Danggui Buxue Tang (Chinese Angelica Decoction): A Sample Trial in TCM Standardization

by Karl W K Tsim

Abstract

The major stumbling block on the internationalization of Traditional Chinese Medicine (TCM) is the lack of a complete set of quality standards that can be recognized and accepted by the international community through an objective and stringent validation process. That is to say, Chinese medicine needs to be standardized. Such a standardization is set by the state and the international regulation authorities who demand scientific proof on the safety, quality and efficacy of TCM. By using the simplest TCM formulation, Danggui Buxue Tang, we hereby present some existing problems and strategies to tackle this task based on the uniqueness of Chinese medicines.

Introduction

Traditional Chinese Medicine (TCM) is a priceless resource that has contributed greatly to the development of herbal medicine worldwide and to the prosperity of the Chinese population in the last several thousand years. Internationalization of TCM applies practices or stipulations to medicine and developed TCM products that can formally enter into the international medicine market. In order to fulfill stringent requirements for pharmaceuticals, TCM products have to follow various challenging rules of standardization.

What is the main concern in the internationalization of Chinese medicine? At present, TCM still lacks a set of complete, strict and objective quality control practice, which can be approved or accepted internationally. That is to say the first task for TCM to enter the international market is to realize its problems in standardization. The standardization of TCM is to establish a scientific evaluation system (or protocol) for the quality, safety and efficacy of TCM according to the guidelines or rulings of the health authority of the national (state) and international governments, so that the manufacturing, sale and use of TCM products can be closely monitored.

Traditionally, TCM is used as a decoction with a specific combination of different herbs as a formula, and which is prepared in unique methodology. These specific requirements of TCM preparation have remained the same until today. The complexity of TCM formulation causes a serious problem in TCM standardization, in particular the complex biological interaction of different compounds within the decoction. Of over tens of thousands of different TCM formulae, Danggui Buxue Tang (DBT) is the simplest, and commonly used by the Chinese for about 800 years. DBT was first described by Lidongyuan, one of the four famous TCM specialists during the Jin and Yuan Dynasties in China. DBT formulation first appeared in
Neiwaishangbianhuolun-Shushangweiqilun (1247 AD). The formulation should contain two herbs: 10 qian Radix Astragali (Huangqi) and 2 qian Radix Angelicae Sinensis (Danggui) in a weight ratio of 5:1 (qian is a weight unit in ancient China, where 1 qian is equal to ~3 g), and boiled in two bowls of water under moderate heat until the final volume is reduced by half. DBT is prescribed to improve menopausal symptoms in women. The patients are advised to drink DBT decoction daily, in order to raise “Qi” and nourish the “Blood” of the individual. Indeed, recent pharmacological results indicated that DBT has the ability to promote hematopoietic function, stimulate cardiovascular circulation, and prevent osteoporosis and anti-oxidation activity.

The Strategy in Standardizing Danggui Buxue Tang (DBT)

For a long period of time, Chinese herbal medicine has encountered problems in addressing the same plant with different names or using the same name to address different plant species. Material of the same name can represent different plants or even animals. The chemical composition of different plants however cannot be the same, and therefore the quality control of TCM is hard to guarantee, and often herbs are misused, resulting in herbal poisoning. The chemical composition of TCM is greatly influenced by weather, geographical environment, soil condition as well as methods of cultivation and processing. Different regions of China can produce excellent quality of certain types of TCM, which are often called “the best growth region” or “authentic source” or “Di Dao.”

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DBT contains only two herbs: Radix Astragali (Huangqi) and Radix Angelicae Sinensis (Danggui). Radix Astragali is the dried roots of *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. (Fam. Leguminosae). The dried roots of *Hedysarum polybotrys* Hand.-Mazz. (Radix Hedysari) have also been used as the substitute of Radix Astragali. Radix Astragali is mainly produced in Shanxi, Heilongjiang, Hebei, Gansu and Inner Mongolia of China. *A. membranaceus var. mongholicus* is the major species used in the market. Saponins, flavonoids, polysaccharides and amino acids are found in Radix Astragali; the content of these active constituents is the highest in a three-year-old plant. By analyzing the active constituents, the best region to produce Radix Astragali is Shanxi. Radix Astragali possesses activities in stimulating the immunity system, improving micro-circulation, anti-oxidation and promoting hematopoietic stem cell multiplication.

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Danggui is the dried roots of *Angelica sinensis* (Oliv) Diels. *A. sinensis* is mainly cultivated in Wudu, Dangchang and Minxian of Gansu. It is also planted in Shanxi, Hubei, Sichuan, Yunnan and Liaoning. The root of *Levisticum officinale* Koch (European Angelica) has also been cultivated on a large scale in China. The roots of *Angelica gigas* (Korea Angelica) and/or *Angelica acutiloba* (Japan Angelica) have also been used as Chinese Angelica in northeast China. The effective constituent of *A. sinensis* roots produced in Gansu is significantly higher than those from other sources. Radix Angelicae Sinensis possesses activities in anti-thrombus, enrichment of the blood, improvement of blood circulation, stimulation of the immunity system and anti-oxidation. Essential oil, ferulic acid, saccharides and amino acids are major chemical constituents in Radix Angelicae Sinensis.
In order to show explicitly the medical theory of TCM formulation, one must abide by TCM principles closely. Application of integrated modern chemistry and pharmacology research can be very useful in understanding the efficacy of TCM formulation and the chemistry behind the theory of complementary herbal interaction (Fig. 3). Taking account all the possible interactions between the herbal constituents in the compound formulation, the extraction of constituents is undertaken from the decoction according to TCM principles. Based on the modern chemical analysis of Radix Astragali and Radix Angelicae Sinensis, the extractions of essential oils, ethanol-soluble components, small molecules (non-polysaccharides) and macromolecules (polysaccharides) from the aqueous extracts are performed to ensure the percentage of yield; the residues are mainly the ineffective constituents such as resin, starch, cellulose, etc. Repetitive quantitative analyses in the major, or active, constituents revealed in DBT were Astragalus-derived astragaloside VI (5%), formononetin (2%), Angelica-derived calycosin (3%), ligustilide (30%), ferulic acid (2%) and n-butylide phthalide (16%). The proportion of the detectable constituents to the total extractable constituents was 58%. These indexes can be taken as the quantitative standards for the quality control of DBT.

After identifying the chemical composition in the DBT extract, the extracts should be tested for respective activities of blood nourishment, immunity improvement and anti-oxidation, so as to verify the parts with biological activity. Using efficacious bioactivity tracing technique, the bioactive components and their respective sources can be determined. The chemical interactions among different constituents in the TCM formula can use the cross design, to mix the bioactive fractions from the schedule above with those non-active fractions for integrative efficacious testing. Chemical components in each single herb can integrate together according to their best proportion.
The effective fractions of DBT are revealed by tracing the bioactivities in strengthening the immunity system, stimulating hematopoietic growth factor and preventing platelet aggregation. In our laboratory, we have isolated four fractions from DBT: the essential oils, ethanol-soluble substances, water-soluble macromolecules and water-soluble small molecules. It showed that the water-soluble macromolecule of DBT possesses remarkable activities of immunity strengthening, stimulation of hematopoietic growth factor and prevention of platelet aggregation. One of these effective components is polysaccharide from Astragulus and Angelica roots. The water-soluble small molecule has activity in preventing platelet aggregation with ferulic acid as its major active ingredient.

Our preliminary results suggest that the biological actions of Radix Astragali-Radix Angelicae Sinensis (5:1) was stronger than Radix Astragali-Radix Angelicae Sinensis (1:1) or other combination of ratio. The experiments also showed the bioactivities are in the following order of magnitude of strength: DBT > aqueous extracts of Radix Astragali > aqueous extracts of Radix Angelicae Sinensis. Such results are in good agreement with the formulation proposed almost 800 years ago, which suggest that the Lidongyuan’s formulation should have a strong base in the original design. Thus, one should not change the ancient TCM formulation without an experimental rationale.

Conclusion
The effectiveness of TCM can stand the test of time. After thousands of years of clinical experience, TCM has gained international recognition in the modern world. Today, it is an international common understanding that medicine must be safe, effective and controllable. But currently, there is still a lack of such practices in most of the TCM products. Currently, TCM raw herbs and manufactured products are not able to show clear indications of efficacy and chemistry. There is no rigorous quality control standard and efficacy testing. These are all obstacles for general acceptance of TCM by the western countries. As the society advances rapidly in the development of science and technology, most people do not believe in secret recipes or formulations that were passed along from ancient forefathers. That is why Chinese medicine needs to be modernized and standardized now, and only then can TCM be recognized on the international market. Otherwise, TCM may not be called “Chinese” traditional medicine any more, because other countries would have adopted this traditional heritage as their own.

The successful research and development of the standard preparations of DBT have great significance in:

1) turning DBT into a product that will meet the international standards, and will provide an effective and safe new TCM preparation for the treatment of anemia;

2) providing a modern methodology in standardizing new TCM drugs from ancient TCM formulation;

3) successfully opening up the international market for TCM products, thus generating income and revenue for China, and also promoting the reputation of TCM on the international stage; and

4) boosting the establishment of Good Agriculture Practice (GAP) of Medicinal Plants and Animals bases for Radix Angelicae Sinensis and Radix Astragali in the rural areas of China.

DBT will only be accepted on the international market because of its stable and reliable ingredients, clear chemistry for each ingredient and detailed documentations on the efficacy experiments and respective clinical trials.
About the Author

Dr Karl W K Tsim graduated from Cambridge University in Biochemistry, and had spent four years at Stanford University as Research Fellow working on Molecular Neurobiology. Currently, he is an Associate Professor at the Department of Biology of Hong Kong University of Science and Technology. He has been working on Traditional Chinese Medicine (TCM) for a number of years, and his major achievement is in developing methodologies for the quality assurance of TCM.

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