

Original Article

The compatibility law of Chinese patent medicines for the treatment of coronary heart disease angina pectoris based on association rules and complex network

Xiaoxue Zhong^{1,2*}, Qingyong He¹, Jiangquan Liao^{1,2*}, Xiangjun Yin^{1,2*}, Guifang Zhao^{1,2*}, Min Li^{1,2}

¹Guang'anmen Hospital, Chinese Academy of Chinese Medical Sciences, Beijing 100053, China; ²Beijing University of Chinese Medicine, Beijing 100029, China. *Equal contributors.

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Abstract: Objective: To analyze the compatibility law of Chinese patent medicines (CPMs) for the treatment of coronary heart disease (CHD) and provide the basis for CPM development. Methods: A total of 248 kinds of CPMs for CHD were collected from the pharmacopoeias published during 1949 to 2014. Computational techniques and datamining analysis were used to analyze the association rules and complex network within these CPMs. Results: These CPMs contain 5.71 ± 4.31 kinds of herb averagely. *Activating blood circulation and eliminating stasis* account for the largest proportion of their functions (125 out of 248, 50.40%). The most commonly used herbs are *Salvia miltiorrhiza* (contained in 122 CPMs, 49.19%), *Notoginseng* (in 82 CPMs, 33.06%) and *Ligusticum wallichii* (in 77 CPMs, 31.05%). The most common double-paired and triple-paired herbs are also identified. The compatibility laws and confidence coefficient were calculated. In the association network of these CPMs, the core herbs are *Salvia miltiorrhiza*, *Notoginseng*, *Ginseng*, *Borneol* and *Ligusticum wallichii*. Conclusion: *Activating blood circulation and eliminating stasis* is the major function of CPMs for CHD. Understanding the association rules in CPMs helps us to comprehend the composition and function laws of CPMs, which is important for the utilization of currently used CPMs, and the development of new CPMs.

Keywords: Coronary heart disease angina pectoris, Chinese patent medicine, compatibility law, association rules, complex network

Introduction

With the rapid development of the society and the aging process, the risk of cardiovascular diseases keeps rising, which makes it a major public health issue. Global Burden of Disease Study 2013 (GBD 2013) had published the systematic analysis for global causes of death from 1990 to 2013 [1], the mortality of ischemic heart diseases (IHD) had raised from 5.7 million to 8.1 million with a growing rate of 41.7%. In China the mortality caused by cardiovascular diseases had also raised from 240.03/100 thousand in 2004 to 268.92/100 thousand in 2010 [2]. The control of coronary heart disease (CHD) is not satisfying in China and the globe. The morbidity and mortality of CHD keep increasing every year, and the secondary prevention does not reach the expectation [3]. CHD has brought up huge burden for

the patients and the society [4-6], the optimization of CHD treatment is urgent.

Traditional Chinese medicine (TCM) might be an excellent complementary and alternative treatment for CHD, as its effectiveness for CHD has been proven [7-11]. The application of TCM is through either decoction/formula or Chinese patent medicine/preparation. Chinese patent medicine (CPM) is composed of several Chinese herbal medicine together to exert certain therapeutic efficacy, which is widely used in clinical practice. The selection of herbs and the production engineering is very prudent and under the supervision of State Food and Drug Administration. The chemical compositions of CPMs are numerous and extremely complex, hence the application of CPM in clinical practice requires experiences and fully acknowledgement of CPMs. To better understand CPM,

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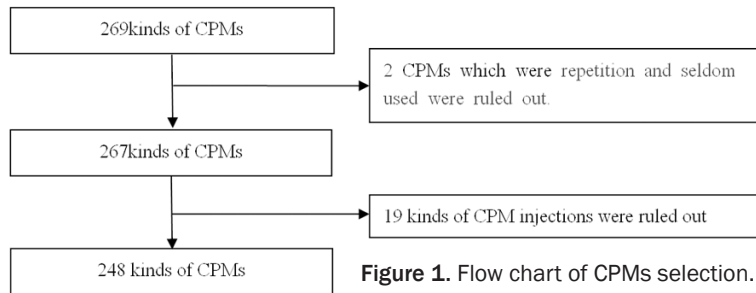


Figure 1. Flow chart of CPMs selection.

studying the patents and combinations of herbs contained in CPMs would be an appropriate way.

Data mining is a method using certain software to collect and analyze the summary patterns. It has been used to study the formula formation and selection in TCM for years. In this research we used data mining to screened out and analyze all the CPMs for CHD published between 1949 and 2014. Association rules and complex network were applied to study the compatibility law of CPMs, hoping to provide indications for the understanding of CPMs and the development of new CPMs.

Materials and methods

Chinese patent medicine inclusion

To study the compatibility law of CPMs, we aimed at those CPMs formally established in official released pharmacopoeias. The pharmacopoeias formally published between 1949 and 2014 in China were searched and those CPMs concerning CHD angina pectoris were collected together.

Inclusion/exclusion criteria

The CPMs documented in official released pharmacopoeias and with the efficacy in treating and preventing CHD were included. Those CPMs fall into these categories were ruled out: Repeatedly collected in different pharmacopoeias; seldom used in clinical practice; CPM injections. Non-herbal ingredients and herbs which are not listed in formal pharmacopoeias were excluded.

Data entry and statistical analysis

All of the herbs in each CPM were documented and inputted into a TCM clinical data warehouse called *Liquorice* to convert and combine

the data of clinical information and CPMs basic elements [12]. The pre-processed data of herbs in CPMs were uploaded to Waikato Environment for Knowledge Analysis (WEKA) platform to perform data mining with FP growth algorithm [13]. With the FP growth algorithm we could uncover the association rules of herbs in

CPMs by calculating the compatibility laws and confidence coefficient.

Results

General information

55 pharmacopoeias were searched, including *Chinese pharmacopoeia 2005*, *Chinese pharmacopoeia 2010*, the 4th, 9th-13th, 15th, 17th, 18th, 21st, 26th-44th editions of *Standards for new medicines to positive*, the 1st to 21st edition of *Pharmaceutical standards of Ministry of Health for Traditional Chinese medicine preparation*, Qi-blood-body fluid section, Cerebral meridian section, lung section and heart section of *National standards for Chinese patent medicines*.

There were 269 kinds of CPMs treating and preventing CHD. Further analysis excluded 2 repeated and seldom used CPMs and 17 injections. Eventually 248 kinds of CPMs were screened out. The process of screening is showed in **Figure 1**. 202 different kinds of herbs (ingredients) were documented in these CPMs. The average amount of herbs in CPMs is 5.71 ± 4.31 , the maximum is 24 and the minimum is 1.

Function categorization of CPMs for CHD

In all types of functions these CPMs exert, “activating blood circulation and eliminating stasis” accounts for the largest proportion (125 out of 248, 50.40%). The frequency of those functions related to “activating blood circulation and eliminating stasis” are listed in **Table 1**, to show the important role of “activating blood circulation and eliminating stasis”.

The formation analysis of herbs in CPMs

CPMs are formed by different kinds of herbs (ingredients) under certain compatibility laws.

Table 1. The functions of CPMs for CHD

Function	Frequency (%)
Activating blood circulation and eliminating stasis	125 (50.40%)
Regulating qi to alleviate pain	45 (18.15%)
Activating meridians to stop pain	28 (11.29%)
Benefiting qi for activating blood circulation	22 (8.87%)
Tonifying qi and yin	10 (4.03%)

Table 2. The most commonly used herbs in CPMs

The single herb	Frequency (%)
Salvia miltiorrhiza	122 (49.19%)
Notoginseng	82 (33.06%)
Ligusticumwallichii	77 (31.05%)
Borneol	64 (25.81%)
Safflower	51 (20.56%)
Ginseng	41 (16.53%)
Radix PaeoniaeRubra	38 (15.32%)
Radix Puerariae	36 (14.52%)
Astragalusmembranaceus	31 (12.5%)

Table 3. The most commonly used double-paired herbs

Double-paired herbs	Frequency (%)
Salvia miltiorrhiza-Ligusticumwallichii	55 (22.18%)
Salvia miltiorrhiza-Notoginseng	49 (19.76%)
Ligusticumwallichii-Safflower	42 (16.94%)
Notoginseng-Borneol	37 (14.92%)
Salvia miltiorrhiza-Borneol	36 (14.52%)
Salvia miltiorrhiza-Safflower	33 (13.31%)
Salvia miltiorrhiza-Radix PaeoniaeRubra	28 (11.29%)
Salvia miltiorrhiza-Ginseng	25 (10.08%)
Salvia miltiorrhiza-Lignum dalbergiaeodoriferae	25 (10.08%)
Salvia miltiorrhiza-Radix Puerariae	24 (9.68%)
Ligusticumwallichii-Radix PaeoniaeRubra	24 (9.68%)
Borneol-Musk	24 (9.68%)
Notoginseng-Ligusticumwallichii	24 (9.68%)
Salvia miltiorrhiza-hawthorn	23 (9.27%)
Borneol-Ginseng	22 (8.87%)
Safflower-Radix PaeoniaeRubra	22 (8.87%)
Ligusticumwallichii-Lignum dalbergiaeodoriferae	22 (8.87%)
Notoginseng-Safflower	22 (8.87%)
Salvia miltiorrhiza-Astragalusmembranaceus	22 (8.87%)
Ligusticumwallichii-Astragalusmembranaceus	21 (8.47%)

The selection of basic ingredients is the foundation of the CPMs formation. The most commonly used herbs is Salvia miltiorrhiza (contained in 122 CPMs, 49.19%), followed by Notoginseng (in 82 CPMs, 33.06%) and Ligus-

ticumwallichii (in 77 CPMs, 31.05%). The most common herbs in CPMs are shown in **Table 2**.

Routine paired herbs usage is common in formation of formulas. Certain combinations of herbs could achieve unique or better efficacy. The most commonly used double-paired herbs are Salvia miltiorrhiza-Ligusticumwallichii (in 55 CPMs, 22.18%), Salvia miltiorrhiza-Notoginseng (in 49 CPMs, 19.76%), and Ligusticumwallichii-Safflower (in 42 CPMs, 16.94%). The double-paired herbs with frequency higher than 20 are listed in **Table 3**.

The most common triple-paired herbs are Salvia miltiorrhiza-Ligusticumwallichii-Safflower (in 28 medicines, 11.29%), Salvia miltiorrhiza-Notoginseng-Borneol (in 26 medicines, 10.48%) and Salvia miltiorrhiza-Ligusticumwallichii-Radix PaeoniaeRubra (in 24 CPMs, 9.68%). The triple-paired herbs with frequency higher than 15 are listed in **Table 4**.

The compatibility law analysis of CPMs

The compatibility law is used to demonstrate the substantial pattern and interaction of the herbs contained in CPMs in computational perspective. The compatibility law of herbs in CPMs was established via Weka and FP growth algorithm. Confidence coefficient (Conf) was calculated and stands for the probability of the appearance of β herb(s) when α herb(s) was contained in a CPM. **Table 5** showed the top 20 compatibility law of herbs.

As shown in **Table 5**, there were 3 associations with Conf >0.8: Lignum dalbergiaeodoriferae- Salvia miltiorrhiza (0.86), Salvia miltiorrhiza, Safflower- Ligusticumwallichii (0.85) and Safflower- Ligusticumwallichii (0.82).

The compatibility laws of them mean that when Lignum dalbergiaeodoriferae is contained in a CPM, the probability of the company of Salvia miltiorrhiza is 86%. So does the rest of them. It showed the deep connections of these paired herbs.

Table 4. The most commonly used triple-paired herbs

Triple-paired herbs	Frequency (%)
Salvia miltiorrhiza-Ligusticumwallichii - Safflower	28 (11.29%)
Salvia miltiorrhiza-Notoginseng - Borneol	26 (10.48%)
Salvia miltiorrhiza-Ligusticumwallichii-Radix PaeoniaeRubra	24 (9.68%)
Salvia miltiorrhiza-Safflower-Radix PaeoniaeRubra	22 (8.87%)
Ligusticumwallichii-Safflower-Radix PaeoniaeRubra	22 (8.87%)
Salvia miltiorrhiza-Ligusticumwallichii-Lignum dalbergiaeodoriferae	20 (8.06%)
Salvia miltiorrhiza-Safflower-Lignum dalbergiaeodoriferae	19 (7.66%)
Ligusticumwallichii-Safflower-Lignum dalbergiaeodoriferae	18 (7.26%)
Salvia miltiorrhiza-Radix PaeoniaeRubra-Lignum dalbergiaeodoriferae	17 (6.85%)
Ligusticumwallichii-Radix PaeoniaeRubra-Lignum dalbergiaeodoriferae	17 (6.85%)
Notoginseng-Ligusticumwallichii-Safflower	17 (6.85%)
Safflower-Radix PaeoniaeRubra-Lignum dalbergiaeodoriferae	16 (6.45%)
Borneol-Toad venom-bezoar	16 (6.45%)
Borneol-Musk-Toad venom	16 (6.45%)
Borneol-Musk-bezoar	15 (6.05%)
Musk-Toad venom-bezoar	15 (6.05%)

Table 5. The compatibility law and Confidence coefficient of herbs in CPMs based on association rules

Association rules		Conf
α herb (s)	β herb (s)	
Lignum dalbergiaeodoriferae	Salvia miltiorrhiza	0.86
Salvia miltiorrhiza, Safflower	Ligusticumwallichii	0.85
Safflower	Ligusticumwallichii	0.82
Radix PaeoniaeRubra	Salvia miltiorrhiza	0.74
Salvia miltiorrhiza, Borneo	Notoginseng	0.72
Ligusticumwallichii	Salvia miltiorrhiza	0.71
Borneo, Notoginseng	Salvia miltiorrhiza	0.7
Ligusticumwallichii, Safflower	Salvia miltiorrhiza	0.67
Safflower	Salvia miltiorrhiza	0.65
Ginseng	Salvia miltiorrhiza	0.61
Notoginseng	Salvia miltiorrhiza	0.6
Borneo	Notoginseng	0.58
Borneo	Salvia miltiorrhiza	0.56
Ligusticumwallichii	Safflower	0.55
Safflower	Salvia miltiorrhiza, Ligusticumwallichii	0.55
Salvia miltiorrhiza, Notoginseng	Borneo	0.53
Salvia miltiorrhiza, Ligusticumwallichii	Safflower	0.51
Notoginseng	Borneo	0.45
Salvia miltiorrhiza	Ligusticumwallichii	0.45
Borneo	Salvia miltiorrhiza, Notoginseng	0.41

The complex network construction and analysis

According to Liquorice analysis, the complex network of compatibility law was constructed

and visualized (**Figure 2**). The key nodes in the complex network are Salvia miltiorrhiza, Notoginseng, Ginseng, Borneo, Ligusticumwallichii, Musk and Safflower. Further analysis of the complex network showed that to develop a new

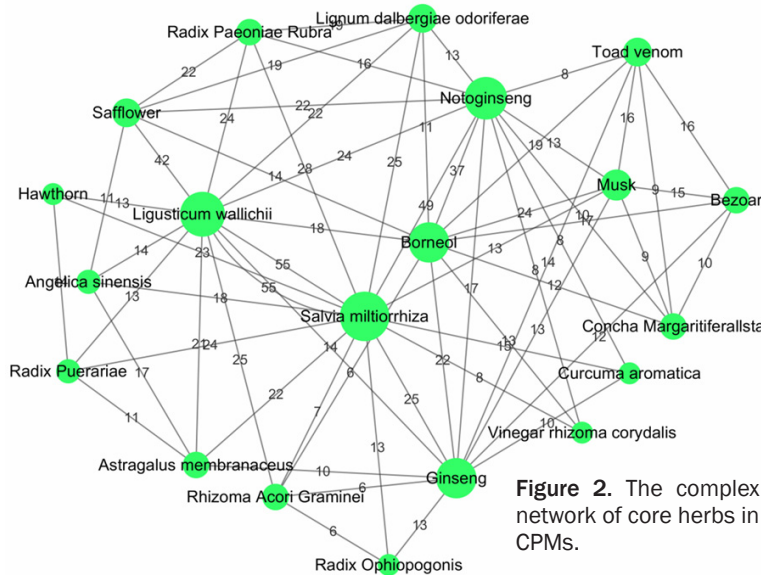


Figure 2. The complex network of core herbs in CPMs.

Table 6. The compatibility law and Confidence coefficient of CPMs for CHD based on complex network

Herbs	Node degree	Edges	Weight
Salvia miltiorrhiza	0.1460674	26	472
Borneo	0.0898876	16	265
Ligusticum wallichii	0.0842697	15	288
Notoginseng	0.0730337	13	241
Ginseng	0.0674157	12	164
Musk	0.0393258	7	103
Safflower	0.0393258	7	163
Toad venom	0.0337079	6	87
Lignum dalbergiae odoriferae	0.0337079	6	109
Astragalus membranaceus	0.0337079	6	92
Rhizoma Acori Graminei	0.0280899	5	31
Angelica sinensis	0.0280899	5	74
Bezoar	0.0280899	5	70
Radix Paeoniae Rubra	0.0280899	5	109
Concha Margaritifera	0.0280899	5	50
Radix Ophiopogonis	0.0280899	5	57
Radix Puerariae	0.0224719	4	62
Curcuma aromatica	0.0224719	4	42
Hawthorn	0.0168539	3	50
Vinegar rhizoma corydalis	0.0168539	3	24

CPM formula, the combination of Salvia miltiorrhiza, Borneo, Ligusticum wallichii, Notoginseng, Ginseng, Musk, Safflower, Toad venom, Lignum dalbergiae odoriferae and Astragalus membranaceus might be preferable choice. The details of nodes in the complex network are shown in Table 6.

Discussion

CHD is a major cause of early morbidity and mortality in most developed countries. Western medication is standard treatment for CHD [14]. Though new medicines for CHD are invented every couple of years, the control of CHD is still not satisfying. Recently, Traditional Chinese medicine has raised the interest as a complementary and alternative treatment for CHD. Researches about TCM with high standards are emerging, especially about CPMs. Unlike herbal decoction, CPMs have fixed and stable ingredients

and proportion, with standard production procedure and engineering.

To use CPMs properly and wisely, we should learn to comprehend both the ingredients and the functions of them. Unlike functions which are intuitive, the combinations of herbs in CPMs can be complicated. The differences between CPMs could be subtle. Hence illustrating the pattern of herbs in CPMs is an approach to understand and better utilize CPMs in clinical practice.

By the computational techniques and data-mining analysis in this study, we found that the most common function of CPMs treating angina pectoris is activating blood circulation and eliminating stasis (50.40%). It is corroborated with our previous study which had found that blood stasis syndrome is the most common syndrome in CHD (56.80%) [15]. And activating blood circulation and eliminating stasis is the standard therapy for blood stasis syndrome. The most commonly used herbs are Salvia miltiorrhiza (49.19%), Notoginseng (33.06%) and Ligusticum wallichii (31.05%).

The modern scientific researches have shown protective effort of them in CHD. Salvia miltiorrhiza could protect vascular endothelial cells, and exert functions of anti-arrhythmic, anti-atherosclerosis, myocardial protection, platelet aggregation suppression, to increase coronary blood flow [16]. Panax Notoginseng Saponins

(PNS) is the major active component of Notoginseng. PNS could improve microcirculation and significantly reduce platelet adhesion and aggregation in CHD patients [17]. Ligusticumwallichii could reduce the expression of IL-1 β in myocardium underwent myocardial infarction by regulating TLR4-NF- κ B signaling pathway and inhibited IL-1 β in hypothalamus by regulating NPY mRNA expression [18].

Paired herbs are herbs that are commonly used concurrently in formula. The herbs' functions in paired herbs are similar or complementary. Combinations of paired herbs could achieve better efficacy. The most common double-paired herbs in CPMs are miltiorrhiza Salvia-wallichiiLigusticum (22.18%), miltiorrhiza Salvia-Notoginseng (19.76%) and wallichiiLigusticum-Safflower (16.94%). The most common triple-paired are Salvia miltiorrhiza-Ligusticum-wallichii-Safflower (11.29%) and Salvia miltiorrhiza-Notoginseng-Borneol (10.48%). These paired herbs represent the sectional pattern of association rules in CPMs, which are the key to the function of activating blood circulation and eliminating stasis.

According to the association rules, we built a complex network of herbs contained in the CPMs. In the complex network there are some core nodes that interact frequently with other nodes, which show the central role of them in the construction of CPM. Salvia miltiorrhiza, Notoginseng, Ginseng, Borneo, Ligusticum-wallichii, Musk, and Safflower are the most central core herbs in the complex network. To create a new formula basing on the complex network, the preferable choices of ingredients would be Salvia miltiorrhiza, Borneo, Ligusticumwallichii, Notoginseng, Ginseng, Musk, Safflower, Toad venom, Lignum dalbergiaeodoriferae and Astragalusmembranaceus.

Conclusion

In this study we explored the characteristics of CPMs for CHD and the association rules in the formation of CPMs. Activating blood circulation and eliminating stasis is the major function of CPMs for CHD, which accords with the fact that blood stasis is the main syndrome in CHD. In the formation of CPMs, certain single and paired herbs as the core ingredients are identified. Understanding the association rules in CPMs helps us to comprehend the composition

and function laws of CPMs, which is important for the utilization of CPMs in clinical practice, and the development of new CPMs.

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Disclosure of conflict of interest

None.

Address correspondence to: Qingyong He, Guang'anmen Hospital, Chinese Academy of Chinese Medical Sciences, Beijing 100053, China. E-mail: heqingyongg@163.com

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