

Study on the Medication Rules of Traditional Chinese Medicine for Acne Treated from Lung Based on Data Mining

Mingyue Yao¹, Chan Zhao^{2,*}, Jiayuan He¹, Juping Ren¹, Fangfang Dong¹, Hui Wang¹

¹First Clinical School of Medicine, Shaanxi University of Chinese Medicine, Xiayang, Shaanxi, 712046, China

²Department of Dermatology, Baoji Hospital of Traditional Chinese Medicine, Baoji, Shaanxi, 721000, China

*Corresponding author

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Abstract: We searched through the Chinese Journal Full-text Database (CNKI), WanFang, and China Science and Technology Journal Database (Vip) to find the literature related to Traditional Chinese Medicine for acne Treated from lung reported in the past 20 years, established a database after screening and used SPSS Modeler 18.0 and SPSS Statistics 26.0 to perform frequency analysis, their natures, flavors and meridian analysis, and cluster analysis. A total of 213 articles were included, involving 219 prescriptions and 156 drugs. The top five herbs were Huangqin, Sangbaipi, Gancao, Pipaye, and Lianqiao; the medicines were mainly cold; bitter, sweet, and spicy in flavor; and the meridians were mainly concentrated in the meridians of the lung, stomach, and heart; and the combination with the highest support is Huangqin to Sangbaipi, reaching 71.23%. High-frequency drugs were divided into 4 clusters after cluster analysis. The data mining method can be used to summarize and analyze the rule of TCM to treat acne from the lung theory and provide certain references for the clinical research of this disease and the development of new drugs.

Acne is a chronic inflammatory disease of the sebaceous glands of the hair follicles, characterized clinically by papules, pimples, pustules, nodules, and cysts. It occurs on the cheeks and forehead, followed by the chest, back, and shoulders, is mostly symmetrically distributed, and is prone to recurrent attacks.[1] According to relevant studies, the incidence and prevalence of acne are increasing linearly[2], and the burden of the disease is also on the rise[3]. Western medicine believes that acne pathogenesis is mainly associated with increased androgen and sebum secretion, abnormal keratinization of follicular sebaceous gland ducts, proliferation of Propionibacterium acnes, and secondary inflammatory reactions[4]. Western medicine often chooses retinoic acid, benzoyl peroxide (BPO), antibiotics, and other treatments, often accompanied by adverse reactions[5-6]. For example, retinoids are most commonly associated with adverse reactions such as cutaneous mucosal, photosensitivity, and skin dryness[7]. And patients are prone to some resistance problems with long-term antibiotic use[8]. Therefore, safe and effective treatment is particularly important for patients. Chinese medicine has been passed down for thousands of years and has a

long history. Acne belongs to the category of "lung wind acne" in Chinese medicine, which often involves multiple organs, but is most common in the lungs. Surgical Insights recorded: "Lung wind acne, the lung blood heat causes this disease, it happens every time on the nose and face, Small bumps on the surface, shaped like a millet, color red, swelling, and pain, broken out of the white powder juice. Over time, a type of flake is formed that is shaped like a white sheet of millet. It is advisable to take Loquat Lung Clearing Drink internally and apply Upside Down Sans externally so that it can be recovered slowly." We can find that the treatment of acne is closely related to the lungs. Acne is a common cause of acne when the lungs are weak and intolerant to external aggressions and when the lungs become hot and depressed. External attack, the lungs are delicate and intolerant, and the formation of heat results in acne, which is a common cause of acne onset[9-10]. This paper aims to collect and collate the literature on the lung-based treatment of acne in traditional Chinese medicine (TCM), and to analyze the medication patterns of lung-based treatment of acne in TCM through data mining techniques, to provide references for the clinical research on lung-based treatment of acne in TCM and the development of new formulas and new medicines[11-12].

1. Data and Methods

1.1. Data Source and Retrieval Method

Literature on acne treatment from the lung theory was searched from the full-text database of Chinese journals (CNKI), Wanfang Data Knowledge Service Platform (Wanfang), and Wipro Chinese Science and Technology Database (VIP), respectively. 3,538 articles were retrieved from the three major databases by using the advanced search function of the CNKI with the search terms "acne" and "lung", and the search time limit of "from 1 January 2001 to 1 January 2021".

1.2. Inclusion Criteria

(1) literature for clinical observation, and diagnosis in line with the Chinese and Western medicine diagnostic criteria of acne; (2) traditional Chinese medicine drug treatment is the main; (3) literature to clarify the effectiveness of treatment, the efficacy of the determination of the standard is clear; (4) drug entry appeared in a different type of evidence, to be recorded separately as a prescription; (5) the selected literature has a complete clinical data.

1.3. Exclusion Criteria

(1) Synthesis, meta analysis, case reports, expert experience, animal experiments, and other types of literature; (2) literature based on other means of treatment, such as Western medicine and external therapeutic methods; (3) only the name of the formula or self-proposed prescription but the composition of the drug is not specific or the drug is incomplete; (4) duplicated the published literature to select one of them to be recorded.

1.4. Data and Information Input and Standardized Processing

Microsoft Excel 2019 software was used to establish a database of Chinese medicine for treating acne from the lung theory. After screening according to the above criteria, a total of 213 documents were eligible for the search, and 219 prescriptions were obtained after extracting the Chinese medicine prescriptions, containing 157 Chinese medicines. We referred the 2020 edition of The People's Republic of China pharmacopoeia[13], the national higher Chinese medicine colleges and

universities planning a textbook eleventh edition of Traditional Chinese Medicine[14] unified specification of Chinese medicine name, natures, flavors, and meridian, such as "fried gardenia" "scorch-fried Cape jasmine fruit" "mountain gardenia" unified specification for "Fructus Gardeniae". For the same traditional Chinese medicine, due to processing, the concocting method is different, the medicinal nature of medicine taste has a big difference in those who are respectively recorded, such as Radix Rehmanniae Recens, Radix Rehmanniae Preparata, etc., and recorded in the four qi, five flavours, Meridian affinity, and other relevant information about each Chinese medicine.

2. Results

2.1. Drug Frequency Statistics

All 219 TCM prescriptions that met the inclusion criteria were entered, and a total of 156 TCM medicines were obtained, with a total frequency of 2437 times, and a total of 30 kinds with a frequency of more than 20, accounting for 79.8% of the total frequency, among which the Chinese herbal medicine with the highest frequency of use was Huangqin, followed by Sangbaipi, Gancao, Pipaye, and Lianqiao. See Table 1.

Table 1: Frequency statistics of high-frequency Chinese medicines (frequency ≥ 20)

No.	Herb	Frequency/ times	Frequency/ %	No.	Herb	Frequency/ times	Frequency/ %
1	Huangqin	171	78.08	16	Shigao	52	23.74
2	Sangbaipi	156	71.23	17	Yejuhua	47	21.46
3	Gancao	152	69.41	18	Dahuang	42	19.18
4	Pipaye	139	63.47	19	Shanzha	36	16.44
5	Lianqiao	114	52.05	20	Yiyiren	36	16.44
6	Mudanpi	93	42.47	21	Baizhi	34	15.53
7	Zhizi	92	42.01	22	Zihuadiding	32	14.61
8	Baihuasheshecao	88	40.18	23	Zhimu	30	13.70
9	Danshen	83	37.90	24	Xiakucao	27	12.34
10	Jinyinhua	83	37.90	25	Zaojiaoci	25	11.42
11	Huanglian	77	35.16	26	Zhebeimu	23	10.50
12	Shengdihuang	72	32.88	27	Danggui	21	9.60
13	Chishao	53	24.20	28	Yinchen	21	9.60
14	Huangbai	53	24.20	29	Digupi	20	9.13
15	Pugongying	53	24.20	30	Fuling	20	9.13

2.2. Statistics on the natures, flavors and meridian of drugs

The 156 kinds of Chinese medicine's natures and flavors were mainly cold (1900 times), bitter (1532 times), sweet (954 times), and pungent (546 times), and the meridians were mainly the lung meridian (1359 times), stomach meridian (1053 times) and heart meridian (1001 times). See Figure 1.



A: Flavors of herbs; B: Natures of herbs; C: Meridian tropism of herbs.

Figure 1: Radar chart of Chinese medicine natures, flavour and meridian.

2.3. Association rule analysis and complex network analysis

SPSS Modeler 18.0 was used to analyze the association rules of 30 high-frequency drugs with a frequency of more than 20 times, as shown in Figure 2. With a support level of more than 30%, a confidence level of more than 80%, and a maximum number of antecedents of 2, the Apriori algorithm was used to analyze the association rules among drugs and the degree of association among the high-frequency drugs for the treatment of acne in terms of the lung theory was obtained, which finally resulted in 22 drug-pair association rules (see Table 2). Among which Huangqin → Sangbaipi had the highest support, followed by Sangbaipi → Pipaye, and Huangqin → Lianqiao.

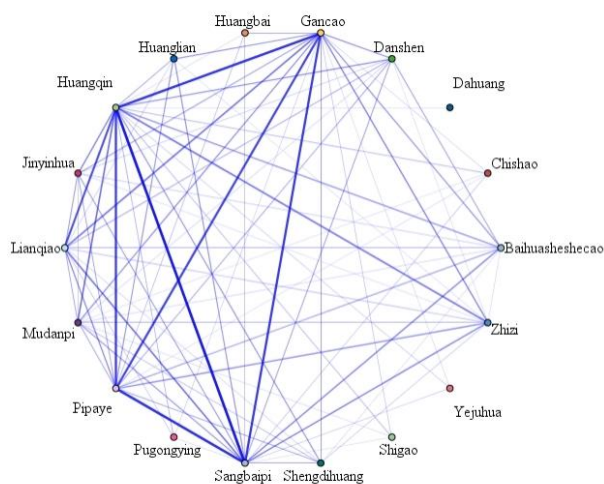


Figure 2: Network diagram of high-frequency drug associations (frequency ≥ 20)

Table 2: High-frequency drug association rule analysis

Latter item	Former item	Support (%)	Confidence (%)
Huangqin	Sangbaipi	71.23	81.41
Sangbaipi	Pipaye	63.47	84.89
Huangqin	Lianqiao	52.05	86.84
Sangbaipi	Pipaye and Huangqin	50.68	84.68
Pipaye	Ganciao and Sangbaipi	50.23	82.73
Sangbaipi	Pipaye and Ganciao	48.40	85.85
Huangqin	Mudanpi	42.47	86.02
Huangqin	Zhizi	42.01	88.04
Huangqin	Jinyinhua	37.90	83.13
Huangqin	Lianqiao and Ganciao	36.53	85.00
Huangqin	Lianqiao and Sangbaipi	36.07	91.14
Huangqin	Shengdihuang	32.88	84.72
Huangqin	Zhizi and Sangbaipi	32.42	90.14
Pipaye	Zhizi and Sangbaipi	32.42	81.69
Huangqin	Baihuasheshecao and Sangbaipi	31.96	81.43
Huangqin	Zhizi and Ganciao	31.51	86.96
Huangqin	Lianqiao and Pipaye	30.59	92.54
Huangqin	Zhizi and Pipaye	30.59	88.06
Sangbaipi	Zhizi and Pipaye	30.59	86.57
Sangbaipi	Lianqiao and Pipaye	30.59	83.58
Ganciao	Lianqiao and Pipaye	30.59	82.09
Ganciao	Zhizi and Pipaye	30.59	80.60

2.4. Cluster analysis

The 30 Chinese medicines with a frequency of more than 20 were analyzed by systematic cluster analysis using SPSS Statistics 26.0 software using average linkage (between groups) and Pearson correlation to generate a tree cluster diagram (see Figure 3). Under the guidance of TCM theory, the

drugs were classified into 4 categories with a class spacing of 24.

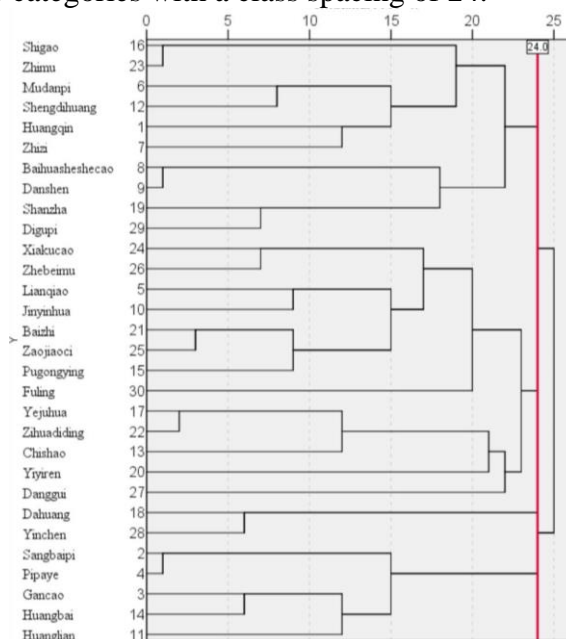


Figure 3: Dendrogram of systematic clustering among high-frequency drugs (frequency ≥ 20)

3. Discussion

Acne is one of the common diseases in dermatology, and ancient medical practitioners often named it pimples, lung winds, and facial blisters[15]. The invasion of external evil into the skin's surface is the key to the occurrence and change of acne. Ancient and modern medical practitioners have applied the theory that "the lung integrates with the skin and hair" to treat acne with remarkable efficacy[16-17]. This theory originates from The Yellow Emperor's Classic of Internal Medicine, for example, in Suwen - The Creation of the Five Organs, it is said that "The lungs are in harmony with the skin, and they nourish the hairs." and in Suwen - A Separate Treatise on the Meridians, it is said that " All the blood in the body passes through many meridians to the lungs, and they transmit their essence to the skin and the hairs." The lungs regulate the secretion and excretion of fluids through the functions of ascending and descending, regulating the waterways, and convergence of blood, thus affecting the functions of the sweat glands and sebaceous glands in the human body. Gas, blood, and fluids are dispersed through the lungs, reaching the head and face orifices, and spreading out to moisten the skin, hair, and muscles. The lungs will be the first to bear the brunt of any external attack, but the lungs are delicate and susceptible to evil attacks that can lead to a lack of power and cause fever, which leads to acne[18-19]. It can be seen that the occurrence of acne is closely related to the lungs, and it is important to treat acne from the lungs.

In the present study, 213 articles on the treatment of acne from the lung theory in Chinese medicine in the past 20 years were included, with 219 prescriptions containing 157 Chinese medicines.

(1) Analysis of drug frequency results: the Chinese medicines whose frequencies were in the top five were Huangqin,Sangbaipi,Gancao,Pipaye,Lianqiao; among them, Huangqin is bitter and cold, and it has the effects of clearing heat and drying dampness, diarrhoeal fire and detoxifying toxins. According to related studies, the intervention of baicalin in acne may regulate the development of inflammatory mediators and reduce the formation of acne scarring in later stages by reducing the levels of IL-4 and MMP-9 in acne model tissues [20]. And baicalin significantly inhibited multiple infections- and inflammation-related pathways activated during acne development [21]. Sangbaipi

is sweet in taste, cold in nature, and belongs to the lung meridian, with the effect of purging the lung to calm panting and inducing diuresis to alleviate edema. Modern pharmacological studies have found that Sangbaipi total flavonoids have anti-inflammatory and analgesic properties, and Sangbaipi Extract plays an antibacterial and antimicrobial role by affecting the intra- and extracellular structure or its related metabolic enzymes [22]. Gancao is sweet in taste and flat in nature, and has the functions of tonifying qi and invigorating spleen, clearing heat and removing toxin, relaxing tension and relieving pain, and harmonizing the actions of all medicinals in a formula. In one study, six flavonoids were isolated from Gancao Extract, and the effects of the six flavonoids on the viability of the cells were evaluated by the MTT method, and it was found to have a stronger antioxidant and anti-inflammatory activity[23]. The licorice triterpenoid saponins and licorice flavonoids in licorice extracts can also affect various aspects of the inflammatory response, and their anti-inflammatory active components synergistically produce anti-inflammatory effects from different mechanisms, inhibition of inflammatory factors, and inhibition of steroid metabolizing enzymes, respectively[24]. Pipaye are bitter in taste and cold in nature, and have the effect of clearing lung heat and relieving cough, directing qi downward to arrest vomiting, and clearing stomach heat. Flavonoids, triterpenoids, organic acids, volatile oils, etc. are the main chemical constituents of Pipaye, triterpenoids can reduce the proportion of tumor necrosis factor, leukocytes, neutrophils, and macrophages, and have some anti-inflammatory effects, and have a strong in vitro and ex vivo antioxidant effects when the concentration of flavonoids is certain[25]. Lianqiao is bitter in taste and cold in nature, with the effects of clearing heat and removing toxin, dispersing swelling and dissipating mass, and dispersing wind-heat. It has been found that among the main active components isolated from forsythia, Forsythia ester glycoside A not only has an antioxidant ability but also can exert anti-inflammatory effects by inhibiting the signaling pathway of pro-inflammatory factors[26]. All of the above high-frequency drugs have anti-inflammatory, antibacterial, and antioxidant effects that effectively treat acne.

(2) The results of the natures, flavors, and meridian analysis: 156 flavor of Chinese medicine is mainly cold, the taste of bitter, sweet, pungent, bitter drugs "can drain, can dry, can be firm", sweet drugs "can be complementary and can be slow", pungent drugs "can disperse", "can move". The sweet herbs are "capable of unifying, harmonizing and moderating" and the pungent herbs are "capable of dispersing". Therefore, the treatment of acne from the lung theory focuses on clearing heat, removing toxin, and cooling blood, as well as activating blood and moving qi, and tonifying and replenishing the middle qi. The lung meridian, stomach meridian, and heart meridian are the main channels, in which the lungs links with all the vessels and govern ascent and dispersion purification and descent, the heart governs blood and vessels, and the stomach governs reception and decomposition (of water and food), and grain. The four qi, five flavor, and meridians together play the role of heat-clearing and fire-purging, cooling blood, and removing toxins.

(3) Analysis of association rules and complex network results: By analyzing the association rules of high-frequency drugs, it was concluded that the highest degree of support was Huangqin to Sangbaipi indicating that this group of drug pairs had the highest number of simultaneous pairings and that the two drugs were located in the top five of the high-frequency drugs in this data mining. Among them, Huangqin can clear heat and dry dampness, drain fire, and resolve toxins in the body, and Sangbaipi can clear lung heat and reduce lung fire. Modern pharmacology shows that this pair of drugs can decrease the serum levels of pro-inflammatory factors IL-1 β and TNF- α , and reduce the number of macrophages, neutrophils, and other inflammatory cells [27]. Therefore, it can be used as the primary pair of drugs in the formula for acne treatment from the lung theory.

(4) Analysis of cluster analysis results: C1 drugs are bitter in taste and cold in nature, mainly belonging to the lung and liver meridians. In the prescription, Shengdihuang, Mudanpi, and Digupi play the role of clearing heat and cooling blood. Huangqin plays the role of clearing heat and drying

dampness, purging fire, and removing toxins. Zhimu plays the role of nourishing yin and moistening dryness. Shigao plays the role of invigorating the spleen and promoting digestion, moving qi, and dissipating (blood) stasis. Shanzha plays the role of stomach tonic and food elimination, circulates qi, and dissipates stasis. Zhizi plays the role of reducing fire, cooling blood, and clearing heat from the upper, middle, and lower triple jiao. Baihuasheshecao plays the role of clearing heat and removing toxins, draining dampness, and relieving Strangury. Danshen plays the role of activating blood and resolving stasis. These Chinese medicinal work together to clear heat and dry dampness, blood-cooling, and remove toxins. C2 is an additional prescription based on the Pei Pa Qing Fei Yin. This prescription is commonly used by ancient and modern dermatologists with remarkable results[28-29]. The drugs in this group are bitter in taste and cold in nature and are mainly attributed to the lung and stomach meridians. The prescription includes Pipaye and Sangbaipi which play the role of clear lung heat and lower lung fire. Huangqin plays the role of clear lung heat in the upper Jiao. Huanglian plays the role of draining fire in the heart and stomach, and fire of stomach in the middle jiao. Huangbai enters the Kidney meridian to clear heat and relieve bone-steaming sensation and can drain damp heat from the lower Jiao. Gancao plays the role of clearing heat removing toxins, and harmonizing the actions of all medicinals in a formula. The combined use of the whole formula can jointly exert the effect of clearing heat from the lungs and stomach. C3 is an additional prescription based on the Xian Fang Huo Ming Yin. This formula is known as "the holy medicine for sores and ulcers, the first formula for surgery". It has remarkable curative effects on sores, ulcers, swellings, and poisons, and is widely used in clinical experience[30]. The drugs in this group are bitter in taste and cold in nature and are mainly attributed to the heart and lung meridians. Jinyinhua, Yejuhua, Pugongying, Zihuadiding, Xiakucao, Zaojiaoci, Lianqiao play the role of clearing heat and removing toxin, dissipating mass, and disperse swelling. Danggui, Chishao plays the role of activating blood and freeing the collateral vessels, resolving swelling, and alleviating pain. Baizhi, Zhebeimu play the role of dissipating mass and dispersing swelling. Yiyiren, Fuling plays the role of promoting urination and draining dampness, fortifying the spleen, and calming the heart. The combination of these herbs can clear heat and remove toxin, dissipate mass and disperse swelling, and activate blood to relieve pain. C4 is an additional prescription based on the Yin Chin Hao soup. The drugs in this group are bitter and cold in nature and are mainly attributed to the spleen and stomach meridians. Yincheng plays the role of clearing heat and draining dampness, combined with Dahuang to purge heat and remove stagnation, expelling blood stasis. In clinical application, Yin Chin Hao soup can effectively relieve symptoms, reduce the extent of skin lesions, inhibit inflammation, improve sex hormone levels, and improve clinical efficacy in patients with acne [31]. The four groups of prescriptions in this data mining include new formulas and additions and subtractions based on classical prescriptions, which can be used as a reference for clinical medication for acne.

4. Summary

This paper summarises and analyses the medication patterns of Chinese medicine in treating acne from the lung theory through data mining methods. This led to the conclusion that the Chinese herbal medicines with the highest frequency were Huangqin, Sangbaipi, Gancao, Pipaye, Lianqiao, with the overall medicinal properties being cold, the medicinal flavours being bitter, sweet and pungent, and the meridians being the lung meridian, the gastric meridian, and the heart meridian, and the most commonly used pair of medicines being Huangqin → Sangbaipi, and that four clustered formulas were derived from the cluster analysis. This study provides a reference for the clinical study of lung-based treatment of acne in Chinese medicine and the development of new formulas and drugs. In addition, there are still some deficiencies in this study, and the drug pairs

and formulas obtained should be verified by future scholars through clinical and mechanistic studies.

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