Dong Quai

Angelica sinensis

Common names

Chinese angelica, dang gui, tang kui

Family

Apiaceae (parsley)

Part used

Root

Background and traditional uses

Dong quai is a cylindrical perennial plant with many roots and rootlets.[1] Native to China and cultivated in Vietnam, dong quai is strongly aromatic with a pungent and bitter taste, and is considered to have warm, bitter, sweet and acrid properties.[2,3]

The first report of the therapeutic application of dong quai was in a traditional Chinese medicine (TCM) monograph from the Qin Han dynasty in 300 A.D, to nourish blood and regulate menstruation, with many records of its use across subsequent Chinese dynasties.[4]

Referred to as the 'female ginseng',[4] the herb has a long history of use in TCM particularly in combination with other herbs for treating women's reproductive issues, as well as for imbalances in heart, liver and spleen channels and to invigorate, enrich, harmonise and tonify the blood.[5,6]

Traditional uses for dong quai are related to blood in heart and liver blood deficiencies, to invigorate blood circulation, relieve pain, regulate menstruation, moisten dry intestines associated with blood deficiency, to ease coughs, dyspnoea, improve immunity, and reduce swelling.[1,2,4,6]

Actions

Primary:[1-5]

- Antianaemic
- Antiarrhythmic
- Anti-inflammatory
- Antiplatelet
- Female tonic
- Hormone modulating
- Depurative
- Spasmolytic

Secondary:[1-5]

- Aperient
- Antioxidant
- Antiproliferative
- Hypoglycaemic
- Immune modulating
- Hepato/nephroprotective

Applications and indications

- For use as a female tonic, and to help tonify the blood, regulate menses and inhibit smooth muscle contraction, thereby assisting dysmenorrhea and infertility.[2,7-9]
- To moisten dry intestines to relieve constipation.[2]
- To stimulate cellular blood building and bone building processes.[10-12,22-24]
- To inhibit platelet aggregation and promote antithrombotic activity.[13]
- Dong quai has also been shown to reduce neurogenic and anti-inflammatory pain,[14-16] and induce apoptosis, senescence and anti-metatastic activity in cancer cell lines.[17-21]

Active constituents and pharmacodynamics

The dong quai plant contains 165 known chemical constituents in total, with over 50 in the root. The primary active constituents are considered to be polysaccharides, organic acids and phthalides.[4] The **polysaccharides** are thought to be responsible for the herbs blood and bone-building, antioxidant and hepatoprotective effects,[10-12,23,26,27] and (Z)-ligustilide for its anti-inflammatory, antinociceptive, antiplatelet and antispasmodic effects,[9,13-15] each via a number of pharmacodynamics actions. Both constituents have demonstrated mechanisms associated with antiproliferative effects.[17-19,21]

The root contains significant concentrations of sugars, specifically fucose, galactose, glucose, arabinose, rhamnose, xylose, arabigalactan, saccharose and hypoxanthine-9-beta-D-ribofuranoside. Other polysaccharides isolated from the root are novel (APS-1a and APS-3a) and acidic (APS-3a, APS-3b, APS-3c) constituents and polysaccharide fractions (APF1, APF2, APF3).[1,4,6]

Phthalides are present in the root and are often used to assess the quality of different herb materials.[4] They represent the essential oil class and consequently have strong olfactory characteristics. Compounds in this category are ligustilide (E and Z), butylidenephthalide (Z), butylphthalide, senkyunolide A-I, senkyunolide P, senkyunolide K, levistolide A, riligustilide, tokinolide B, neocnidilide, (Z)-6,7-epoxyligustilide, angelicide and 2,4-dihydrophthalic anhydride.[1,3,4,6]

Constituents with benzene rings of **organic acids** and their esters are also located in the roots. They include phenylpropanoids ((E)-ferulic acid, coniferyl ferulate); benzenoids (valerophenone-O-carboxylic acid, vanillin acid); succinic acid, nicotinic acid, folic acid coumarins (angelol G, angelicone, umbelliferone), linoleic acid, palmitic acid and oleic acid.[1,3,4]

Summary of clinical evidence

Female tonic

Several human studies have investigated the use of herbal combinations that included dong quai for the treatment of menopausal symptoms.[7,8]

In a placebo-controlled study, 55 postmenopausal women (45-65 years) experiencing at least three hot flushes over 24 hours, as well as night sweats, were randomly divided into either treatment or placebo groups.[7] Over 12 weeks, the treatment group (n=22) was given 375mg dong quai and 150mg *Matricaria chamomilla* (chamomile) daily in divided dosages (five tablets between meals) while the placebo group (n=23) had identical non-active tablets. At the end of the study period, there was a significant difference in the frequency and intensity of hot flushes from baseline compared with the placebo group (90-96% vs 15-25%, p<0.001), with the effects observed from the first month of treatment in the active group (68%±2% reduction of hot flushes during the day and 74±4% at night). Sleep disturbances, fatigue, mood and concentration also improved in the treatment group compared with placebo.[7]

Similar results were observed in a subsequent randomised, double-blind, placebo-controlled trial assessing the efficacy of dong quai in combination with *Actaea racemose* (black cohosh), *Silybum marianum* (milk thistle), *Trifolium pretense* (red clover), *Panax ginseng* (American ginseng) and *Vitex agnus-castus* (chaste tree) for menopausal symptom relief.[8] Healthy pre- and post-menopausal women aged 44-65 years were given the herbal combination that included 75mg dong quai root extract (standardised to 1% lingustilides) (n=19) or placebo (n=16) twice daily for three months. The active treatment group had a significant reduction in menopausal symptoms compared with placebo. By the end of the study period, there was a reduction in both the number of hot flushes (by 73% versus 8% in placebo, p=0.044) and night sweats (by 69% vs 29%, p=0.027) in the active treatment group. The treatment group also had a decrease in hot flush intensity and improved sleep quality (80% lower than baseline vs 35% of placebo group). At the end of the treatment period 47% of women experienced complete cessation of hot flushes compared with 19% in placebo group.

Antianaemic and blood building

An animal study investigated the mechanistic effect of powdered dong quai root on iron homeostasis in rat models of iron-deficiency anaemia.[10] Rats were fed an iron deficient diet combined with blood-letting three times weekly for two weeks and subsequently randomly divided into three groups – intragastric administration with dong quai polysaccharides (named ASP) (1g/kg daily for 14 days), injection with recombinant human erythropoietin (rhEPO) daily for three days or intragastrical administration of saline daily for 14 days. ASP was observed to significantly inhibit hepcidin expression (by 13.4% vs 31.8% in the rhEPO group vs no significant change in controls) and increase EPO secretion. ASP also inhibited two pathways involved in hepcidin expression, SMAD4 gene in the liver (by 64.7% v no significant difference in rhEPO group) and C/EBP-alpha expression (49.4% v 75.9% with rhEPO).[10] Similar results were observed in another rat study assessing the pathways involved in inhibition of hepcidin by ASP.[11]

A further study investigated the potential haematopoietic-associated mechanisms of polysaccharide fractions from a crude dong quai extract in a mice model.[12] Following incubation of dong quai and ASP with mice spleen cells, ASP was observed to stimulate secretion of interleukin-6 and secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). Mice administered with 2.3mg/kg/day of ASP had significantly accelerated recovery of haemoglobin to normal levels following blood loss compared with controls (p<0.05).

Antiproliferative

ASP induced senescence in acute myelogenous leukaemia (AML) CD34+ and CD38- stem cells in two separate *in vitro* investigations via similar mechanisms.[17,18] Treatment of cell lines with ASP observed that inducement of AML senescence was likely a consequence of the upregulation of tumour suppressor p16-Rb, p53 and p21 proteins and downregulation of CDK4 and cyclin E.

In another *in vitro* study, proliferation of human chronic erythromegakaryoblastic leukaemia K562 cells was inhibited by ASP through the arrest of cell cycle division at the G0/G1 phase and stimulation of the JAK2/STAT5 pathway.[19] An investigation into the impact of ASP on invasive ductal carcinoma cell lines (T47D) observed inducement of apoptosis via the cAMP response element binding protein (CREB) pathway.[20] The specific apoptotic signalling pathways affected were caspase protease enzyme activity, inhibition of cellular membrane potential, cytochrome c release and translocation of Bax, PARP and Apaf1 proteins.

Another constituent from dong quai, Z-lingustilide (LIG) was found to influence the Nrf2 pathway *in vitro*, specifically by inducing mRNA and protein expression of Nrf2 and downstream target genes (HO-1, NQ01, UGT1A1), decreasing methylation of Nrf2 promoter CpG region and inhibiting DNA methyltransferase activity.[21]

Spasmolytic

An *in vitro* study looked at the effects of the LIG constituent from dong quai on rat uterine contractions.[9] LIG demonstrated antispasmodic activity through several mechanisms, including inhibition of spontaneous periodic contraction (LIG 2-8mcg/ml, 95% CI 2.7-6.1), and reduction of prostaglandin (PGF2 alpha) and acetylcholine chloride-induced contractions by 95.3% and 73.9% respectively (LIG 8mcg/ml). LIG also significantly affected oxytocin-induced contraction of the uterine horns as well as potassium (K+) depolarisation-induced contractions by significant levels at a dose of 2mcg/ml (95% CI 2.5-4.1mcg/ml).[9]

Antithrombotic and antiplatelet

In a rat model, the effect of LIG on platelet aggregation and coagulation time was investigated.[13] Rats were administered with 10 or 40mg/kg of LIG or aspirin intragastrically daily for three days, with blood samples taken one hour following administration. Both dosage levels of LIG significantly reduced thrombus formation in rat arteriovenous shunt thrombosis similar to the antithrombotic effects of 40mg/kg of aspirin. Coagulation factors were not affected by LIG, suggesting antiplatelet mechanisms may be involved.[13]

Anti-inflammatory and analgesic

An ethyl acetate fraction and LIG constituent from dong quai have exhibited anti-inflammatory and analgesic effects.[14-16] In one study, rat microglia were pre-treated with LIG one hour (2.5, 5, 10 and 20mmol/L) before lipopolysaccharide (LPS)-induced inflammation occurred.[14] LIG significantly reduced LPS-induced nitric oxide (NO) synthesis, TNF-alpha and interleukin-1 beta (IL-1 beta), MCP-1, NF-kappaB (NFkB), COX-2 and iNOS concentrations, ($p<0.01$) compared with LPS treatment only.

Similar results were observed in an assessment of the effects of an ethyl acetate fraction of dong quai on macrophages and BALB/c mice. Pre-treatment with dong quai resulted in significant inhibition of NFkB activity, TNF-alpha, IL-6, MIP-2 and NO concentrations following LPS and interferon stimulated inflammation. Mice orally administered with 1.56mg/kg of dong quai also decreased serum TNF-alpha and IL-12p40 levels, with ferulic acid and LIG significantly reducing NFkB activity.[16]

Bone building

Several *in vitro* studies on dong quai extracts have demonstrated its support for bone building activites.[22-24] In a rat osteoarthritis *in vitro* and *in vivo* model, ASP stimulated IL-1 beta inhibited proteoglycan synthesis by increasing mRNA expression of aggrecan and glycosyltransferases.[23] A subsequent study by the same group observed that in human primary chondrocytes treated with ASP or IL-1 beta, ASP stimulated IGF-1 and IGF1R gene expression, resulting in increased production of UDP-sugars and glycosoaminoglycan synthesis.[22]

Antioxidant

Several preliminary investigations have demonstrated that constituents from dong quai exhibit antioxidant activity.[19,25,26] In a rabbit model, ASP was administered orally for 40 days at doses of 150 or 300mg/kg prior to performance of a cerebral ischaemia reperfusion (CIR) operation. Compared with CIR animals, those in the ASP group demonstrated significantly reduced oxidative damage and augmentation of antioxidant enzyme activity in the brain.[25]

In an *in vitro* study, ASP fractions effectively inhibited H(2)O(2)–induced decrease of cell viability and SOD activity, malondialdehyde (MDA) formation and reduced glutathione depletion. It also protected macrophages by inhibiting the release of excess NO and ROS induced by high levels of H(2)O(2).[26]

Hepatoprotective

Mildly hyperglycaemic BALB/c mice with type 2 diabetes were fed a high fat diet (HFD) for six weeks and subsequently orally administered ASP at doses of 100, 200 and 400mg/kg for four weeks.[27] ASP was observed to protect against multiple low-dose streptozotocin (STZ) and HFD-induced liver damage, specifically reducing ALT/ASP levels and reducing hepatic apoptosis via upregulation of Bax and downregulation of Bcl-2 in the liver. It also prevented hyperglycaemia, stimulated hepatic glycogen synthesis and insulin secretion following upregulation of liver insulin signalling proteins (IRS-2, PI3K, Akt, p-Akt and GLUT2) and PPARγ.[27]

Similar results were observed in a separate mice model study, where an assessment of plasma and liver homogenate from mice following carbon tetrachloride- and drug-induced liver damage found that oral administration of ASP (60, 120 and 240mg/kg/d) to mice for three days resulted in a hepatoprotective effect.[28] Specifically, compared with controls, all ASP-treated mice had significant reductions in plasma ALT, ASP, gamma-GT and MDA ($p<0.01$) and increases in SOD activity ($p<0.01$).[28]

Dosage summary

Liquid extract (1:2): 30-60mL weekly[3,29,20]
Dried herb equivalent: 2.5-15g dried root daily[3,29,30]
Relief of menopausal symptoms: 150mg root extract daily[8]

Safety information

- Use during pregnancy and lactation is not advised.[3,29,30]
- According to the TCM treatment paradigm, dong quai is contraindicated in individuals with diarrhoea associated with weak digestion, haemorrhagic disorders, acute viral infections including cold and influenza, predisposition to spontaneous abortion and in the first trimester of pregnancy.[30]
- Use in individuals with cancer, diarrhoea, haemorrhagic diseases or with hypermenorrhoea is not advised.[29]
- Contraindicated in individuals hypersensitive to members of the *Apiacea* family.[29]
- Concomitant use with anticoagulant medication may have an additive effect so is not recommended unless advised by a healthcare professional.[3]

References

1. European Medicine Agency (EMA). Assessment report on *Angelica sinensis* (Oliv.) Diels, radix. Committee on Herbal Medicinal Products [online]. London: EMA, 2013. Viewed 15 Dec 2017, http://www.e-lactancia.org/media/papers/AngelicaSinensis-EMA2013.pdf
2. Herbal Medicine Database: Yin Yang House. Accessed 4 November 2016 from https://theory.yinyanghouse.com
3. World Health Organization (WHO). *Radix Angelica sinensis*. Monographs on selected medicinal plants, vol. 2. Geneva: WHO, 2004.
4. Wei WL, Zeng R, Gu CM, et al. *Angelica sinensis* in China - A review of botanical profile, ethnopharmacology, phytochemistry and chemical analysis. J Ethnopharmacol 2016;190:116-141.
5. Dang gui monograph. TCM information database. Viewed 3 Dec 2016, http://bidd.nus.edu.sg/group/TCMsite/HerbDetails.aspx?HBID=202&Search=1health
6. Hook IL. Danggui to *Angelica sinensis* root: lost in translation? Are potential benefits of a TCM lost to European women? A review. J Ethnopharmacol 2014;152(1):1-13.
7. Kupfersztain C, Rotem C, Fagot R, et al. The immediate effect of natural plant extract, *Angelica sinensis* and *Matricaria chamomilla* (Climex) for the treatment of hot flushes during menopause. A preliminary report. Clin Exp Obstet Gynecol 2003;30(4):203-206.
8. Rotem C, Kaplan B. Phyto-female complex for the relief of hot flushes, night sweats and quality of sleep: randomized, controlled, double-blind pilot study. Gynecol Endocrinol 2007;23(2):117-22.
9. Du J, Bai B, Kuang X, et al. Ligustilide inhibits spontaneous and agonists- or K+ depolarisation-induced contraction of rat uterus. J Ethnopharmacol 2006;108(1):54-58.
10. Liu JY, Zhang Y, You RX, et al. Polysaccharide isolated from *Angelica sinensis* inhibits hepcidin expression in rats with iron deficiency anaemia. J Med Food 2012;(10):923-929.
11. Zhang Y, Li MM, Zeng F, et al. Study to establish the role of JAK2 and SMAD1/5/8 pathways in the inhibition of hepcidin by polysaccharides from *Angelica sinensis*. J Ethnopharmacol 2012;144(2):433-440.
12. Liu PJ, Hsieh WT, Huang SH, et al. Hematopoietic effect of water-soluble polysaccharides from *Angelica sinensis* on mice with acute blood loss. Exp Hematol 2010;38(6):437-445.
13. Zhang L, Du JR, Wang J, et al. Z-ligustilide extracted from *Radix Angelica sinensis* decreased platelet aggregation induced by ADP *ex vivo* and arterio-venous shunt thrombosis *in vivo* in rats. Yakugaku Zasshi 2009;129(7):855-859.
14. Wang J, Du JR, Wang Y, et al. Z-ligustilide attenuates lipopolysaccharide-induced proinflammatory response via inhibiting NF-kB pathway in primary rat microglia. Acta Pharmacologica Sinica 2010;31:791-797.
15. Du J, Yu Y, Ke Y, et al. Ligustilide attenuates pain behaviour induced by acetic acid or formalin. JEthnopharmacol 2007;112(1):211-214.
16. Chao WW, Hong YH, Chen ML, et al. Inhibitory effects of *Angelica sinensis* ethyl acetate extract and major compounds of NF-kB trans-activation activity and LPS-induced inflammation. J Ethnopharmacol 2010;129(2):244-249.
17. Jia DY, Liu J, Li CP, et al. Biological mechanisms of human-derived leukemia stem cells senescence regulated by *Angelica sinensis* polysaccharide. Zhonguo Zhong Yao Za Zhi 2015;40(1): 12-117.
18. Liu J, Xu CY, Cai SZ, et al. Senescence effects of *Angelica sinensis* polysaccharides on human acute myelogenous leukemia stem and progenitor cells. Asian Pac J Cancer Prev 2014;14(11):6549-6556.
19. Wang L, Jiang R, Song SD, et al. *Angelica sinensis* polysaccharide induces erythroid differentiation of human chronic myelogenous leukemia k562 cells. Asian Pac J Cancer Prev 2015;16(9):3715-3721.
20. Zhou WJ, Wang S, Hu Z, et al. *Angelica sinensis* polysaccharides promotes apoptosis in human breast cancer cells via CREB-regulated caspase-3 activation. Biochem Biophys Res Commun 2015;467(3):562-569.
21. Su ZY, Khor TO, Shu L, et al. Epigenetic reactivation of Nrf2 in murine prostate cancer TRAMP C1 cells by natural phytochemicals Z-ligustilide and Radix Angelica sinensis via promoter CpG demethylation. Chem Res Toxicol 2013,26(3):477-485.
22. Wen Y, Li J, Tan Y, et al. *Angelica sinensis* polysaccharides stimulated UDP-sugar synthase genes through promoting gene expression of IGF-1 and IGF-1R in chondrocytes: promoting anti-osteoarthritic activity. PLoS One 2014;9(9):e107024.
23. Qin J, Liu YS, Liu J, et al. Effect of *Angelica sinensis* polysaccharides on osteoarthritis *in vivo* and *in vitro*: a possible mechanism to promote proteoglycans synthesis. Evid Based Complement Alternat Med 2013;2013: 79476124.
24. Kong L, Zhao Q, Wang X, et al. *Angelica sinensis* extract inhibits RANKL-mediated osteoclastogenesis by downregulated expression of NFATc1 in mouse bone marrow cells. BMC Complementary Altern Med 2014;14:481.
25. Ai S, Fan X, Fan L, et al. Extraction and chemical characterization of *Angelica sinensis* polysaccharides and its antioxidant activity. Carbohydrate Polymers 2013;94(2):731-736.
26. Yang X, Zhao Y, Zhou Y, et al. Component and antioxidant properties of polysaccharide fractions isolated from *Angelica sinensis* (Oliv.) Diels. Biol Pharm Bull 2007;30(10):1884-1890.
27. Wang K, Tang Z, Zheng Z, et al. Protective effects of *Angelica sinensis* polysaccharide against hyperglycemia and liver injury in multiple low-dose streptozotocin-induced type 2 diabetic BALB/c mice. Food Funct 2016;7: 4889-4897.
28. Ji P, Wei Y, Sun H, et al. Metabolomics research on the hepatoprotective effect of Angelica sinensis polysaccharides through gas chromatography-mass spectrometry. Journal of Chromatography B Analyt Technol Biomed Life Sci 2014;18(973C):45-54.
29. Dong quai monograph. Health Canada 2012. Viewed 3 Mar 2017, http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monoReq.do?id=842&lang=eng
30. Bone K, Mills S. Principles and practice of phytotherapy, 2nd ed. Sydney: Churchill Livingstone Elsevier, 2013.

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