus (undated-c)

*LD not specified (i.e., LD_{50}, LD_{LO}, etc.)
Abbreviations: i.p. = intraperitoneal; i.v. = intravenous; LD_{50} = lethal dose for 50% of test animals; n.p. = not provided

When a single oral dose of an alcoholic extract of *A. sinensis* (5000 mg/kg) was administered in male and female Wistar rats, no deaths occurred; the extract was "virtually nontoxic" (Taesotikul et al., 1998 abstr.). In Swiss mice and rabbits, oral administration of an extract formulation from a mixture of *A. sinensis*, *Ligusticum wallichii*, and *Achyranthes bedentata* (up to 200 g/kg) did not affect body weight or hemoglobin production. Although an LD_{50} could not be established, 200-4000 mg/kg/day was suggested (Dao et al., 1998).

When i.p. injected into mice, ferulic acid (LD >350 mg/kg) caused behavioral changes (ataxia, rigidity, and alterations in motor activity) (ChemIDplus, undated-b). When i.v. injected into mice, behavioral changes (altered sleep time, including changes in righting reflex) and pleural thickening were observed (RTECS, 2006).

9.1.4 Short-term and Subchronic Exposure

Daily oral administration of an alcoholic extract of *A. sinensis* suspended in water (25, 50, or 100 mg/kg) for 3 months caused no significant changes in body or tissue weights. Hematology and histopathology also had no significant findings and no further details were provided (Taesotikul et al., 1998 abstr.).

9.1.5 Chronic Exposure

No data were available.

9.1.6 Synergistic/Antagonistic Effects

Dong quai has been reported to have many synergistic effects with various chemicals. See also Section 10.0 for additional beneficial effects of Dong quai and its constituents.

Effects on Reproductive Parameters

A. sinensis was observed to have a protective role on cartilage tissue and in the proliferation and differentiation of neural stem cells from hypoxic embryonic rats (H. Yu et al., 2005, 2006). A mixture of *A. sinensis* ligustici leech protected and repaired injury to the testis and experimental varicocele and improved the activity of end epididymis spermatozoa (e.g., increased curvilinear velocity) in rats (Guan et al., 2007). Toki-shakuyaku-san (Dang-Gui-Shao-Yao-san) extract powder (800 mg/kg) administered to pregnant spontaneously hypertensive rats increased fetal weight and placental blood flow, indicating its potential to improve fetal development in toxemia in pregnancy. [Toki-shakuyaku-san is composed of six crude drugs, one being *A. Radix*] (Watanabe et al., 1989).

Effects on Cytotoxicity of Other Chemicals

In male ICR mice, polysaccharides from the root of *A. sinensis* (subcutaneous [s.c.]; 5, 10, or 25 mg/kg) had a protective effect on bone marrow and gastrointestinal tissues against the cytotoxicity of cyclophosphamide (CY). It significantly increased the rate of recovery of white blood cell numbers, blood vessel numbers, and proliferating cell numbers in the gastric and duodenal mucosae of CY-treated mice (Hui et al, 2006). The ethanol extract of *Angelicae Radix* significantly inhibited the interferon (IFN)-γ and tumor necrosis factor (TNF)-α-mediated cytotoxicity to rat thyroid cells. It also suppressed IFN-γ-induced aberrant thyroid cell major histocompatibility complex class II antigen expression (Shon et al., 2004). In aged rats, Danggui Shaoyao San and its disassembled prescriptions had an antagonistic effect against the inhibition of isoprel on lymphocyte proliferation (He et al., 2003 [PMID:14666767]). In bovine heart, ferulic acid inhibited cytochrome c-induced apoptosis (F. Yang et al., 2007).

Miscellaneous Effects

A. sinensis (100 or 200 mg/kg) alleviated bleomycin-induced pulmonary fibrosis in Sprague-Dawley rats (Chai et al., 2003). The methanolic extract of *Radix Angelica Sinensis* and the *n*-hexane fraction of the extract (1000 mg/kg) significantly improved amnesia induced by scopolamine and cycloheximide as measured by the passive avoidance test (Hsieh et al., 2000 [PMID:10999445]). In rabbits, *A. sinensis* significantly lowered the prothrombin time after cotreatment with warfarin (Lo et al., 1995 [PMID:7588995]). Coadministration of *A. sinensis* extract, alone or in combination with *Radix astragalus* (Huangqi) extract, with praziquantel provided treatment to rabbits with hepatic fibrosis secondary to schistosomiasis (He et al., 2006). A low molecular weight fraction of an aqueous extract of *A. sinensis* had a protective effect in mice against lethal endotoxemia and sepsis; this was partly via reduction of the systemic accumulation of a late proinflammatory cytokine, the high mobility group box 1 protein (H. Wang et al., 2006).

An effective component of *A. sinensis* Diels, sodium ferulate (100 mg/kg) improved acetaminophen-induced liver toxicity in mice. It inhibited the activity of serum alanine aminotransferase, prevented depletion of liver glycogen and glutathione, increased liver homogenate and microsomal gluathione S-transferase activities, and reduced malondialdehyde

content, mitochondria, and liver microsomal membrane fluidity (Wang and Peng, 1994 [PMID:8010094]).

9.1.7 Cytotoxicity

Using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay, four constituents of *Angelicae Sinensis Radix* were found to be cytotoxic against the mouse lymphocytic leukemia (L1210) and human leukemia (K562) cell lines. (*Z*)-ligustilide was the most cytotoxic compound against both L1210 and K562 cancer cell lines; IC_{50} values were 2.27 and 4.78 µM, respectively. The 3-3′a, 8-7′a dimeric (*Z*)-ligustilide neodiligustilide showed moderate cytotoxicity; IC_{50} values were 5.45 and 9.87 µM, respectively. The polyacetylenes 11(*S*),16(*R*)-dihydroxy-octadeca-9*Z*,17-dien-12,14-diyn-1-yl acetate and 3(*R*),8(*S*)-falcarindiol were only cytotoxic against the L1210 cell line; their IC_{50} values were 2.60 and 2.87 µM, respectively (Q.C. Chen et al., 2007 [PMID:17615675]). Aqueous extracts of *A. sinensis* root (0.5-2500 µg/mL) were cytotoxic to mouse maloncytes in culture at higher concentrations; pretreatment of the extract with polyvinylpolypyrrolidone reduced cytotoxicity by reducing the coumarin content (Raman et al., 1996 [PMID:8953431]).

Dong quai also has cytotoxic effects against cancer cells. Examples are presented below. [See also Section 9.5.]

The acetone extract of *A. sinensis* had a dose-dependent antiproliferative effect on several human cancer cells (A549, HT29, DBTRG-05MG, and J5); IC_{50} values ranged from 35 to 50 µg/mL at 24 hours after treatment. It induced G1/S arrest and activated the mechanism of apoptosis in the human cancer cells (Y.L. Cheng et al, 2004 [PMID:15261763]). An extract of *A. sinensis* also inhibited proliferation of B16-BL6 metastatic mouse melanoma cells. The migration capacity of the cells was significantly inhibited, while no effect was seen on invasion capacity. *A. sinensis* regulated bidirectionally the adhesion of the cells to the basement component laminin. In the mouse spontaneous melanoma model, continuous treatment with the extract (3.67 mg/kg) markedly decreased the lung metastatic nodes number and volume (Gu et al., 2007 [PMID:17634038]). The chloroform extract of *A. sinensis* suppressed the growth of malignant glioblastoma multiforme (GBM) brain tumor cells both *in vitro* and *in vivo* (rats and humans) via cell cycle arrest and apoptosis, without being cytotoxic to fibroblasts. The volumes of *in situ* GBM were also reduced (Tsai et al., 2005 [PMID:15867250]). In a follow-up study, *n*-butylidenephthalide was the major component isolated from the chloroform extract. It was highly cytotoxic to various rodent and human tumor cells (GBM, neuroblastoma, lung cancer, hepatoma, melanoma, teratoma, breast cancer, and leukemia); IC_{50} values ranged from 15-76 µg/mL (Tsai et al., 2006). The acetone and chlorophenol extracts of Dong quai were also found to have antiproliferative and proapoptotic effects *in vitro* on GBM 8401 cells; proliferation was inhibited by 30-50%. Cathepsin B expression and vascular endothelial growth factor were also inhibited. *In vivo*, both extracts inhibited tumor growth by 30-60% in nude mice while also significantly inhibiting mirovessel formation (W.H. Lee et al., 2006 [PMID:17085958]). The ethanol extract of *Angelica radix* and the methanol and hexane partition layers were seen to have cytotoxic effects on the HepG2, HeLa, MCF7, and SW626 cells. The greatest effects were on HepG2 and HeLa cells by the methanol and hexane partition layers; cell growth was inhibited by 99% at 100 µg/mL (Han et al., 2000).

Radix *A. sinensis* was cytotoxic to human embryonic intestinal cells (Int407) at "normal doses" as an herbal remedy, reducing percentage viability by 90%, but was not cytotoxic to human colon adenocarcinomas cells (Caco-2) (Lam et al., 2000 abstr.) Angelica polysaccharides inhibited the proliferation of human erythroleukemia K562 cells *in vitro* and induced their differentiation toward erythrocyte and granulocyte series (Zheng and Wang, 2002 [PMID:12585175]).

9.2 Reproductive and Teratological Effects

When pregnant white Swiss mice (n=10/group) were s.c. injected with an aqueous extract of *A. sinensis* Diels (0.05-0.2 mL) two times per day for five days, no effects on fertility were observed (Matsui et al., 1967). When spontaneously hypertensive rats (n=7-10/group, 12 weeks old) were administered daily doses of Toki-shakuyaku-san extract powder (800 mg/kg) in saline from day 1 to 20 of pregnancy, increased placental blood flow (46±4 versus 40±/mL/min/100g; $p<0.05$) and fetal body weight (3.51±0.08 versus 3.46±0.06, $p<0.05$) occurred compared to rats only given saline. The development of small-for-date baby, measured by the mean minus 1SD of fetal weight, was decreased by Toki-shakuyaku-san (5% in rats given drug with water versus 15% in rats given water only and 15% in rats given drug with saline versus 65% in rats given saline only). A tendency toward increased number of fetuses per dam was reported, but this was not significant. No changes in blood pressure were observed (Watanabe et al., 1989).

See also Section 9.1.6.

9.3 Carcinogenicity

No data were available.

9.4 Initiation/Promotion Studies

No data were available for Dong quai.

In female CD-1 mice initiated with 7,12-dimethylbenz[*a*]anthracene (DMBA) and promoted with 12-*O*-tetradecanoylphorbol-13-acetate (TPA), topical application of ferulic acid (10 µmol) with TPA inhibited the number of TPA-induced tumors per mouse by 35% and the percentage of animals with tumors by 7%; at a higher dose (50 µmol), the numbers were 97% and 80%, respectively (M.-T. Huang et al., 1988). However, when skin tumors were initiated in male NMRI Swiss mice using DMBA followed by promotion with TPA for 15 weeks, the addition of ferulic acid (200 µg, daily for 6 days) resulted in no inhibitory effect (Lesca, 1983 [PMID:6317220). A dehydrogenation polymer of ferulic acid was able to inhibit tumor promotion by TPA in the DMBA-treated skin of female ICR mice. Topical application of the polymer (5 mg) before that of TPA significantly decreased papillomas (3.2 tumors/mouse [20.3% of the controls] and 65% of mice developed tumors] and prolonged the latent period prior to the onset of tumors (7 versus 5 weeks). The monomeric ferulic acid exhibited no inhibitory effects (Asanoma et al., 1994 [PMID:7923605]).

9.5 Anticarcinogenicity

Numerous studies, particularly *in vitro* assays, have been published regarding the anticarcinogenic effect of Dong quai and its constituents. Examples are included in this section. [Note: See also Section 9.1.7.]

Dong quai (Drug, Extract, etc.)

When *Angelica radix* (crude drug, 640 mg/kg) was administered to DDY mice in drinking water before and after transplantation of Ehrlich tumors, a high survival rate was reported (51 days compared to 36 days for controls). Complete cure rate (89%) was also high compared to controls (0%). In tumor-free controls, *Angelica radix* produced a survival rate of 100%. When given p.o. as an initial stimulating agent, a relatively high level of TNF activity was observed (350 [assessed from dilution factor] versus 0 for controls) (Haranaka et al., 1985 [PMID:3851690]).

Polysaccharides: A low molecular weight (~3000) polysaccharide isolated from the rhizome of *A. sinensis* (Oliv.) Diels, had strong antitumor activity on Ehrlich ascites tumor-bearing mice; additionally, immunostimulating activities were observed *in vitro* and *in vivo* (Choy et al., 1994 [PMID:7992813]). In another study, total polysaccharides isolated from *A. sinensis* (Oliv.) Diels were examined for antitumor effects on three kinds of murine tumor models *in vivo* (sarcoma 180, leukemia L1210, and Ehrlich ascetic cancer). The polysaccharides increased the production of ascetic liquids in Ehrlich ascites tumor-bearing mice and prolonged survival in mice bearing Ahrlich ascites and L1210. An inhibitory effect on the growth of sarcoma 180 was not observed. In *in vitro* experiments, total polysaccharides had inhibitory effects on invasion and metastasis of human hepatocellular carcinoma cells (Shang et al., 2003 [PMID:12970885]).

Extracts: The acetone extract of *A. sinensis* exhibited antiproliferative effects on some human cancer cells (Y.L. Cheng et al, 2004 [PMID:15261763]). An extract of *A. sinensis* also inhibited proliferation of B16-BL6 metastatic mouse melanoma cells (Gu et al., 2007 [PMID:17634038]). [Note: Further details of these studies can be found in Section 9.1.7.]

Mixtures: DBT, alone or in combination with CY, inhibited tumor growth in EL-4 tumor-bearing mice and prolonged survival time compared to controls; additionally, significant improvements in various immune indices were observed (Yuan et al., 2008 [PMID:18184552]). In another study, the combination of *A. sinensis* with CY was more potent in treating transplanted tumors in mice than either agent alone (Gao and Yang, 1997). Antitumor effects of the decoction were also seen in mice s.c. injected with LZEJ-C2 cells, an EJ-Ha-ras transformed cell line, as well as *in vitro* in LZEJ and LZEJ-C2 cells (Hsieh et al., 2003 [PMID:12784917]).

Ferulic Acid

Ferulic acid (100 mg/kg, given as 5 i.p. injections before and after carcinogen treatment) was able to inhibit the formation of benzo[*a*]pyrene-induced lung tumors in male A/J mice by ~30% (6.0±0.8 versus 10.2±1.4 tumors/mouse) (Lesca, 1983 [PMID:6317220). In female ICR-Ha mice, ferulic acid (0.06 mmol/g) was able to significantly suppress benzo[*a*]pyrene-induced forestomach neoplasia (3.0±0.4 versus 5.0±0.5 tumors/mouse) (Wattenberg et al., 1980).

When ferulic acid was administered during the initiation or post-initiation phase to male F344 rats given azoxymethane, the incidence and multiplicity of intestinal tumors were reduced. Statistical significance was seen with treatment during the initiation phase with 250 and 500 ppm for the entire intestine (32 and 36% incidence, respectively, versus 68%) and with 250 ppm for the large intestine (0.32±0.47 versus 0.68±0.63 multiplicity). In addition, a lower incidence of

adenomas and adenocarcinomas was observed compared to controls; a significant difference in adenocarcinomas incidence was seen with treatment during the initiation phase with both doses for the entire intestine (23 and 32%, respectively, versus 68%) and for the large intestine (23 and 27%, respectively, versus 59%). [Noted: Ferulic acid significantly decreased the number of aberrant crypt foci per colon] (Kawabata et al., 2000 [PMID:10893437]). In another rat study, ferulic acid markedly reduced the incidences of tongue carcinomas and preneoplastic lesions when given in the diet (500 ppm) after exposure to 4-nitroquioline-1-oxide (Mori et al., 1999 [PMID:10625957]).

Other Constituents

The arabinoglucan APS-1d, extracted from the roots of *A. sinensis* (Oliv.) Diels, significantly inhibited the proliferation of human cervix carcinoma HeLa cells and lung carcinoma A549 cells *in vitro*, as well as the growth of the tumors on the mice transplanted with S180 tumor cells (Cao et al, 2006a). *n*-Butylidenephthalide, isolated from the chloroform extract of *A. sinensis*, was antitumorigenic against GBM tumors *in vivo* and *in vitro*. *In vivo*, s.c. injection of *n*-butylidenephthalide suppressed the growth of the human GBM tumor, DBTRG-05MG, and the rat GBM tumor, RG2, in nude mice and syngenic rats, respectively. Additionally, *n*-butylidenephthalide had antitumor effects on *in situ* tumors; it significantly decreased tumor volume of RG2 cells that were intracerebrally injected into the striatum of rats, as well as prolonged survival of rats (Tsai et al., 2006). When 3-*n*-butylphthalide (an Angelica constituent but isolated here from celery seed oil from *Apium graveolens*) was administered to benzo[*a*]pyrene-induced tumorigenic mice, forestomach tumor incidence was decreased from 68% to 30% and tumor multiplicity was reduced by ~67% (Zheng et al., 1993 [PMID:8446516]).

9.6 Genotoxicity

No data were available for Dong quai.

Ferulic acid (100-10,000 µg/plate) was negative for mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 in the presence and absence of metabolic activation (CCRIS, 2002).

9.7 Cogenotoxicity

No data were available.

9.8 Antigenotoxicity

No data were available.

9.9 Immunotoxicity

No data were available for Dong quai.

When 5-methoxypsoralen (bergapten; coumarin derivative found in Dong quai) was orally administered to guinea pigs, an association between serum concentration and the appearance of phototoxicity (mainly in the epidermis) was observed. Compared to 8-methoxypsoralen, the phototoxicity was lower, likely due to its reduced concentration in the epidermis (Kornhauser et al., 1982 [PMID:7100920]).

9.10 Other Data

Additional toxicological and pharmacological effects of Dong quai are provided in the following section. Studies where Dong quai was combined with additional herbs are not included, unless the effects of Dong quai alone could be evaluated or information on Dong quai alone on the endpoint evaluated was available. Further, Dong quai extracted from *Angelica* species other than *Angelica sinensis* are not included. However, it is noted that most studies evaluated showed that Dong quai obtained from and extracts of other *Angelica* species produce similar effects to those observed for *Angelica sinensis* extracts.

Endocrine System

In Vitro Studies

There are conflicting results in the literature on the effects of Dong quai in the endocrine system; most studies available have focused on its potential estrogen-like effects. Amato and colleagues (2002 [PMID:11875334]) showed that Dong quai significantly increased MCF-7 cellular proliferation in a dose dependent manner. The maximal increase was 16-fold over control levels at a 1:500 dilution [Noted: Antagonism studies were not conducted.] Similar effects in MCF-7 cells were observed by Elm et al. (2005 abstr.). Elm and colleagues (2005 abstr.) also showed Dong quai extracts (a) weakly bound to ERs, (b) weakly increased cellular proliferation in MCF-7 cells, and (c) did not increase cellular proliferation of BT-20 cells (human breast cancer cell line which is negative for ERs) at dilutions up to 1:50. [Noted: Extract type was not provided.] Furthermore, studies using MCF-7 and T47D cells showed that the effects of Dong quai extracts are greater in T47D cells when compared to MCF-7 cells (Houghton et al., 2005 abstr.). The authors propose that the efficacy difference is related to the difference in the levels of ERα and ERβ in the two cell lines, higher levels of ERβ are present in T47D cells.

However, while these studies suggest that the extracts produce estrogen-like effects other studies contradict these results. Lau et al. (2005 [PMID:16278617]) showed that the water extract of Dong quai increased MCF-7 and BT-20 cellular proliferation, as measured by MTT. The cellular proliferation effects in MCF-7, but not BT-20, cells were blocked by 4-hydroxytamoxifen, suggesting the effects in BT-20 cells occur through a non-ER mediated mechanism. In studies conducted by J. Liu et al. (2001 [PMID:11368622]), Dong quai methanol extracts showed minimal affinity for human recombinant ER receptors (IC_{50} >50 µg/mL). At a concentration of 20 µg/mL, Dong quai extracts minimally upregulated progesterone receptor mRNA levels (0.07 fold) in Ishikawa cells and pS2 expression (0.25 fold) in S-30 cells (ER-negative MDA-MB-231 breast cancer cells transfected with ERα). Kim et al. (2008) showed that ethanol extracts of *A. sinensis* did not produce estrogenic or antiestrogenic effects, using yeast cells that express human ER, estrogen response elements, and β-galactosidase. Oerter Klein et al. (2003) obtained similar results using methanol extracts of Dong quai. Furthermore, Amato et al. (2002 [PMID:11875334]) showed that Dong quai extracts did not increase gene expression in cells transiently transfected with human ERα or ERβ.

Compared to the above studies, Rosenberg Zand et al. (2001 [PMID:11580929]) showed that ethanol extracts of Dong quai (tested as stock, 10-, 100- and 1000-fold dilutions) had significant anti-estrogenic and anti-androgenic activity, as measured by pS2 and prostate-specific antigen (PSA) levels in BT-474 human breast cancer cells. These studies showed that the extract

inhibited pS2 production (measure of estrogen activity) up to 50% and PSA production (measure of androgen activity) up to 75%.

In Vivo Studies
As with the *in vitro* studies, there are conflicting *in vivo* results. An *A. sinensis* ethanol extract (100 and 300 mg/kg/day for 7 days) was estrogenic in ovariectomized rats, stimulating the uterine histoarchitecture, producing significant cornification of the vaginal epithelium and reducing serum luteinizing hormone concentration. The extract further increased uterine weight. In intact rats, *A. sinensis* extract (100 and 300 mg/kg/day for 5 days) prolonged estrus (67%) (Circosta et al., 2006 [PMID:16691630]). Comparatively, Amato and colleagues (2002 [PMID:11875334]) treated ovariectomized CD-1 mice with 500 µL/day (via gavage) with alcohol herbal extracts for 4 days. Animals were euthanized on day 5 and uteri were weighed. Dong quai extracts had no significant effect on uterine weight.

Enzyme Effects
Overall, these studies show that extracts of *A. sinensis* can modify the activity of a variety of enzymes, including metabolic enzymes such as cytochrome P450.

Ethanol extracts of *A. sinensis* (2.5% v/v) decreased CYP3A activity, as measured by testosterone 6β-hydroxylation) by less than 40% of control levels. When prescriptions containing various concentrations of *A. sinensis* (3.0 to 44.4% w/v) were evaluated, moderate inhibitory effects were observed. The formulated prescription and the ether extract of Huoxue Zhitong, which contained 44.4% *A. sinensis*) showed similar inhibitory effects on CYP3A (approximately 50% inhibition) while the non-extractable components were not active. (L.Q. Guo et al., 2001). J.H. Wang et al. (2000) showed that a 50% ethanolic extract of *A. sinensis* inhibited tyrosinase activity.

Tang et al. (2006 [PMID:17006975]) gavaged male rats with aqueous and ethanol extracts of Dong quai for 6 days. The authors stated that the daily doses were equivalent to 3 g (dry herbal material)/kg. The animals were killed and livers removed for assessment of microsome protein content and cytochrome P450 activity. Both aqueous and ethanol extracts increased liver microsome protein content and decreased cytochrome P450 levels. The aqueous extract of Dong quai increased the activities of CYP2D6 and CYP3A and decreased the activities of CYP1A2, CYP29, and CYP2E1. The ethanol extracts decreased CYP1A2, CYP2C9, CYP2E1, and CYP3A and increased CYP2D6 activities. [Noted: The authors note that some effects are significant, but identification of the significant changes is not provided.]

ASP Enzyme Effects
A. sinensis polysaccharides (ASP) also produced effects on drug metabolizing enzymes. Ding et al. (2001 [PMID:11509139], 2004) conducted *in vivo* studies with ASP to evaluate the effects produced. Male mice were treated with 30, 60, and 120 mg/kg per day for 7 days. Animals were then killed and enzyme activities assessed. Results showed that ASP increased P450 levels and activities of numerous metabolic enzymes (e.g., NAPH-cytochrome C reductase and aniline hydroxylase), but then decreased levels and activities at higher test concentrations. The authors propose that the observed biphasic effect may be related to the immunoactivity effects of ASP.

Xia et al. (2003 [PMID:15015291]) showed similar results in naïve and prednisolone (PSL) treated mice. ASP increased cytochrome P450 levels and metabolic enzyme activities (e.g., glutathione S-transferase, NADPH-cytochrome c reductase, and aniline hydroxylase activities). When mice were treated with ASP, PSL-induced changes (i.e., decreased glutathione content and increased enzyme activities) were restored to control levels.

Recently, C. Yu et al. (2006) reported that Radix *A. Sinensis* induced transcription of CYP3A4 in HepG2 cells that were transiently transfected with human PXR gene.

Gene Expression

A majority of the literature reviewed indicates that *A. sinensis* down-regulates gene expression. Shen et al. (2006) showed that the A3 fraction of *A. sinensis* dose-dependently inhibits Cox-2 mRNA transcription in rat uterus *in vivo*. Zhong et al. (2007 [PMID:17605235]) showed that in *A. sinensis* down-regulated transcription of transforming growth factor beta-1 (TGF-□1) approximately 60% in lung tissues in radiation exposed mice. Similar results on TGF-□1 expression were reported by Han et al. (2006 [PMID:16669709]). Xie et al. (2006) showed that *A. sinensis* extract reduced expression of TNF-α and TGF-β1 in lung tissues in the late phases of radiation induced pneumonitis in mice. Guo and Wang (2007) showed that *A. sinensis* down-regulated expression of collagen I, collagen II, connective tissue growth factor, and alpha smooth muscle actin in rats with bleomycin-induced pulmonary fibrosis.

Y. Wu et al. (2007) showed that *A. sinensis* reduced the number of neurons expressing c-Fos and neuron-specific enolase in rat embryo cerebrums after exposure to hypoxic conditions. The authors suggest that c-Fos regulation could play a role in the neuroprotective effects observed.

Q. Gao et al. (2007) conducted microarray studies in human MG-63 osteosarcoma cells to assess effects on gene expression by a Chinese herbal medicine and its components (e.g., *A. sinensis*). Studies showed that *A. sinensis* specifically upregulated 473 genes.

A. sinensis effects on expression of vascular endothelial growth factor and its receptor Flt-1 appears to be cell-type specific. Q.Z. Shi et al. (2007) showed that administration of *A. sinensis* increased expression of vascular endothelial growth factor (VEGFR) and its receptor Flt-1 in bone marrow stromal cells of mice exposed to radiation. Comparatively, Lam et al. (2008 [PMID:17497682]) showed that *A. sinensis* extract increased VEGFR expression and decreased Flt-1 expression.

Cellular Effects

There are conflicting results on the effects of *A. sinensis* extracts on cellular proliferation and apoptosis. Q. Lu et al. (2006 [PMID:16806164]) and Liang and He (2006 [PMID:16671548]) showed that the *A. sinensis* component ligustilide inhibited cellular proliferation of vascular smooth muscle cells. Further, Chor et al. (2003 abstr.) showed that *A. sinensis* extracts, when applied to rat T6 cells, decreased the number of cells in G1 phase and increased the number of cells in the sub G0/G1 phase. These results suggest that the extracts possessed anti-proliferative and pro-apoptotic activities. Comparatively, X. Chen et al. (2006 [PMID:16687249]) and Ye et al. (2001a [PMID:11213366], 2001b [PMID:11331080]) reported that *Angelica* extracts induced proliferation in murine bone marrow mononuclear and gastric epithelial cells. Q. Yang et al.

(2002 [PMID:12204429]) showed that the aqueous extract of *A. sinensis* produced a biphasic effect on human osteoprecursor cell proliferation; proliferation was increased at lower concentrations (e.g., <125 µg/mL) and inhibited at higher concentrations (e.g., >250 µg/mL).

In addition to effects on cellular proliferation, Dong quai induced differentiation of mesanchymal stem cells and migration of gastric epithelial cells (Dong et al., 2005; Ye et al., 2001a [PMID:11213366]).

Neurotoxicity

Overall, the studies reviewed suggest that Dong quai is not neurotoxic, but rather neuroprotective. Hu et al. (2007) evaluated the mechanism of JD-30, a constituent of Danggui Shaoyao San, in enhancing cognition. Studies showed that JD-30 did not affect population spike amplitude in the CA1 area of hippocampal slices alone, but ameliorated the effects produced by amyloid beta-protein fragment 25-35. Zhou et al. (2007) showed that *A. sinensis* and sodium ferulate promoted neurological function and diminished infarct volume and cerebral edema in Wistar rats that were subjected to focal cerebral ischemia.

Recent studies have focused on the neuroprotective effects of ligustilide. Peng et al. (2007) showed that ligustilide (20 or 80 mg/kg, p.o.) decreased, in a dose dependent manner, brain edema, infarct size, and neurobehavioral impairment in rats where focal ischemia was induced. Kuang et al. (2008 [PMID:17889286]) also showed that ligustilide prevented cognitive deficits and increased choline acetyltransferase and decreased acetylcholinesterase activity.

Circulatory System

Overall, studies have shown that *A. sinensis* is protective in the pulmonary system. Zhong et al. (2007 [PMID:17605235]) and Han et al. (2006) showed that *A. sinensis* inhibited the development of radiation-inducted pulmonary fibrosis in irradiated mice. The authors further suggested the effect was related to the down-regulation of TGF-beta1 (see Gene Expression section). Additional effects produced by *A. sinensis* extracts include, but not limited to, decreased cellular permeability and platelet adhesion, increased angiogenesis, reduced serum triglyceride levels, and reversing oxidative damage (Fan et al., 2001 [PMID:15575163]; D. Gao et al., 2005 [PMID:16313116]; H. Meng et al., 2006; Xiaohong et al., 2000 [PMID:11081469]; S. Yan et al., 2000; Zhui et al., 2000 [PMID:11081467]). Xin et al. (2007) showed that the aqueous soluble fraction of *A. sinensis* also mitigated effects produced by doxirubican (e.g., bradycardia and increased QT interval).

Two studies have shown that *A. sinensis* can increase international normalized ratio (reviewed by Stedman, 2002 [PMID:12016550]). This effect may lead to excessive bleeding and bruising.

Recent studies show that the cardioprotective effects observed with application of *A. sinensis* extracts can be attributed, in part, to ligustilide and ferulic acid. Studies with these chemicals have shown that they can reduce induced aortic tension *in vitro*, induced vasodilation in rat mesenteric artery preparations, induced vasorelaxation in isolated rat aorta preparations, increase cerebral blood flow, inhibit proliferation of smooth muscle cells, and inhibit platelet aggregation (Cao et al., 2006b [PMID:16807126]; S.S.K. Chan et al., 2007 [PMID:17222996]; Du et al.,

2007 [PMID:17597507]; Hsieh et al., 2002 [PMID:12221605]; B.H. Wang and Ou-Yang, 2005 [PMID:16007232]; H. Yu et al., 1999 [PMID:12212033]).

A. sinensis and its constituents and APS-iron complex also have a variety effects in blood including enhancing hematopoiesis, inhibiting thrombus formation, and reversing the effects of iron deficiency anemia (K.P. Wang et al., 2007; P.P. Wang et al., 2007 [PMID:18180896]; Y. Wang and Zhu, 1996 [PMID:9206201]; Xu and Feng et al., 2001 [PMID:12584852]).

Antioxidant

Numerous studies have shown that *A. sinensis* aqueous extracts and Angelica polysaccharide sulfates were shown to possess antioxidant activity in a variety of assay systems (Jia et al., 2007 [PMID:17571770]; Li and Wang, 2004 [PMID:14985912]; S.J. Wu et al., 2004 [PMID:15742346]; X. Yang et al., 2007a [PMID:17917256], 2007b [PMID:18047788]). Studies further show that sodium ferulate also has antioxidant effects (Traoré et al., 2003 [PMID:12454431]; Wang and Yang, 2005).

Additional Effects

A. sinensis extract and Dong quai have been shown also to interact with histamine H_1, 5-HT_{1A}, 5-HT_7, and γ-aminobutyric acid receptors (Deng et al., 2006a, 2006b [PMID:17144247]; Liao et al., 1995 [PMID:7480361]; M. Shi et al., 1995 [PMID:7646782]).

Additional activities ascribed to *Angelica* extracts and its active constituents include, but are not limited to, anxiolytic, insecticidal, and antifungal activity (S.W. Chen et al., 2004; Meepagala et al., 2005 [PMID:16222793]; Miyazawa et al., 2004). *A. sinensis*, in combination with *Astragalus monholicus*, was shown to have a nephroprotective and gastric protective effects (Cho et al., 2000 [PMID:10865452]; Li et al., 2000 [PMID:11775225]; Ye et al., 2001a [PMID:11213366], 2001b [PMID:11331080]; Y.W. Zhang et al., 2006 [PMID:16523407]). Numerous studies also have shown that the *A. sinensis* extracts, Dong quai preparations, and APS have varied immunomodulatory effects. These effects include, but are not limited to, stimulation of induced- and non-induced-lymphocyte proliferation, inhibited carageenen-induced release of prostaglandin E2, enhanced phagocytic function of macrophages, enhanced erythrocytic C3b receptor rosette rate, increased IL-2 production and activities, and increased IFN-γ release and activity (Y.F. Chu et al., 2005a,b; Hu et al., 1991; S. Lu et al., 1997 [PMID:12572476]; S.J. Lu et al., 1989 [PMID:2695109]; Shan et al., 2002 [PMID:12914316]; Xia et al., 2001).

10.0 Structure-Activity Relationships

No data were directly applicable. (See Appendix C for the activity of some constituents.)

11.0 Online Databases and Secondary References

11.1 Online Databases

National Library of Medicine Databases (TOXNET)
ChemIDplus
EMIC and EMICBACK
HSDB
IRIS

STN International Files

AGRICOLA	IPA
BIOSIS	MEDLINE
BIOTECHNO	NIOSHTIC
CABA	NTIS
CANCERLIT	Registry
EMBASE	RTECS
ESBIOBASE	TOXCENTER

TOXCENTER includes toxicology data from the following files:

Aneuploidy	ANEUPL*
BIOSIS Previews® (1969-present)	BIOSIS*
CAplus (1907-present)	CAplus
International Labour Office	CIS*
Toxicology Research Projects	CRISP*
Development and Reproductive Toxicology	DART®*
Environmental Mutagen Information Center File	EMIC*
Epidemiology Information System	EPIDEM*
Environmental Teratology Information Center File	ETIC*
Federal Research in Progress	FEDRIP*
Health Aspects of Pesticides Abstract Bulletin	HAPAB
Hazardous Materials Technical Center	HMTC*
International Pharmaceutical Abstracts (1970-present)	IPA*
MEDLINE (1951-present)	MEDLINE
Pesticides Abstracts	PESTAB*
Poisonous Plants Bibliography	PPBIB*
Swedish National Chemicals Inspectorate	RISKLINE
Toxic Substances Control Act Test Submissions	TSCATS*

*These are also in TOXLINE. Missing are TOXBIB, NIOSHTIC®, NTIS.

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Appendix A: Units and Abbreviations

ºC = degrees Celsius
µg/L = microgram(s) per liter
µg/mL = microgram(s) per milliliter
µM = micromolar
bw = body weight
CY = cyclophosphamide
DAD = diode array detection
DBT = Danggui Buxue Tang
DMBA = dimethylbenz[*a*]anthracene
DOS = danggui oral solution
ER = estrogen receptor
F = female(s)
g = gram(s)
g/cm^3 = gram(s) per cubic centimeter
g/mL = gram(s) per milliliter
GBM = glioblastoma multiforme.
GC = gas chromatography
h = hour(s)
Hg = mercury
HPLC = high-performance liquid chromatography
i.p. = intraperitoneal(ly)
i.v. = intravenous(ly)
kg = kilogram(s)
L = liter(s)
LC = liquid chromatography
LD_{50} = lethal dose for 50% of test animals
M = male(s)
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
MS = mass spectrometry
n.p. = not provided
NTP = National Toxicology Program
PMID = PubMed identification
ppm = parts per million
PSA = prostate-specific antigen

TCM = traditional Chinese medicine
TNF = tumor necrosis factor
TPA = 12-*O*-tetradecanoylphorbol-13-acetate

Appendix B: Description of Search Strategy

Dong Quai
(CAS Nos. 308068-61-3 [root] and 299184-76-2 [extract]))

Internet searches with the Google, Google Scholar, and Froogle search engine(s) were done in June and July 2006. Appendix A includes selected URLs from the searches. Specific web sites were also used, e.g., PubMed, TOXLINE, ChemIDplus, www.inchem.org, and the Phytochemical and Ethnobotanical Databases (http://sun.ars-grin.gov:8080/npgspub/xsql/duke/plantdisp.xsql?taxon=87). Fee-based searches were done in the following database files on STN International: Registry, three food science databases (FSTA, FOMAD, and FROSTI), a business database (PROMT), and the usual biomedical files. The strategy in the fee-based searches involved inclusion of all the synonyms identified by ILS up to the date of the search and initial retrieval of database records for reviews. Literature searches for information about certain constituents were usually limited to the NLM databases. An update search was done on April 8, 2008, in the usual biomedical databases for new publications in 2006-2008. Most of the 1389 search results from queries using synonyms were on therapeutic and preventive uses of different formulations containing dong quai with other herbs. Another 32 results were on ligustilide. Only 149 database records were printed in full for possible inclusion in the report.

The histories of the online sessions in 2006 and 2008 are given below:

```
     FILE 'PROMT' ENTERED AT 17:02:25 ON 30 JUN 2006
L1          206 S (TANG OR DANG OR DONG)(W)(KWEI OR KUEI OR GWI OR QUA OR QUAI OR GUI OR KWAI)
L2          198 S DONG(W)QUAI OR DANGGUI OR DANG(W)GUI
L3          210 S L1 OR L2
L4           56 S L3 AND (SALES OR RANK OR POPULAR?)

     FILE 'MEDLINE, AGRICOLA, CABA, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS,
     TOXCENTER' ENTERED AT 17:13:00 ON 30 JUN 2006
L5          356 S L1
L6           11 S TAN KUE OR DAN GUI OR XIONG GUI
L7            1 S TANGKWEI OR TANGKUEI OR TANGGWI OR TANGQUA OR TANGQUAI OR TANGGUI OR TANGKWAI
L8          236 S DANGKWEI OR DANGKUEI OR DANGQUA OR DANGQUAI OR DANGGUI OR DANGKWAI OR DANGGWI
L9            1 S DONGKWEI OR DONGKUEI OR DONGGWI OR DONGQUA OR DONQUAI OR DONGQUAI OR DONGGUI OR
                DONGKWAI
L10          23 S YUNGUI OR QINGUI
L11         624 S L5 OR L6 OR L7 OR L8 OR L9 OR L10
L12        1458 S ANGELICA(W)SINENSIS OR CHINESE(W)ANGELICA OR ANGELICA(W)POLYMORPHA(2A)SINENSIS
L13         866 S ANGELICA(2A)(ROOT OR RADIX)
L14         821 S L13 NOT ARCHANGELICA
L15        2410 S L11 OR L12 OR L14
                SET DUPORDER FILE
L16        1528 DUP REM L15 (882 DUPLICATES REMOVED)
                ANSWERS '1-334' FROM FILE MEDLINE         334
                ANSWERS '335-365' FROM FILE AGRICOLA       31
                ANSWERS '366-542' FROM FILE CABA          177
                ANSWERS '543-1034' FROM FILE EMBASE       492
                ANSWERS '1035-1040' FROM FILE ESBIOBASE     6
                ANSWERS '1041-1078' FROM FILE IPA          38
                ANSWERS '1079-1225' FROM FILE BIOSIS      147
                ANSWERS '1226-1528' FROM FILE TOXCENTER   303
L17          32 S L16 AND REVIEW/DT
                SAVE L17 X400REVU/A
L18        1496 S L16 NOT L17
                SAVE L18 X400BIOMED/A
L19          34 S LIGUSTILIDE AND L18
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```
L20         336 S LIGUSTILIDE NOT L18
L21          16 S L20 AND (TOXIC? OR ADVERSE(W)EFFECT?)
L22          16 SORT L21 1-16 TI

     FILE 'REGISTRY' ENTERED AT 17:38:01 ON 30 JUN 2006
                E CIS-LIGUSTILIDE/CN
L23           1 S E3
                E TRANS-LIGUSTILIDE/CN
L24           1 S L3
                E TRANS-LIGUSTILIDE/CN
L25           1 S E3
                E LIGUSTILIDE/CN
L26           1 S E3

     FILE 'MEDLINE, AGRICOLA, CABA, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS,
     TOXCENTER' ENTERED AT 17:42:40 ON 30 JUN 2006
L27          22 S L18 AND ALKALOID?
L28          22 DUP REM L27 (0 DUPLICATES REMOVED)
L29          22 SORT L28 1-22 TI
```

After examination of 1,496 titles from the biomedical databases in 2006, 160 full records were printed from MEDLINE (68), EMBASE (42), CABA (19), BIOSIS (14), TOXCENTER (8), AGRICOLA (5), and IPA (4). An additional 31 records were printed from the food science databases. Later, additional synonyms were found in a World Health Organization monograph (WHO, 2002) [which was not located by searching www.inchem.org] and some additional retrievals were found in MEDLINE (PubMed) by use of "radix angelicae sinensis." When the major synonyms were used in a PubMed search on July 6, 2006, it was noted that 42% of the 298 records retrieved were for publications written in Chinese, 16% did not have abstracts, and nearly one-third were for drug combinations (dang gui followed by other Chinese words). Such problems were observed in the fee-based results as well.

STN International files MEDLINE, AGRICOLA, CABA, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS, and TOXCENTER were searched simultaneously on April 8, 2008, to update the 2006 searches. Synonyms that had previously yielded few results were not used, but some terms that had not been used in the 2006 strategy were added to the most commonly used names. One important plant synonym, Chinese angelica, was omitted. A check of PubMed on September 2, 2008, however, found only one additional result for 2006-2008 (Zhang et al., 2007 [PMID:17571768]) (regarding anti-tumor activity of the polysaccharides). The history of the April 2008 online session is shown below:

```
                  ACTIVATE X400NAMES/Q
                  ---------
L1                QUE  DONG QUAI OR DANG GUI OR DANGGUI OR ANGELICA? SINENSIS
                  ---------
L2          3947 S L1
L3             0 S CAN(W)QUI OR DANGDANGGUI OR DUONG(W)QUI OR HANDANGGUI OR
                  HASHSHAT(W) ALMALAK
L4             2 S KARA(W)TOKI OR MIN(W)GUI OR TAN(W)QUI
L5             0 S L4 NOT L2
L6          1694 S L2 AND (2006-2008)/PY
L7           519 S LIGUSTILIDE
L8           431 S L7 NOT L6
                  SET DUPORDER FILE
L10         1389 DUP REM L6 (305 DUPLICATES REMOVED)
             102 ANSWERS '1-102' FROM FILE MEDLINE
               7 ANSWERS '103-109' FROM FILE AGRICOLA
              84 ANSWERS '110-193' FROM FILE CABA
             166 ANSWERS '194-359' FROM FILE EMBASE
               3 ANSWERS '360-362' FROM FILE ESBIOBASE
               6 ANSWERS '363-368' FROM FILE IPA
              28 ANSWERS '369-396' FROM FILE BIOSIS
```

```
            993 ANSWERS '397-1389' FROM FILE TOXCENTER
L11        1389 SORT L10 1-1389 TI
                SAVE L11 X400UPDATE/A
L12         648 S RADIX(4A)ANGELICAE(W)SINENSIS
L13           0 S L12 NOT L1
L14          79 S L8 AND (2006-2008)/PY
L15          32 DUP REM L14 (47 DUPLICATES REMOVED)
             15 ANSWERS '1-15' FROM FILE MEDLINE
              2 ANSWERS '16-17' FROM FILE AGRICOLA
              1 ANSWER '18' FROM FILE CABA
              7 ANSWERS '19-25' FROM FILE EMBASE
              1 ANSWER '26' FROM FILE ESBIOBASE
              6 ANSWERS '27-32' FROM FILE TOXCENTER
L16          32 SORT L15 1-32 TI
                SAVE L16 LIGUSTILIDE/A
```

Most of the search results for dong quai were on therapeutic and preventive uses of different formulations containing dong quai and other herbs. Approximately 600 titles began with phrases such as "(A) Chinese medicine/herbal/medical/medicinal/traditional;" another 57 began "Traditional Chinese medicinal/medicine."

A total of 149 full records were printed after examination of the titles in answer sets L11 and L16. The database tallies follow:

```
MEDLINE FILE          76
CABA FILE             12
AGRICOLA FILE          3
EMBASE FILE           30
ESBIOBASE FILE         2
BIOTECHNO FILE         0
IPA FILE               3
BIOSIS FILE           14
TOXCENTER FILE         9
```

Appendix C: Constituents of Dong Quai Root

Approximately 45% of the dong quai root is soluble in 70% ethanol. The classes of compounds identified in the more than 60 species in the genus *Angelica* root include coumarins, polyacetylenes, chalcones, sesquiterpenes, and polysaccharides. *A. sinensis* root was reported to contain alkylphthalides, coumarins and furocoumarins, terpenes, phytosterols, organic acids, polysaccharides, and polyacetylenes (polyynes) (Bhatti et al., 2004; Deng, 2005 diss.). A number of the alkylphthalides and their dimers also were reported in the essential oil extracted from *A. sinensis* and are listed in Deng (2005 diss.). The alkylphthalides were the major constituents identified in the essential oil. *Z*-Ligustilide was the main phthalide found in the root (5%) and the essential oil (45-60%) (Yi et al., 2007b [PMID:17638355]). The amount of essential oil extracted from the *A. sinensis* root is only 0.4-0.7% (Deng, 2005 diss.; WHO, 2004). Several of the constituents commonly reported for *A. sinensis* root extracts, including quantitation when available, are listed in the following table.

Ferulic acid and the phthalides were reported to be the major biologically active compounds in *A. sinensis* root. These compounds are also common to other plants in the Umbelliferae (Apiaceae) family (Budavari, 1996). Similar phthalides and phthalide dimers, the alkyne falcarindiol, and coniferyl ferulate were found in herbal medicines such as *Ligusticum chuanxiong*, *Ligusticum porteri*, and *Levisticum officinale* (lovage). Higher concentrations of phthalides and ferulic acid were reported in methanolic extracts of *L. chuanxiong* compared with extracts from *A. sinensis* (Yi et al., 2007a; Zschocke et al., 1998).

Huang et al. (2004) identified 82 of 97 constituents separated in the essential oil of powdered dong quai root from Gansu province in China. The root was prepared by the "standard extraction process" according to the Chinese Pharmacopoeia [possibly steam distillation or boiling water extraction, the "ancient preparation" referred to by Dong et al., 2006)]. Of the 76 compounds that were quantified, 45 had concentrations from 1 to >4% (only 4 were >4%). The yields of extracts from main root and root fiber were 0.512% and 0.453%, respectively. Chemical classes of compounds identified included numerous terpenes; alkanes, alkenes, alkylbenzenes; two alkynes; one cumarin (5,7,8-trimethyldihydrocoumarin) alcohols and phenols; aldehydes and ketones; carboxylic acids; and phthalides. The ligustilides comprised 18.72% of the essential oil, (equivalent to 958 ppm in the dong quai root.) Ferulic acid, falcarinol, and falcarinol were not identified.

Steam distillation of crude *A. sinensis* drug gave a product (presumably the essential oil) that contained ~16-40 ppm safrole (Liu et al., 1989). Safrole is reasonably anticipated to be a human carcinogen (NTP, 2004). Isosafrole, which has also been reported as a constituent of the distillant, has insufficient evidence for carcinogenicity (category 3) accorcing to IARC (IARC, 1998).

A methanolic extract of *A. sinensis* root (6.75% total yield) was partitioned into petroleum ether (3.35%), chloroform (0.71%), *n*-butanol (0.49%), and water (1.98%). The chloroform and/or petroleum ether extracts inhibited serotonin and GABA receptors and were antiestrogenic and cytotoxic. The activities of the other extracts were much lower and they were not investigated further. Chromatographic techniques were used to isolate 23 compounds. Sucrose (62.5 ppm based on weight of root) was the major compound identified. The others ranged in

concentrations from 0.09 to 6.25 ppm. *Z*-Ligustilide (6.25 ppm) and *Z*-butylidenephthalide (3.75 ppm) represented 80.3% of the nine phthalides (12.45 ppm) identified; falcarindiol (6.01 ppm) represented 81.5% of the three alkynes (7.37 ppm); and ferulic acid (0.16 ppm); two esters (2.79 ppm) one furocoumarin, imperatorin (0.25 ppm), and one phytosterol, stigmasterol (2.5 ppm), also were isolated (Deng, 2005 diss.). [The lower concentrations of phthalides found compared with Huang et al. (2004) may be due to instability during the multiple extraction steps and/or different extraction media.]

General differences in constituents from dried roots (200 g) extracted with solvents having different polarities were seen using Fourier-Transform Infrared (FT-IR) and two-dimensional (2-d) correlation IR spectroscopies. The major lipophilic components in the petroleum ether extract (extract weight 3.5 g) included the ligustilides (45% by extract weight [1.75% ext.; 7900 ppm ligustilides in root]) and other γ-lactones (phthalides) as well as carboxylic acids and their esters, terpenoids, and "greases." Carbonyl compounds also were strongly represented. No hydroxyl peaks were observed. The spectra of the alcoholic extract (95% ethanol; yield 19.25 g) and boiling-water extract (yield 85.75 g) were similar (minor differences in the carbonyl compounds and more were found in the ethanol extracts than in the water extracts). Although all of the extracts had the characteristic peaks of the polysaccharides (said to be "one of the main effective constituents" in *A. sinensis*, the polysaccharides were very different in the two polar extracts. The extraction residue contained plant fiber polysaccharides (cellulose or hemicellulose and lignins), glycoprotein, and vegetable protein (Liu et al., 2006).

Table. Major constituents of interest in *Angelica sinensis* root extracts and root essential oil

Constituent	Chem. Class	CASRN	Essential Oil Extract/Nonpolar Solvent	Essential Oil Extract/Polar Solvent	Biological Activities	References[a]
Bergapten; 5-Methoxypsoralen; Heraclin	Psoralen	484-20-8	1810 ppm (leaf oil)		Carcinogen., Genotox., Antimitot./prolif., Antithrombotic	PED; EMEA (2007)
Safrole; 1,2-Methylenedioxy-4-allylbenzene	Other	94-59-7	16-40 ppm		Carcinogen., Genotox., Antithrombotic	PED; EMEA (2007); Liu et al. (1989)
Isosafrole (trans form)	Other	120-58-1	+		Carcinogen.	PED
Scopoletin	Coumarin	92-61-5		+	Anti-carcin., Anti-mutagen., Cytotox., Hormonal	PED
Umbelliferone; 7-Hydroxycoumarin	Coumarin	93-35-6		+	Anti-carcin., Anti-mutagen., Antimitot./prolif.	PED
Ferulic acid; 3-Methoxy-4-hydroxycinnamic acid; 3-(4-Hydroxy-3-methoxyphenyl)-2-propenoic acid; Caffeic acid 3-methyl ether	Other	1135-24-6	N.D.	0.16 ppm (MeOH); 442 ppm (MeOH) (mean of means); 149 ppm (boiling water); max. 940 ppm in plant (PED)	Anti-carcin., Anti-mutagen., Antimitot./prolif., Antiestrogenic, Antithrombotic	PED; Deng (2005 diss.) (MeOH); Dong et al. (2006) (boiling water)[b]; Yi et al. (2007a) (MeOH)
Falcarindiol	Other: Alkyne		N.D.	6.01 ppm (MeOH); 70% EtOH	Anti-mutagen., Cytotox., Antithrombotic	PED; Deng (2005 diss.) identified four new diynes as well; Wang et al. (2005) found much higher concentrations of phthalides than of falcarindol

Constituent	Chem. Class	CASRN	Essential Oil Extract/Nonpolar Solvent	Essential Oil Extract/Polar Solvent	Biological Activities	References[a]
Falcarinol; Paraxynol	Other: Alkyne; Diyne	21852-80-2	N.D.	+	Anti-carcin., Cytotox., Antimitot./prolif., Antithrombotic	PED[c]
Z-Ligustilide	Phthalide			6.25 ppm (MeOH); 7317 ppm (MeOH) (mean of means)		Deng (2005 diss.); Yi et al. (2007a)
Ligustilide; 3-Butylidene-4,5-dihydroxyphthalide	Phthalide	4431-01-0	73.98%	131 ppm (boiling water)		PED; Dong et al. (2006)
Z-Butylidenephthalide; *Z*-Ligusticum lactone	Phthalide			3.75 ppm (MeOH); 70% EtOH		Deng (2005 diss.); Wang et al. (2005); WHO (2004)
Senkyunolide A	Phthalide			145 ppm (MeOH) (mean of means)		Yi et al. (2007a)
Senkyunolide H	Phthalide			161 ppm (MeOH) (mean of means); 70% EtOH		Wang et al. (2005) also detected senkyunolide D and sedanenolide A; Yi et al. (2007a)
Alloocimene	Terpene (linear)	673-84-7	3.75%			Huang et al. (2004)
Carvacrol	Terpene	499-75-2	3.78%			PED; Huang et al. (2004)
Butylidenephthalide; 3-Butylidenephthalide (642376)	Phthalide	551-08-6	4.78%			PED; Huang et al. (2004)
Ligustilides	Phthalide		18.72%			Huang et al. (2004)
beta-Pinene	Terpene	127-91-3	2.3-17%			EMEA (2007)
cis-beta-Ocimene	Terpene	3338-55-4	12.18%			PED
Citronellyl acetate	Terpene	150-84-5	3.4-10.3%			EMEA (2007)

Constituent	Chem. Class	CASRN	Essential Oil Extract/Nonpolar Solvent	Essential Oil Extract/Polar Solvent	Biological Activities	References[a]
alpha-pinene	Terpene	80-56-8	5.78% (see comment); 0.6-6.1%			EMEA (2007); Huang et al. (2004)
3-Methyl-2-octene	Other: alkene		4.1-13.8%			EMEA (2007)
Heraclinin	Psoralen	2880-49-1	3000 ppm			EMEA (2007)
Ostruthole	Psoralen	642-08-0	1750 ppm			EMEA (2007)
Anethole; 1-Methoxy-4-(1-propenyl)benzene	Other: (Estragole isomer)	104-46-7	700 ppm			Huang et al. (2004)
Isoimperatorin	Psoralen	482-45-1	590 ppm			EMEA (2007)
Heraclenol	Psoralen	31575-93-6	380 ppm			EMEA (2007)
Oxypeucedanin	Psoralen	737-52-0	350 ppm (leaf)			EMEA (2007)
Archangelicin	Fpsoralen ("angular")	2607-56-9	290 ppm (root oil)			PED; EMEA (2007)

[a]The reference PED is the Phytochemical and Ethnobotanical Databases, which does not identify the extracting solvents used. Biological activities usually included in a Toxicological Review were selected from the activities listed by the PED unless otherwise specified.
[b]Wang et al. (2007) did not detect ferulic acid in a 70% ethanolic extract of Gansu province dong quai. The dried powder to solvent ratio was 1:10. (L.-F.) Huang et al. (2004) did not detect ferulic acid in the essential oil.
[c]Huang et al. (2004) did not find it in the essential oil. The only alkynes found were 1-tridecyn-4-ol at 1.27% and unquantitated 3-decyn-2-ol.

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