



# Danggui Buxue Tang (Astragali Radix and Angelicae Sinensis Radix) for menopausal symptoms: A review



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## ABSTRACT

**Background:** Traditional Chinese medicine (TCM) has contributed greatly to human health in past several thousand years. Today, the development of TCM is facing two obstacles: (i) quality control of herbal extract; and (ii) action mechanisms not known.

**Objectives:** Among thousands of complex TCM formulations, Danggui Buxue Tang (DBT) is the simplest one. DBT is used to treat ailments in women and contains only two herbs, Astragali Radix (Huangqi; AR) and Angelicae Sinensis Radix (Danggui; ASR). The weight ratio of AR to ASR in DBT must be 5:1, as stipulated in AD 1247. By using DBT as a model formula, we develop a strategy to reveal the complexity of a traditional TCM formula.

**Results:** There are 3 levels of research directions: (i) the preparation of DBT and its rationale behind; (ii) the traditional theory of DBT is elucidated by chemical and biological determinations; and (iii) the action mechanisms of DBT are revealed.

**Conclusion:** Through the chemical, biological, genomic and proteomic studies, a possible direction in resolving the preparation mythologies, pharmacological and mechanistic analyses of a TCM decoction is being proposed here.

## 1. Introduction

Traditional Chinese medicine (TCM) is a treasure that has contributed greatly to the prosperity of Chinese population for several thousand years and to the development of traditional medicine worldwide. Out of over US\$ 50 billion trading from international herbal market today, China picks up only a meager 10% market share, but China produces over 90% of raw materials in supplying the market. The value of international herbal market is expected to increase at least by 3–4 folds in the year of 2050 (Booker et al., 2012). Although consumers are taking TCM every day worldwide, they still do not know exactly what they are taking, and how that works in their bodies. The major hurdle on internationalization of TCM is lacking a complete set of quality standards that can be recognized by international community. Being more problematic, the action mechanism of any

TCM therapy has never been resolved. According to the old theory of herbal formula in TCM, each decoction consists of four elements: *Jun* (king), *Chen* (minister), *Zuo* (assistant) and *Shi* (servant), which have to be worked harmoniously together in order to achieve a therapeutic purpose. In general, TCM is being used as a water decoction having a specific combination of different herbs as a formula, and which has to be prepared in a unique methodology. These specific requirements of TCM preparation have not been changed until today. Having a herbal mixture generates serious problems in defining quality control and in figuring out their action mechanisms.

Amongst over hundreds of thousands of complex TCM formulae, Danggui Buxue Tang (DBT) is the simplest one having clinical usage in Chinese population for over 800 years (Gao et al., 2007a), and so far there are no reported of side effects. DBT was first described by Li Dongyuan in <Neiwaishangbianhuolun Shushangweiqilun> in 1247

**Abbreviations:** TCM, Traditional Chinese Medicine; DBT, Danggui Buxue Tang; AR, Astragali Radix; ASR, Angelicae Sinensis Radix; Erk1/2, Extracellular Signal-Regulated Kinase; ERα, Estrogen Receptor α; HIF-1α, Hypoxia-Inducible Factor-1α; FSC, Feedback System Control; NF-κB, Nuclear Factor-Kappa B; NO, Nitric Oxide; eNOS, Endothelial NO synthase; CFS, Chronic Fatigue Syndrome

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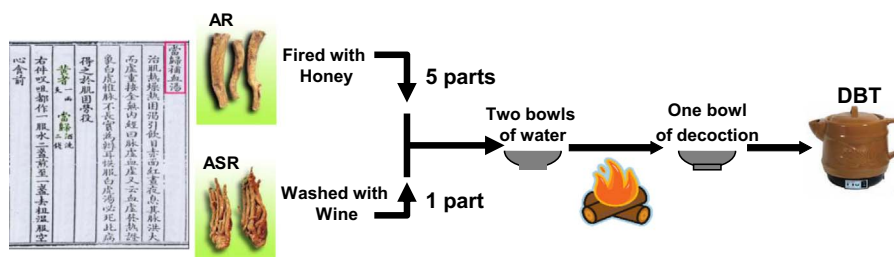
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**Fig. 1.** Preparation of DBT decoction. According to ancient medicinal book written by Li Dongyuan in 1247 CE, 5 parts of honey-treated AR and 1 part of wine-processed ASR are boiled together in two bowls of water at moderate heat until the final has been reduced to one bowl.

CE (Fig. 1). The herbal formula contains only two herbs: 10 qian Astragali Radix (AR; roots of *Astragalus membranaceus* (Fisch.) Bunge or *Astragalus membranaceus* (Fisch.) Bunge var. *mongholicus* (Bunge) P.K. Hsiao, Huangqi in Chinese) and 2 qian Angelicae Sinensis Radix (ASR; roots of *Angelica sinensis* (Oliv.) Diels, Danggui in Chinese) (qian is a weight unit in ancient China, where 1 qian is equivalent to ~3 g). The herbs of 30 g AR and 6 g ASR in 5:1 ratio are boiled together in 2 bowls of water at moderate heat until the final volume is reduced by half. Besides, AR has to be processed by honey, and ASR has to be processed with wine before the boiling of two herbs together. Here, AR serves as *Jun*, ASR serves as *Chen* in DBT decoction. According to ancient TCM theory, DBT was used in nourishing “qi” and enriching “blood”. Today in clinics, DBT is being used to mitigating women menopausal illnesses. The reduction of 17- $\beta$ -estradiol is the major cause for the development of menopause. The menopausal women are suggested to have estrogen replacement therapy (ERT) in preventing the syndromes; however, side effects have been reported during ERT, e.g. high risks of getting breast cancer and cardiovascular diseases (Choi et al., 2011). Therefore, patients are eager to find safer treatment, e.g. TCM, for menopause. The preparation method of DBT is facing a lot of challenges today; because TCM practitioners do not follow this rigid regulation. To understand the rationale of a TCM herbal mixture, DBT was chosen as an example for verification. By using various experimental methods, we aimed to resolve the therapeutic purposes of DBT formula, as well as to determine the important of distinct preparation method in making a better herbal decoction.

## 2. Preparation method of DBT

The chemical compositions of AR and ASR are influenced by the cultivated conditions, e.g. weather, geographical environment and soil condition, as well as the methods of cultivation and processing (Ma et al., 2002; Zhao et al., 2003). In sourcing of TCM, “the best growth region” or “authentic source” or “Di Dao” is referring to the best herb being collected. The sourcing of AR and ASR is the first priority in optimizing the quality of DBT. By comparing the levels of isoflavonoids, astragalosides, polysaccharides, amino acids and trace elements collected from AR of different growing sources, the 3-year-old AR from Shanxi contained higher amounts of ingredients (Ma et al., 2000a, 2000b). The chemical constituents of ASR, including ferulic acid, ligustilide, angelic acid, brefeldin A and butylidenephthalide were higher in 2-year-old ASR collected from Gansu (Zhao et al., 2003). The source of herbs in making DBT is important as to ensure maximal chemical and pharmacological properties.

The amount of water used in boiling of herbal mixture, i.e. 30 g AR + 6 g ASR as written in the original prescription of DBT, did not spell out specifically (Li et al., 2009; Zhang et al., 2013). Li Dongyuan mentioned 2 bowls of water in 1247 CE (Fig. 1). The only way to guess “2 bowls of water” is based on the size of a bowl coming from that period of time. In general, a typical bowl from 12th century in China could be ranged from 200 to 300 mL, and thus we considered 500 mL should be corresponding to 2 bowls of water. By revealing the amounts

of chemical ingredients in DBT, prepared by varied amounts of water, the best chemically decoction was demonstrated, as written in the ancient prescription (Song et al., 2004).

From ancient literatures, the DBT formulation should have AR and ASR in a weight ratio of 5:1. The rationale of this specific formulation has never been given. The chemical compositions and pharmacological activities of DBT extracts, prepared by boiling AR and ASR at different ratios, were determined. Most of the analyzed chemicals, e.g. astragaloside IV, calycosin, formononetin, ferulic acid and total saponins, total flavonoids and total polysaccharides showed much better solubilities in 5:1 (AR: ASR) ratio of DBT (Dong et al., 2006). The amount of ligustilide was the lowest in 5:1 DBT preparation. Indeed, ligustilide played a role in suppressing the estrogenic, osteogenic and erythropoietic functions in cultured MCF-7, MG-63 and HEK293 cells (Zheng et al., 2014). The chemical distinction of DBT, as compared to a simple mixture of AR+ASR extract, was verified by  $^1\text{H-NMR}$  metabolic profiling. DBT showed distinction to the water extracts of its constituent herbs (Chan et al., 2014). In parallel, DBT at 5:1 ratio also showed much better pharmacological properties, as compared to other groups, i.e. AR and ASR at different ratios from 1:1 to 10:1 (Dong et al., 2006).

The boiling of herbal mixture by moderate heating is an essential factor in preparing the best DBT: the procedure is aiming to extract higher bio-active ingredients in the decoction. By taking DBT extracts every 5 min during the boiling procedure from room temperature to boiling under gentle heating of ~2 h, the chemical composition of decoction was revealed. The amounts of astragaloside IV, calycosin, formononetin, calycosin-7-O- $\beta$ -D-glucoside and ononin increased in a time- and temperature-dependent manner: the amounts of these chemicals reached a peak at 2 h. The glycosidic residues of calycosin-7-O- $\beta$ -D-glucoside and ononin could be hydrolyzed forming calycosin and formononetin, respectively. The hydrolytic efficiency was affected by pH, temperature and amount of herbs (Zhang et al., 2014). Interestingly, the heated ASR/AR did not able to show such activity, suggesting a possible enzymatic reaction here.

The processing of herbal materials is considered to be important in preparing a better herbal decoction. According to historical description in DBT preparation, AR had to be fried with honey, while ASR had to be pre-treated with yellow wine (a typical wine in China at ~15% ethanol) before the boiling process. The honey-fried AR in DBT did not affect the properties of DBT, except that tasted well. The processing of ASR is referring to the treatment of herbs with yellow wine. DBT prepared by wine processed-ASR showed a marked different, chemically, to that did not (Zhan et al., 2013). The chemical composition of DBT, generated by wine-treated ASR, was significantly different from the one without wine-treated ASR, in particular the levels of volatile oil (Zhan et al., 2013). In line to this observation, the inclusion of volatile oil in DBT preparation significantly decreased the amount of astragaloside IV, calycosin, formononetin, total saponins and total flavonoids in the final water extract (Zhan et al., 2014). Besides, the volatile oil suppressed the pharmacological properties of DBT (Zhan et al., 2014). Thus, ASR volatile oil was believed as a negative regulator for the pharmacological properties of DBT, supporting the specific requirement of wine treatment of ASR. In contrast, the processed ASR showed

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