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

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Abstract— Efforts are being made to investigate the mechanical characteristics of Cenosphere and e- galass fibres reinforced Al7075 in this current project. Cenosphere, a low-density, low-cost reinforcing material, is a byproduct of coal combustion in thermal power plants and is readily accessible. As a result, Al 7075 metal matrix with cenosphere as reinforcement can easily overcome the cost barrier and may serve as the best supplement with varied physical and mechanical qualities for servicing a broad variety of applications providing wide usage in today's world. Variations in the E-glass and cenosphere were used to create the specimens. The specimens used in the tensile test were constructed in accordance with ASTM specifications. Improved features including improved specific strength, specific modulus, damping capacity, and superior wear resistance may be achieved by using metal matrix composites (MMCs) instead of ordinary alloys. The great strength-to-weight ratio of aluminium composite MMCs makes them the most popular.

Key words: Al7075 alloy composite, E-glass, MMCs, and short E-glass fibres

have cast doubt on SHLI's safety. Future research would benefit from a streamlined synopsis of the SHLI studies that have already been published

new studies, particularly those that are inherently unquantifiable and unrepeatable, like qualitative reviews.

A bibliometric approach has been proposed as a means of explaining this "quality crisis" and providing an alternative in situations when there is not enough information to conduct a review study. Researchers in the SHLI field have documented such bibliometric studies that use the prevalence of keywords in published articles as measures of

While the quantity of published papers in a given field of study doubles every eight years,[7] it is becoming more and more challenging to conduc

the scope of the study.[8,9] Although this is a new field of study, there are a few caveats to keep in mind, such as the limited number of indicators and the lack of consistency between them. neglected to do study on the field's outline, which includes concepts like innovation, progress, bottlenecks, and hotspots. To overcome these shortcomings, one solution is to implement scientific mapping based on the notion of a complex network. This technique can visualise

aspects of a pool of articles that are not visible using more traditional methods.103rd day Scientific mapping is able to depict the development and structural links of subjects in a certain field by examining knowledge domains.14 Insights into new information and underexplored areas of study may be revealed by this mapping, which reveals the interconnections, overlaps, interactions, and evolution of knowledge units. One of the applications made to enable scientific mapping is CiteSpace, which has seen widespread usage across various domains.15 One famous contemporary formula, Shuanghuanglian (SHL), is made from three medicinal herbs: scutellaria (Scutellaria baicalensis Georgi), honeysuckle flower (Lonicera japonica Thunb.), and forsythia fruit (Forsythia suspensa (Thunb.) Vahl).16 Oral liquid, injectable, pill, and tablet are some of the dosage forms of SHL that have been produced so far. For the treatment of bacterial and viral respiratory illnesses, including tonsillitis, pneumonia, and upper respiratory tract infections, SHLI is often administered as a solution or powder.17 According to traditional Chinese medicine, SHLI dissipates harmful heat and toxicants and dissipates wind heat. In 2001 and 2009, there were reports of serious adverse drug reactions (ADRs) to SHLI, including allergic reactions and dyspnea.Research in both the lab and the clinic has shown that SHLI is effective in reducing viral replication and lung damage (18, 19).20,21 The use of SHLI to treat COVID-19 infections is also very promising. Because vaccinations and particular medications take months, if not years, to produce, one of the main ways to deal with a newly emerged virus is to look into current medications and other substances that might work as effective remedies.22 The Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai, China) and the Wuhan Institute of Virology, CAS (Wuhan, China) collaborated on a research that discovered that SHL oral liquid, an oral formulation that uses the same chemicals as SHLI, might suppress SARS-CoV-2.23,24. We anticipate that this discovery will refocus attention on SHL formulations, particularly SHLI, on a global scale. Research on SHLI has been well documented, and it would be helpful for researchers to have a scientific map that shows the development and structural linkages of these studies. Therefore, the purpose of this study is to examine the development and emerging trends in SHLI hot topics by creating a CiteSpace term co-occurrence map of SHLI studies.

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 pub- lished 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 arti- cles. 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 vali- dated, 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 data- base. 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 ≥30. If the number of citations was <30 we quit the mapping, but still used these articles as back- ground 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 in- formation regarding these parameters and their functions can be found in a previous report.[15] As is recommended by the developer of CiteSpace[15] and in accordance with previous studies,[25e29] 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,[30] (c) burstiness (abbreviated as B),[30] (d) modularity (Q),[31] (e) silhouette (abbreviated as S),[30] and (f) qualitative results of representative labels generated by two types of algorithms (tf*idf[32] and log-likelihood ratio (LLR)[33]).

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 ampli- tude 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,[34–36] 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 e1 to 1, respec- tively. 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,[12] 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 assump- tions; therefore, their results can be complementary to each other.

Network layouts and representation

The resulting keyword co-occurrence map shows various in- formation 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 character- izes 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 conno- tation are manually merged by the "Alias List" function as described in a previous report.[15] 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 upper- most 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 thick- nesses. 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 auto- matically by the LLR algorithm. The results of the two other text- mining algorithms can be explored through several more mouse clicks.[15]

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 remain- ing 19 articles (<30) were not sufficient to build a separate scientific map, and the full texts were retrieved to provide background in- formation 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 ¼ 614), animal experiments (n ¼ 45), *in vitro* experiments (n ¼ 16), processing and detection techniques (n ¼ 126), and literature reviews (n ¼ 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 ¼ 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 gener- ating the network shown in Fig. 2. The largest node "Shuan-ghuanglian 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 merit- ing 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 uccessful 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.

Time slice	Selected lines/Candidate nodes		Selected lines/Candidate lines
1992e1994	100/152		424/424
1995e1997	100/497		500/559
1998e2000	100/502		431/471
2001e2003	100/296		347/347
2004e2006	100/172		364/364
2007e2009	100/273		376/376
2010e201	100/255	224/224	
2013e2015	100/199	245/245	
2016e2018	100/151	224/224	
2019e2020	100/112	119/119	
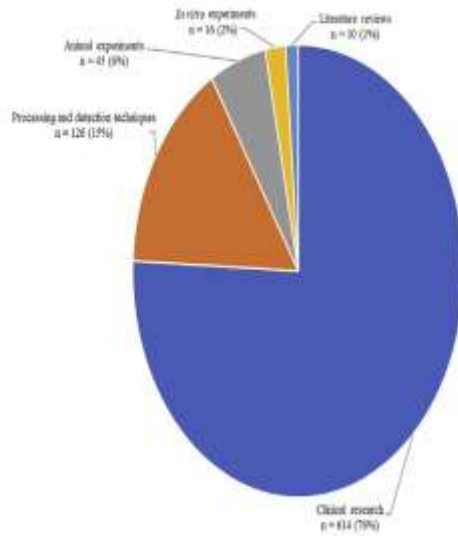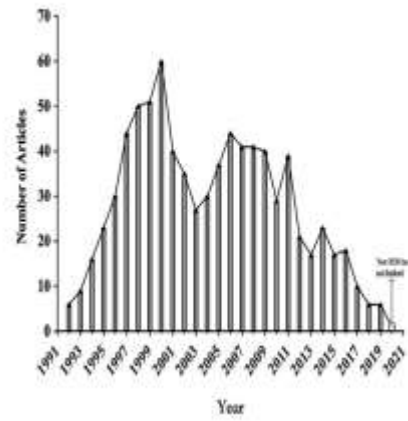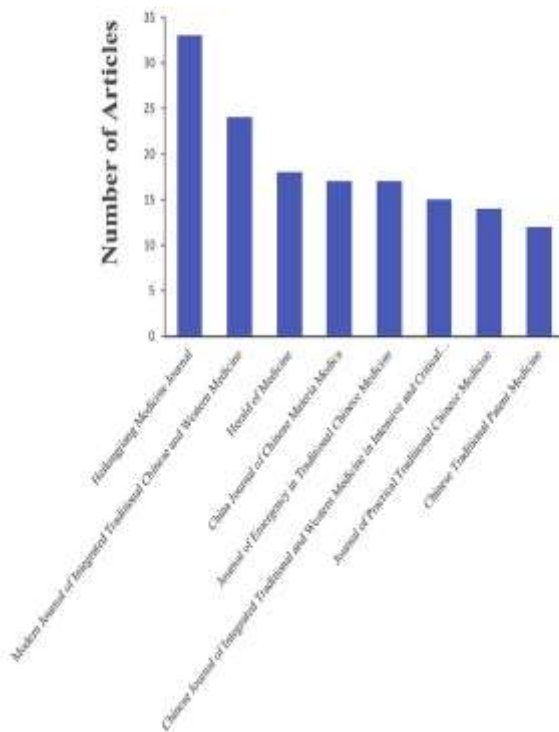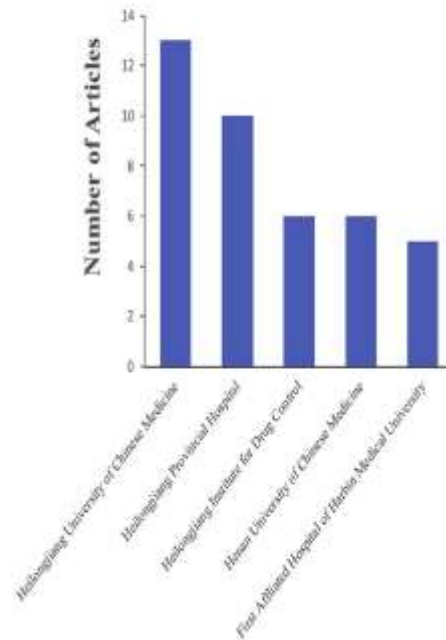
Fig. 1. General bibliometric features of the retrieved articles. (A) The types of published studies; (B) The yearly trends in the numbers of published articles from 1992 to 2020; (C) Top 8 journals that published the largest number of SHLI-focused articles; (D) Top 5 institutes where the largest number of the first authors of the published SHLI-focused articles are bas

It can be seen that before the year 2000, most SHLI studies focused on clinical and production techniques rather than labora- tory experiments. In contrast to modern medicine, where novel drugs are generally developed by the synthesis of artificial com- pounds with no previous evidence of their safety, traditional Chi- nese 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 opti- mizing 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 Moni- toring, China in 2004 and 2009,[32,33] 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 keywords "adverse events" and "The 2nd CM pharmaceutical fac- tory of Harbin"

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 se- vere adverse drug events with SHLI. This effect also corresponds with the high burstiness of the keyword "Clinical observation" (B ¼ 7.35, 2006e2019).

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 ¼ 9.83, 2008e2019) and the high frequency of the

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.

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 algo- rithms tend to be more specific terms than those chosen by human experts. Interpretation from a multi-label perspective has the po- tential to provide additional insights complementary to bias-prone expert reviews, and provides a support for interpreting the nature of specialties.[37]

Table 3
Nodes with burstiness values higher than 3.0.

Node*	Used year
Shuanghuanglian injection	1992
The 2nd CM pharmaceutical factory of Harbin	1992
Adverse effect	1992
Shuanghuanglian powder injection	1992
Baicalin	1992
Clinical observation	1992
Shuanghuanglian for injection (under lyophilization)	1992
Affecting factors	1992

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.
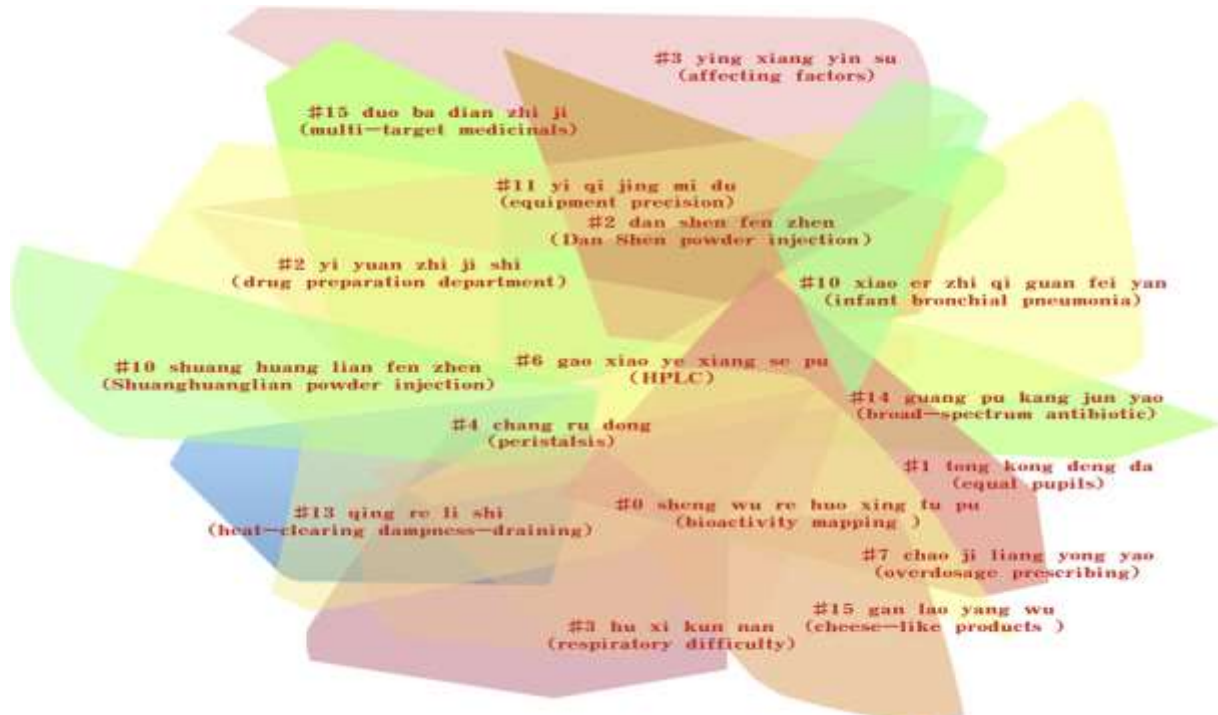

Fig. 3. CiteSpace-generated network with clustered keywords.
Note: Cluster names in this picture were originally displayed in Chinese Characters, herein they are presented in both Pinyin and English for the ease of readers. HPLC: high performance liquid chromatography.

Table 4
The six individual clusters that demonstrated meaningful field focus.

Cluster number	Number of nodes contained	Sihouette	tf*idf-
0	56	0.99	Bioact
1	45	0.91	Equal
2	44	0.87	Drug
3	43	0.85	Difficu
4	37	0.88	Perista
5	33	0.94	Dansh

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 finger- print" 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 corre- sponds 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.[38] 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.[39] 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, Na- tional 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 Simi- larity Detection.[38] 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 verifi- cation 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 Or- ganization's Guidelines for the Assessment of Herbal Medicine (1996), the British Pharmacopoeia (1986), the Indian Pharmaco- poeia (1998), and the US Pharmacopeia (1999e2001).[38] The ob- jectives 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 interna- tionally 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.[40] 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.[41] The tf*idf-generated label "equal pupils" is an important physical examination for anaphylactic shock, indi- cating 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.[40] 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.[42]

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 contamina- tion.[43] As CMIs mostly contain complex ingredients, the prepara- tion 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 chemi- cal or physical changes and thus increase the amount of particulate matter.[44] This is particularly the case for the preparation of CMIs, such as SHLI, which intrinsically have components of mixed prop- erties. 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.[45] 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 in- structions, and the time of the drug injection after preparation should be carefully controlled.[46]

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 mar- keted based on putative, empirical effectiveness without first demonstrating safety and efficacy through clinical trials, as is required for pharmaceutical drugs.[47–49] 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%e100% in patients who undergo abdominal sur- gery,[50,51] and no appreciably effective medicine has yet been developed.[52] Some studies have reported the effectiveness of peristalsis in preventing the symptoms of intra-abdominal adhe- sions by overcoming the obstruction.[53] 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 exper- imental and clinical studies on the topic with satisfactory results being obtained.[54] 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 im-

provements.[54] 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,[55] chronic pelvic in- flammatory disease,[56] and acute viral myocarditis.[57] 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 (#0e#3) focus on providing evidence for, or enhancing the quality of, SHLI from a "purely" science-based perspective, whereas two (#4e#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 evi- dence supporting the efficacy of a medicine does not extrapolate back to the authenticity of any historical putative theories. Re- searchers 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

"Shuanghuanglian injection" (n = 112) is the second most common term, with "Shuanghuan-glian powder injection" being the most used (F = 235). Given the apparent similarity in meaning between these phrases, we dug deeper into the CiteSpace Pennant Diagram Function for specific node observations. We observed that "Shuanghuanglian powder injection" is commonly used in articles discussing the chemical components and pharmacological effects of SHLI, whereas "Shuanghuanglian injection" is more commonly associated with safety, clinical practice, and head-to-head trials. Since "Shuanghuanglian injection" can convey a more general meaning that encompasses all the derivative products, the usage of these distinct titles is reasonable. Our position is that SHLI's medical names should be standardised. The term "Adverse events" ranks third in terms of frequency of use. As mentioned in the section on Cluster #1, the safety concerns about SHLI are evident in the keyword use. This should come as no surprise.

Research medication comes from the 2nd CM pharma-ceutical plant of Harbin, which ranks as the fourth most popular term. Using a drug manufacturer as a keyword is frequent in CMI research, but it often makes little sense for the study of chemical medications, so this is rather intriguing. This is likely due to the fact that various manufacturers employ vastly different chemical components while making CMIs. We think this is an issue that needs further investigation because, after years of work on fingerprint component identification, SHLI components still haven't been standardised.

Among the most common search terms, "chlorogenic acid" ranks ninth. This molecule is an important part of SHLI, which is responsible for its medicinal benefits and some of its negative effects, such allergies.59 A number of plants include chlorogenic acid or other pharmacologically active components, and an overabundance of these actions in particular herbs might lead to unwanted side effects.45 This issue, known as "off-target" consequences, is also present in the process of developing chemical medications.

Similarly unhelpful ideas for field research are suggested by other frequently used keywords like "Shuanghuanglian" (ranked 6th), "Powder injection" (7th), and "Prepared CM remedy" (8th). We should anticipate their use since, on occasion, writers may choose only one or two keywords to characterise the area of research.

The bursting
In contrast to frequency, which shows a consistent interest area for certain terms over time, burstiness examines statistically significant fluctuations in keyword use over brief intervals. The high prevalence of the field's defining keywords growing in tandem with the total number of articles in the field may explain, like frequency, some of the burstiness noticed. Shuanghuanglian injection, Shuan-ghuanglian powder injection, and Shuanghuanglian for injection (under lyophilizing) were therefore omitted from the subsequent discussion. The emphasis on studying the effectiveness of SHLI through clinical trials, beginning in 2006 and continuing to the present, is emphasised by the keywords "The 2nd CM pharmaceutical factory of Harbin" (B ¼ 9.83, 2008e2019; the history of its usage as a keyword has been covered in the section on Frequency) and "Clinical obser-vation" (B ¼ 7.35, 2006e2019). While there are valid concerns about using evidence-based medicine to study CM, this emphasis suggests that evidence-based medicine's status as the clinical practice gold standard might keep impacting SHLI studies and the field of CM as a whole. The SHLI family of SHL formulations may suppress SARS-CoV-2.23,24 according to promising results from a recent investigation. So, in the next months—or maybe even years—the explosiveness of this term will continue to soar. Several major adverse drug reaction (ADR) instances that garnered public attention between 2008 and 2011 coincide to the surge of the term "Adverse effect" (7.35). While a prior study on terrorist incidents did reveal that news coverage affected the emphasis of academic research, it would not be surprising to see a same pattern in the healthcare sector. The fingerprint analysis and other chemical-level SHLI research are related to the term "Baicalin" (B ¼ 4.79, 2006e2019), which is one of the main therapeutic chemical components of SHLI. Similar to the popularity of evidence-based studies at the general level, this keyword's usage in SHLI research indicates that researchers are increasingly bringing new ideas and methods to the table.

Since the term "Affecting factor" (3.42, 2010e2019) does not really provide a clear definition, we dug deeper into the papers that used it. We discovered that this term is often used to describe the many sources of SHLI's negative effects. The compounds in SHLI that cause the ADRs have not been identified after years of research. A number of studies in recent years have started to look at potential multi-factoral causes of SHLI ADRs, including differences in production methods, storage conditions, and individual vulnerability.

We observed a rising trend in research that investigate SHLI utilising current approaches from science-based viewpoints, as shown by the frequency and burstiness analyses. The safety of SHLI is another area of intense interest, with researchers beginning to rule out single-factor to multi-factor explanations.

Conclusion

Bibliometric analysis helped identify the main subject categories of SHLI studies and the historical trajectory of research hotspots. As the benefits and safety of SHLI were more widely recognised, the hotspots changed in response. Bioactivity fingerprint, adverse drug reaction (ADR) mechanism and cause identification, appropriate preparation, clinical evidence collection, and effectiveness in illnesses with no effective therapy and combination use are the five main areas of focus in SHLI research. In order to identify the specific areas of SHLI research that need more investigation, academics should zero in on these five broad subject areas. The present

investigation suggests that the current trend towards studying SHLI using cutting-edge approaches grounded on scientific principles will likely persist. Future research may also concentrate on the novel understanding of ADRs as having several causes.

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