

Pharmacological and Biochemical Action of Angelica Sinensis (Dong Quai): Natural Product with Therapeutic Potential

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Abstract: The medicinal plants as well as the herbs are an important aspect of traditional Chinese medicine and even an enriched source of various chemicals. Among the medicinal herbs, Angelica sinensis, also known as Dong Quai is the most popular used as Chinese medicine. The main compounds found in the acetone extract of Angelica sinensis(AS-AC) are ferulic acid, butylidenephthalide, ligustilide, brefeldin A, angelicide, B-sitosterol, butyl phthalide, calcium channel-blocking compounds (which relax visceral organ muscle), carvacrol, coumarins (at least six coumarin derivatives(coumarin content in Dong Quai does not promote phototoxic, carcinogenic or mutagenic effects, but exerts antispasmodic and vasodilatory effects)) including: angelol, angelicone; essential oils, consisting mainly of Ligustilide, N-butylidenphthalide; ferulic acid, flavonoids, fixed oil, furanocoumarins, nicotinic acid, phytosterols, polysaccharides, stigmasterol, vitamins E, A and B12. This traditional Chinese herbal medicine has various pharmacological and toxicological effects i.e. Cardiovascular effects, Neurological effects, Musculoskeletal effects, Immunological effects/Amineoplastic activity/Antimicrobial activity, Anti-Inflammatory activity, Dermatological effects, Carcinogenicity, Estrogenic effects, Gastrointestinal effects. The aims of this review are to summarize the history and an account of the adverse effects and potential interactions of Dong Quai, and a discussion about therapeutic effects of this herb.

Keywords: Angelica Sinensis, Chinese medicine, Dong Quai, medicinal plant, Pharmacological and biochemical action, Toxicological effects.

1. INTRODUCTION

Natural plants as well as herbs have been used to treat disease and maintain health. In China more than 4500 herbs and 350 minerals (and even animal extracts) are routinely applied to patients as a mixture or formula. Traditional medicine involving Chinese herbs is currently gaining a lot of attention due to its quite promising effect, as well as its better clearance, resulting in less accumulation and lower toxicity. Since several active compounds have been found in some herbs, certain herbal medicine products can possess many biological activities. Practitioners of traditional Chinese medicine believe that disease primarily arises from imbalances in the body. The therapeutic purpose of a Chinese doctor is therefore to bring the human body back into equilibrium. Herbal drugs are used with the goal of restoring this balance by nourishing the body, including the energy, qi (breath circulation), and spirit to maintain health rather than to treat a particular disease or medical condition. This mindset reflects an emphasis on preventive medicine. Treatments undertaken with this goal are called Fu Sheng and are given as complementary therapy intended to reduce the side effects of conventional Western medical treatment. Chinese herbal medicine is independent of conventional Western concepts of medical diagnosis and treatment. One aspect of Chinese medicine is to bolster resistance to disease by strengthening a person's immunity. Chinese herbs attempt to prevent and treat physiological imbalances, such as those caused by cancer and other diseases, with combinations of herbs, minerals, and plant extracts. Diseases that cannot be cured by modern medical treatments, such as diabetes and cancer, may be alleviated by traditional Chinese medicine. The use of Chinese herbs not only depends on its active ingredients and clinical results, but also on people's belief. Many Chinese herbs have become very popular and have been used as alternative medicine for certain diseases, such as cancer, because of their

effectiveness and lower adverse reactions compared to modern medicine. Even though many herbs have been recognized for their efficacy, some toxicity can be found, especially with their impurities. Traditional Chinese herbal medicines (TCHM) are increasingly used throughout the world, as they are considered to be effective and to have few side-effects and so that the Quality control of active ingredients and impurities are necessary for herbal medicine in order to obtain the optimum action. Danggui (Chinese Angelica root; Dong Quai; *Angelica sinensis* (Oliv.) Diels) is a traditional Chinese herbal remedy with a long history of use in China, Korea and Japan. Even today it is still one of the herbs most commonly used by Traditional Chinese Medicine (TCM) practitioners in China, as well as Europe.

2. HISTORY AND TRADITIONAL USES

An aromatic herb, Botanical Name: *Angelica sinensis*, *Angelica polymorpha* (Dong Quai should not be confused with *Angelica* root or *Angelica* seed), Plant Family: Umbelliferae, Apiaceae .Common Name: Bai zhi, Chinese Angelica, Dang gui, Dong Qua, Dong Quai, Tan kue, Tang kuei, Tang kwei. Dong Quai root has been used for centuries throughout the East. It is a biennial or perennial member of the carrot family that can be found in meadows and damp places in Europe, Asia, Canada, and the northern United States. It has white to greenish-white flowers that bloom from May to August growing to a height of 3 to 6 feet [1 to 2 meters], in June it bears white flowers, and in the fall, a seeded fruit. The name Dong Quai means "proper order". Dong Quai is known historically as a female remedy and has been referred to as "empress of the herbs," "sovereign herb for women," and "the female ginseng." Historic uses include treatment of migraine, headaches, neuralgia, arthralgia, menstrual disorders, amenorrhea, menopausal syndromes, dysmenorrhea, menorrhagia, anemia, abdominal pain, injuries, and having Cardiovascular effects, Neurological effects, Musculoskeletal effects, Immunological effects/Amineoplastic activity/Antimicrobial activity, Anti-Inflammatory activity, Dermatological effects, Carcinogenicity, Estrogenic effects, Gastrointestinal effects and premenstrual syndrome . It is also said to ensure healthy pregnancies and easy deliveries. 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 also has been used to treat a variety of ailments including, dehydration, lumbago, hypertonia, nervous disorders, 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 sub chronic studies. Dong Quai extracts has 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. Active constituents of Dong Quai include vitamins A, B and E, as well as numerous phytochemicals and minerals, including calcium and magnesium. Dong Quai contains active coumarin compounds such as psoralen, bergapten, angelicton and osthole [regarded as a brain stimulant, possibly due to its ability to increase blood flow].

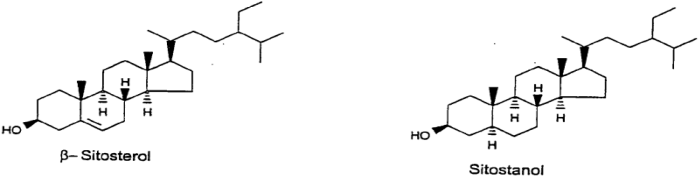
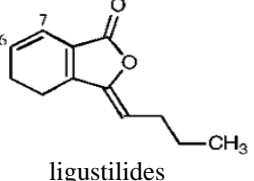
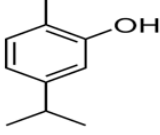
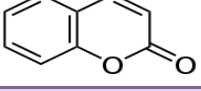
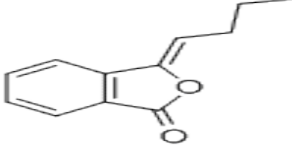
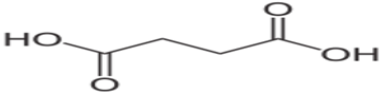
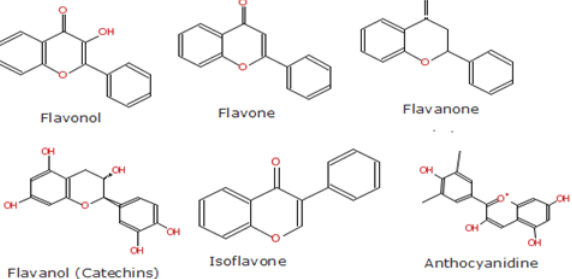


Fig. 1. *Angelica sinensis*

3. MAJOR CONSTITUENTS

Numerous constituents have been isolated with phthalides, ferulic acid and polysaccharides showing biological activities. 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 immune stimulating polysaccharide. 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.

TABLE 1

Plant Constituents of Dong Quai	Structure of some constituents
B-sitosterol	 <p style="text-align: center;">β-Sitosterol Sitostanol</p>
Alkyl phthalides (Ligustilides, Angelicide, and Butyl phthalide)	 <p style="text-align: center;">ligustilides</p>
Carvacrol	
Coumarins (at least six coumarin derivatives) including: Angelol Angelicone	
Calcium channel-blocking compounds (which relax visceral organ muscle)	
N-butylidenphthalide	
Organic acids (Ferulic, Succinic, and Myristic),	<p>Chemical structure of succinic acid.</p> 
Flavonoids	 <p style="text-align: center;">Flavonol Flavone Flavanone Flavanol (Catechins) Isoflavone Anthocyanidine</p>

Fixed oil	
Furanocoumarins (Archangelicin, Bergapten, and Imperatorin)	<p>Furan + Coumarin = Furanocoumarins</p> <p>Psoralen Derivatives of this isomer are called "linear furanocoumarins"</p> <p>Angelicin Derivatives of this isomer are called "angular furanocoumarins"</p>
Nicotinic acid	
Phytosterols	
Polysaccharides	<p>Polysaccharide</p>
Stigmasterol	
Vitamins E, A and B12	<p>Vitamin E (α-tocopherol)</p>

3.1. Phthalides:

Phthalides consist of monomeric phthalides such as Z-ligustilide and phthalide dimers. The majority of the phthalides identified is relatively non-polar, the fraction of which can be extracted with solvents such as hexanes, pentane, petroleum ether, methanol, 70% ethanol and dichloromethane. The amount of Z-ligustilide in Danggui varies between 1.26 and 37.7 mg/g dry weight. Z-ligustilide facilitates blood circulation, penetrates the blood brain barrier to limit ischemic brain damage in rats and attenuates pain behavior in mice. Preclinical studies have indicated that AS and Z-ligustilide may also relax smooth muscle in the circulatory, respiratory and gastrointestinal systems. Numerous phthalide derivatives have been isolated from Angelica species. The major constituent is Z-ligustilide (61–69% in the essential oil), with other phthalides such as E-ligustilide, Z-butylenephthalide, 3-butylphthalide, 3-butyldiene-4-hydroxy-phthalide, senkyunolide A, 6, 7-epoxylicustilide, senkyunolideF, senkyunolide H, senkyunolideI, 6, 7-dihydroxylicustilide and phthalide dimers including riligustilide, levistolide A, and senkyunolide. Extensive investigations have been carried out and published on the biological activities of ligustilide, including inhibition of uterine contractions, vasodilation, decrease in platelet aggregations, analgesic, and anti-inflammatory effects, attenuation of lipopolysaccharide-induced pro-inflammatory response and endo-toxic shock. Ligustilide is stated to be neuro protective, to inhibit vascular smooth muscle cells proliferation, to be anti-depressant and serotonergic and a novel transient receptor potential cation channel (TRPA1)-activator. N-butylenephthalide inhibits angiogenesis in vitro and in vivo and endothelial sprouting. The pharmacokinetics of ligustilide in humans are little understood, but animal studies have found that after oral administration of ligustilide was absorbed at only the highest dose (500mg/kg) and rapidly eliminated. The main metabolic reactions of phthalides appear to be conjugation with glutathione, cysteine, glucuronic and sulfuric acids.

3.2. Organic acids (i.e. Ferulic acid and coniferylferulate):

Danggui contains many organic acids. For example, ferulic acid isolated from Danggui is widely used as the marker compound for assessing the quality of Danggui and its products. Methanol, methanol-formic acid (95:5), 70% methanol,

70% ethanol, 50% ethanol or diethyl ether-methanol (20:1) is used as the initial extraction solvent. The amount of ferulic acid in Danggui varies between 0.21 and 1.75 mg/g dry weight. Abundant in rice bran, wheat, barley, tomato, sweet corn and toasted coffee, ferulic acid is an antioxidant, anti-inflammatory and anti-cancer agent and apart from its effects against Alzheimer's disease, it possesses anti-hyperlipidemia, antimicrobial and anti-carcinogenic properties. The activity of processed *Angelica sinensis* root is also linked to the ferulic acid (FA) content (Chinese Pharmacopoeia, B.P.: British Pharmacopoeia; European Pharmacopoeia). This content varies significantly depending on the methods of extraction and analyses. FA rarely occurs freely in plants but more usually as its unstable ester coniferyl ferulate which has actions similar to FA, but stronger. Ferulic acid is stated to possess numerous bioactivities mostly associated with its anti-oxidant and radicals scavenging activities. These effects include anti-inflammatory, antithrombotic, anti-coagulant and cardio protective, neuro protective after cerebral ischemia, radio protective by inhibiting of gamma radiation induced DNA strand breaks and inhibitory of oxytocin-induced mouse uterine contraction invitro. Results in humans show that after oral ingestion peak plasma concentrations of FA were reached within 1h and declined over 24h. The peak time for maximal urinary excretion was approximately 7h and there covering the urine, on the basis of total free ferulic acid and feruloyl glucuronide excreted, was 11–25% of that ingested.

3.3. Polysaccharides:

Biochemical and medical researchers have recently been interested in the anti-tumor and immunomodulatory effects of polysaccharides. The efficacy of Danggui is associated with its various polysaccharides which are extracted with water as the initial extraction solvent. Polysaccharides from Danggui consist of fructose, galactose, glucose, arabinose and xylose. Danggui contains a neutral polysaccharide and two kinds of acidic polysaccharides. Interest in the bioactivities of polysaccharides isolated from AS has recently increased. Chemically polysaccharides isolated from fresh roots are reported to consist of uronic acid [8.6%] and the sugars rhamnose, arabinose, mannose, glucose and galactose. A polysaccharide extracted from dried, defatted *Angelica sinensis* roots was determined to have a molecular weight of 78kDa and to consist of 95% sugars, mainly arabinose, glucose and galactose, while two homogenous polysaccharides: APS-1a contains the sugars galactose, arabinose and glucose and APS-3a, galactose, arabinose and glucose. Several acidic polysaccharides have also been isolated and fractionated, with different fractions showing various activities. In common with other plant-derived high molecular weight polysaccharides, those from AS have been shown to have immunomodulatory actions. In addition they are reported to be antioxidant, myeloprotective, cardio protective, have anti-tumor and analgesic effects and promote proteoglycan synthesis by chondrocytes which is of potential relevance to osteoarthritis. Some fractions have been reported to have thrombopoietic and hematopoietic properties by inhibiting hepcidin expression suggesting their use for treating iron deficiency anemia, while APS-1a and-3a could be used as radioprotective agents for promoting bone marrow hematopoiesis. Hepatoprotective and antidiabetic activities have also been suggested.

4. PHARMACOLOGICAL / TOXICOLOGICAL EFFECTS

4.1. Cardiovascular Effects:

Cardiac arrhythmia, Cardiovascular disorders can be treated by AS. It dilates blood vessels and increases blood flow without affecting heart rate. It lowers blood pressure and also lowers vascular resistance palpitations. It promotes blood circulation reduces pulmonary hypertension and strengthens the heart stroke (decreases the amount of brain damage following a stroke). Dong Quai is included in combinations for circulatory and liver conditions due to its ability to reduce the viscosity of blood. The antispasmodic and soothing effects of Dong Quai have made it the herb of choice in treating conditions such as hypertension and high blood pressure. By soothing the arteries and calming the vascular system, it lowers stress on the heart Researchers have isolated seven coumarin derivatives in Dong Quai that may have vasodilating and Antispasmodic effects that may improve circulation, lower blood pressure, and dilate coronary arteries. These effects may be mediated through calcium channel blockade or inhibition of phosphodiesterase activity. Nitric oxide (NO) is synthesized with nitric oxide synthase (NOS) which includes three different isoforms, namely endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). While nNOS and eNOS are induced under different conditions, their activation relies on intracellular Ca²⁺ for binding calmodulin. Due to its vasodilative effects, eNOS is considered neuro-protective. Hypertension and a lack of endothelium-derived relaxing factor activity are found in eNOS knockout mice. Moreover, the cerebral infarction size is larger in a model of eNOS mutant mice with middle cerebral artery occlusion (MCAo). Therefore, eNOS has a vasodilation effect and is neuro-protective by increasing the blood flow. It is possible

that Danggui increases NO formation and relaxes the endothelium, thereby limiting infarction size. In rabbits on a high-lipid diet, treatment with ferulic acid, an active component of Danggui, increases the generation of NO, thereby inhibiting platelet aggregation on endothelium and proliferation of smooth muscles and preventing leucocytes adhering to the endothelium. Z-Ligustilide (3-butylidene-4, 5-dihydrophthalide), a component of Danggui, inhibits (4-8 µg/ml) the spontaneous contraction of isolated rat uterus in a dose-dependent manner. Moreover, Z-Ligustilide may also inhibit prostaglandin F-2a, oxytocin, acetylcholine chloride and potassium depolarization-induced uterine contraction, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited, suggesting that Ligustilide modulates the function of uterine tissue and has a non-specific anti-spasmodic effect. Z-Ligustilide enhances the recovery of conjunctival capillary and venue diameter after dextran T500 administration to rabbits and increases the number of opened capillaries as well as blood flow, suggesting that Z-Ligustilide improves microcirculation. Ferulic acid is the main organic acid component of Danggui. Ferulic acid (10-3 mol/L) relaxes the phenylephrine-induced contraction of aorta ring in spontaneous on rat (SHR) whereas the effects of ferulic acid may be partially blocked by pretreatment of the aorta with NGnitro- L-arginine methyl ester (L-NAME, 10-4 mol/L) which inhibits the production of NO from L-arginine . Ferulic acid (10-3 mol/L) reduces the production of thromboxane B2 in the aorta ring of SHR. Ferulic acid (10-4 mol/L) also significantly reduces the generation of NADPH-dependent production of the superoxide anion and enhances the acetylcholine-induced vasodilation whereas hydroxyhydroquinone (HHQ) inhibits this effect. Taken together, ferulic acid reduces blood pressure in SHR via effects on (1) eNOS; (2) the inhibition of thromboxane B2 to relax aorta ring; (3) reactive oxygen species (ROS) scavenging activity to increase the availability of NO in endothelial cell of aorta. Pre-treatment with AS (15 g/kg daily for 4 weeks) decreases doxorubicin-induced (15 mg/kg intravenously) myocardial damage and serum aspartate aminotransferase levels in male ICR mice. Human umbilical vein endothelial cells (HUVECs) treated with AS water extract activate VEGF gene expression and the p38 pathway, thereby increasing angiogenic effects of HUVECs both in vitro and in vivo. Excess adipose tissue can lead to insulin resistance and increases the risk of type II diabetes and cardiovascular diseases. Water and 95% ethanol extracts of AS effectively decrease fat accumulation in 3T3-L1 adipocytes and reduce triglyceride content .Dong Quai has also been purported to have a high iron content which may prove efficacious in the treatment and prevention of iron deficiency anemia. Other reported cardiovascular effects include inhibition of platelet aggregation via inhibition of platelet serotonin release; prolongation of the refractory period; and reduction of atherosclerotic plaque formation. It is claimed to stimulate hematopoiesis secondary to its vitamin B12 (0.25–0.4 mg/100 g dried root), folic acid, and biotin content. Cardio vascular side effects include excessive bleeding.

4.2. Neurologic Effects:

The findings of an in vitro study in murine neurocyte culture suggest Dong Quai may accelerate the growth of neurocyte processes and prevent decline in process branch number. Dong Quai may promote neurocyte growth and delay age-related nerve atrophy in humans. It prevents Insomnia and spasms, relieves stress and calms the nerves and stimulates the central nervous system Z-ligustilide treatment decreases the level of malondialdehyde (MDA) and increases the activities of the antioxidant enzymes glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) in the ischemic brain tissues in ICR mice; meanwhile there is a decrease in Bax and caspase-3 protein expression. Z-ligustilide increases the choline acetyltransferase activity and inhibits the acetylcholine esterase activity in ischemic brain tissue from Wistar rats. AS extract protects Neuro 2A cell viability against b-amyloid (Ab) peptide induced oxidative damage by ROS, MDA and glutathione (GSH) and rescues mitochondrial trans membrane potential levels-ligustilide inhibits the TNF-a-activated NF-B signaling pathway, which may contribute to Z-ligustilide's protective effect against Ab peptide-induced neurotoxicity in rats. AS methanol extract significantly attenuates Ab1-42 induced neurotoxicity and tau hyperphosphorylation in primary cortical neurons. AS polysaccharides (18.6% saccharose) reduce myocardial infarction size and enhance cardiotrophon-1 levels, serum GSH levels, serum SOD levels, GSH-Px activity and brain caspase-12 expression in Wister rats treated with a single oral dose (100, 200, 300 mg/kg) daily for two months. The tranquilizing and sedative effects that have been attributed to Dong Quai may help alleviate of mood swings and irritability in premenstrual syndrome . Dong Quai has also been recommended for the treatment of migraine headaches.

4.3. Musculoskeletal Effects:

AS can be used to prevent neuralgia and muscular-skeletal injuries. Components of Dong Quai may be capable of relaxing smooth muscle of visceral organs, including the intestines and uterus, via calcium channel blockade. The water-soluble, nonvolatile extract causes uterine stimulation, while the alcoholic extract (an essential oil with a high boiling

point) relaxes the uterus. This relaxation may help reduce the pain associated with menstrual cramps. Osthole, a coumarin derivative found in the root, and ferulic acid, a volatile oil component, have been shown to inhibit platelet function. A Dong Quai root preparation administered intravenously was also shown to prolong prothrombin time in humans.

4.4. Immunologic Effects/Antineoplastic Activity/Antimicrobial Activity:

Hematological immunological problems can be treated. Inhibition of experimentally induced immunoglobulin E (IgE) production has been demonstrated with aqueous extracts of Dong Quai. Thus, the herb may prove useful in the treatment and/or the prevention of allergic symptoms. However, a polysaccharide isolated from Dong Quai has been demonstrated to have an immunostimulant effect, and to have an antitumor effect in murine models. Thus, it may prove to have efficacy in the treatment of cancer. The coumarins found in Dong Quai purportedly stimulate macrophages, enhancing phagocytosis. Treatment of BALB/c mice spleen cells with AS polysaccharide (100 µg/ml) increases the production of IL-2 and IFN-g and decreases the production of IL-4. An acidic polysaccharide fraction isolated from AS stimulates female BALB/c murine peritoneal macrophages to produce higher levels of nitric oxide (NO) via the induction of iNOS gene expression. The AS polysaccharide (mannose, rhamnose, glucuronic acid, galacturonic acid, glucose, galactose, arabinose, xylose)-dexamethasone conjugate demonstrates a therapeutic effect on trinitrobenzenesulfonic acid-induced ulcerative colitis in rats and the systemic immunosuppression caused by dexamethasone. Four hydrosoluble fractions of AS polysaccharide exert the most conspicuous mitogenic effects on phagocytic activity and NO production by female ICR mouse peritoneal macrophages. AS polysaccharide treatment rescues BALB/c mice from retro-orbital bleeding induced anemia and increases IL-6, granulocyte macrophage colony stimulating factor (GM-CSF) concentrations in spleen cells. Ferulic acid, an antioxidant from AS, decreases H₂O₂-induced IL-1b, TNF-a, matrix metalloproteinase-1 and matrix metalloproteinase-13 levels and increases SRY-related high mobility group-box gene 9 gene expression in chondrocytes. AS induces the proliferation of ICR murine bone marrow mononuclear cells by activating ERK1/2 and P38 MAPK proteins. Pretreatment with 50 mg/kg AS increases serum colony-stimulating activity together with IFN-g and TNF-A levels in the spleen mononuclear cells of *Listeria monocytogenes* infected BALB/c mice. Other immunostimulatory actions include possible B-lymphocyte mitogenic activity, complement activation, interferon production, and interleukin-2 production. Dong Quai may have activity against both Gram-negative and Gram-positive bacteria.

4.5. Anti-Inflammatory Activity:

Ferulic acid, a phenolic compound of Dong Quai, was found to exert analgesic and anti-inflammatory activity in both the early and late phases of the inflammatory process in laboratory animals. The analgesic action is said to be 1.7 times greater than that of aspirin. Histamine-mediated inflammation is not affected by Dong Quai. Pro-inflammatory cytokines, such as IL-1b and TNF-a, are increased in the brain tissue of transient middle cerebral artery occlusion (MCAo) rats. IL-1 up-regulates the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), P-selectin and E-selectin in the endothelium. These adhesion molecules facilitate the translocation of activated leukocytes into the ischemic core. Moreover, nuclear factor-B (NF-B) is also activated in the ischemic core. Moreover, paeoniflorin reduces IL-1b, TNF-a, ICAM-1 and leucocytes [30]. Therefore, anti-inflammation, such as inhibition of pro-inflammatory cytokine and ICAM-1, is very important in treating cerebral infarction. Ferulic acid (eg 80 and 100 mg/kg, i.v.) reduces the size of cerebral infarction and neurological deficit scores and inhibits ICAM-1 and NF-B expression in transient MCAo rats. The anti-inflammatory action of ferulic acid is, at least in part, important in its therapeutic effect on cerebral infarct. Moreover, ferulic acid (eg 100 mg/kg, i.v.) exerts anti-inflammatory action by reducing the generation of 4-hydroxy-2-nonenal (4-HNE), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and apoptosis in the reperfusion period after cerebral ischemia, thus providing neuroprotection. This neuro-protection by ferulic acid is thought to occur via enhancing gamma-amino butyric acid type B1 (GABAB1) receptor expression to against p38 mitogen activated protein kinase (MAPK)-mediated NO-induced apoptosis. Danggui reduces inflammatory cell infiltration and TNF-a and TGF-β1 mRNA expression; it also reduces TNF-a and TGF-β1 positive cells in radiation-induced pneumonitis in mice. Danggui polysaccharides reduce TNF-a levels in the colon mucosa during intra-colon enema with 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) and ethanol in rats. Both Danggui and ferulic acid exert anti-inflammatory effects.

4.6. Carcinogenicity:

As noted previously, the furocoumarins, psoralen and bergapten, can induce photosensitization. These agents are also photocarcinogenic, and mutagenicity persists even in the absence of light. As with photosensitization, risks attributable to human consumption of Dong Quai have not been documented. Safrole, a component of the essential oil of Dong Quai,

has also demonstrated carcinogenicity and its ingestion are not recommended. AS had a dose-dependent antiproliferative effect on human cancer cell lines derived from the lung, brain, liver, and colorectal tissue. Their results also demonstrated that the AS-C induced the arrest of human cancer cells and activated the mechanism of apoptosis. A low-molecular weight polysaccharide from the *Angelica sinensis* rhizome and proved its strong antitumor and immunostimulatory activities. Additional polysaccharides have since been identified from *Angelica sinensis*: APS-1, APS-3a, APS-3b, and APS-3c. These display diverse structural features and antitumor activities: e.g., the backbone of APS-1 consists of (1, 4)- α -D-glucopyranosyl residues, its branches being (1, 6)- α -D-glucopyranosyl residues with a terminal β -L-arabinofuranose residue. Notably, APS-1 had antitumor effects in vitro, especially against human cervical cancer HeLa cells. This antitumor activity coincided with a greater expression of mRNAs encoding interferon-gamma, interleukin-2, and interleukin-6 in splenocytes, as well as greater nitric oxide and TNF-gamma production in macrophages. Butylidenephthalide was recently identified as the active component of AS-AC. Natural phthalide compounds such as butylidenephthalide are considered to be candidate antitumor agents. Indeed, butylidenephthalide has proven anticancer potential against colon cancer. As well as its antitumor effect, butylidenephthalide has demonstrated an ability to prevent benzo[a]pyrene-induced stomach cancer in mice. Butylidenephthalide and other agents (senkyunolide A and Z-ligustilide) act synergistically to reduce tumor cell proliferation. A synergistic antiproliferative effect is noted when butylidenephthalide is combined with the chemotherapeutic drug 1, 3-bis (2-chloroethyl)-1-nitrosourea (carmustine or BCNU). This synergism is mediated by downregulation of the gene MGMT, which encodes the DNA repair enzyme O-6-methylguanine-DNA methyltransferase. AS extract induces apoptosis and causes cell cycle arrest at G0/G1 in brain tumor cell lines. AS extract also decreases the expression of the angiogenic factor vascular endothelial growth factor (VEGF) in brain astrocytoma. Moreover, n-butylidenephthalide and Z-ligustilide are cytotoxic against brain tumor cell lines and leukemia cells. The three main AS phthalides, namely n-butylidenephthalide, senkyunolide A and Z-ligustilide, decrease cell viability of colon cancer HT-29 cells dose dependently. The PC12 cells with Z-ligustilide attenuates H₂O₂-induced cell death, attenuates an increase in intracellular reactive oxygen species (ROS) level, decreases Bax expression and cleaves caspase-3 and cytochrome C. A novel polysaccharide (50 mg/kg, 100 mg/kg) isolated from AS inhibits the growth of HeLa cells in nude mice via an increased activity in the caspase-9, caspase-3 and poly (ADP-ribose) polymerase (PARP).

4.7. Estrogenic Effect:

Dong Quai is purported to contain phytoestrogens and is used for treatment of conditions of both high and low estrogen levels. These phytoestrogens are reportedly lower in potency than animal estrogens. However, in conditions of low estrogen, they are said provide adequate estrogen replacement, while in conditions characterized by high estrogen levels, these lower potency phytoestrogens are thought to compete with estrogen for estrogen binding sites. Use of Dong Quai is also recommended for amenorrhea, dysmenorrhea, and menorrhagia. Dong quai has also been reported to enhance regularity of menstrual cycles, control premenstrual symptoms, and alleviate some signs and symptoms of menopause. Premenstrual syndrome (PMS) symptoms such as cramps respond well to the calming effect of this herb. Dong Quai is a mainstay treatment for menstruation and menopause disorders in traditional Chinese medicine. Herbal alternatives that include Dong Quai in their formulas may relieve night sweats, mood swings, hot flashes, bloating, and heavy bleeding. Dong Quai also offers an alternative to risky hormone replacement therapy (HRT) treatments, which have been under scrutiny in recent years. Despite these uses, it is unclear if Dong Quai actually contains phytoestrogens. For applying a dose in healthy woman the change mainly has seen on endometrial thickness, vaginal cytology, Kupperman index and patient diary of vasomotor symptoms. No changes in serum estrogen, estradiol, sex hormone binding globulin (SHBG), blood pressure, or weight. Adverse effects included burping, gas, and headache, which occurred with similar frequencies in both the place. Dong Quai has been called the “female ginseng” and is an excellent women’s herb. It helps an woman for- amenorrhea, balances and treats many female systems and cycles ,controls dysmenorrhea (painful menstruation) , endometriosis ,female tonic ,helps combat premenstrual tension ,helps women resume normal menstruation after using birth control pills, improves fetal nourishment during pregnancy ,infertility ,infrequent periods, irregular menstruation (regulates the menstrual cycle) ,menopausal symptoms, especially hot flashes ,menstrual cramps, menorrhagia (excessive loss of blood during a period) ,premenstrual syndrome (PMS), especially when combined with Black Cohosh ,powerful herb for the female reproductive system ,produces a balancing effect on estrogen activity ,reduces spontaneous uterine contractions ,regulates uterine contractions, regulates uterine function ,stimulates as well as relaxes uterine muscles ,stimulates the uterus during childbirth ,strengthens internal reproductive organs, uterine bleeding ,uterine cramping

,weakness and headaches associated with menstrual disorders ,and for menopausal symptoms. It has been used for centuries in China for maintaining a healthy menstrual cycle. Most of the actions of Dong Quai depend on the presence of coumarins, phyosterols, polysaccharides and flavonoids. Dong Quai helps to promote uterine health and regulate the menstrual cycle. Coumarins dilate blood vessels, stimulating the central nervous system and increasing blood flow throughout the body. They may also relax the smooth muscles of the uterus, which would help to explain the herb's traditional use for menstrual cramps.

4.8. Dermatological Effects:

Dong Quai is known as a beauty tonic. The herb has been found to benefit the complexion by improving circulation in the skin and by detoxifying, thus helping to clear blemishes. Dong Quai has been used in the treatment of eczema, neurodermic dermatitis, and psoriasis in Chinese medicine. Psoralen and bergapten, two of the furocoumarins found in Dong Quai, are photoreactive and have the potential to cause severe photodermatitis. Dong Quai helps skin tone as it enriches the blood and improves circulation. Dong Quai is an important herb for women whose skin is sallow, dry and lacking a healthy glow. Astragalus is often used in combination with Dong Quai to further improve the circulation of blood in the skin making it more supple and healthy. Dong Quai's reputation as a female tonic. Psoralens induce skin melanization in the presence of light and have been employed in the treatment of skin depigmentation and psoriasis. The risk of phototoxicity in humans from ingestion of Dong Quai has not been characterized. Dong Quai has also shown an inhibitory effect against many bacteria including hemolytic *Streptococcus* and *Shigella*. It has a mild sedative effect, and a pain relieving effect.

5. DRUG INTERACTIONS AND OTHER SIDE EFFECTS

Dong Quai should not be used if following medications is taken:

1. Blood Thinning Agents such as Warfarin (Dong Quai can increase the potency). If any anticoagulant (blood-thinning) medication or a nonsteroidal anti-inflammatory drug (such as ibuprofen) have to be taken, then physician recommendation is needed before trying Dong Quai as it will have additive blood thinning and anti-inflammatory properties.
 2. Blood-thinning herbs although extremely uncommon, combining Dong Quai with other herbs that thin the blood may possibly increase the risk of bleeding in some people.
 3. Herbs that should be used only under strict supervision when combined with Dong Quai include: Feverfew (*Tanacetum parthenium*), Garlic (*Allium sativum*), Ginger (*Zingiber officinale*), Ginkgo (*Ginkgo biloba*), Ginseng (*Panax ginseng*), Licorice (*Glycyrrhiza glabra*), Chinese skullcap (*Scutellaria baicalensis*), Turmeric (*Curcuma longa*).
 4. Hormone medications: Estrogens, Progesterone.
 5. Oral contraceptives: Tamoxifen, Faloxifene.
 6. Herbs or Medications causing Sun Sensitivity: St. John's Wort can cause sun sensitivity so it should not be used with Dong Quai which can cause the same reaction.
 7. Other Medications: Heparin, Ticlopidine.
- * Dong Quai also contains substances called psoralens that can react to sunlight, especially in fair skinned people.
 - * Dong Quai may have a mild laxative effect, and menstrual bleeding may increase when taking Dong Quai.
 - * Stop taking Dong Quai if a skin rash or photosensitivity develops.
 - * Don't take Dong Quai if you are pregnant or nursing. As with all herbal and dietary supplements, you should always inform your physician about what you are taking in order to avoid potentially dangerous drug interactions.
 - * High doses of Dong Quai can cause some fair-skinned people to become more sensitive to sunlight causing: rashes, skin inflammation.

Dong Quai should not be used during:

- ❖ first trimester of pregnancy because it may affect the muscular functioning of the uterus (however in traditional Chinese medicine Dong Quai is used routinely to calm the fetus and nowhere is it contraindicated)
- ❖ during breast-feeding
- ❖ with a tendency to spontaneous abortion
- ❖ with a bleeding tendency
- ❖ for women with very heavy periods
- ❖ when suffering from abdominal bloating
- ❖ when suffering from chronic diarrhea
- ❖ when suffering from a cold or flu
- ❖ with acute viral infections such as colds or influenza
- ❖ with increased menstrual flow or hemorrhagic disease

A 46-yr-old black female experienced an increase in INR from 2–3 to 4.05–4.9 after taking 565 mg of Dong Quai once or twice daily for 4 wk. The patient's past medical history included rheumatic heart disease, stroke, and atrial fibrillation. Medications included 5 mg/d of warfarin, 0.25 mg/d of digoxin, and 20 mg/d of furosemide. Upon challenge from Dong Quai, her INR decreased to 3.41 after 2 wk, and then to 2.48 2 wk later, with no change in warfarin dose. Because a study in rabbits showed that 2 g/kg of Dong Quai increased prothrombin time (PT) but did not alter warfarin pharmacokinetics, the authors suspected a pharmacodynamics mechanism for the interaction. They also hypothesized that warfarin might displace a component of Dong Quai from protein binding sites or inhibit its metabolism, thus increasing its plasma levels and effect on PT.

6. TOXICOLOGICAL DATA

6.1. Acute Toxicity:

The LD50 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 LD50 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).

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)	LD50/LC50
A. Sinensis (Oliv.) Diels		
root extract		
i.v.	Mouse, (sex and strain n.p.)	LD50 = ~100 g/kg
dried root; ethanol-water (1:1) extract		
oral	mouse, male, strain n.p.	LD50 = 50.0 mL/kg
i.p.	mouse, male, strain n.p.	LD50 = 38.0 mL/kg
Ferulic acid		
i.v	Mouse (sex and strain n.p.)	LD50 = 857 mg/kg
i.p	Mouse (sex and strain n.p.)	LD > 350 mg/kg*
3-Butylidenephthalide		
oral	Rat (sex and strain n.p.)	LD50 = 1850 mg/kg
dermal	Dermal Rabbit (sex and strain n.p.)	LD50 >5000 mg/kg

*LD not specified (i.e., LD50, LDLO, etc.) Abbreviations: i.p. = intraperitoneal; i.v. = intravenous; LD50 = lethal dose for 50% of test animals; n.p. = not provided.

7. CONCLUSION

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 sub chronic studies. Dong Quai extracts have been reported to have synergistic effects with various chemicals and have anti proliferative 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 anti-carcinogenic 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. 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.

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