

# Orthogonal Stimulus-Response as a Tool to Formulate Traditional Chinese Medicinal Herbal Combination

## - New Scientific-Based TCM Herbal Formulating Method -

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### Key Words

traditional chinese medicine, crude herbs combination, antihypertension, orthogonal stimulus-response

### Abstract

**Objectives:** There is an increasing number of complex diseases that are progressively more difficult to be controlled using the conventional “single compound, single target” approach as demonstrated in our current modern drug development. TCM might be the new cornerstone of treatment alternative when the current treatment option is no longer as effective or that we have exhausted it as an option. Orthogonal stimulus-response compatibility group study is one of the most frequently employed formulas to produce optimal herbal combination for treatment of multi-syndromic diseases. This approach could solve the relatively low efficacy single drug therapy usage and chronic adverse effects caused by long terms administration of drugs that has been reported in the field of pharmacology and medicine

**Methods:** The present review was based on the Science Direct database search for those related to the TCM

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and the development of antihypertensive TCM herbal combination using orthogonal stimulus-response compatibility group studies approach.

**Results:** Recent studies have demonstrated that the orthogonal stimulus-response compatibility group study approach was most frequently used to formulate TCM herbal combination based on the TCM principles upon the selection of herbs, and the resulting formulated TCM formula exhibited desired outcomes in treating one of global concerned complex multi-syndromic diseases, the hypertension. These promising therapeutic effects were claimed to have been attributed by the holistic signaling mechanism pathways employed by the crude combination of herbs.

**Conclusion:** The present review could serve as a guide and prove the feasibility of TCM principles to be used for future pharmacological drug research development.

### 1. Introduction

In 21st century, the awareness of global scientists towards the increasing numbers of complex diseases that are difficult to control using single drug therapy approach has been ignited, especially with multi-syndromic disease such as hypertension being on the rise.

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At this point, the synthetic drugs that are currently available in the market has become not only insufficient but incapable to be used to fully tackle the unceasingly increase of new and complex conditions that hits our community at a large scale. At best, synthetic medication is used for damage control of symptoms without providing a wholesome cure towards these diseases. Fundamentally, the concept of the modern drug development is based on “single compound, single target” philosophy, whereby treating a particular symptom by targeting an exact protein with the use of a single compound [1]. However, the lifestyles of the living organisms are constantly change day-to-day as the society continuously develops, thus the number of complex, multi-syndromic diseases are constantly being introduced. Therefore, the biggest challenge for the global scientists in this era is to search for alternatives as a true solution instead of solely defending the typical reductionism approach of modern drug development.

As a matter of fact, there is potentially a promising alternative avenue that exists and has been well-practiced and refined via continuous constructive studies and trials in the few thousand years that it has been around. Traditional Chinese medicine (TCM) could potentially be the edge towards a better solution for a holistic treatment of our patients, and is exactly what our modern scientists are looking for, the perfect alternative. However, there biggest concern has been a lack of scientific research and studies done to determine the exact consistency and safety of this alternative we speak of and based on the typical modern drug development approach, we know that every newly developed drug needs to pass through the evaluation of safety, pharmacology and efficacy tests upon clinical use in human. Up to this point, TCM has only had about over a thousand years of clinical profile evidences to concretely prove their efficacy as well as safeness towards the use in human to fight against variety of diseases but not much of laboratory based scientific studies being done on it [2]. Although the approach employed for treatment is based on the principles of TCM to treat disease and is on opposite ends of the scale of difference from the western approach, but evidences has shown that the TCM-practicing physicians in China has had experience in treating diseases competently with the use of either acupuncture, Qigong, Tuina or combination of herbal medicines [3].

According to the TCM principles, an individual is considered as “healthy” only when the internal body environment is in harmony and have balance in all five fundamental elements (wood, fire, metal, water and earth) as well as their Yin and Yang [4]. Once there is imbalance, even a slight one, syndromes would appear based specifically on elements that goes off balance and subsequently lead to various conditions towards the human body. Despite having multiple choices in treatment choices in the standard TCM practice, herbal medicines concoction has been one of the most abundantly used option for treatment. Generally, there are 1894 types of medicinal drugs recorded in the Compendium of Materia Medica, and amongst all of those recorded, 1094 are of medicinal herbs. According to Shen Nong’s herbal classic, different types of the medicinal herbs will be selected and customized for a concoction as a TCM prescription which is specifically used to treat differ-

ent types of syndromes caused by the diseases of the body. Typically, the roles of each herb selection within a TCM prescription can be categorized into four types including sovereign, minister, assistant and envoy drugs [5]. Furthermore, most of the TCM prescriptions will be processed using decoction method with different types of adjuvant such as wine, vinegar, herbal juice, oil, lime or honey. The adjuvant itself will cause a certain physical or chemical transformation on the medicinal herbs, which will directly enhance the efficacy whilst counteract the toxicity of the crude drugs by altering its pharmacokinetic behavior [6].

Despite sole guarding of the typical modern drug research approach, recently, there is an increasing number of global researchers whose focus are on herbal medicine whereby these traditional treatment approach of choice are being evaluated by identifying the specifics of crude TCM herbs such as their therapeutic effects towards certain complex diseases. In the present review, one of the most worldwide threatening diseases, hypertension will be taken as an example and further discussed based on the most frequently used drug development approaches employed in recent publications. As it is common knowledge amongst us, hypertension exists since a couple of decades ago, and from the trend of evolution of modern antihypertensive drugs, the classes of synthetic antihypertensive compounds that are recommended to be consumed by patients are changed from time-to-time with the aim of achieving the targeted blood pressure lowering effects, but the lack of efficacy and the chronic adverse effects are still frequently being reported in the current practice [7, 8].

There is a new scientific-based orthogonal stimulus-response compatibility group studies approach frequently used in recent publications to develop new combinations of TCM herbs for treatment of hypertension. Interesting point to note that all these published results demonstrated desirable outcomes exhibiting promising vasodilatory effects as well as antihypertensive effects. In fact, the typical nature of crude TCM herbs combination has a “multi-component, multichannel” properties, which is the main reason which attributes the promising therapeutic effects over single drug therapy, and this have fulfilled the criteria for treating complex diseases via using holistic mechanisms of actions [9-13]. In this review, all the successfully developed TCM herbal formula using the orthogonal stimulus-response approach will be further elaborated. This could serve as a crucial guideline for future drug development research in treating complex diseases.

## 2. Methods

The present review was completed based on the Science Direct database search for studies related to the TCM and the development of antihypertensive TCM herbal combination using orthogonal stimulus-response compatibility group studies approach.

### 3. Results & Discussion

#### 3.1. Orthogonal stimulus-response compatibility group study in formulating antihypertensive TCM herbal combination

Based on the philosophy and principles of TCM, a typical TCM practitioner will prescribe a TCM herbal combination specific for each patient based on the syndromes projected by their body. As aforementioned, the selection of the herbs for TCM prescription is based on their capability to counteract the syndrome as a whole. Taking hypertension as an example, recent publications have shown a new development of TCM herbal combinations using the orthogonal stimulus-response approach. There are three major syndromes that would appear in a hypertensive patient; fire, phlegm-fluid retention, and deficiency syndromes [3, 14]. Others common symptoms that would appear in a hypertensive patient would be headache, fatigue, dizziness and neck stiffness.

Recently, there were two research articles which focus on the usage of TCM principles and the orthogonal stimulus-response approach to formulate a new TCM herbal combination in treating hypertension. A crude 50% ethanolic extract combination of *Glycyrrhiza uralensis*, *Gastrodia elata*, *Atractylodes macrocephala*, *Poria cocos*, and *Citri reticulatae* were found to exhibit a promising vasodilatory effects at the optimal ratio of 2.71:1.14:1:5.57:7.14. The orthogonal stimulus response  $L_{36}$  ( $6^6$ ) formula was used to formulate this combination by using the *in vitro* aortic rings assay [15]. Furthermore, this TCM formula demonstrated optimal blood pressure lowering effect in *in vivo* spontaneous hypertensive rat (SHR) models. According to the results shown, the systolic (SBP) and diastolic blood pressure (DBP) as well as the mean arterial pressure (MAP) were successfully decreased after 28 days of sub-chronic oral administration of this TCM formula combination, and this formula was then termed as Banxia Baizhu Tianma Tang [16].

The second TCM formula namely BPAid was successfully developed by using similar approach with the  $L_{25}$  ( $5^5$ ) formulation. The 50% ethanolic extract combination of *Uncaria rhynchophylla*, *Pueraria thomsonii*, *Panax notoginseng*, and *Alisma orientale* at the ratio of 5.32:2.44:9.24:1 were shown to significantly cause *vasodilatory* effects in isolated aortic rings at lower  $EC_{50}$  value as compared to either one of the single herbs within its combination [17]. The antihypertensive effects *in vivo* was found similar to Banxia Baizhu Tianma Tang at which BPAid significantly lowered the SBP, DBP and MAP of SHR models after 28 days consecutive oral administration [18]. A significant point to take notice would be that there was no adverse effect that has been reported from their toxicology studies after 28 days of sub-chronic oral administration, thus proving the safety of TCM herbal combination to be used in the patient sub-chronically.

Apart from this, there was another example establish-

ing the significance of antihypertensive TCM formula by combining the vasoactive compounds extracted from the TCM herbs with the orthogonal stimulus-response  $L_{25}$  ( $5^6$ ) formulation. The best vasodilatory effects exhibited from the combination of gastrodin, baicalin, tetramethylpyrazine and puerarin on the norepinephrine pre-contracted isolated aortic rings was found at a ratio of 5.33:1:2.67:5.33 [19]. The vasodilatory effect of the combined vasoactive compounds was proved stronger than any of its single compound and there were another research completed that found a combination of pinosresinol diglucoside, rhynchophylline, puerarin and anthraquinone aglycone at a ratio of 2:4:4:1 elicited stronger vasodilatory effects in norepinephrine pre-contracted isolated aortic rings compared to either one of it single drug, and was seen to produce relatively significant results when it is being compared to calcium channel blocker (CCB), verapamil which is widely used in treatment of hypertension in modern therapy. In fact, four of these pure compounds are the vasoactive compounds isolated from *Eucommia ulmoides*, *Uncaria rhynchophylla*, *Radix pueraria* and *Cassia semen*, respectively [20].

Generally, there are three key information that could be speculated from the findings presented above, the results of these research clearly presented the competency of combined drugs over single drugs in terms of exhibiting vasodilatory effects, the orthogonal stimulus-response compatibility study approach could be used to formulate TCM formula in terms of treating complex diseases, and the crude extracts of the herbs could provide promising therapeutic effects rather than single compounds due to holistic mechanisms of actions whilst providing cost-effective beneficial from the commercial viewpoint as compared to pure compound [21-24].

### 4. Conclusion

TCM has been around in the Chinese community as the mainstay approach towards treatment of ailments long before the development of modern, western therapy. With the continuous development of synthetic medication with targeted therapy on patients, we have reached a saturation point whereby we are almost at the brink of exhaustion of resources of synthetic medication that is functional towards the treatment of multi-syndromic conditions namely, hypertension. Thus, TCM could potentially be our rescue medication, an alternative towards the situation. Difficulties in standardization process of raw herbs and lack of scientific evidence to support the safety, toxicity and efficacy of these medicinal herb is the only thing in the way of bringing TCM to the common global playing field of medicine in which they become a standard choice of consideration when it comes to treatment option. Thus, TCM should be adopted in the efficacy-driven approach rather than a mechanism-centered paradigm since it has been applied clinically in control of human diseases since a few thousand years ago. Its efficacy and safety obtained via its clinical usage should be treated as evidence to allow for its usage in modern practices. In terms of the efficacy-driven

approach, the mechanisms of actions should only be investigated to enhance the therapeutic effects once after the clinical efficacy of the drugs is firmly demonstrated, as the efficacy of the drugs towards certain disease treatment is the main objective for every novel drugs development. To wrap it all up, the current review should serve as a stepping stone for global scientists in terms of understanding the capabilities that TCM possesses and to continue in pursuing the development for a more holistic and effective approach for treatment of complex condition with the usage of orthogonal stimulus-response approach in formulation of TCM herbal combination.

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## Conflict of interest

The authors declare that there are no conflicts of interest.

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