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## Outlining the keyword co-occurrence trends in Shuanghuanglian injection research: A bibliometric study using CiteSpace III

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### ABSTRACT

**Objective:** To explore the evolvement and new trends in the use of Shuanghuanglian injection (SHLI).

**Methods:** China National Knowledge Infrastructure (CNKI), PubMed, and Embase were extensively searched using the search terms “Shuanghuanglian injection” and “Shuanghuanglian fenzhen” to retrieve articles relevant to SHLI (1992–2020). Retrieved articles were further investigated by two authors to exclude those unrelated to SHLI. The bibliographical references of the included articles were exported as raw data and then treated using the CiteSpace tool to visualize the mapping of the SHLI research domain. Essential clusters and highly frequent keywords were quantified for further analysis. The clusters were automatically labeled by the algorithm of tf\*idf for objective analysis. Basic bibliometric features, including article types and yearly trend in article numbers were also determined and discussed.

**Results:** The modules of the keywords of interest presented clear boundaries with a high modularity score ( $Q = 0.73$ ). High-confidence clusters were identified, including bioactivity fingerprint ( $S = 0.99$ ), equal pupils ( $S = 0.91$ ), drug preparation department ( $S = 0.87$ ), difficulty in respiration ( $S = 0.85$ ), peristalsis (0.88), and Danshen powder injection ( $S = 0.94$ ). The characteristic keywords in terms of frequency and burstiness were Shuanghuanglian powder for injection ( $F = 235$ ,  $B = 5.22$ ), SHLI ( $F = 112$ ,  $B = 11.39$ ), and adverse drug reactions (ADRs;  $F = 104$ ,  $B = 7.35$ ).

**Conclusion:** In the field of SHLI study, there are five major topic categories: bioactivity fingerprint; ADR mechanism and cause detection; proper preparation; clinical evidence accumulation; and efficacy in diseases with no effective treatment and combination usage. The trend for using modern methodologies from a science-based perspective to study SHLI will continue to exist. The causes of multi-factorial ADRs may be an important topic for future studies.

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### Introduction

The efficacy of Shuanghuanglian injection (SHLI) has long been proven from a variety of clinical evidence.<sup>1–6</sup> However, the safety of SHLI is being critically questioned because of a number of adverse drug reactions (ADRs), and this topic has captured the attention of researchers. A clear outline of the published SHLI studies may provide directions for the focus of future research.

With the rapid evolvement of scientific research, the number of published papers doubles every 8 years,<sup>7</sup> simultaneously there is an increasing difficulty of carrying out new studies, and this is especially true for the types of studies that are intrinsically lacking in quantification and repeatability, such as qualitative reviews.

In an attempt to account for this “quality crisis” and to supplement the cases where the data is insufficient for a review study, the concept of a bibliometric perspective has been introduced. In SHLI research, such bibliometric studies have been reported using the frequency of keywords in published papers as metrics of focus magnitude.<sup>8,9</sup> As an emerging area of research, these studies are not without limitations, which include the small number of indicators and relatively low levels of coherence among these indicators,

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leaving the outline of the field of focus (such as hotspots, innovation, progression, and bottlenecks) under-researched. To address these insufficiencies, scientific mapping based on the theory of a complex network that can visualize facets of a pool of articles, which cannot be visualized using more conventional methods, can be adopted.<sup>10–13</sup>

By looking at knowledge domains, scientific mapping can picture the progression and structural relationships of the topics in a particular area.<sup>14</sup> This mapping can show how knowledge units connect, overlap, interact, and evolve with each other, and thus provide insights into emerging knowledge and areas of focus that may be currently overlooked. CiteSpace is one of the software programs developed to allow scientific mapping, and this software has been extensively used in many areas.<sup>15</sup>

Shuanghuanglian (SHL) is a well-known modern formula prepared from three medicinal herbs, honeysuckle flower (*Lonicera japonica* Thunb.), scutellaria (*Scutellaria baicalensis* Georgi), and forsythia fruit (*Forsythia suspensa* (Thunb.) Vahl).<sup>16</sup> To date, SHL has been developed in a variety of dosage forms, including capsule, tablet, oral liquid, and injection. SHLI is usually formulated as either a solution or powder, and is commonly used to treat upper respiratory tract infections, pneumonia, tonsillitis, and other respiratory diseases caused by bacteria or viruses.<sup>17</sup> From the perspective of Chinese herbology, SHLI clears pathogenic heat/toxicants and expels wind-heat. Although cases of severe ADRs to SHLI, such as allergy and dyspnea, were reported in 2001 and 2009,<sup>18,19</sup> the efficacy of SHLI in inhibiting viral replication and alleviating lung injury has been proven in laboratory and clinical studies.<sup>20,21</sup> SHLI also has great potential for treating COVID-19 infections. When a novel virus emerges, investigating existing medicines and other compounds that might function as effective treatments is one of the major approaches to tackle the virus, because vaccines and specific medicines take months, if not years, to develop.<sup>22</sup> A joint study conducted by the Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai, China) and the Wuhan Institute of Virology, CAS (Wuhan, China) found that SHL oral liquid, an oral formulation using same ingredients as SHLI, could inhibit SARS-CoV-2.<sup>23,24</sup> We expect that this finding will bring formulations of SHL, including SHLI, back into the international research spotlight. As such, a scientific mapping presenting the progression and structural relationships of the great number of existing studies of SHLI would facilitate a fully informed starting point for researchers. Therefore, in this research, by depicting the keyword co-occurrence map of SHLI studies using CiteSpace, we aim to explore the evolution and new trends in SHLI hot topics.

## Material and methods

### Data source and collection

On the 30th February 2020, articles were retrieved from the China National Knowledge Infrastructure (CNKI), Medline (PubMed entry), and Embase (ovid entry) with no limitations on the published date. Our search terms were “Shuanghuanglian injection”, “Shuanghuanglian fenzhen” and the Boolean combination of the two. The detailed search strategies can be found in Supplementary Data.

The retrieved articles were imported into Endnote to remove duplicates. Two authors (QZ and GR) then separately read the titles and abstracts to exclude those articles with topics irrelevant to SHLI. It should be noted that a bibliometric study is insensitive to the precision, but sensitive to the extensiveness, of included articles. This tolerance is the result of the frequency-based algorithm of keyword connecting and clustering that ignores minor noise. Therefore, in a bibliometric study we should avoid using extremely

rigid inclusion constraints as is required by other types of studies, such as a meta-analysis.

Because the establishment of a method for manual association between keywords in different source languages has yet to be validated, as well as the fact as indicated in a pilot search that studies of SHLI are overwhelmingly more frequently reported in China-based journals, our mapping was majorly focused on the Chinese database. Articles retrieved from English-language databases were also treated in CiteSpace to outline a separate scientific map of the area only if the number of citations was  $\geq 30$ . If the number of citations was  $< 30$  we quit the mapping, but still used these articles as background information for our qualitative discussion.

The retrieved articles were saved as indexing records and transformed into an executable format using the “Data → Import/Export” function of CiteSpace.

### Parameter settings

A pilot study showed that the earliest SHLI article was published in 1992; therefore, for the present study we set the timespan from 1992 to 2020. Other parameters included time slice duration, node type, slice content, line strength, and pruning method. More information regarding these parameters and their functions can be found in a previous report.<sup>15</sup> As is recommended by the developer of CiteSpace<sup>15</sup> and in accordance with previous studies,<sup>25–29</sup> we have used the following settings: a duration of 3 years was set for every time slice (resulting in 8 consecutive slices); node type was set as “Keyword”; treated articles were set as the top 100 keywords in each slice (ranked according to how often they were used); line strength was set to cosine; and the pruning method was set as MST + pruning the sliced network.

### Interpretation of network evaluation indicators

To judge whether the network was successfully established and to explore the potential scientific data, several qualitative and quantitative evaluation indicators reported by CiteSpace were determined and interpreted. These indicators were (a) frequency (abbreviated as F), (b) sigma,<sup>30</sup> (c) burstiness (abbreviated as B),<sup>30</sup> (d) modularity (Q),<sup>31</sup> (e) silhouette (abbreviated as S),<sup>30</sup> and (f) qualitative results of representative labels generated by two types of algorithms (tf\*idf<sup>32</sup> and log-likelihood ratio (LLR)<sup>33</sup>).

For interpretation, frequency is a series of values that quantify the importance of each node by how often it is presented in the included nodes, and it can be used to tease out weighted focuses of the field. In the present paper, we looked at keywords with  $F > 10$ .

Sigma identifies the innovativeness of the topic, if there is any, then quantifies it. Typically, higher sigma values indicate more innovation. In the present paper, we set a value for sigma  $> 10$  as reflecting the potential novelty of a field.

Burstiness, another important node indicator, ranks the amplitude of usage surges for keywords with significant changes in usage frequency (we would not expect CiteSpace to report anything if there were no significant changes identified). According to previous studies,<sup>34–36</sup> a keyword with  $B > 3$  can be considered to have a meaningful value for burstiness and we used this cutoff for the present analysis.

The values for Q and S ranged from 0 to 1 and  $-1$  to 1, respectively. These indicators are used to assess how well the field is split into clusters (each cluster represents a particular research focus). CiteSpace only calculates an overall value for S, whereas for Q both an overall value and individual values for each cluster are reported. A Q value close to 1 indicates better-defined clusters and an S value close to 1 indicates confidence in how the nodes are clustered. According to a previous report,<sup>12</sup> we considered that the results

with both  $Q > 0.3$  and an overall  $S$  value  $S > 0.6$  indicated successful clusters, and any individual cluster with  $S > 0.8$  as having a meaningful research field focus worth further discussion.

The results of  $tf*idf$ , LLR, and mutual information (MI) provide qualitative information about the research focus of each cluster. The algorithms are developed based on different text-mining assumptions; therefore, their results can be complementary to each other.

#### Network layouts and representation

The resulting keyword co-occurrence map shows various information including the executing version of CiteSpace, computing speed, slice profile, the node, and other network evaluation values mentioned above.

In the middle of the map is the CiteSpace-visualized merged network based on several networks corresponding to the snapshots of consecutive slices we have set. The merged network characterizes the development of the field over time, showing the most important footprints of the related research activities. The network is merged in a semi-automatic manner, i.e. the duplicate nodes and lines among slices are automatically merged through the built-in algorithm of CiteSpace, and different nodes with the same connotation are manually merged by the “Alias List” function as described in a previous report.<sup>15</sup> Each dot represents a keyword in the network (we call this dot a node in the present study). CiteSpace can generate networks of other types of nodes, such as term, author, reference, and keyword. As we have set the node type as “Keyword”, the nodes in this study solely represent keywords. The lines that connect nodes are co-occurrence links (these correspond to the scientific topic in question). The colors of these nodes and lines are designed to show when a connection was made for the first time, and we can distinguish them by referring to the uppermost caption.

In the merged network, the size of a node is proportional to how many times a keyword is used. The keyword usage history is visualized in terms of “tree rings” of different colors and thicknesses. The thickness of a ring is proportional to how many times the keyword is used in a particular period that is represented by the ring color. Nodes with usage bursts are visualized by rings colored in red.

Individual nodes can be aggregated into clusters based on their interconnectivity to represent strong relationships in the field in question. This aggregation will generate another picture, where nodes and links are replaced by clusters with labels displayed in red prefixed by the cluster number (#). The labels are identified automatically by the LLR algorithm. The results of the two other text-mining algorithms can be explored through several more mouse clicks.<sup>15</sup>

**Table 1**

Number of included nodes and lines and the total number of candidate nodes and lines.

Time slice	Selected lines/Candidate nodes	Selected lines/Candidate lines
1992–1994	100/152	424/424
1995–1997	100/497	500/559
1998–2000	100/502	431/471
2001–2003	100/296	347/347
2004–2006	100/172	364/364
2007–2009	100/273	376/376
2010–2012	100/255	224/224
2013–2015	100/199	245/245
2016–2018	100/151	224/224
2019–2020	100/112	119/119

## Results

A total of 270 and 234 articles in English were retrieved from Medline and Embase, respectively. After duplicate removal, 299 articles remained. Through manual examination, 280 articles were further excluded because of their irrelevance to SHLI. The remaining 19 articles (<30) were not sufficient to build a separate scientific map, and the full texts were retrieved to provide background information for the qualitative discussion.

A total of 811 articles were retrieved. The number of resulting nodes and lines before merging are shown in Table 1. A knowledge map showing how the field of SHLI progressed over time was successfully generated.

#### General features of the retrieved articles

The types of studies in the 811 retrieved articles included clinical studies ( $n = 614$ ), animal experiments ( $n = 45$ ), *in vitro* experiments ( $n = 16$ ), processing and detection techniques ( $n = 126$ ), and literature reviews ( $n = 10$ ) (Fig. 1A). The number of articles on a yearly basis peaked in the year 2000, followed by a sharp decrease until the number essentially plateaued during the first ten years of the 21st century with modest fluctuations. However, the last decade has seen a steady decline in the number of articles (Fig. 1B). The journals publishing the 8 highest numbers of SHLI articles are shown in Fig. 1C, with the *Heilongjiang Medicine Journal* ranking highest ( $n = 33$ ). The research institutes of the first authors who published SHLI articles are overwhelmingly located in Heilongjiang Province, China (Fig. 1D).

#### General features of the keyword co-occurrence network

A pair of different nodes with the same notation “双黄连粉针” and “双黄连粉针剂” was identified and manually merged as one node. Finally, 551 nodes with 746 lines were included for generating the network shown in Fig. 2. The largest node “Shuanghuanglian powder injection” is located in the middle right of the picture, which represents the highest frequency of usage. The red peripheral ring of this node indicates significant burstiness meriting further exploration. The node’s inner rings with a variety of different colors indicate the consistent focus on this topic over 24 years, but we can also determine that this keyword was most frequently used from 1995 to 1998 because the thickest ring is a light blue color. Other nodes with a relatively large size can also be readily identified. To explore the importance of the nodes in terms of frequency and burstiness, the values of nodes with  $F > 20$  are shown in Table 2 and values of nodes with  $B > 3.0$  are shown in Table 3. No values for  $\sigma > 10$  were found, indicating a lack of novelty in the topics in the field of SHLI.

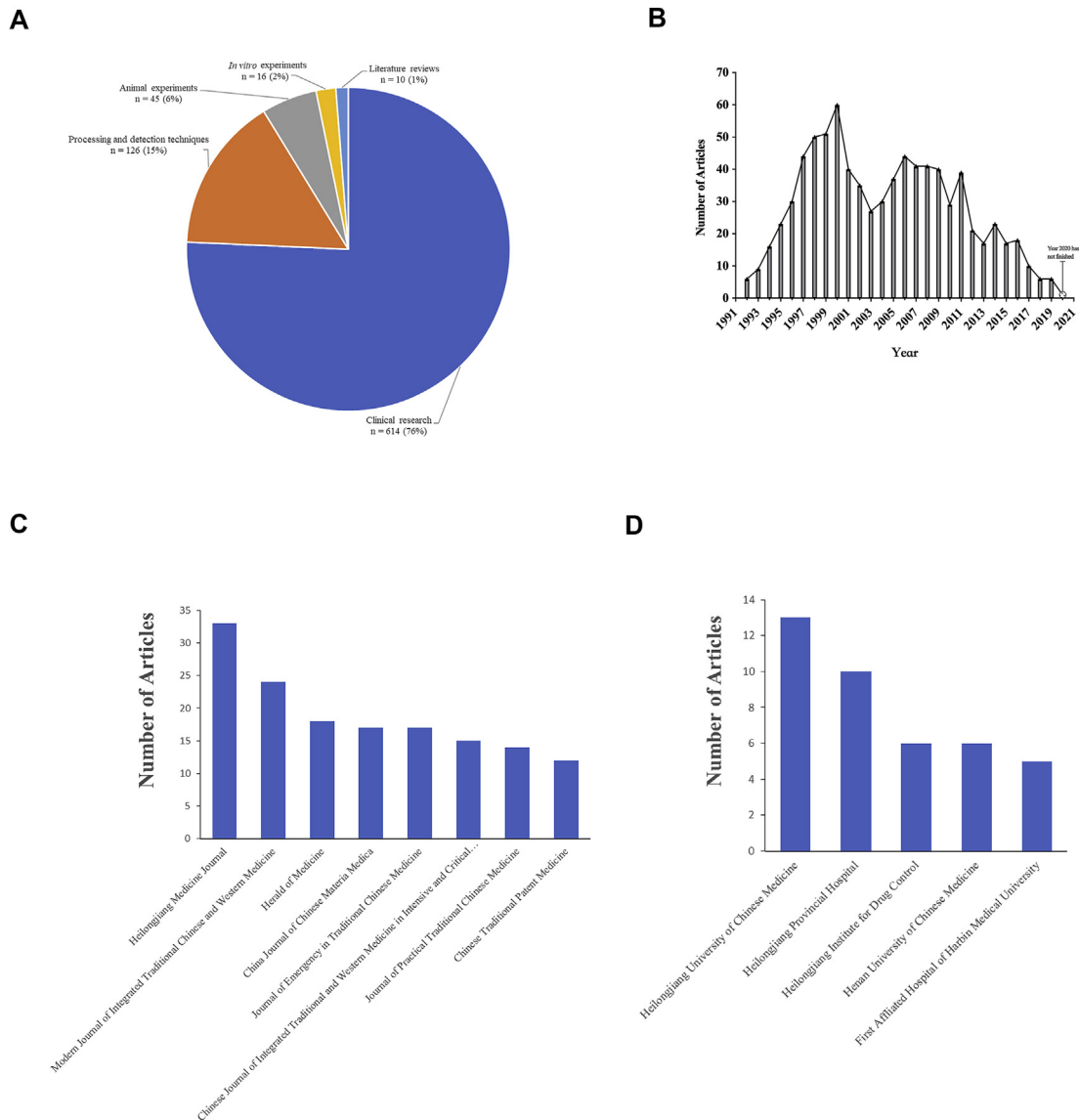
#### General features of the network with clustered keywords

The network with clustered nodes is illustrated in Fig. 3. The overall  $Q$  and  $S$  values were 0.73 and 0.68, respectively, indicating a successful clustering. Six individual clusters were found to have a meaningful field focus (Table 4).

## Discussion

#### General features of the included articles

Among the 811 included articles, the largest number of articles was on clinical research, followed by processing and detection techniques. Laboratory experiments only comprised 7.5% of the total.



**Fig. 1.** General bibliometric features of the retrieved articles. (A) The types of published studies; (B) The yearly trends in the numbers of published articles from 1992 to 2020; (C) Top 8 journals that published the largest number of SHLI-focused articles; (D) Top 5 institutes where the largest number of the first authors of the published SHLI-focused articles are based.

It can be seen that before the year 2000, most SHLI studies focused on clinical and production techniques rather than laboratory experiments. In contrast to modern medicine, where novel drugs are generally developed by the synthesis of artificial compounds with no previous evidence of their safety, traditional Chinese medicine (TCM) has had thousands of years of clinical application, which may minimize concerns over severe adverse effects. This makes a thorough exploration into the mechanism of action of Chinese medicines (CM) less appealing to TCM researchers than a clinical demonstration of their putative efficacy, and even less appealing to pharmaceutical enterprises compared with optimizing techniques for production.

Interestingly, as SHLI was proven to be not as safe as previously thought, from two reports from the National Center for ADR Monitoring, China in 2004 and 2009,<sup>32,33</sup> interest was again directed into the area of clinical studies, because post-market reevaluation of the medicine began to appear necessary. This further added to the

number of clinical studies. Modest peaks in the number of published SHLI studies were seen soon after these reports were published, indicating that these trends may be the result of concerns over severe adverse drug events with SHLI. This effect also corresponds with the high burstiness of the keyword “Clinical observation” ( $B = 7.35$ , 2006–2019).

In the province where most manufacturers have production licenses for SHLI and also where the severe adverse events were reported, it is reasonable that local institutes will have a strong interest in SHLI studies. This local interest is demonstrated by the fact that, of the top five institutes where the largest number of the first authors of the published SHLI-focused articles is based, four are in Heilongjiang Province. This also corresponds to the high burstiness of the keyword “The 2nd CM pharmaceutical factory of Harbin” ( $B = 9.83$ , 2008–2019) and the high frequency of the keywords “adverse events” and “The 2nd CM pharmaceutical factory of Harbin”.

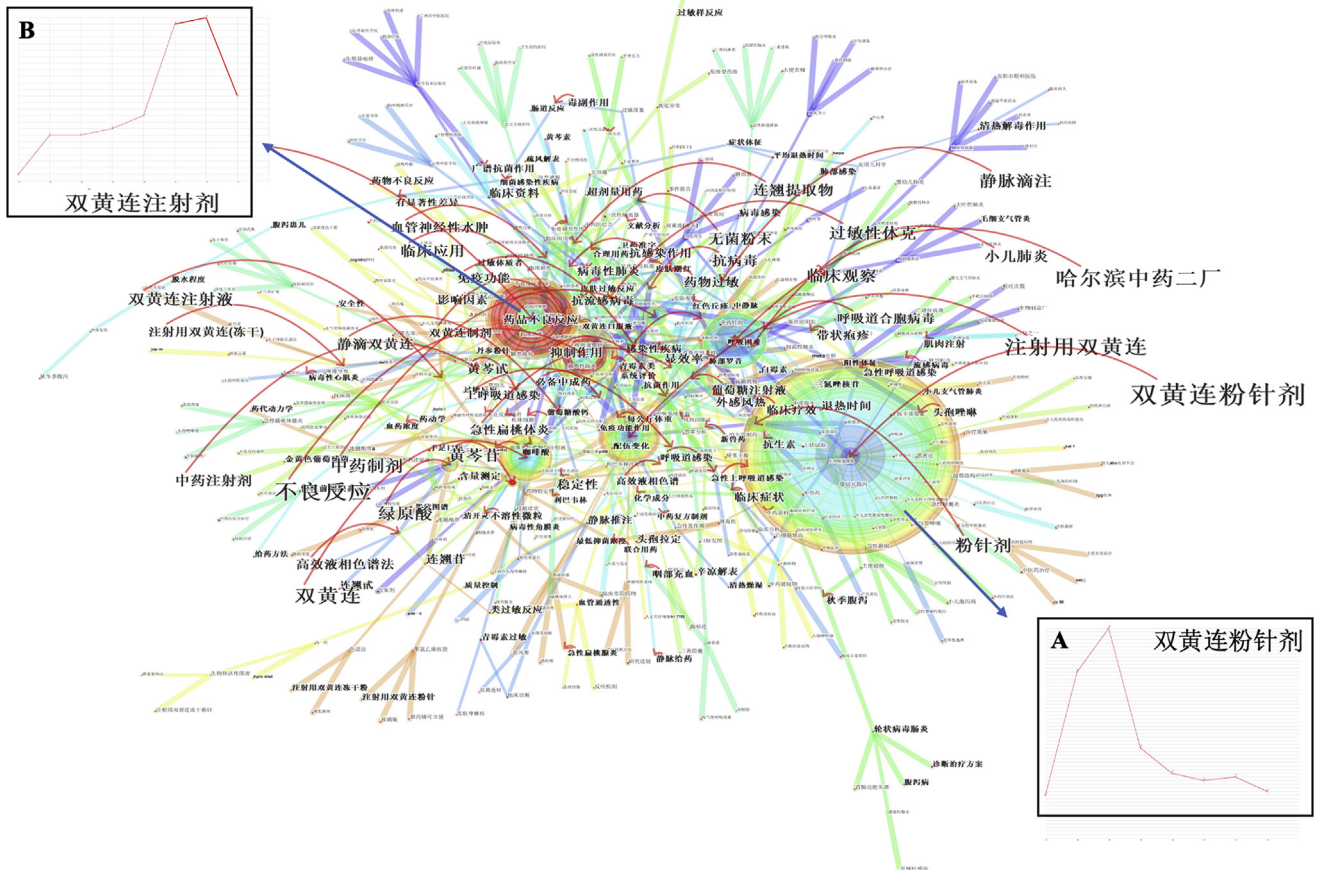


Fig. 2. CiteSpace-generated keyword co-occurrence network.

**Table 2**  
Nodes with frequency higher than 20.

Frequency	Node*	Cluster
235	Shuanghuanglian powder injection	#0
112	Shuanghuanglian injection	#3
104	Adverse effect	#4
94	Shuanghuanglian for injection	#4
85	The 2nd CM pharmaceutical factory of Harbin	#14
79	Shuanghuanglian	#2
42	Powder injection	#12
39	Prepared CM remedy	#1
31	Cholorogenic acid	#6
29	Intravenous infusion	#1

**Note:** \*Node names in this column were originally displayed in Chinese Characters, herein they are presented in English for the ease of readers. CM: Chinese medicine.

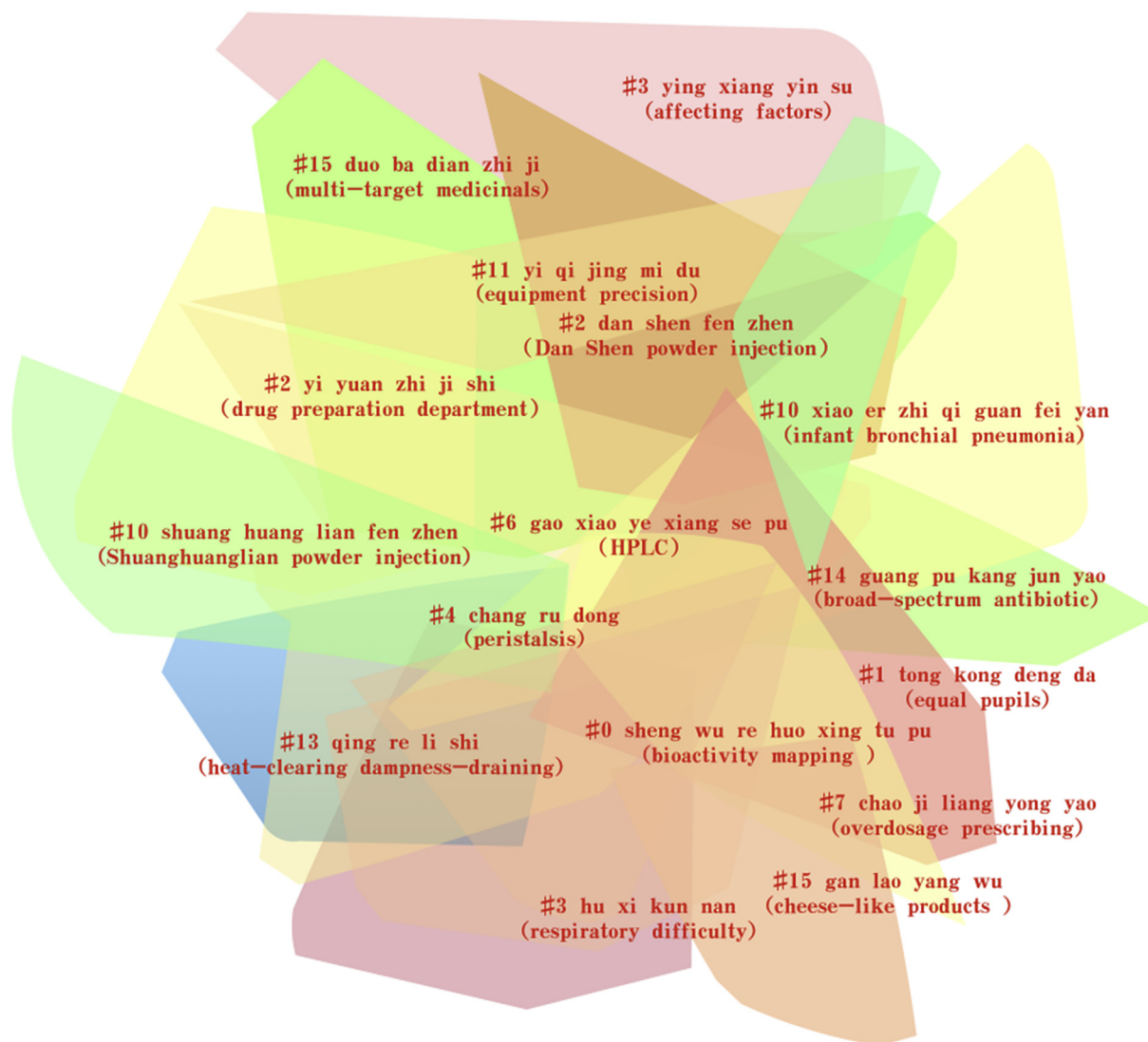
**Table 3**  
Nodes with burstiness values higher than 3.0.

Node*	Used year	Burstiness	Duration	Cluster
Shuanghuanglian injection	1992	11.39	2008-2019	#3
The 2nd CM pharmaceutical factory of Harbin	1992	9.83	1993-1997	#14
Adverse effect	1992	7.35	2008-2011	#4
Shuanghuanglian powder injection	1992	5.22	1998-2000	#0
Baicalin	1992	4.79	2006-2019	#6
Clinical observation	1992	4.57	1993-1998	#8
Shuanghuanglian for injection (under lyophilization)	1992	3.59	2010-2019	#11
Affecting factors	1992	3.42	2010-2019	#9

**Note:** \*Node names in this column were originally displayed in Chinese Characters, herein they are presented in English for the ease of readers. CM: Chinese medicine.

Exploring the topic categories for SHLI studies

The identified meaningful clusters may point to particular areas of research focus because each cluster is considered to be a group of tightly coupled keywords based on topic interconnectivity. A thorough exploration of the clusters under the computer-aided guidance of multiple cluster labels can lead to information on the studies of SHLI. Note that, as has been pointed out by the developer of CiteSpace, cluster labels chosen from the computer-aided algorithms tend to be more specific terms than those chosen by human experts. Interpretation from a multi-label perspective has the potential to provide additional insights complementary to bias-prone expert reviews, and provides a support for interpreting the nature of specialties.<sup>37</sup>



**Fig. 3.** CiteSpace-generated network with clustered keywords.

**Note:** Cluster names in this picture were originally displayed in Chinese Characters, herein they are presented in both Pinyin and English for the ease of readers. HPLC: high performance liquid chromatography.

**Table 4**

The six individual clusters that demonstrated meaningful field focus.

Cluster number	Number of nodes contained	Sihouette	tf*idf-generated label*	LLR-generated label*
0	56	0.99	Bioactivity mapping	Shuanghuanglian sterile injection powder
1	45	0.91	Equal pupils	Allergic shock
2	44	0.87	Drug preparation department	Shuanghuanglian for injection
3	43	0.85	Difficulty in respiration	Keratitis
4	37	0.88	Peristalsis	Shuanghuanglian for injection administration
5	33	0.94	Danshen powder injection	Powder injection

**Note:** \*Node names in this column were originally displayed in Chinese Characters, herein they are presented in English for the ease of readers. LLR: log-likelihood ratio.

#### Cluster #0

The largest cluster, #0, starts in 2006 and contains 56 key words (Fig. 2 and Table 4). The tf\*idf-generated label “bioactivity fingerprint” represents a widely-adopted methodology for research into SHLI, and it is very interesting to find that the label “lyophilized SHLI powder for injection” generated by the LLR algorithm corresponds to the form of the drug used in this methodology. Thus, the interest in this area is to be expected.

Bioactivity fingerprint analysis is a quality control model that

builds upon spectroscopic and chromatographic technologies, which is different from traditional quality control models in the sense that fingerprinting looks at the “complete information” or comprehensiveness of the chromatogram, and displays integrated quality information.<sup>38</sup> Fingerprint analysis was introduced to the study of SHLI and many other herbal medicines because this analysis can be better adapted to CM than conventional methods as it analyzes the overall effective components of an individual herb or a combination of herbs. For example, Wen used an immune

fingerprint to screen for the allergenic components of SHLI by enzyme-linked immunosorbent assay (ELISA) combined with high performance liquid chromatography (HPLC)/mass spectrometry (MS), and 22 components in SHLI were found that could be adsorbed by specific anti-IgE antibodies and the sensitization of SHLI could be changed by different administration methods.<sup>39</sup> The use of a bioactivity fingerprint is regarded as a great improvement from the conventional modern drug-centered single component analysis for herbal medicine, the efficacy of which partly depends on how the components work together.

In addition to the stimulus provided by its sound compatibility with CM, bioactivity fingerprint analysis has support from China's governmental funding and international regulations. In 2002, National Medical Products Administration launched an initiative in collaboration with 48 academic institutions to perform fingerprint identification on 74 types of CM injection (CMI), including SHLI (a lag effect is expected, which causes this analysis to appear as a research focus in 2006). The bureau also issued the Guideline for Standardized Procedure of Chinese Medicine Fingerprint Test, and designed two pieces of software for Fingerprint-based CM Similarity Detection.<sup>38</sup> The guideline provides clear requirements and procedures for laboratory and instrumentation facilities, sample and reference collection and preparation, proper conditions for testing, operational processes, and the methods for result verification and checking. The software is able to compute and compare an entire body of CM chromatographic peaks, so that component fingerprint similarity can be quantified. These research efforts have contributed to a rigorously-designed, technically-sound platform for the practice of CM fingerprinting, and a good number of studies have been performed. Outside of China, fingerprinting is listed in the US Food and Drug Administration's Guidance for Industry Botanical Drug Products (drafted in 2000), the World Health Organization's Guidelines for the Assessment of Herbal Medicine (1996), the British Pharmacopoeia (1986), the Indian Pharmacopoeia (1998), and the US Pharmacopoeia (1999–2001).<sup>38</sup> The objectives of these guidelines are to address the uncertainty and variation in the chemical components of medicinal plants and to enhance the authentication and control of the quality of herbal extracts. Thus, at least to some extent, interest has been aroused in SHLI fingerprinting in the hope that SHLI might enjoy an internationally wider acceptance.

#### Cluster #1

Cluster #1 comprises 45 key words. The labels together indicate that this cluster focuses on the ADRs of SHLI (Fig. 2 and Table 4). Over the past decades, the clinical applications of CMIs have experienced robust growth with ever-improving quality control and processing techniques. However, this growth has been accompanied by an increasing number of reports of ADRs, which has aroused considerable safety concerns.<sup>40</sup> From the LLR-generated labels of this cluster, we were able to identify that the most frequently reported ADR was “anaphylactic shock”, which was first reported in 1993.<sup>41</sup> The tf\*idf-generated label “equal pupils” is an important physical examination for anaphylactic shock, indicating the emphasis on the surveillance of this reaction during the clinical application of SHLI. Unfortunately, the concerns from an academic perspective were justified by the occurrence of several severe ADRs arousing public interest between 2006 and 2009. Because of the increasing number of extremely serious ADRs, the Chinese government temporarily suspended sales of four types of CMIs, including SHLI. A previous literature review found a decrease in the literature reporting an ADR from CMIs, including SHLI, after sales were suspended.<sup>40</sup> To further advance the development of CMIs, a comprehensive clinical reappraisal of CMIs is urgently needed to guide the clinical application of CMIs and reduce the

incidence of ADRs.<sup>42</sup>

#### Cluster #2

Cluster #2 is labeled as “Shuanghuanglian injection” by LLR and as “hospital drug preparation room” by tf\*idf, indicating concerns regarding the preparation of SHLI (Fig. 2, Table 4). Indeed, the standardized preparation of the drug requires uniform cleanroom management and a low possibility of drug mixture contamination.<sup>43</sup> As CMIs mostly contain complex ingredients, the preparation processes are varied. The compatibility of different solvents, or if the mixtures are left standing for a long time after preparation, may cause the precipitation of certain ingredients through chemical or physical changes and thus increase the amount of particulate matter.<sup>44</sup> This is particularly the case for the preparation of CMIs, such as SHLI, which intrinsically have components of mixed properties. A systematic review highlighted the fact that particulate matter present in SHLI will increase in amount after being prepared as an infusion, and using normal saline as the solvent can minimize the amount of particulate matter.<sup>45</sup> The study also found significant variations in the SHLI components among different producers and among different batches of the same producer. Therefore, to reduce the incidences of ADRs, it is crucial that the solvent selection for SHLI should be strictly in accordance with the manufacturer's instructions, and the time of the drug injection after preparation should be carefully controlled.<sup>46</sup>

#### Cluster #3

It is interesting that the labels generated by the two algorithms for this cluster have considerably different connotations (Fig. 2). The tf\*idf gives “difficulty in breathing”, which relates to an ADR, whereas LLR gives “keratitis”, one of the indications of SHLI (Table 4). By closer exploration of the articles, we found that this cluster focuses on clinical trials of SHLI that tested both its efficacy and safety. Most CMIs, such as SHLI, are produced, sold, and marketed based on putative, empirical effectiveness without first demonstrating safety and efficacy through clinical trials, as is required for pharmaceutical drugs.<sup>47–49</sup> With growing interest in the therapeutic effectiveness of SHLI, and safety-based concerns, increasing efforts have been directed toward acquiring scientific proof and conducting evidence-based evaluations regarding the efficacy and safety of SHLI.

#### Clusters #4 and #5

These two clusters, unlike the broader perspectives of the four clusters described above, provide a further breakdown of the research topics of SHLI (Fig. 2). Cluster #4 identifies interest in a very promising new indication, intestinal peristalsis, as labeled by td\*idf (Table 4). Intra-abdominal adhesions following abdominal surgery represent a major unsolved problem, with a high reported incidence of 90%–100% in patients who undergo abdominal surgery,<sup>50,51</sup> and no appreciably effective medicine has yet been developed.<sup>52</sup> Some studies have reported the effectiveness of peristalsis in preventing the symptoms of intra-abdominal adhesions by overcoming the obstruction.<sup>53</sup> According to the theory of TCM, SHLI may exert effectiveness by eliciting the peristaltic action of the intestines. This possibility has attracted a number of experimental and clinical studies on the topic with satisfactory results being obtained.<sup>54</sup> Such studies are especially meaningful, because they explore the use of CMIs for patients who have conditions where there are no known effective treatments or when standard therapies have not been tolerated or have failed to lead to improvements.<sup>54</sup> As can be identified from both the labels (Table 4), studies from cluster#5 investigated the effectiveness of SHLI when used in tandem with compound Danshen in dealing with a variety of heat-toxin-based diseases or symptoms, including pain after



radiotherapy for nasopharyngeal carcinoma,<sup>55</sup> chronic pelvic inflammatory disease,<sup>56</sup> and acute viral myocarditis.<sup>57</sup> Interestingly, the underlying rationale for combining these seemingly unrelated types of medicine derives from the TCM theory that removing blood stasis enhances the clearance of heat-toxin (heat-toxin in the sense of TCM is arguably similar to inflammation in modern medicine).

It is very interesting that, among the six categories of topics identified by CiteSpace, four (#0–#3) focus on providing evidence for, or enhancing the quality of, SHLI from a “purely” science-based perspective, whereas two (#4–#5) focus on seemingly modern studies following an ancient TCM rationale. This is a vivid reflection of the status quo of the entire CM research area, where there exists a dispute over whether or not ancient TCM theory should be adhered to in scientific studies. In recent decades, the adherence to TCM theory has been declining. In the present analysis, the number of SHLI studies conducted from a CM perspective alone was not sufficient to form a cluster, and the researchers in CM must conduct studies under the framework of scientific methodologies. However, even the aggregation of positive results from studies of CM cannot contribute to any validation of ancient TCM theory, because evidence supporting the efficacy of a medicine does not extrapolate back to the authenticity of any historical putative theories. Researchers still need to focus on validation of the theory itself.

#### *Exploring the importance of keywords*

The importance of an individual keyword to the entire network can be determined by the frequency and burstiness. Keywords with high importance can be considered to represent hotspots in the field.

#### *Frequency*

The most frequently used keyword ( $F = 235$ ) is “Shuanghuanglian powder injection”, followed by “Shuanghuanglian injection” ( $n = 112$ ). Because the meanings of these keywords are seemingly similar, we conducted further exploration using the Pennant Diagram Function of CiteSpace for individual node observations. We found that the term “Shuanghuanglian powder injection” is typically used in articles focusing on the pharmacological effects and chemical components of SHLI, while “Shuanghuanglian injection” is most strongly related to reviews and reports on the safety, clinical practice, and head-to-head trials. The use of these different terms is understandable because “Shuanghuanglian injection” may imply a broader connotation that covers all the derivative products. However, we believe the standardization of the medicinal names for SHLI is necessary.

The 3rd most frequently used keyword is “Adverse events”. The safety concerns regarding SHLI have been elaborated in the section on *Cluster #1*, and it is not surprising to find that these concerns are reflected in the keyword usage.

The 4th most frequently used keyword “The 2nd CM pharmaceutical factory of Harbin” reflects the source of the medicine used in studies. This is very interesting because in general for the study of chemical drugs, the use of a drug manufacturer as a keyword does not make any sense, whereas it is a common practice in CMI studies. The reason for this is probably because the chemical components of a CMI vary greatly between different manufacturers. Despite years of effort in fingerprint component identification, the components of SHLI have not yet been standardized and we believe that this is a problem meriting further exploration.

The 9th most frequently used keyword “Cholorogenic acid” is one of main chemical components of SHLI that both exerts the therapeutic efficacy,<sup>58</sup> and accounts for some of the side effects, such as allergy.<sup>59</sup> Many herbs contain pharmacologically active

compounds, such as cholorogenic acid, and some herbs may cause side effects through excessive biological effects.<sup>45</sup> This problem is also found in the development of chemical drugs, where it is termed as “off-target” effects.

Other high-frequency keywords, such as “Shuanghuanglian” (6th), “Powder injection” (7th), and “Prepared CM remedy” (8th) do not indicate very useful notions for exploration of the field. We would expect the use of such words because sometimes authors select one or two keywords that are only used to define the field of study.

#### *Burstiness*

Unlike frequency, which indicates a stable field of interest from some keywords, burstiness looks at statistically significant fluctuations in keyword usage over a short period of time. Similar to the frequency, some of the burstiness detected may be the result of the high prevalence of the keywords used for defining the field increasing in parallel with the growth in the entire number of articles in the field. Therefore, we excluded some keywords from further discussion, including Shuanghuanglian injection, Shuanghuanglian powder injection, and Shuanghuanglian for injection (under lyophilizing).

The keywords “The 2nd CM pharmaceutical factory of Harbin” ( $B = 9.83$ , 2008–2019; the background of its use as a keyword has been discussed in the section on Frequency) and “Clinical observation” ( $B = 7.35$ , 2006–2019) highlight the focus on investigating the efficacy of SHLI through clinical trials, starting from 2006 to the present. This focus indicates that although there are a number of limitations and criticisms of applying evidence-based medicine to the study of CM,<sup>60–62</sup> the position of evidence-based medicine as the gold standard of clinical practice may continue exerting leverage on SHLI studies, if not the entire CM field. Promising results from a recent study have shown that the family of SHL formulations, including SHLI, may have an inhibitory effect on SARS-CoV-2.<sup>23,24</sup> Thus, we can expect a further surge in the burstiness of this keyword in the coming months, or even years.

The surging of the keyword “Adverse effect” (7.35) during 2008–2011 corresponds to several serious ADR events arousing public interest over roughly the same time period. The influence of publicized events on the focus of academic research has already been identified in a previous study on terrorist attacks, and it is not unexpected to find a similar trend in the healthcare area.

The keyword “Baicalin” ( $B = 4.79$ , 2006–2019), as one of the major therapeutic chemical components of SHLI, corresponds to the fingerprint analysis and other SHLI studies at a chemical level. The use of this keyword is evidence for the prevalence of applying modern methodologies and perspectives to SHLI studies that echoes the popularity of general-level evidence-based studies.

The keyword “Affecting factor” (3.42, 2010–2019) is not so self-explanatory, so we conducted further exploration of the articles using this keyword. We found that this keyword is used to describe the multiple causes of the adverse effects of SHLI. Years of efforts to determine the chemicals in SHLI that cause the ADRs has not yet revealed a definitive culprit. In recent years, some researchers have begun to investigate multi-factorial causes for the ADRs of SHLI, such as variations in the manufacturing techniques, product storage conditions, and susceptibility of individuals.

From the frequency and burstiness analyses, we found an increasing trend for studies that explore SHLI using modern methodologies from science-based perspectives. Another hotspot is the safety of SHLI, with the focus shifting from single-factorial to multi-factorial possibilities.

#### **Conclusion**

By conducting bibliometric research, the evolution route of

hotspots in research, as well as the major topic categories of SHLI studies were determined. The hotspots evolved along with increasing awareness of the safety and efficacy of SHLI. In the field of SHLI study, there are five major topic categories: bioactivity fingerprint; ADR mechanism and cause detection; proper preparation; clinical evidence accumulation; and efficacy in diseases with no effective treatment and combination usage. Further analysis should focus on these five major topic categories to accurately determine the branched hotspots of SHLI studies. According to the current analysis, it can be assumed that the trend for using modern methodologies from science-based perspectives to study SHLI will continue. The new perspective of multi-factorial causes for ADRs may also be a focus for future studies.

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## Declaration of competing interest

The authors declare no conflict of interest.

## CRediT authorship contribution statement

**Qin Zhang:** Conceptualization, data curation, methodology, formal analysis, and writing – original draft. **Guang Rong:** Conceptualization, software, visualization, and writing – review & editing. **Qinggang Meng:** Conceptualization, supervision, and funding acquisition. **Mang Yu:** Data curation, project administration, and methodology. **Qingyu Xie:** Software and visualization. **Jian Fang:** Formal analysis.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jtcm.2020.05.006>.

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