Analysis of Chinese Medicine Compound in Treatment of Urticaria with Rheumatic Fever

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Abstract. Purpose: To explore the rules of prescriptions of modern clinical Chinese medicine compound prescriptions in treatment of urticaria with rheumatic fever, and to provide a reference for the clinical treatment. Methods: The literature on the treatment of urticaria with rheumatic fever with medicine compound prescriptions from October 1st, 1949 to January 1st, 2021 in China National Knowledge Infrastructure (CNKI) was searched to establish an Excel database of medicine prescriptions, and data analysis was performed by SPSS Statistics22.0 and SPSS Modeler18.0. Results: A total of 52 articles are included in this study, involving 54 medicine prescriptions and 97 Chinese medicines with a cumulative frequency of 623 times. Among them, 39 Chinese medicines are used more than 4 times, with the highest frequency of Fangfeng. They are mainly pungent, cold in nature, with the channel tropism of liver and lung. There are 19 second-order association rules for mining TCM association rules, with the first five rules ranked in the descending order of confidence as follows: Fangfeng + Scutellaria baicalensis, Jingjie + Anemarrhenae Rhizoma, Fangfeng + Anemarrhenae rhizoma, Fangfeng + Arctium fruit, Fangfeng + Jingjie, with 103 third-order associations and 124 fourth-order associations, which are consistent with the actual clinical application. Conclusion: The modern clinical treatment of urticaria with rheumatic fever is based on "dispelling wind to relieve exterior syndrome", and also on "curing deficiency", "resolving dampness", "suppressing hyperactive liver for calming endogenous wind", and "promoting blood circulation and removing blood stasis". The data provides reference for the clinical treatment of the disease and Chinese medicine research.

Keywords: Chinese medicine compound; Urticaria with rheumatic fever; Dosing pattern; Data mining.

1. Introduction

Urticaria is a common dermatological disease, and the treatment is quite tricky because of its complex etiology and unknown mechanism. In traditional Chinese medicine, urticaria is called "Yi Zhen" and "Fengzhen Kuai", which is caused by internal and external factors, such as deficiency of endowment, weakness of Qi and blood, and loss of defensive Qi. External factors are mostly caused by wind-cold or wind-heat of liver on the surface of the skin, or by eating fish, shrimps, or thick tastes that turn heat into wind; or due to loss of harmony within the seven emotions and insects. Among them, urticaria with rheumatic fever is one of the more common types of urticaria in clinical practice. Chinese medicine is most commonly used because of its rapid absorption, flexible use, and significant therapeutic effects. In this study, the literature on the treatment of urticaria with rheumatic fever with medicine compound prescriptions from October 1st, 1949 to January 1st, 2020 in China National Knowledge Infrastructure (CNKI) is summarized. 54 medicine prescriptions are analyzed by association rules and cluster analysis to explore the characteristics of the modern clinical use of Chinese medicine compound prescriptions in the treatment of urticaria with rheumatic fever and the rules of formulae, aiming to provide references for its treatment.
2. Materials and Methods

2.1 Literature Research

Search "Chinese medicine" + "urticaria with rheumatic fever" or "Chinese medicine" + "Yi Zhen" or "Chinese medicine" + "Feng Zhen" and other subject terms in China National Knowledge Infrastructure (CNKI). The search period was from October 1st, 1949 to January 1st, 2020.

2.2 Inclusion Criteria

Type of literature: randomized controlled trials or clinical research literature; study subjects: consistent with the diagnosis of urticaria with rheumatic fever; content of literature: Chinese medicine compound as the main treatment, with a clear medicine prescription, uses the Chinese medicine compound alone or with other methods such as western medicine and acupuncture, and Chinese medicine dosage forms are soup, gel, tablet, pill, powder, wine, etc.

2.3 Exclusion Criteria

The literature on medicines and compounds not explicitly given in the prescriptions; review literature; literature on animal experiments; literature on clinical cases and summaries of personal experience; literature on cellular and histological studies; only one duplicate article is retained; literature on Chinese medicine compound as adjuvant therapy.

3. Research Methodology

3.1 Data Processing

The names of the medicines in the prescriptions involved in the included literature are standardized according to the Pharmacopoeia of the People's Republic of China and Chinese Medicine for aliases, misspellings and abbreviations, such as "Chanyi" is unified as "Cicada slough" ("Chantui"), and "nanxing" is unified as "rhizoma arisaematis"("Tiannanxing") etc.; "Shengancao", "Jiugancao" and "Gancao" in the prescriptions are unified as Glycyrrhiza uralensis fisch ("Gancao").

3.2 Statistical Methods

According to the established inclusion and exclusion criteria, after data processing, an Excel prescription database is established for the literature that met the requirements, including number, literature title, source journal, publication time, prescription name, and medicine composition. The data are imported into SPSS Statistics22.0 for data mining, including frequency, nature and flavor, channel tropism, association analysis, and cluster analysis.

4. Results

4.1 Literature Inclusion

According to the inclusion and exclusion criteria, a total of 125 papers on the use of Chinese medicine in the treatment of urticaria with rheumatic fever are retrieved, and 52 papers are finally included, involving 54 prescriptions of Chinese medicine, screened and checked by NoteExpress 3.2 software.

4.2 Analysis of the Frequency, Nature and Flavor, Channel Tropism of Medicines in the Treatment of Urticaria with Rheumatic Fever

According to the inclusion and exclusion criteria, a total of 54 formulas meeting the criteria are screened in this study, involving 97 Chinese medicines with a total frequency of 623 times, among which 39 high-frequency Chinese medicines (frequency ≥4). In order of frequency, they are Fangfeng,
Glycyrrhiza uralensis fisch, Cicada slough, Dried rhizome of rehmannia, etc., with a total of 542 frequencies, accounting for 87.00% of the total. See Table 1 and Table 2 for details.

### Table 1. High-frequency Chinese medicine for urticarial with rheumatic fever

| Number | Medicine                          | Frequency / (times) | Efficacy classification          | Number | Medicine                          | Frequency / (times) | Efficacy classification                                                                 |
|--------|-----------------------------------|---------------------|----------------------------------|--------|-----------------------------------|---------------------|-----------------------------------------------------------------------------------------|
| 1      | Fangfeng                          | 45                  | Relieving exterior syndrome      | 21     | Peppermint                       | 9                   | Relieving exterior syndrome                                                             |
| 2      | Glycyrrhiza uralensis fisch       | 41                  | Curing deficiency               | 22     | Semen sesamum nigrum             | 8                   | Curing deficiency                                                                      |
| 3      | Cicada slough                     | 37                  | Relieving exterior syndrome     | 23     | Duckweed                         | 7                   | Relieving exterior syndrome                                                            |
| 4      | Dried rhizome of rehmannia        | 34                  | Clearing heat                   | 24     | Radix lithospermi                | 7                   | Clearing heat                                                                          |
| 5      | Jingjie                           | 29                  | Relieving exterior syndrome     | 25     | Cortex mori                      | 5                   | Facilitating Expectoration, suppressing cough and relieving dyspnea                     |
| 6      | Moutan bark                       | 26                  | Clearing heat                   | 26     | Ligusticum wallichii             | 5                   | Promoting blood circulation and removing blood stasis                                  |
| 7      | Danggui                           | 24                  | Curing deficiency               | 27     | Schizonepeta spike               | 5                   | Relieving exterior syndrome                                                            |
| 8      | Arctium fruit                     | 22                  | Relieving exterior syndrome     | 28     | Radix cynanchi paniculati        | 5                   | Dispelling wind-dampness                                                               |
| 9      | Gypsum Fibrosum                  | 19                  | Clearing heat                   | 29     | Chrysanthemum                    | 5                   | Relieving exterior syndrome                                                             |
| 10     | Kuh-seng                          | 19                  | Clearing heat                   | 30     | Mutong                           | 5                   | Clearing dampness and promoting diuresis                                               |
| 11     | Honeysuckle                       | 18                  | Clearing heat                   | 31     | Astragalus mongholicus           | 4                   | Curing deficiency                                                                      |
| 12     | Anemarrhenae Rhizoma             | 17                  | Clearing heat                   | 32     | Keel                             | 4                   | Calming the nerves                                                                    |
| 13     | Radix peoniae rubra               | 16                  | Clearing heat                   | 33     | Safflower                        | 4                   | Promoting blood circulation and removing blood stasis                                  |
| 14     | Forsythia                         | 16                  | Clearing heat                   | 34     | Fructus mume                     | 4                   | Inducing astringency                                                                   |
| 15     | Cortex Dictammi                  | 16                  | Clearing heat                   | 35     | Golden cypress                   | 4                   | Clearing heat                                                                          |
| 16     | Scutellaria baicalensis           | 15                  | Clearing heat                   | 36     | Smilax glabra rhizome            | 4                   | Clearing heat                                                                          |
| 17     | Atractylodes lancea               | 15                  | Eliminating dampness            | 37     | Cortex lycii radicis             | 4                   | Clearing heat                                                                          |
| 18     | Bombyx batryticatus              | 13                  | Suppressing hyperactive liver for calming endogenous wind | 38 | Danshen                           | 4                   | Promoting blood circulation and removing blood stasis                                  |
| 19     | Fructus kochiae                   | 12                  | Eliminating dampness            | 39     | Cortex cereis                    | 4                   | Promoting blood circulation and removing blood stasis                                  |
| 20     | Tribulus terrestris               | 11                  | Suppressing hyperactive liver for calming endogenous wind |        |                                   |                      |                                                                                         |
Table 2. High-frequency Chinese medicines for urticaria with rheumatic fever in nature and favor and channel tropism

| Nature and favor & Channel tropism | Frequency/(times) | Frequency / (%) | Nature and favor & Channel tropism | Frequency/(times) | Frequency / (%) |
|-----------------------------------|-------------------|-----------------|-----------------------------------|-------------------|-----------------|
| Pungent                           | 17                | 30.90           | Liver                             | 25                | 25.25           |
| Sweet                             | 16                | 29.09           | Lung                              | 18                | 18.18           |
| Bitter                            | 16                | 29.09           | Heart                             | 12                | 12.12           |
| Salty                             | 2                 | 3.64            | Stomach                           | 11                | 11.11           |
| Astrigent                          | 2                 | 3.64            | Spleen                            | 8                 | 8.08            |
| Sour                              | 1                 | 1.82            | Kidney                            | 8                 | 8.08            |
| Tasteless                          | 1                 | 1.82            | Bladder                           | 7                 | 7.07            |
| Cold                              | 21                | 53.85           | Large intestine                   | 4                 | 4.04            |
| Warm                              | 10                | 25.64           | Small intestine                   | 3                 | 3.03            |
| Neutral                           | 7                 | 17.95           | Gall bladder                      | 2                 | 2.02            |
| Cool                              | 1                 | 2.56            | Pericardium                       | 1                 | 1.01            |

4.3 Cluster Analysis of High Frequency Medicines for Urticaria with Rheumatic Fever

Cluster analysis of high frequency medicines is performed by SPSS Statistics22.0. The results show that the high frequency Chinese medicines for the treatment of urticaria with rheumatic fever could be divided into four categories. The first category is Moutan bark. The second is Fangfeng, Cicada slough, Glycyrrhiza uralensis fischn, Dried rhizome of rehmannia. The third is Atractylodes Lancea, Semen sesami nigrum, Kuh-seng, Anemarrhenae Rhizoma, Gypsum Fibrosum, Arctium fruit, Danggui, Jingjie. The fourth is Radix paeoniae rubra, Forsythia, Cortex Dictamni, Honeysuckle, Bombyx batryticatus, Scutellaria baicalensis, Fructus kochiae, Tribulus terrestris, Peppermint, Schizonepeta spike, Duckweed, Radix lithospermi, Astragalus mongholicus, Safflower, Ligusticum wallichii, Cortex lycii radices, Smilax glabra rhizome, Golden cypress, Radix cynanchi paniculate, Fructus mume, Mutong, Danshen, Cortex mori, Keel, Cortex cereis. The specific results are shown in Figure 1.

![Figure 1. Cluster Analysis of High Frequency Medicines for Urticaria with Rheumatic Fever](image)

4.4 Analysis of Association Rules of Chinese Medicines for Treatment of Urticaria with Rheumatic Fever

According to the database established for the treatment of urticaria with rheumatic fever, the association rules between the high-frequency in 54 medicine prescriptions are analyzed by the Apriori
algorithm in SPSS SPSS Modeler18.0 software, setting the number of antecedents as 1, 2 and 3 respectively, with a minimum support of 25% and a minimum confidence level of 85%. After the analysis, they are ranked in descending order of support.

4.4.1 Second-Order Association Rules

There are 19 second-order associations, and the top 4 with support > 30% and all confidence levels of 100% are selected and listed. The highest support is that of Jingjie → Fangfeng with 53.70% and the improvement is 1.41%. The details are shown in Table 3.

"Support" represents the frequency of occurrence of both the antecedents and the consequents, and the result shows that the highest support is 53.70%, which means that the frequency of occurrence of Jingjie and Fangfeng together is higher. "Confidence" represents whether the consequent will definitely appear when the antecedent appears, and the result shows that the highest confidence level is 100%, which indicates that when Jingjie appears, there is a high probability that Fenfeng will appear. "Elevation" represents the ratio of "the frequency of the antecedent appearing in the presence of the consequent" to "the frequency of the antecedent", with elevation > 1 representing positive correlation, elevation < 1 representing negative correlation, and elevation = 1 representing no correlation. See Table 3 for details.

Table 3. Analysis of the second-order association rules of Chinese medicine for urticaria with rheumatic fever (top 4)

| Number | Antecedent 1 | Consequent 1 | Support degree/ (%) | Confidence level/ (%) | Elevation degree/ (%) |
|--------|--------------|--------------|---------------------|-----------------------|-----------------------|
| 1      | Jingjie      | Fangfeng     | 53.70               | 100                   | 1.41                  |
| 2      | Arctium fruit| Fangfeng     | 40.74               | 100                   | 1.41                  |
| 3      | Anemarrhena Rhizoma | Jingjie | 31.48               | 100                   | 2.18                  |
| 4      | Anemarrhena Rhizoma | Fangfeng | 31.48               | 100                   | 1.41                  |

4.4.2 Third-order Association Rules

Table 4. Analysis of the third-order association rule of Chinese medicine for urticaria with rheumatic fever (top 14)

| Number | Antecedent 1 | Consequent 1 | Support degree/ (%) | Confidence level/ (%) | Elevation degree/ (%) |
|--------|--------------|--------------|---------------------|-----------------------|-----------------------|
| 1      | Dried rhizome of rehmannia + Glycyrrhiza uralensis fisch | Fangfeng     | 50.00               | 100                   | 1.41                  |
| 2      | Dried rhizome of rehmannia + Cicada slough | Jingjie      | 48.15               | 100                   | 1.41                  |
| 3      | Jingjie + Glycyrrhiza uralensis fisch | Glycyrrhiza uralensis fisch | 44.44               | 100                   | 1.41                  |
| 4      | Jingjie + Cicada slough | Fangfeng     | 44.44               | 100                   | 1.41                  |
| 5      | Arctium fruit + Glycyrrhiza uralensis fisch | Fangfeng     | 38.89               | 100                   | 1.41                  |
| 6      | Arctium fruit + Cicada slough | Fangfeng     | 37.04               | 100                   | 1.41                  |
| 7      | Jingjie + Dried rhizome of rehmannia | Fangfeng     | 37.04               | 100                   | 1.41                  |
| 8      | Moutan bark + Cicada slough | Fangfeng     | 35.19               | 100                   | 1.41                  |
| 9      | Danggui + Jingjie | Fangfeng     | 33.33               | 100                   | 1.41                  |
| 10     | Anemarrhena Rhizoma + Jingjie | Fangfeng     | 31.48               | 100                   | 1.41                  |
| 11     | Anemarrhena rhizoma + Fangfeng | Jingjie      | 31.48               | 100                   | 2.18                  |
| 12     | Arctium fruit + Dried rhizome of rehmannia | Glycyrrhiza uralensis fisch | 31.48               | 100                   | 1.62                  |
| 13     | Arctium fruit + Dried rhizome of rehmannia | Fangfeng     | 31.48               | 100                   | 1.41                  |
A total of 103 third order associations are selected, and the top 14 with support > 30% and all confidence levels of 100% are listed. The highest support is Dried rhizome of rehmannia + Glycyrrhiza uralensis fisch → Fangfeng with 50.00% and 1.41% improvement. The details are shown in Table 4.

4.4.3 Fourth-order Association Rules

There are 103 fourth-order associations, and the top 8 with support > 30% and confidence level of 100% are selected and listed. The highest support is raw Dried rhizome of rehmannia + Glycyrrhiza uralensis fisch + Cicada slough→ Fangfeng with 44.44% and 1.41% improvement. See Table 5 for details.

Table 5. Analysis of fourth-order association rules for urticaria with rheumatic fever (top 8)

| Number | Antecedent | Consequent   | Support degree(%) | Confidence level(%) | Elevation degree(%) |
|--------|------------|--------------|-------------------|---------------------|--------------------|
| 1      | Dried rhizome of rehmannia + Glycyrrhiza uralensis fisch + Cicada slough | Fangfeng | 44.44 | 100 | 1.41 |
| 2      | Jingjie + Glycyrrhiza uralensis fisch + Cicada slough | Fangfeng | 37.04 | 100 | 1.41 |
| 3      | Arctium fruit + Glycyrrhiza uralensis fisch + Cicada slough | Fangfeng | 35.19 | 100 | 1.41 |
| 4      | Jingjie + Dried rhizome of rehmannia + Glycyrrhiza uralensis fisch | Fangfeng | 33.33 | 100 | 1.41 |
| 5      | Arctium fruit + Dried rhizome of rehmannia + Glycyrrhiza uralensis fisch | Fangfeng | 31.48 | 100 | 1.41 |
| 6      | Arctium fruit + Dried rhizome of rehmannia + Fangfeng | Glycyrrhiza uralensis fisch | 31.48 | 100 | 1.41 |
| 7      | Moutan bark + Glycyrrhiza uralensis fisch + Cicada slough | Fangfeng | 31.48 | 100 | 1.41 |
| 8      | Jingjie + Dried rhizome of rehmannia + Cicada slough | Fangfeng | 31.48 | 100 | 1.41 |

5. Discussion

Urticaria with rheumatic fever belongs to the category of "Yi Zhen" in Chinese medicine, which is an allergic skin disease characterized by the appearance of wind masses on the skin with itching. The treatment of urticaria with rheumatic fever mostly uses pungent medicines, followed by sweet and bitter ones. Pungent medicines have the effect of dispersing, moving Qi and invigorating blood, which dispel and relieve depression, relieving the skin of the deficiency heat and real heat. Sweet medicines can nourish Yin and blood, and bitter medicines can clear fire and heat, which have a targeted therapeutic effect on the etiology of wind-heat pathogens that consume blood. Shennong Ben Cao Jing states: "treated cold syndrome with heat nature medicines, treating heat syndrome with cold nature medicines". Cold medicine in the treatment of urticaria with rheumatic fever is in the highest frequency of application, in line with the basic clinical guidelines for the use of medicines, while cold medicine is easy to cause cool to suppress pathogenic factors. Therefore, it is helpful in the treatment of urticaria with rheumatic fever application of warm medicine to penetrate the pathogen and relieve depression. The treatment mainly uses the medicines related to liver and lung. The liver and the defensive Qi are "connected by the same Qi", and the defensive Qi is closely related to the skin diseases. Moreover, the liver affects the function of the defensive Qi, which has an important impact on skin diseases. The lung is the master of the skin and hair, and if the lung defense is not solid, the wind pathogen will take advantage of the deficiency to enter the body and cause the disease.

According to statistics, Fangfeng reaches the highest frequency in the treatment of urticaria with rheumatic fever. Modern experimental studies have shown that Fangfeng has good antiallergic and
antipruritic effects in the treatment of skin diseases. In terms of the classification of functions of Chinese medicine, exterior syndrome-relieving medicines and heat-clearing medicines are most frequently used. In addition, medicines for curing deficiency, resolving dampness, suppressing hyperactive liver for calming endogenous wind, and promoting blood circulation and removing blood stasis, etc. shall also be used, which not only tally with the etiology of wind-heat disease but also fully embody the ideology of treatment based on syndrome differentiation.

High frequency traditional Chinese medicine for urticaria with rheumatic fever can be divided into 4 categories. The first category is Moutan bark. It is bitter, pungent and slightly cold, and enters the heart, liver and blood, which is in favor of clearing blood heat. As a skin medicine, Moutan bark helps to treat skin diseases, which leads the medicine directly to the disease and is good for achieving the ideal clinical effect. The second is Fangfeng, Cicada slough, Glycyrrhiza uralensis fisch, Dried rhizome of rehmannia. Fangfeng is slightly warm and Cicada slough is cold, so the combination of cold and warmth penetrates the surface to disperse pathogen and dispel wind-heat; Glycyrrhiza uralensis fisch is neutral and Dried rhizome of rehmannia cools blood and nourishes Yin, so the four medicines work together to dispel wind-heat and cool blood and nourish Yin. The third is Atractylodes Lancea, Semen sesami nigrum, Kuh-seng, Anemarrhenae Rhizoma, Gypsum Fibrosum, Arctium fruit, Dansheng, Jingjie, which is an addition to Wai Ke Zheng Zong of eliminating wind and dampness, clearing heat and nourishing blood. It is effective in treating urticaria with rheumatic fever and relieving itching, and also it is suitable for the treatment of urticaria with rheumatic fever with damp symptoms. The fourth is Radix paeonae rubra, Forsythia, Cortex Dictamni, Honeysuckle, Bombyx batryticas, Scutellaria baicalensis, Fructus kochiae, Tribulus terrestris, Peppermint, Schizonepeta spike, Duckweed, Radix lithospermi, Astragalus mongholicus, Safflower, Ligusticum wallichii, Cortex lycii radices, Smilax glabra rizhrome, Golden cypress, Radix cynanchi paniculate, Fructus mume, Mutong, Danshen, Cortex mori, Keel, Cortex cereis, Forsythia, Honeysuckle, Peppermint. Schizonepeta spike owns the effects of Yinqiao powder in Wen Bing Tiao Bian, to dispel wind to relieve exterior syndrome and to clear away heat and toxic material.

From the analysis of the second-order association rule, it can be seen that Jingjie-Fengfeng is the most supported medicine pair for the treatment of urticaria with rheumatic fever. Modern pharmacological studies have found that Jingjie-Fengfeng has good anti-allergic effects, which inhibits the release of histamine and reduces the allergic reactions in the systemic line. From the analysis of the third-order and fourth-order association rules, it concludes that in addition to medicines for dispelling wind and relieving exterior syndrome and clearing heat, medicines for tonifying Qi, such as Glycyrrhiza uralensis fisch, and medicines for nourishing Yin and nourishing Blood, such as Dried rhizome of rehmannia and Dansheng, are also used in the treatment of urticaria with rheumatic fever. Modern pharmacological research shows that its active ingredients have various effects in anti-inflammatory, multi-channel regulation of immunity, enhancement of body resistance, sedation and analgesia. Dried rhizome of rehmannia and Dansheng nourish Yin and nourish blood; wind-heat diseases tend to move blood and consume blood, so nourishing Yin and nourishing blood medicines can supplement the deficiency of blood. The analysis of the second and third order association rules revealed that Anemarrhenae Rhizoma is more widely used. It tastes both bitter and sweet, and cold in nature, which is good at clearing heat and fire, nourishing Yin and moistening dryness, and is most suitable for the treatment of urticaria with rheumatic fever in which the heat pathogen injures Yin.

In this study, by using data analysis method, the composition of modern clinical Chinese medicine compound prescriptions for the treatment of urticaria with rheumatic fever, the nature and taste, the rules of association, and the cluster analysis are collated, and the characteristics of the modern treatment of urticaria with rheumatic fever and the rules of prescriptions are systematically analyzed. It is concluded that the treatment of urticaria with rheumatic fever is based on "dispelling wind to relieve exterior syndrome", and also on "curing deficiency", "tonifying blood", "resolving dampness" and "suppressing hyperactive liver for calming endogenous wind". The treatment is based on the cause, and the principle of "treating heat syndrome with cold nature medicines" and "dispelling wind to relieve exterior syndrome" is combined with the treatment principle of "using cold and warmth"
and "eliminating pathogen and strengthening vital Qi ", which reflects the way of thinking of Chinese medicine in terms of discriminatory treatment and holistic concept. The data fully reflects the characteristics of modern clinical Chinese medicine compound prescriptions for the treatment of urticaria with rheumatic fever and the rules of formulae, which is expected to provide reference for the clinical treatment of this disease and Chinese medicine research.

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