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In silico method for studying property combination of traditional Chinese herbs

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Abstract *Objective:* This paper discusses the composition of prescription qualitative, quantitative design principles and methods based on herbal property combination, describing the method application in new prescription design.
Method: Qualitative property-combination pattern (PP) calculation was based on bipartite graphing and performing a greedy algorithm which was designed to optimize obtaining a new herbal prescription. Quantitative PP calculation was based on the qualitative computation. To calculate the Euclidean distance for the PP of the new prescription, an optimized algorithm for solving the unknown minimum Euclidean distance was used with, the new weighted proportions. Finally, non-linear optimization software was used to find the minimum Euclidean distance.
Results: Using the PP of classic prescription Large Yin-Nourishing Pill, applying quantitative PP calculation a new prescription was created. Mathematical algorithms based on property combinations of traditional Chinese herbs can be applied to identify compatibility and synergies of herbs within prescriptions, especially classic formulas.
Conclusion: In silico methods can then be used to create new prescriptions or modify existing ones depending on need. This type of automated approach may increase efficiency in designing new drugs based on Chinese herbs.

Introduction

In traditional Chinese medicine (TCM), the characteristics, or properties, of an herb determine its actions (mechanisms) and clinical application. The major categories of herbal properties are: four natures, five tastes, channels entered, direction of action, and toxicity. Modern research has allowed for scientific understanding of the properties of

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herbs, and is elucidating the mechanisms of the properties and their clinical applications. For example, Liang et al used integrative bioinformatics analysis to determine the chemical components of hot and cold property herbs.[1]

While there is an abundance of TCM research on herbal properties, it has been difficult to translate the results into clinical applications and new drugs. Therefore, applying computational methods may be an efficient approach toward amalgamating the essence of the various herbal properties into utilitarian value. In our previous studies, we used in silico methods to explore herbal property combination as applied to medicinal-efficacy correlation,[2,3] compatibility principles for combining herbs,[4] and formulation principles of herbal prescriptions.[5] In this study, we continue our investigation by applying software-based technology to combine the core herbal properties of the four natures, five tastes, and channels entered to establish a medicinal-efficacy correlation.

Methods

Concepts of property combination and property-combination pattern

In this study, property combination (PC) is a concept that includes the nature, taste, and channel entered of an herb, which helps in the study of synergy among other herbs in a prescription.[6] Property-combination pattern (PP) refers to multiple property combinations of herbs with the same or similar efficacy recurring in a prescription.[5]

Qualitative and quantitative computation of property-combination pattern

Qualitative computation

In mathematics, a bipartite graph is a special graph that can display the relationship between two sets of objects when the characteristic between the sets of objects needs to be known. The uniqueness of a bipartite graph is that there is no connection among objects in the same set. A greedy algorithm is a mathematical problem-solving approach that finds the optimal solution for each step of a complex process, without reconsidering the choices.

Thus, in this study, qualitative PP calculation was based on bipartite graphing[7] and performing a greedy algorithm,[8] which was designed to optimize obtaining a new herbal prescription. The PP of a classic TCM prescription served as a template, and application of bipartite graphing and greedy algorithm construction were then used to generate the new PP.

A bipartite graph was created by assigning herbs and PCs to respective sets A and B to reveal the relationship between each herb and its PCs. For example, Fig. 1 shows a set of Chinese herbs (A) and a set of PCs (B) that represent a binary coverage. This process aims to find the fewest herbs in set A that can cover the PCs in set B.

The greedy algorithm would then be applied with each step seeking the optimal solution. Again, using Fig. 1 as the example, herb 3 would be selected because it is associated with the three PCs cold-bitter-stomach, cold-bitter-bladder, and cold-bitter-liver. However, herb 3 is not associated with the PCs of warm-sour-spleen and warm-sour-stomach, whereas herb 1 is. Herb 2 is associated with two of the same PCs that are associated with herb 3, that is, cold-bitter-bladder and cold-bitter-stomach. For this reason, herb 2 is eliminated from consideration. Thus, herb 1 is chosen as the target herb and based on the greedy algorithm, herbs 1 and 3 are associated with all PCs without any overlap of coverage (Fig. 1).

Quantitative computation

Quantitative PP calculation was based on the qualitative computation. To calculate the Euclidean distance for the PP of the new prescription, an optimized algorithm for solving the unknown minimum Euclidean distance was used with the new weighted proportions. Finally, non-linear optimization software was used to find the minimum Euclidean distance.

The new prescription was calculated as follows:

A classic formula, F, contains n herbs, set of f_{ij} using PC "j" of herb "i" in prescription F, $i = 1, 2, 3\ldots n$; $j = 1, 2, 3\ldots m$ (m represents PCs in the classic recipe),

$$fij=\begin{cases}1 & i \ \ contains \ \ j\\ 0 & i \ \ contains \ \ no \ j\end{cases}$$

$i = 1, 2, 3\ldots n$, $j = 1, 2, 3\ldots m$.

The prescription's jth PC can be expressed as

$$F_j=(x_1 \ \ x_2 \ \ \cdots \ \ x_n)(f_{11} \ \ f_{21} \ \ \cdots \ \ f_{n1})^T$$

where F_j is the jth combination of prescription PC, $j = 1, 2, 3\ldots m$; and x_i represents the weight percentage of the herb "i" in the prescription, $i = 1, 2, 3\ldots n$.

The PC of n herbs in the prescription constitutes an m-dimensional matrix, that is PC matrix Y,

$$Y=\begin{pmatrix} f_{11} & f_{12} & \cdots & f_{1m}\\ f_{21} & f_{22} & \cdots & f_{2m}\\ \cdots & \cdots & \cdots & \cdots\\ f_{n1} & f_{n2} & \cdots & f_{nm}\end{pmatrix}$$

$X=(x_1 \ \ x_2 \ \ \cdots \ \ x_n)$ as the percentage of the amount of drug matrix.

The PP of the classic prescription can be expressed as F:

$$F=(F_1 \ \ F_2 \ \ \cdots \ \ F_m)$$
$$=(x_1 \ \ x_2 \ \ \cdots \ \ x_n)\begin{pmatrix} f_{11} & f_{12} & \cdots & f_{1m}\\ f_{21} & f_{22} & \cdots & f_{2m}\\ \cdots & \cdots & \cdots & \cdots\\ f_{n1} & f_{n2} & \cdots & f_{nm}\end{pmatrix}=X\cdot Y$$

The PC m in the calculation method of the PP of the classic prescription was used according to the number of PCs in the classic formula PC.

New prescription design based on PP

Qualitative design

Herb-PC data was converted into binary variables, in which an herb that is of a given PC was assigned 1, and one that is not of a given PC was assigned 0 (Table 1). Using MATLAB programming (Math Works, Natick, MA, USA) and the greedy

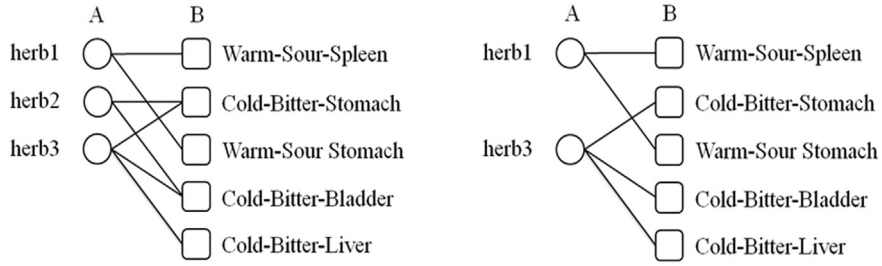

Fig. 1 Bitartate graph depicting minimal coverage between herbs and their property combinations in a prescription.

Table 1 Local binary-state variables of Chinese herb PCs.

Herbs	Cold-bitter-kidney	Cold-bitter-bladder	Cold-bitter-lung	Cold-salty-liver	Warm-sweet-liver	Cold-salty-kidney
Phellodendron bark	1	1	0	0	0	0
Anemarrhena root	0	0	1	1	0	0
Cooked rehmannia root	0	0	0	0	1	0
Tortoise plastron	0	0	0	0	0	1
Arrowhead	0	1	1	0	0	
Figwort	1	0	1	0	0	1

algorithm, based on the concept of minimal coverage bipartite graph, a new prescription was designed.

Quantitative design

Quantitative design was then performed based on the PP of a chosen classic prescription. Design steps involved:

1) Calculating the PP of the classic prescription, namely the target PP.
2) Creating a new prescription based on qualitative design and identifying the new PC square pattern matrix.
3) Setting the quality proportions of each herb of the new prescription to unknowns, and establishing a function of the PP of the new prescription containing unknowns.
4) Calculating the Euclidean distance for the PP of the new prescription and target prescription, using the optimization algorithm, which yielded the new prescription constitution ratio.

Results and discussion

New herbal prescription design based on property-combination patterns

We designed several new herbal prescriptions using bipartite graphing and greedy algorithm application. Herein, we present an example of a new prescription.

The classic prescription Large Yin-Nourishing Pill (*da bu xin wan*; LYNP) was first described by *Danxi's Experiential Therapy*. This formula is comprised of phellodendron bark (*Phellodendron chinense* C.K.Schneid.), anemarrhena root, cooked rehmannia root [*Rehmannia glutinosa* (Gaertn.) DC.] and tortoise plastron. The overall action of the formula is to nourish yin to reduce pathogenic fire. Using the PP of LYNP as a template, applying bipartite graphing and the greedy algorithm a new prescription was created comprised of arrowhead [*Sagittaria trifolia L. var. sinensis* (Sims.) Makino], tortoise plastron, cooked rehmannia root [*R. glutinosa* (Gaertn.) DC.], and figwort (*Scrophularia ningpoensis Hemsl.*).

Compare the PP of the new prescription with the PP of the original prescription, as shown in Fig. 2.

As can be seen from Fig. 2, the new prescription has the same PP as the original prescription. The main PC of the original prescription is cold-sweet-kidney and cold-bitter-kidney. The cold-sweet-kidney has the effect of clearing heat, promoting production of fluid, dieresis and moistening dryness. The quantitative result of cold-bitter-kidney is less than the original prescription, and the cold-salty-kidney is more than the original prescription. The main PC of the new prescription is cold-sweet-kidney and cold-salty-kidney. The cold-salty-kidney has the effect of

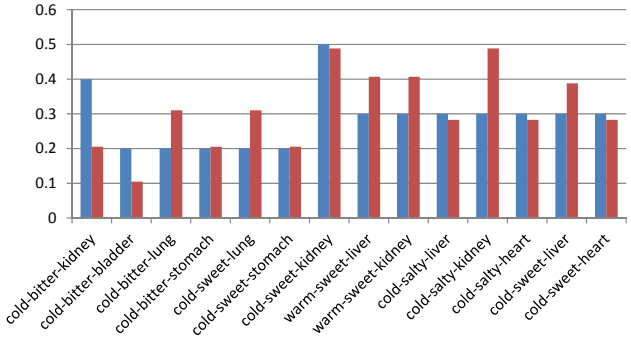

Fig. 2 Comparing the PP of the new prescription with the PP of the original prescription.

softening and resolving hard mass, subsiding yang and benefiting kidney. So the new prescription has the main effect of promoting production of fluid, moistening dryness and benefiting kidney, which conforms to the principle of nourishing kidney Yin for Yin deficiency constitution adjustment, and the drug can be used as ingredients to meet the need of Yin deficiency constitution people daily physical adjustment required.

We have also applied in silico application of PC and PP in traditional Chinese food therapy (also known as diet therapy). Using this methodology, our group designed medicinal diet recipes for treating diabetes.[9] Another area of research is prescription adjustment for health maintenance. For example, if an individual is not actually ill with symptoms, but through TCM diagnostics is found to have a constitutional subclinical problem, such as deficiency or excess, PC and PP application can tailor-adjust an existing formula for the individual. This pilot study was performed according to our strategy based on the calculation. Thus, further experimental studies are required to validate the conclusions.

Conclusion

Mathematical algorithms based on property combinations of traditional Chinese herbs can be applied to identify compatibility and synergies of herbs within prescriptions, especially classic formulas. In silico methods can then be used to create new prescriptions or modify existing ones depending on need. This type of automated approach may increase efficiency in designing new drugs based on Chinese herbs.

Author contributions

YW and YQ conceived and designed the project. YH and FD designed and performed the experiments. YH wrote the paper. YW read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Fei L, Li L, Wang ML, et al. Molecular network and chemical fragment-based characteristics of medicinal herbs with cold and hot properties from Chinese medicine. *J Ethnopharmacol*. 2013; 148:770—779.
2. Xiao B, Wang Y, Guo WJ, et al. Relationship between Chinese herb nature combination and function. *World Sci Technol*. 2010; 12:902—908.
3. Gu H, Wang Y, Yan SR, et al. Analysis on Chinese herbal nature combination of stopping vomiting. *Chin J Tradit Chin Med Pharm*. 2011;26:2497—2499.
4. Gu H, Wang Y, Xiao B, et al. Study on compatibility of couplet medicines based on medical nature combination. *Chin J Inf Tradit Chin Med*. 2010;17:99—101.
5. Li M, Gu H, Zhai HQ, et al. Preliminary analysis of the discipline from Yan Zhenghua's prescription to treatment of stomach pain based on medical nature combination mode. *World Sci Technol*. 2012;14:1648—1651.
6. Wang Y, Zhang YL, Shi XY, et al. Framework for nature-effect relationship research of Chinese medicinals based on nature combination. *World Sci Technol*. 2012;14:1798—1802.
7. Newman MEJ, Watts DJ, Strogatz SH. Random graph models of social networks. *Proc Natl Acad Sci USA*. 2002;99:2566—2572.
8. Yu YX, Ma SQ. 1-Neighbour knapsack problem and prospective greedy algorithm of intentional islanding in active distribution network. *Sci China (Technol Sci)*. 2014;3:568—577.
9. Ma L, Yan SR, Li XH, et al. The nature combination patterns based formula design method of medicated diet. *Chin J Chin Mat Med*. 2014;39:2392—2395.