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Original Paper

Based on the Molecular Mechanism of CiteSpace Sanqi Total Saponin and the Prevention and Treatment of Renal Fibrosis, Hot Spot Visualization Analysis

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Abstract

This study aims to study the current situation, hot spots and development trends of Sanqi total saponins in the prevention and treatment of renal fibrosis through a visual map, in order to provide a direction and trend for the research of traditional Chinese medicine on the prevention and treatment of renal fibrosis. Method: By using CiteSpace visualization software, the relevant literature on the use of Sanqi total saponins in the CNKI database for the treatment of renal fibrosis was visually analyzed, including posting trends, authors, institutions and keywords, and the corresponding knowledge map was generated. Results: From 2005 to 2022, a total of 1,533 documents were included in the research results. From 2008 to 2017, an average of 99 articles were published every year, accounting for 67.5% of the total number of articles published. Among them, the number of articles published in 2010 and 2013 reached 114, the highest in previous years. At the same time, Yang Min is the author who has published the most articles, with a total of 29 papers. Beijing University of Traditional Chinese Medicine is the main research institution in this field. Through cluster analysis of research hotspots, ten clusters were obtained, including rats, left ventricular reconstruction, oxidative stress, drug interaction, astragaloside, apoptosis, matrix metalloproteinase-9,oleoside, lipopolysaccharide, atherosclerosis, etc. Future research focuses include oxidative stress, autophagy process, Sanqi total saponins,

inflammatory response, cell proliferation and apoptosis, and pharmacokinetics. Conclusion: The knowledge map reveals the research status and research hotspots of Sanqi total saponins in the prevention and treatment of renal fibrosis, including oxidative stress, inflammation, cell proliferation and apoptosis, which will become the focus of research on the prevention and treatment of renal fibrosis in traditional Chinese medicine in the future. However, the collaboration between research authors and scientific research institutions lacks closeness, lacks core authors, and has not yet formed an influential research organization. The depth and breadth of research need to be further enhanced.

Keywords

Panax notoginseng total saponins, CiteSpace, molecular mechanism, prevention and control, visual analysis

1. Introduction

Radix Notoginseng is the root of the genus Panax in the Araceae family. It has the effects of nourishing the body, stopping bleeding, promoting blood circulation, eliminating swelling and relieving pain. Mainly produced in Yunnan, Guangxi, Sichuan and other places, it is a traditional Chinese medicinal herb.

Panax notoginseng is a kind of medicinal herb with complex chemical composition, which contains a series of active substances such as saponins, panax notoginseng, amino acids, flavonoids, phytosterols, volatile oils, trace elements and so on. Panax notoginseng total saponins are the main physiological active substances in Panax notoginseng, which include a variety of monomer saponins, including Rbl, Rb2, Rc, Rd, R93, Rh2 and so on. They are the effective active ingredients extracted from Panax notoginseng in the Araceae family. A modern pharmacological study has found that the drug has a variety of effects, such as vasodilation, improvement of microcirculation disorders, reduction of myocardial oxygen consumption, inhibition of platelet aggregation, prolongation of coagulation time, reduction of blood lipids, scavenging of free radicals, anti-inflammatory and anti- oxidation. These effects may help to improve the microcirculation of the fundus and the ischemic and hypoxic state of the retina. This article briefly summarizes the research status of Panax notoginseng total saponins in the prevention and treatment of renal fibrosis, and discusses the potential mechanism of its effects on hyperlipidemia, hypertension, myocardial ischemia, anti-shock, arrhythmia, atherosclerosis, cardio-cerebral ischemia, renal fibrosis, anti-thrombosis, anti-inflammation, swelling and analgesia, immune regulation and intelligence. After summarizing the published literature, this paper summarizes the pharmacological effects of Panax notoginseng total saponins (PNS). Through the use of CiteSpace visualization software, a large number of scientific literature can be intuitively displayed on the atlas through a reasonable and ingenious spatial layout, so as to quickly understand the structure, rules and distribution of scientific knowledge. In this way, the time and energy of reading literature can be saved, and the main research directions and achievements can be quickly understood. The amount of literature on the prevention and treatment of clinical diseases with Panax notoginseng total saponins is large,

which is very time-consuming and labor- intensive to read. The use of CiteSpace visualization software can help people to master the relevant scientific knowledge more quickly.

2. Materials and Methods

2.1 Data Collection

Data were obtained from CNKI; Literature type: journal literature; Language: Chinese; Search style: Subject = (" renal fibrosis "+" hyperlipidemia "+" hypertension "+" myocardial ischemia "+" arrhythmia "+" atherosclerosis "+" renal fibrosis "+" cardio-cerebral ischemic "+" arrhythmia ") and full text = (" notoginseng "+" notoginseng total saponin "+" pharmacology "+" traditional "+" prescription "+" single taste traditional Chinese medicine (TCM) ", "effective traditional

Chinese medicine "Materia medica" + "Chinese patent medicine" + "prescription" + "single Chinese medicine" + "effective extract of Chinese medicine" + "anti-thrombosis" + "anti-inflammation" + "swelling and analgesia" + "immune regulation"); The retrieval time span: January 2005 to December 2022. The literature search time was December 16, 2022.

2.2 Literature Processing and Data Download Format

Refworks was used to export the literature to download_***.txt format files, and then CiteSpace5.8.R3 software was used to convert the raw data to Webof Science format, and CiteSpace5.8.R3 was used for analysis.

2.3 Parameter Settings

(1) CiteSpace software data setting, analysis type: author cooperation (including author, institution and country); Co-occurrence (author key words); Counting method: complete counting; Threshold selection: the minimum number of papers (author, institution, country) is 6; The remaining parameters were set as the default Settings of the software.

(2) CiteSpace software data Settings, time slice: from 2005 to 2022, every 2 years as a time slice; Node type: keywords; Extract node threshold: Top 50 per slice; Pruning options: Minimum spanning tree + merge pruned network; The remaining parameters are set to the default Settings of the software.

3. Get Results

3.1 Annual Trend Chart of Publications

From January 2005 to December 2022, a total of 1533 North Nuclear and CSSCI papers on Panax notoginseng total saponins in the prevention and treatment of renal fibrosis were published in China. After excluding 67 duplicate, irrelevant and missing articles, 1466 articles were finally included in the journal. Figure 1 shows that from 2005 to 2007, the number of articles published was less than 50, which was the early stage of the study. During the period of 2007-2008, the development speed was very fast, and the number of articles published continued to increase, with an average of more than 80 articles published per year. From 2008 to 2017, the number of papers published remained stable and fluctuating, with an average annual number of 99 papers, accounting for 67.5% of the total number of

papers published. Among them, the annual number of published papers in 2010 and 2013 both reached 114, which was the highest in the past year. The main type of published papers was clinical research. According to the statistics of the number of articles published each year, a trend chart of the publication was made, as shown in Figure 1 for details.

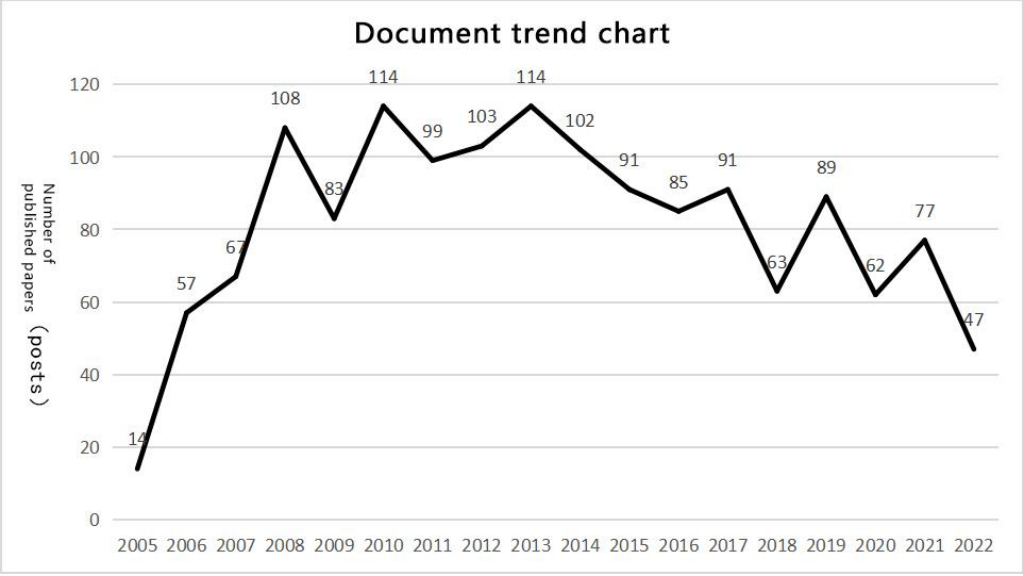

Figure 1. Trend Chart of Publications on Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022

3.2 Collinear Map of Authors' Cooperation

Analyzing the authors and their cooperative relationships can help us to fully understand the core academic groups and high-yield authors in the field of Panax notoginseng total saponins research. CiteSpace software (version 5.8.R3) was used to import the data into CiteSpace after standardized processing of sample literature. In the CiteSpace tool, select "Author" as the analysis project, set the time range from 2005 to 2022 in the database analysis, and select the parameter k=6. In this way, a co-occurrence map of authors related to Panax notoginseng total saponins can be generated (see Figure 2), where each node represents an author, and the lines between nodes represent the cooperative relationship between different authors. The results of operation show that the network contains 146 nodes, 171 lines, and the network density is 0.0162. In the research field of Panax notoginseng total saponins in the prevention of renal fibrosis, the authors selected 146 authors through the co-occurrence knowledge graph, and 171 connections were established between them. The number of articles published by the top six authors was Yang Min (29 articles), Deng Changqing (28 articles), Huang Xiaoping (22 articles), Fu Yongsheng (19 articles), Deng Zhijun (16 articles), and Guo Jiewen (15 articles). The number of papers published by high-yield authors in this field is small, and the number of papers published by the first six authors only accounts for 8.8% of the total literature, which indicates that the number of core authors is insufficient. For authors who published at least 4 articles, the visual

analysis of the cooperative network was performed, in which the size of nodes represented the number of papers published by the authors, and the lines between nodes represented the strength of cooperation. From the figure, it can be clearly observed that the gray cluster is the largest group, in which Yang Min is the largest node, representing the largest number of his publications. The members who form a stable research group with him include Fu Yongheng, Pan Jingqiang, Deng Zhijun and Guo Jiewen, among others. The main research direction of this team is the mechanism and efficacy of Panax notoginseng total saponins in the prevention and treatment of RF. There is relatively much cooperation within the team, but there is a lack of cooperation lines between various teams, so the core research team needs to be formed. See Figure 2 for the number of articles and cooperation among literary authors.

Figure 2. Author Network of Literature on Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022 2.3 Map of Literature Institutions and Cooperative Relationships

It is helpful to understand the overall situation of the core research institutions of Panax notoginseng total saponins in the field of renal fibrosis research through effective analysis of the publishing institutions and their cooperative relationships. CiteSpace software was used to standardize the sample literature, and the data were imported into it. Select "Institution" as the analysis item in the CiteSpace tool, and when analyzing the selected database, the time range is 2005-2022. By drawing the co-occurrence map, the overall distribution of institutions related to the research field of Panax notoginseng total saponins in the prevention and treatment of renal fibrosis can be analyzed. Universities and affiliated hospitals are not merged, but other secondary units of the same institution can be merged. Each node in the figure represents a research institution, and the lines in the figure reflect the cooperative relationship between different institutions. The running result is the number of

nodes N=111, the number of connections E=36, and the network Density Density=0.0059. In the field of Panax notoginseng total saponins in the prevention and treatment of renal fibrosis, an author's co-occurrence knowledge map selected 111 institutions and established 36 connections between these institutions. According to the number of publications, the top six institutions were: Beijing University of Chinese Medicine (23 articles), Guangzhou Hospital of Traditional Chinese Medicine (19 articles), Guangxi University of Traditional Chinese Medicine (13 articles), Guangzhou University of Traditional Chinese Medicine (12 articles), Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine (11 articles), and Medical Research Center of Guangdong General Hospital (8 articles). Traditional Chinese medicine universities and their affiliated hospitals are the main research institutions, and institutions in Beijing and Guangzhou have published more articles than those in other provinces. Guangzhou University of TCM has quite a number of cooperative ties. As shown in the figure, the pathophysiology laboratories of Beijing University of Traditional Chinese Medicine, Guangxi University of Traditional Chinese Medicine and Hunan University of Traditional Chinese Medicine, which have a high number of publications, mainly cooperate with institutions in the same region, but have less cooperation with other institutions. See Figure 3.

Figure 3. Institutional Cooperation Network of Panax Notoginseng Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022

3.3 Keyword Analysis

3.3.1 Co-occurrence Analysis of High-frequency Keywords

When analyzing the knowledge graph, the research topics and research hotspots of a certain field can be obtained through the keyword analysis. In the keyword contribution network picture constructed by

Citespace software, each node represents a keyword, and the size of the node reflects the frequency of keyword occurrence. The resulting Keyword co-occurrence map is shown in the following figure, which is obtained through the "keyword" function of Citespace. According to this data, it can be observed that there are 188 nodes in the graph, which are connected to each other by 195 lines, and the network density is 0.0111. See Figure 4.

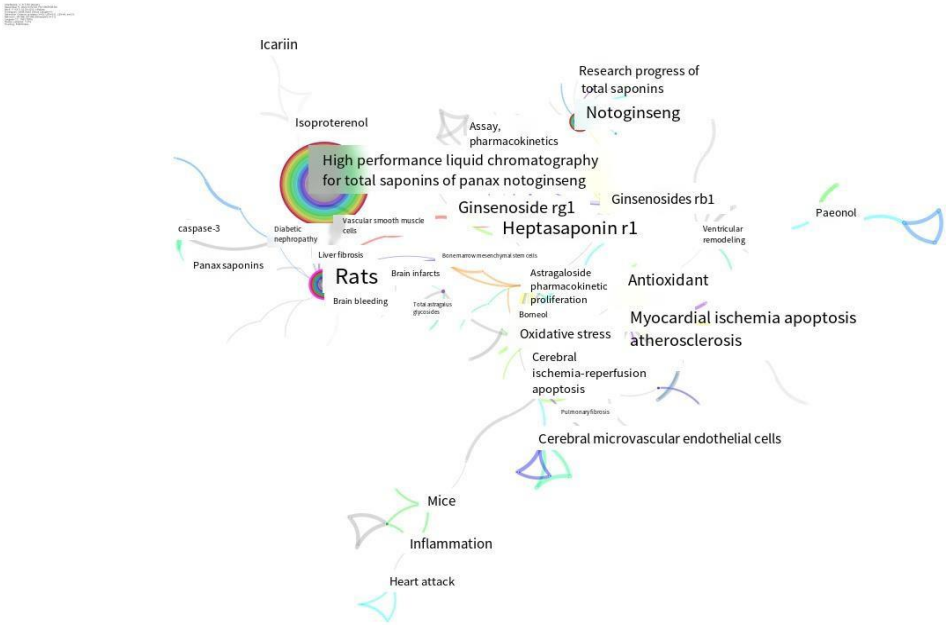

Figure 4. Keyword Co-occurrence Network of Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022

The top 10 keywords in terms of frequency and centrality were screened out. High-frequency keywords represented the hotspots and trends of scientific research, and keywords with intermediate centrality no less than 0.01 were of great significance. Meaningless keywords were required to be deleted, abbreviations, synonymous academic words and synonyms were merged, and keywords with frequency ≥9 were counted. Keywords included Panax notoginseng total saponins, rat, oxidative stress, apoptosis, astragaloside iv, cerebral ischemia- reperfusion, proliferation and antioxidant, and these keywords were related to mediation center. See Table 1.

Table 1. High Frequency Keywords of Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis (Frequency ≥9)

Serial number keywords centrality frequency	Serial number keyword centrality frequency
1 Panax notoginseng total saponins 0.15 1216	11 Ventricular remodeling 0.24 22
2 rats 0.62 105	12 Astragaloside iv 0.69 21
3 panax notoginseng 0.12 87	13 Proliferation 0.28 20

4 Oxidative stress 0.28 40	14 Content determination 0.03 16
5 Ginsenoside rg1 0.02 38	15 Research progress 0.01 11
6 Apoptosis 0.28 37	16 Inflammation 0.05 9
7 Cell apoptosis 0.11 24	17 mice 0.13 9
8 Panax notoginsenoside r1 0.15 24	18 Diabetic nephropathy 0.11 9
9 Cerebral ischemia reperfusion 0.27 24	19 Icariin 0.02 9
10 Atherosclerosis 0.01 23	20 Antioxidant 0.27 9

3.3.2 Keyword Cluster Analysis

After keyword clustering analysis using CiteSpace5.8.R3, a knowledge map was generated containing high-frequency keywords of Panax notoginseng total saponins prevention and control research from 2005 to 2022. The name of each cluster was the keyword with the highest frequency in the cluster. Each cluster represents a row, and the wider the line drawn in the time region, the closer the cluster is. The tightness from high to low was "#0 rat", "#1 left ventricular remodeling", "#2 oxidative stress", "#3 drug interaction", "#4 astragaloside iv", "#5 apoptosis", "#6 matrix metalloproteinase-9", "#7 Icariin", "#8 lipopolysaccharide", and "#9 atherosclerosis". In the upper left panel, the number of network nodes is 188, the number of connections is 195, the network density is 0.0111, the network modularity is 0.8455 (greater than 0.5), and the weighted average contour is 0.9625 (greater than 0.8). Meanwhile, the harmonic mean of Q and S is 0.9002 (greater than 0.8). These results show that the resulting cluster structure is significant and each cluster has sufficient similarity to make the clustering reasonable and convincing. See Figure 4.

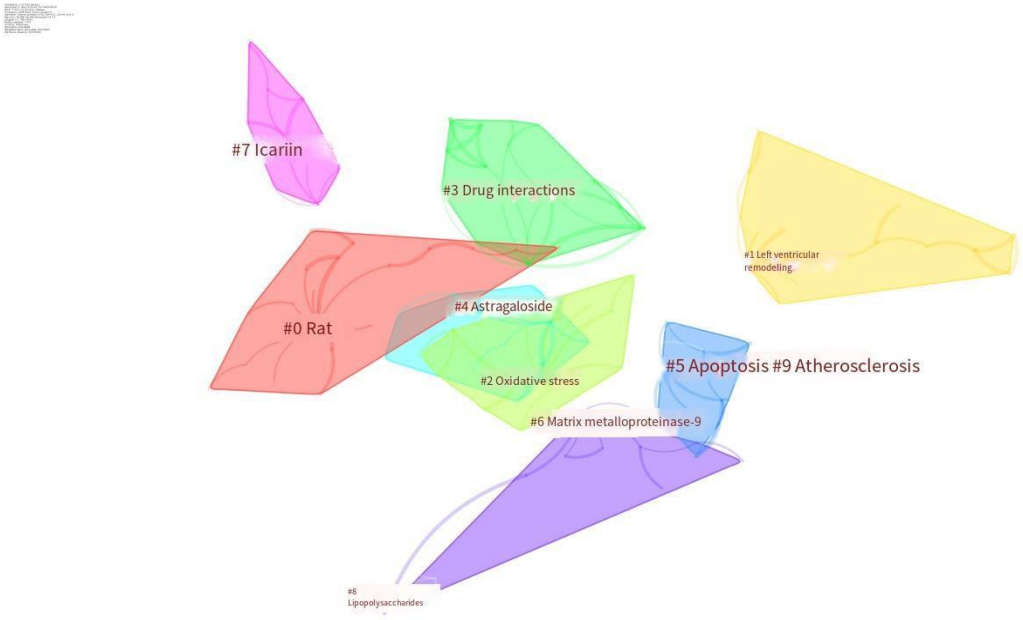

Figure 4. Cluster Diagram of Keywords of Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022

3.3.3 Time Plot Analysis of Keywords

Citespace software was used to make a timeline map to analyze the duration and evolution trend of research hotspots of Panax notoginseng total saponins in the field of renal fibrosis. The evolution map of keywords was arranged from left to right in chronological order, and the size of square nodes in the map was proportional to the frequency of keywords. By using CiteSpace software, the evolution analysis of the research hotspots of the selected literature was carried out. In the time range from 2005 to 2022, the slice length was set to 1, and the node type was set as key words, and the evolution results of the keyword clustering were shown in the figure. There are 188 nodes and 195 lines in the atlas, and the density value is 0.0111. In this case, the Q value is 0.8455, indicating that the divided structure is very obvious. The time plot analysis of the keywords of Panax notoginseng total saponins in the treatment of renal fibrosis can intuitively show the evolution path of each cluster keyword. Certain nodes in Figure 5 are marked with red outer circles, indicating that these nodes are key turning points. The years from 2005 to 2007 were the hot spots of research. During this period, the main directions of attention were liver fibrosis, mechanism of action, Panax notoginseng total saponins, panax notoginseng saponins, ginsenosides, ischemia-reperfusion, and atherosclerosis. From 2007 to 2010, the research focus included nuclear factor-kB, connective tissue growth factor, extracellular matrix, drug interaction, astragalus saponins, experimental research and lipopolysaccharide. From 2010 to 2013, I used proliferating cell nuclear antigen, cytokines, astragaloside iv, bcl-2 and energy metabolism. From 2013 to 2016, thrombin, MMP-9, cardiac fibroblasts, pc12 cells, and inflammatory response were studied. 2016-2019: vascular endothelial growth factor, nf-kb p65, blood-brain barrier, macrophages, renal ischemia-reperfusion injury; 2019-2022 Molecular docking and cerebral ischemia. See Figure 5.

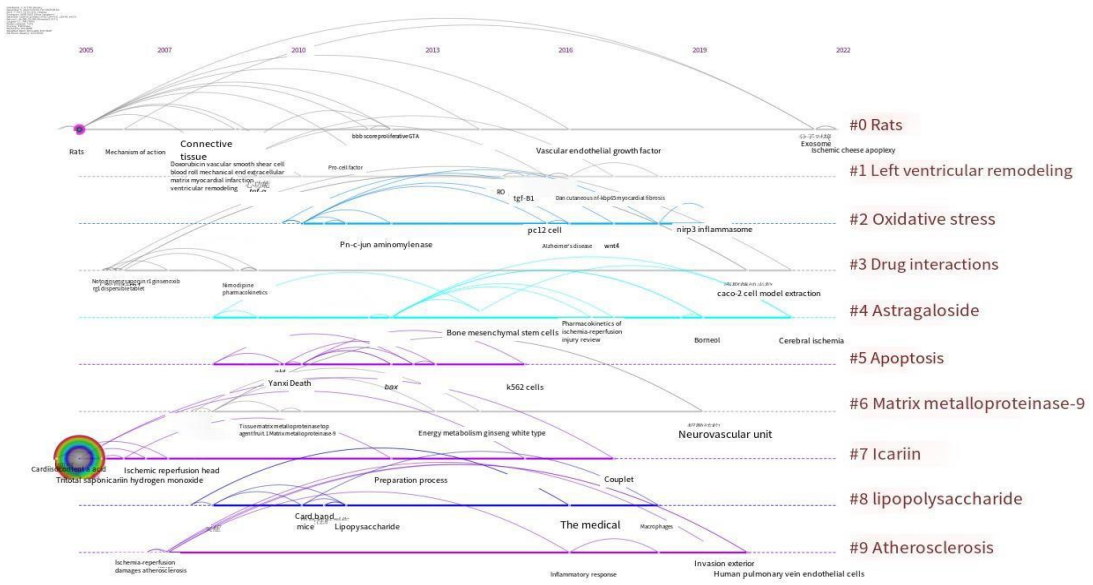

Figure 5. Keyword Time Map of Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022

3.3.4 Time Zone View Analysis

Research hotspots are constantly changing and vary from period to period. CiteSpace software shows the method of Timezone View literature citation network. By collecting keywords in the first time zone, sorting them in chronological order, and generating keywords co-current zone map through beautification adjustment, the research process of hot topics in the time dimension is clearly displayed. According to the co-occurrence of keywords, by setting the time slice to 1 year and keeping the other parameters unchanged, the keyword co-occurrence map was generated by clicking Run. Select "Layout" in the shortcut control panel of the visualization interface, and select "Timezone View" under "Visualizations" to get the original map. By adjusting the parameters to further beautify the map, the hot zone map of the research on pannotoginseng saponins in the prevention and treatment of renal fibrosis from 2005 to 2022 was obtained, as shown in Figure 6.

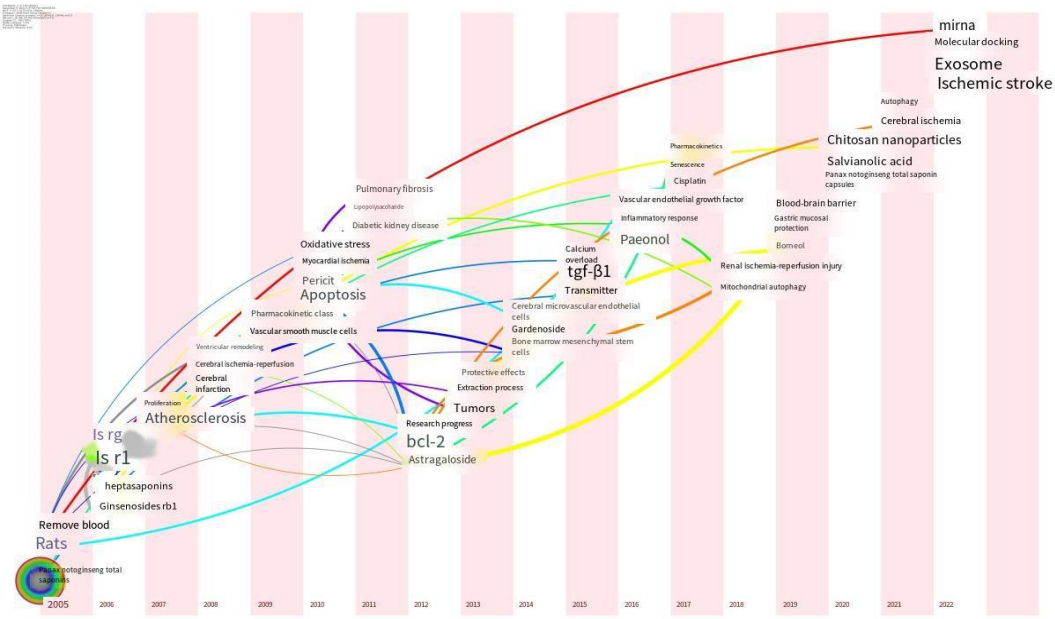

Figure 6. The Visual Area View of Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022

3.3.5 Keyword Emergence Analysis

The above keywords were included in the above keyword co-occurrence map for further processing. Use The shortcut function key "Burstness" of the visual interface to enter the burst detection function area, and modify the parameters, The Number of States=2, γ=0.8, Minimum Duration=3. Then click "View" to view the results of burst detection. In the final results, 24 keywords with high emergence value appeared in the research of Panax notoginseng total saponins in the prevention and treatment of renal fibrosis from 2005 to 2022. The following figure is sorted according to the emergence time of the keywords, and there are a total of 24 high-emergence keywords, arranged in order from far to near. In Figure 7, "Strength" shows the representation of the emergence intensity, where "Begin" and "End"

represent the time points of the emergence start and end, respectively, while the red line segment represents the time period of the emergence.

According to the figure, the keywords with high emergence intensity are "astragalus iv (7.08)", "ventricular remodeling (6.39)", "ginsenoside rg1 (5.96)", "borneol (5.27)", "Panax notoginseng total saponins r1 (4.71)", "brain microvascular endothelial cells (4.51)", etc. This indicated that these keywords were the frontier topics of researchers' attention in the corresponding period. In terms of the time span of burst duration, "ginsenoside rg1 (5 years)", "pharmacokinetics (5 years)", "research progress (4 years)", "pharmacokinetics (3 years)", "vascular smooth muscle cell (3 years)", "high performance liquid chromatography (3 years)", and "panax notoginsenoside r1 (2 years)" lasted longer. This means that these fields have been the focus of scholars for a long time, and some of them are even hot topics.

Frontier keywords will constantly change over time, showing a phased evolution as a whole. Therefore, this study will divide the research frontier of Panax notoginseng total saponins in the prevention and treatment of renal fibrosis according to the time stage. In this process, the keywords that suddenly appeared and had great influence were selected for analysis. It can be clearly seen from Figure 7 that during 2005-2008, the emergence of keywords was mainly focused on the research of Panax notoginseng total saponins on myocardial hypertrophy, atherosclerosis, ventricular remodeling and cerebral infarction. From 2009 to 2011, the research focus was on the pharmacokinetics of ginsenoside, an active component extracted from Panax notoginseng, against vascular smooth muscle cells in mice with myocardial ischemia and pulmonary fibrosis. From 2012 to 2022, the research focus was on the extraction process of Panax notoginseng total saponins, the intrinsic mechanism of action of cerebral vessels, cell proliferation, apoptosis, and pharmacokinetics. A variety of drug-related terms and concepts are covered in the glossary, including apoptosis, research progress, extraction process, brain microvascular endothelial cells, paeonol, pharmacokinetics, astragaloside iv , borneol, proliferation and apoptosis. Among them, oxidative stress, autophagy, Panax notoginseng total saponins, inflammation, cell proliferation and apoptosis are still the research directions and hotspots in the future.

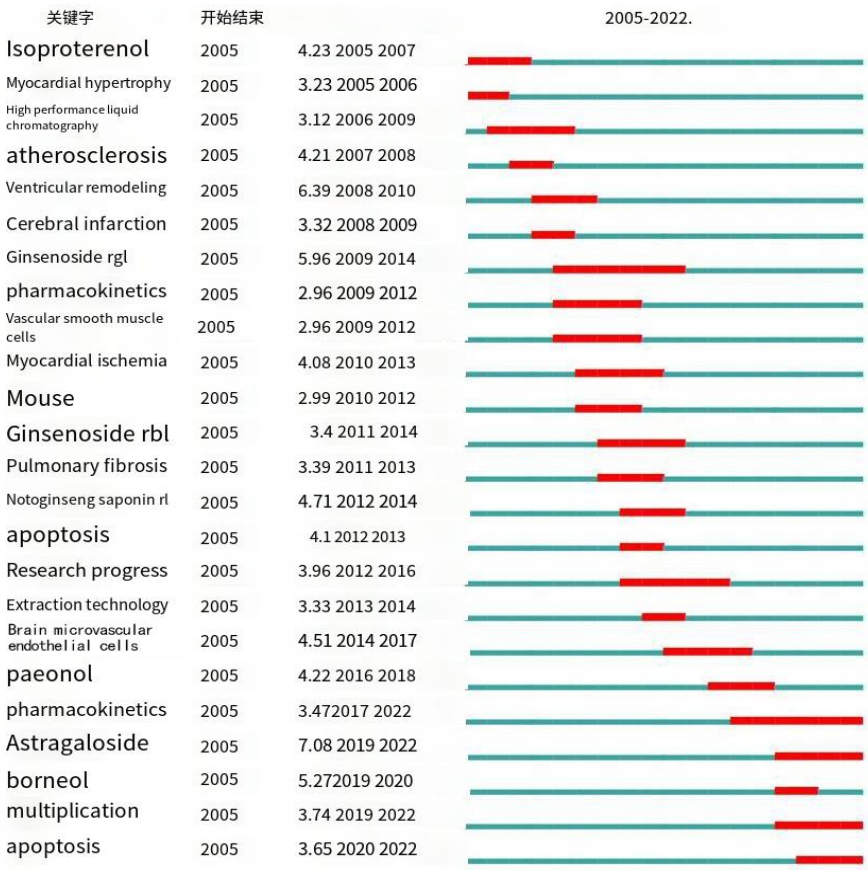

Figure 7. Emergence Diagram of Key Words of Panax Notoginseng Total Saponins in the Prevention and Treatment of Renal Fibrosis from 2005 to 2022

4. Discussion

Renal fibrosis is a chronic progressive fibrotic disease, which is a necessary stage in the development of many chronic kidney diseases. Due to the stimulation of various pathogenic factors such as trauma, infection, inflammation, blood circulation disorders, and immune response, its inherent cells are damaged, and a large number of collagen deposits and accumulation occur in the later stage of development, resulting in gradual sclerosis of the renal parenchyma and the formation of scars, until the kidney completely loses its organ function. The process of fibrosis and sclerosis of intrinsic cells in the kidney is also the process of renal fibrosis, which is characterized by abnormal deposition of extracellular matrix (ECM).

Panax notoginseng, a rare traditional Chinese medicine, has a long history (Yuan, Zhang, Ju, et al., 2021) of being widely used in the treatment of cardiovascular and cerebrovascular diseases, such as coronary heart disease and angina. Panax notoginseng has a long history, which contains saponins with dammarane type tetrocyclic triterpene parent nucleus structure, mainly including ginsenoside Rg1, ginsenoside Rb1, ginsenoside Re, panax notoginseng saponside R1 and ginsenoside Rd (Wang, Guo, Zhou, et al., 2016). These components have been widely used in many fields. In recent years, the

clinical effects of Panax notoginseng total saponins (PNS) and the medicinal materials of Panax notoginseng total saponins have been well studied and verified (Wu, 2011; Tao, Guo, Liu, et al., 2008) in the treatment of RF. Pharmacological studies have found that its mechanism of action is mainly as follows: first, it can reduce the aggregation of inflammatory cells. Second, it can play a role by reducing the expression of rheumatoid arthritis related factors in kidney tissue. Third, it can inhibit the expression of integrin and the fibrosis marker transforming growth factor (TGF) -β1 in the kidney. Fourth, it can inhibit the differentiation of renal tubular epithelial cells. Fifth, it can inhibit the proliferation of human renal interstitial myofibroblasts. Sixth, it can regulate and reduce the accumulation of collagen matrix (Zhang, Yin, Liu, et al., 2012).

4.1 Number of Publications

Bibliometric analysis showed that in the past 17 years, the research literature on the use of Panax notoginseng total saponins in the treatment of renal fibrosis showed a peak from 2008 to 2013, and then the number of publications gradually decreased. Most of the journals mainly focused on the field of clinical research, while some researches focused on other fields such as pharmacokinetics, extraction process and research progress.

4.2 High-yielding Authors and Institutions

Between 2005 and 2022, Yang Min, Deng Changqing, and Huang Xiaoping became the leading researchers in the field, ranking in the top three in terms of the number of publications, indicating their influence in the study of the mechanism of action of TCM. Among them, Yang Min has published the largest number of articles. The idea is that Panax notoginseng total saponins can significantly reduce the progression of renal fibrosis, increase the activity of intracellular superoxide dismutase (SOD), reduce the rate of mitochondrial damage, and improve the viability of damaged cells. In addition, Panax notoginseng total saponins also reduced the expression of extracellular matrix cell adhesion molecule (ICAM-1), monocyte chemoattractant protein 1 (MCP-1) and Caspase-3 in endothelial cells (VEC). Panax notoginseng total saponins can prevent and treat renal fibrosis by improving the antioxidant indexes of damaged cells and reducing the expression of cytokines related to renal fibrosis, thus improving oxidative stress injury of VEC. According to the cited literature, the experimental study of Panax notoginseng total saponins in the prevention and treatment of renal fibrosis and the molecular mechanism of traditional Chinese medicine treatment were mainly studied. The universities, affiliated hospitals and research institutes of TCM in various provinces/cities had formed a cooperative model, and Beijing University of Chinese Medicine was the most prominent institution, followed by Guangzhou Hospital of Traditional Chinese Medicine and Guangxi University of Traditional Chinese Medicine. The cooperation among various institutions is not close, and more is based on internal cooperation, indicating that the research strength of pannotoginseng saponins in the prevention and treatment of renal fibrosis has not yet formed a joint force, which restricts its long-term development to a certain extent. It is necessary to strengthen the communication and cooperation between multiple regions and institutions to promote the continuous progress of research.

4.3 Research Hot Topics

Recent studies have shown that Panax notoginseng total saponins, rat, Panax notoginseng, oxidative stress, ginsenoside rg1, proliferation and apoptosis, Panax notoginseng total saponins r1, and cerebral ischemia- reperfusion have become high-frequency keywords and cluster labels that have received much attention in the research field. These keywords have high centrality, long research span and prominent occurrence frequency in the research field, and have been the research hotspots for a long time.

Panax notoginseng total saponins: can inhibit the proliferation of renal tubular epithelial cells and the secretion of total collagen caused by ureaplasma, thus slowing down the process of renal tubulointerstitial fibrosis and improving renal function. Zhang, Chen, Liu et al. (2005) used flow cytometry and immunofluorescence to detect the effects of Panax notoginseng total saponins at different concentrations on transforming growth factor-β1 (Tgf-β1) -induced α-smooth muscle actin (α-SMA) expression in HK-2 cells. The effects of Panax notoginseng total saponins at different concentrations on TGF-β1-induced α-SMA expression in HK-2 cells were also examined at the gene level by reverse transcription- polymerase chain reaction (RT-PCR). It was found that PNS inhibited Tgf-β1 induced transdifferentiation of HK-2 cells in a time - and dose- dependent manner, and had a certain reversal effect on the transdifferentiation phenotype of HK-2 cells. Based on this finding, it can be speculated that PNS may delay the progression of renal tubulointerstitial fibrosis by inhibiting the transdifferentiation of renal tubular epithelial cells, which may be one of the mechanisms of PNS in the treatment of renal fibrosis. It was found that IL-1α could promote the transformation of renal tubular epithelial cells into myofibroblasts, leading to the expression of α-smooth muscle actin, and also promoting the deposition of extracellular matrix component fibronectin. However, Panax notoginseng total saponins can inhibit the transdifferentiation and extracellular matrix secretion of normal rat renal tubular epithelial cells induced by IL-1α. In addition, the inhibitory effect of PNS on α-smooth muscle actin expression was positively correlated with the inhibitory effect on fibronectin secretion (Wang, Fan, Liu, et al., 2004). Su, Li, Fan et al. (2005) conducted experimental observations to study the effect of Panax notoginseng total saponins on renal interstitial fibrosis in rats with unilateral ureteral obstruction. The results showed that after unilateral ureteral obstruction in rats, renal interstitial fibrosis gradually occurred, and there was an increase in the number of cells with proliferating cell nuclear antigen and the expression of α-smooth muscle actin in the obstructed kidney. However, PNS can significantly inhibit the differentiation and proliferation of renal tubular cells into myofibroblasts, thereby reducing the synthesis of extracellular matrix and alleviating the degree of renal interstitial fibrosis. These results suggest that PNS has a positive effect on renal interstitial fibrosis.

Ginsenoside Rg1: can reduce the excessive secretion of inflammatory factors in the process of renal fibrosis, reduce the infiltration of inflammatory cells, reduce the damage of renal intrinsic cells, proliferation and apoptosis abnormalities, and finally reduce the excessive deposition of ECM, glomerular sclerosis, peritubular capillary necrosis and obstruction, and slow down interstitial fibrosis

(Wang & Wang, 2019). Under the stimulation of various pathogenic factors such as infection, inflammation, blood circulation disorders and immune response, the structure of renal tissue changes, produces fibroblasts and epithelial-mesenchymal transition, and promotes the synthesis of ECM. TGF-β and its signal transduction pathway TGF-β/Smad play an extremely key role in the pathological process of renal fibrosis.

Ginsenoside Rg1 can delay renal interstitial fibrosis by increasing the expression of hepatocyte growth factor and inhibiting the expression of TGF-β1 in renal interstitium (Hu, Wu, Li, et al., 2014). The application of Panax notoginseng injection can repair the metabolic disorder (Gao, Wei, Weng, et al., 2013), improve anemia and slow down renal injury in rats with renal interstitial fibrosis. Inhibiting the activation of TGF-β1/P38MAPK signaling pathway may be related to the protection of kidney. PNS can inhibit the transformation of renal tubular epithelial cells to mesenchymal cells and renal interstitial fibrosis by reducing the expression of Tgf- β 1 and Gremlin. Deng (2016) found that Astragalus and Sanqi mixture can improve the renal function indexes of rats with chronic kidney disease, reduce renal pathological damage and collagen deposition area, and delay the progression of renal fibrosis by inhibiting the P38MAPK signaling pathway.

Oxidation and antioxidation: The imbalance of defense mechanisms is the key to the development of renal interstitial fibrosis, and oxidation and antioxidation play an important role in this process. GSH and T-SOD are common antioxidants, and their levels/activities reflect the antioxidant capacity of tissues. MDA, a compound produced by the peroxidative breakdown of arachidonic acid, is used as a primary assessment of oxidative stress. Panax notoginseng total saponins can improve renal injury by increasing glutathione (GSH) level and superoxide dismutase (T-SOD) activity and reducing advanced glycation end products (AGEs) level in rat kidney.

Proliferation and apoptosis: they play important roles in the normal function of the body and the development of diseases. Some researchers have pointed out that there is an imbalance between the development of kidney disease and the abnormal increase and apoptosis of kidney tissue cells. Proliferation of cells present in renal intermediates. The increased secretion of extracellular matrix will affect the local blood supply in the renal interstitium, leading to ischemia and hypoxia of renal tubular epithelial cells, and then cause degeneration and necrosis of renal tubular cells, inflammatory cell infiltration and apoptosis. Bcl-2 and Bax are the key members of bcl- 2 gene family. Bcl-2/Bax is a key factor regulating the degree of cell apoptosis, and Bax plays a crucial role in promoting cell apoptosis. Studies on the mechanism of nephrotoxicity induced by cyclosporine A found that it increased the expression of Bax in the renal tubulointerstitium, while reducing the expression of Bcl-2, resulting in a decrease in the Bcl-2/Bax ratio. These results suggest that apoptosis plays A major role in the renal interstitial fibrosis induced by csa. Recently, Chinese researchers have studied the relationship between renal tubulointerstitial lesions and the progression of chronic kidney disease by using in situ end labeling and immunohistochemistry. Recent studies have shown that renal tubulointerstitial damage and fibrosis are associated with cell proliferation and apoptosis dysregulation. Among them, the moderate

damage of renal tubulointerstitium is mainly manifested by cell proliferation. At the same time, the expression of apoptosis-related gene Bax is also significantly increased in the aggravation of renal tubular lesions. In vivo and in vitro, proximal tubular cells have been confirmed to be the target cells of apoptotic cell death after ischemia and toxic injury. The loss of renal tubular cells due to excessive apoptosis affects the remodeling and effective repair of the kidney after injury, thereby aggravating renal interstitial fibrosis (Sun & Zhou, 2005).

The results of keywords analysis showed that the research hotspots of the anti-renal fibrosis mechanism of Panax notoginseng total saponins into blood can be summarized as follows: (1) to study the material basis and action pathway of its drug effect, so as to explore the mechanism of its anti-renal fibrosis. Researchers are identifying the biological processes and signaling pathways that Panax notoginseng total saponins may affect after entering the blood, including intracellular signal transduction, apoptosis, proliferation, matrix breakdown, as well as PI3KAKT, Rap1, HIF-1, FoxO, etc. (2) Apoptosis is caused by oxidative stress leading to the accumulation of free radicals, lipid oxidation, and membrane rupture. Apoptosis is a secondary molecular mechanism of oxidative stress. The combination of the above components and targets reveals the multi-component, multi-target and multi-pathway mechanism of Panax notoginseng total saponins in the treatment of renal fibrosis. (3) For experimental studies, the Chinese literature found mainly focused on the field of rat as a research model.

The frontier topics in the research field can be reflected by the emergence words, and the research history of traditional Chinese medicine in the prevention and treatment of renal fibrosis can be observed from the changes of these keywords. Oxidative stress is the core of research in this field. The initial research focused on the composition and pharmacokinetics of traditional Chinese medicine, and then turned to vascular endothelial disease and the mechanism of Panax notoginseng total saponins. Animal experiments were mainly carried out in the early stage of this field, and then focused on clinical studies, molecular mechanisms and cellular studies. Studying the molecular mechanisms of oxidative stress, apoptosis and autophagy and the relationship among them will be the mainstream direction of research in this field.

This study summarizes the importance of being able to provide effective information for potential collaborators and institutions, and provides the possibility and development direction for researchers to explore and better understand the mechanism of Panax notoginseng total saponins in the prevention and treatment of renal fibrosis.

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