Research Article

Mechanism of Xinfeng Capsule in the Treatment of Hypercoagulable State of Ankylosing Spondylitis Based on Data Mining and Network Pharmacology

Xu Li,1 Jian Liu,2 Yanyan Fang,3 Mingyu He,1 Fanfan Wang,1 and Qi Han1

1Graduate School, Anhui University of Traditional Chinese Medicine, Hefei 230038, China
2Department of Rheumatism Immunology, The First Affiliated Hospital, Anhui University of Chinese Medicine, Hefei 230031, China
3Department of Clinical Data Center, The First Affiliated Hospital, Anhui University of Chinese Medicine, Hefei 230031, China

Correspondence should be addressed to Jian Liu; liujianahzy@126.com

Received 24 November 2021; Accepted 2 March 2022; Published 17 March 2022

Academic Editor: Rui Liu

Copyright © 2022 Xu Li et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Ankylosing spondylitis (AS) is a rheumatism that mainly affects the axial bones and joints. Xinfeng capsule (XFC) is a preparation with a remarkable clinical effect that is used in our hospital. And it has definite curative effect and less side effects in the treatment of AS.

Objective. Data mining and network pharmacology were used to analyze the efficacy of Chinese medicine Xinfeng capsule on treating the hypercoagulable state of ankylosing spondylitis and the underlying mechanism behind it.

Methods. Clinical data were collected and compiled from the Department of Rheumatology and Immunology of the First Affiliated Hospital of Anhui University of Chinese Medicine. Cluster analysis was used to investigate herbs that frequently used to treat AS, Apriori module was used to analyze the association rules between herbs and laboratory indexes, and the random walk model was used to reveal the therapeutic efficacy of XFC against AS. The TCMSP database was used to acquire the active components and targets of XFC, and the GeneCards and OMIM database were used to obtain the targets of AS. Afterward, an active ingredient-target network was established and core targets were screened for; overlapping targets were screened for the protein-protein interaction (PPI) network analysis, the Gene Ontology (GO) enrichment analysis, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. Molecular docking was adopted to investigate the interactions between main active components and core targets.

Results. Frequently used herbs could be divided into three groups, and according to the analysis of Apriori module, there is a strong correlation between XFC and the improvement of ESR and hs-CRP, and the results of the random walk model demonstrated that the effect of XFC on improving PLT, ESR, and hs-CRP was superior to the use of traditional Chinese medicine alone. In total, 103 active compounds of XFC and 59 overlapping targets were obtained. The PPI relationships were obtained through the STRING database, and 13 core targets were identified. 1786 GO enrichment results and 205 KEGG enrichment results were obtained, including NF-kappa B signaling pathway, TNF signaling pathway, and IL17 signaling pathway. The outcomes of molecular docking revealed a close relationship between the active compounds of XFC and core targets.

Conclusion. This study demonstrated that XFC can effectively improve the hypercoagulable state and the inflammatory indices of AS patients through data mining, and it has a strong correlation with the clinical improvement of inflammation. The active compounds of formononetin, triptolide, quercetin, and kaempferol may be the key active components of XFC in regulating AS, possibly through inhibiting the activation of NF-kappa B signaling pathway to improve hypercoagulable state.

1. Introduction

Ankylosing spondylitis (AS) is an autoimmune disease that has a high incidence, mainly manifested as spinal inflammation and chronic connective tissue lesions [1]. It is closely related to the human leukocyte antigen-B27 gene (HLA-B27) [2], the incidence rate of AS is about 0.3% and is greater in males [3], and the ratio of male to female ranges from 2 : 1 to 9 : 1 [4]. The commonly used drugs are nonsteroidal anti-inflammatory drugs and sulfonamides, which are
anti-inflammatory and analgesic, controlling the development of the disease and reducing the disability rate; yet there are certain side effects. There is an early understanding of AS from traditional Chinese medicine with a rich theoretical basis and clinical experience in its treatment.

Xinfeng capsule (XFC) is a preparation with a remarkable clinical effect that is used in our hospital. It is mainly composed of four herbs: Astragalus membranaceus (Huang Qi:HQ), Coix seed (Yi Yi Ren:YR), Tripterygium wilfordii (Lei Gong Teng:LGT), and centipede (Wu Gong:WG). XFC has been used in clinic for more than 10 years, and it has definite curative effect and less side effects in the treatment of AS [5].

As a new scientific method, network pharmacology is based on the analysis of network data and system biology. The combination of traditional Chinese medicine and network pharmacology has bridged the gap between modern medicine and traditional medicine [6].

The clinical efficacy of traditional Chinese medicine on treating AS is valid, as it improves the immune inflammations indices of AS patients [7, 8], but the prescription remained complex and variable [9], which hindered the further exploration of its exact mechanism. Therefore, this study conducted data mining research on the prescriptions of traditional Chinese medicine and laboratory indicators of hospitalized patients and is aimed at exploring the mechanism of XFC used to treat ankylosing spondylitis through the method of network pharmacology, so as to provide a basis for the clinical application of XFC.

2. Materials and Methods

2.1. Materials. Clinical data from hospitalized AS patients in the Department of Rheumatology and Immunology of the First Affiliated Hospital of Anhui University of Chinese Medicine between July 2009 and June 2021 were collected and compiled. The dataset includes usage records of XFC and Chinese herbal medicines, and the value of laboratory indicators includes PLT, hs-CRP, and ESR. 1040 datasets were acquired, among them, 710 received Chinese medicine alone as control groups, and 330 were treated with XFC combined with Chinese medicine as experimental groups.

2.2. Cluster Analysis. Any Chinese herbal medicine that was prescribed to individual patients was assigned 1, and those not used were assigned 0. The compatibility of Chinese herbal medicines, and the value of laboratory indicators were acquired, Among them, 710 received Chinese medicine alone as control groups, and 330 were treated with XFC combined with Chinese medicine as experimental groups.

2.3. Association Rules. Any Chinese herbal medicine that was prescribed to individual patients was assigned 1, and those not used were assigned 0; any improvement in the laboratory indices was also assigned 1, otherwise 0. The Apriori module in SPSS Clementine client v. 11.1 was used to determine the correlation between Chinese herbal medicine and laboratory indicators. The minimum support rate was 30%, the confidence level was 50%, and the lift was >1. Apriori was used to establish relationships between items. Individual drug and index were used as variables. The formula is as follows:

\[ \text{Support}(X \rightarrow Y) = \frac{\sigma(X \cup Y)}{N}, \]

\[ \text{Confidence}(X \rightarrow Y) = \frac{\sigma(X \cup Y)}{\sigma(X)}, \]

\[ \text{Lift}(X \rightarrow Y) = \frac{\text{confidence}(X \cup Y)}{\sigma(Y)}, \]

where \( X \rightarrow Y \) represents an association rule, \( X \) (left-hand side (LHS)) represents the set of laboratory indices, and \( Y \) (right-hand side (RHS)) represents herbs, and \( \sigma(X) \) is the probability of the itemset \( X \) occurring; \( \sigma(X \cup Y) \) is the union of itemsets \( X \) and \( Y \), and \( \sigma(X \cup Y) \) is the probability when \( X \) and \( Y \) occur together. Support(\( X \rightarrow Y \)) represents the probability of itemset \( (X, Y) \) occurring within the total itemset, and confidence(\( X \rightarrow Y \)) is the probability of \( Y \) occurring in the presence of \( X \). Lift is the ratio of the probability that itemset \( Y \) appears in the presence of \( X \) to the probability of \( Y \) appearing. Support and confidence are usually used to eliminate insignificant associations, and lift indicates the effectiveness of the association rules.

2.4. Random Walk Model. The random walk model evaluation in the index laboratory was realized using the Oracle 10 g tool; Peng’s random walk model was used to refer [10], and according to the ideas of this model, the changing process of efficacy indicators such as symptom signs, physicochemical indices, and certain scale indicators, clinically can reflect the effects of the corresponding treatment options; hence, PLT, hs-CRP, and ESR were used as the indexes for the random walk model evaluation.

2.5. Screening of Active Ingredients and Targets. The compounds in XFC consisting of four Chinese herbs were acquired from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmspw.com), which is a Chinese herbal medicine platform [11]. Based on the rules of optimal toxicokinetic ADME, drug-likeness (DL) \( \geq 0.18 \), and oral bioavailability (OB) \( \geq 30\% \), the bioactive components of XFC were chosen. However, the active components of centipede (WG) were zero according to the criteria; therefore, the literature was searched to supplement the compounds. Then, the targets were corrected by the UniProt database to establish the gene symbol of active compounds.

2.6. Acquisition of AS Associated Targets. The keyword “ankylosing spondylitis” was searched for in the GeneCards (http://www.genecards.org/) and OMIM databases (http://www.omim.org/); AS related targets were recognized and filtered, with duplicate targets deleted to establish the targets of
AS. Targets of AS and XFC were collected and visualized through R 4.1.1.

2.7. Construction of Active Component-Target Network. Based on the aforementioned active ingredients of traditional Chinese medicine, potential targets were intersected with those related to AS, and 59 targets were obtained and introduced into the Cytoscape 3.8.2 software for constructing the active component-target network.

2.8. PPI Network Structure and Screening of Core Targets. Overlapping targets relating to both AS and XFC were selected for molecular docking. The mol2 format file of active compound structure was downloaded on the TCMSP platform, along with the 3D structure of the corresponding target from PBD (https://www.rcsb.org/), the molecular docking of the target and active components was carried out by the AutoDock 4.2.6 software, and the visualization was achieved by PyMOL 2.5.2. The best affinity and minimum binding energies are conformations as final docking results.

3. Results

3.1. Cluster Analysis of Herbs in AS Therapy. A cluster analysis of the herbs used for therapy was conducted, at 20 Euclidean distances; herbs could be categorized into three groups (Figure 1).

| Indices (LHS, X) | Herbs (RHS, Y) | Support (X) (%) | Confidence (X → Y) (%) | Lift |
|------------------|---------------|----------------|------------------------|------|
| PLT↓             | Angelicae Sinensis Radix | 32.53 | 52.07 | 1.16 |
| hs-CRP↓          | XFC           | 31.761 | 66.97 | 1.098 |
| hs-CRP↓          | Herba Hedyotidis | 40.038 | 66.346 | 1.087 |
| ESR↓             | XFC           | 31.761 | 52.424 | 1.039 |
| ESR↓             | Herba Hedyotidis | 40.038 | 52.404 | 1.039 |
| ESR↓             | Dandelion     | 61.983 | 52.329 | 1.038 |

2.9. Bioinformatics Analysis. Both Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were carried out using the R 4.1.1 clusterProfile V3.12.0. The GO enrichment analyzed biological processes, cellular composition, and molecular functions, whereas the KEGG pathway analyzed important biological pathways.

2.10. Molecular Docking. The core targets and main components were selected for molecular docking. The mol2 format file of active compound structure was downloaded on the TCMSP platform, along with the 3D structure of the corresponding target from PBD (https://www.rcsb.org/), the molecular docking of the target and active components was carried out by the AutoDock 4.2.6 software, and the visualization was achieved by PyMOL 2.5.2. The best affinity and minimum binding energies are conformations as final docking results.
### 3.2. Association Rule Analysis of Herbs and Laboratory Indices.

The minimum support rate was 30%, the confidence was 50%, and the lift was >1. Apriori was used to establish relationships between herbs and laboratory indices (Table 1).

### 3.3. Random Walking Model of Laboratory Indices.

The PLT improvement coefficients in the control and experimental groups were 0.081 and 0.164, respectively, and the clinical significance lies within the improvement of each index, which requires 23.030 steps and 10.730 steps to be taken, respectively. The improvement coefficients of hs-CRP were 0.260 and 0.387, respectively, and the clinical significance was the need to take 6.630 and 4.330 steps, respectively, for an improvement to be seen in each of the combined indices. The improvement coefficients of ESR were 0.243 and 0.295, respectively, and the clinical significance was walking for 7.400 and 5.940 steps, respectively, for improvement in each composite measure to occur (Table 2 and Figure 2).

| Index | Group      | Maximum random fluctuation | Walking positive growth rate | Random fluctuation power law value | Improvement coefficient | Comprehensive evaluation records | Ratio  |
|-------|------------|-----------------------------|-----------------------------|-----------------------------------|-------------------------|---------------------------------|--------|
| PLT   | Control group | 66                          | 0.044                       | 0.327 ± 0.14                      | 0.081                   | 811                             | 23.030 |
|       | Experimental group | 71                          | 0.093                       | 0.308 ± 0.098                      | 0.164                   | 432                             | 10.730 |
| hs-CRP| Control group  | 254                         | 0.151                       | 0.417 ± 0.117                      | 0.260                   | 976                             | 6.630  |
|       | Experimental group | 189                         | 0.231                       | 0.350 ± 0.110                      | 0.387                   | 488                             | 4.330  |
| ESR   | Control group  | 216                         | 0.135                       | 0.365 ± 0.118                      | 0.243                   | 889                             | 7.400  |
|       | Experimental group | 129                         | 0.168                       | 0.353 ± 0.122                      | 0.295                   | 436                             | 5.940  |

**Table 2: Random walking model of laboratory indices.**

**Figure 2:** Random walking model of laboratory indices. Note: Blue line signifies the experimental group. Green line symbolizes the control group. The length of the horizontal line grows with the number of steps. Vertical line height grows with the effect of the intervention.

### 3.4. Active Components of Screening for XFC.

The components of Astragalus membranaceus (Huang Qi: HQ), Coix seed (Yi Yi Ren: YYR), Tripterygium wilfordii (Lei Gong Teng: LGT), and centipede (Wu Gong: WG) were acquired from the TCMSP database and searched from literature. 103 active compounds and 212 potential targets of XFC were obtained. 1961 AS targets were obtained by screening the GeneCards database and OMIM database. Through inspecting the intersection of drug and disease targets, 59 overlapping targets were identified (Figure 3).
3.5. Active Component Target Network Construction. The active component target network, which can intuitively reflect the interactions between active ingredients and targets, was designed using the Cytoscape v3.8.2 software (Figure 4). Red nodes indicate active components of Astragalus membranaceus, blue nodes represent active components of Coix seed, green nodes symbolize active components of Tripterygium wilfordii, purple nodes symbolize active components of centipede, and light blue represents the common components between Astragalus membranaceus and Tripterygium wilfordii. The presence of an interconnection indicates a relationship between components and targets. The size of nodes indicates the magnitude of the degree value, and the greater the degree, the greater the number of nodes it is connected to, hence the greater the regulatory function of the whole network. The top four active ingredients identified from the degree value were as follows: formononetin, triptolide, quercetin, and kaempferol.

3.6. PPI Network Structure and Screening of Core Targets. 59 overlapping targets were uploaded to the STRING database to export the TSV text. The PPI network built by Cytoscape 3.8.2 is shown in Figure 5(a), with 59 nodes and 762 edges in total. After double network topology analysis, 13 key targets that were screened out are shown in Figure 5(c): IL4, IL6, IL10, VEGFA, PTGS2, IL6, CCL2, IFNG, IL8, IL1B, TNF, EGF, and RELA.
TNF, IL1β, VEGFA, IL10, CCL2, PTGS2, CXCL8, EGF, STAT3, NFκBIA, and IFNG.

3.7 GO and KEGG Analyses. The Go analysis contained the following aspects: biological process (BP), cellular components (CC), and molecular function (MF). In the end, 1786 GO enrichment results were obtained. The upper 10 of BP, CC, and MF are shown in Figure 6. BP mainly involved responses to lipopolysaccharide, bacterially derived molecules, and cellular responses to biotic stimulus. CC was mainly related to the outer side of the plasma membrane, the membrane raft, and membrane microdomain. MF was mainly involved in cytokine activity and receptor ligand activity, along with that of signaling receptor activator activity.

205 KEGG enrichment results were obtained, and Figure 7 demonstrates 20 important pathways ($q$ value < 0.05), and some played essential roles, such as the NFκB signaling pathway, TNF signaling pathway, and IL17 signaling pathways. The potential pathways were mainly involved with inflammatory responses, antiviral functions, and immune regulation.

3.8 Molecular Docking. The main active components, such as formononetin, triptolide, quercetin, and kaempferol, were docked with IL6, CCL2, TNF, and IL4 of the core targets. The results showed that all targets and molecules were successfully docked, as shown in Table 3. The smaller the binding energy value, the more stable the binding was. Some docking results were selected in this study, as displayed in Figure 8.

4. Discussion

Previous studies of our team have discovered that the formation of AS might be related to cytokine disorder, and the NFκB signaling pathway was related to overactivation [13], the clinical efficacy of traditional Chinese medicine in the treatment of AS has been demonstrated, and its use has been widely accepted due to its simple combination, flexibility, and proven positive outcome [14]; the use of traditional Chinese medicine under the guidance of the principle of syndrome differentiation and treatment yielded satisfactory curative effects for various disease manifestations during the progression of AS, such as limited lumbar and spinal activity and morning stiffness [15, 16].

The present study made use of data mining to explore the usage rules of Chinese herbal medicine for AS treatment in our hospital and verified its efficacy. Three groups of commonly used Chinese herbal combinations for AS treatment were obtained through cluster analysis, and treatment modalities mostly adopted the methods of tonifying Qi and strengthening of the spleen, dispelling wind, and dehumidification, promoting blood circulation and removing blood stasis. The results of association rules showed that XFC has a strong correlation with the improvement of ESR and hs-CRP. The improvement of PLT, ESR, and hs-CRP in the experimental group was superior to those in the control.
group as shown in the random walk model, and the experimental group had a lower number of walking steps compared to the control group, hence supporting the effectiveness of XFC in treating AS. Data mining results showed that XFC can effectively improve the hypercoagulable state and inflammatory indexes of AS patients, regulate the hypercoagulable state and inflammatory response, and has a strong correlation with the improvement of hypercoagulable state and inflammation.

Network pharmacology [17, 18], which involves system biology and computer technology analysis, could be used to investigate the mechanism of action of drugs. In the active component-target network of XFC, 103 active compounds were selected. Four of the major compounds, including formononetin, triptolide, quercetin, and kaempferol, were recognized as active components of XFC. Triptolide can significantly reduce the severity of collagen induced arthritis. It not only has anti-inflammatory effect, but also has the ability to prevent bone destruction [19]. Formononetin is one of the major active components of Astragalus membranaceus [20], and it shows a wide range of physiological effects beneficial to health through estrogen dependent and independent mechanisms [21]. Quercetin is a natural flavonoid compound with a variety of biological activities, and it

| Core targets (PDB ID) | Active ingredients | Binding energy (kcal/mol) |
|-----------------------|---------------------|---------------------------|
| IL6 (1ALU)            | Quercetin           | -7.0                      |
| CCL2 (1DOK)           | Quercetin           | -7.5                      |
| TNF (2ZPX)            | Triptolide          | -8.5                      |
| IL4 (1HZI)            | Triptolide          | -6.9                      |
| IL4 (1HZI)            | Formononetin        | -6.3                      |
| TNF (2ZPX)            | Kaempferol          | -8.5                      |
can reduce chondrocyte apoptosis and extracellular matrix degradation [22]. Kaempferol, also known as polyphenols, is a type of flavonoids seen in many plants. Studies have identified that it can obviously promote the osteogenic differentiation of mesenchymal stem cells and osteoblasts [23].

The topological parameters of identifying key nodes were calculated through the PPI network, and 13 targets were found to be the core targets for XFC in the treatment of AS, including IL4, IL6, TNF, IL1β, VEGFA, IL10, CCL2, PTGS2, CXCL8, EGF, STAT3, NFκBIA, and IFNG. These targets are related to host immunity, oxidative stress, and other pathogenic microorganisms. IL6 is a pleiotropic cytokine with numerous biological functions, which is involved in the pathogenesis of a variety of rheumatic diseases [24]. IL10 is an anti-inflammatory factor, and it has a high expression level in patients with AS, which represents an inhibitory feedback pathway and an inhibitory response to inflammation [25]. Through animal experiments, it was found that IL10 also inhibited synovial proliferation and promoted articular cartilage repair [26]. The high expression of PTGS2 can cause the proliferation of fibroblast-like synovial cells, affect the expression levels of TNF-α, IL1β, and IL6 in the serum, and aggravate the inflammatory response [27].

Go and KEGG enrichment analyses showed that XFC could control immune pathway processes. XFC was involved in biological process such as responses to lipopolysaccharide,
bacterially derived molecules, cellular responses to biotic stimulus, cytokine activity, receptor ligand activity, and signaling receptor activator activity. Results of the KEGG pathway enrichment analysis illustrated that most targets were enriched in NF-kappa B signaling pathway, TNF signaling pathway, and the IL17 signaling pathway.

Previous studies from our group found that XFC could significantly improve the status of AS disease activity and immune-inflammatory indicators, and the mechanism could be contributed to inhibiting the activation of the NF-κB signaling pathway [28–30]. NF-kappa B pathway has been proved to be one of the main transcription factors involved in the abnormal expression of inflammatory cytokines in AS, expressed as the abnormal activation of NF-kappa B signaling pathway and increased secretion of inflammatory cytokines lead to deposition of immune complexes and to play in the treatment of AS.

Molecular docking was also performed to forecast complex interactions between four active components and protein targets. The binding energy further confirmed the reliability of the docking results and showed great bonding characteristics. The results demonstrated that formononetin, triptolide, quercetin, and kaempferol could have crucial roles to play in the treatment of AS.

5. Conclusion
The study has demonstrated that XFC can improve the hypercoagulable state and the inflammatory indices of AS patients, and it has a strong correlation with the clinical improvement of inflammation. The mechanism of XFC used to treat hypercoagulable state of AS was analyzed through network pharmacology, and its possible molecular mechanism involves multiple components. The active compounds of formononetin, triptolide, quercetin, and kaempferol may be the key components of XFC in regulating hypercoagulable state of AS and may do so through the NF-kappa B signaling pathways. However, there are some limitations in this present study, and clinical experimental validation of superior quality is needed to support the results concluded.

Data Availability
All the datasets are available by conduct with the corresponding author.

Conflicts of Interest
The authors declared no conflicts of interest associated with this work.

Authors’ Contributions
Jian Liu conceived and directed this study. Xu Li wrote the manuscript. Yanyan Fang provided support for the data mining section. Mingyu He, Fanfan Wang, and Qi Han collected the data required.

Acknowledgments
This work was supported by the Anhui Provincial Laboratory of Applied Basic and Development Research of Modern Internal Medicine of Traditional Chinese Medicine (2016080503b041), the National Natural Science Foundation of China (82104817), the Scientific Research Project of the Chinese Society of Ethnic Medicine (2020zy323–350102), the Key Laboratory of Xin’an Medicine, Ministry of Education (No. 2020Xayx08), and the Scientific Research Project of Anhui Provincial Health Commission (ahwj2021b036).

References
[1] W. Zhu, X. He, K. Cheng et al., “Ankylosing spondylitis: etiology, pathogenesis, and treatments,” Bone Res, vol. 7, no. 1, p. 22, 2019.
[2] J. D. Taurog, A. Chhabra, and R. A. Colbert, “Ankylosing spondylitis and axial spondyloarthritis,” The New England Journal of Medicine, vol. 374, no. 26, pp. 2563–2574, 2016.
[3] R. Wang and M. M. Ward, “Epidemiology of axial spondyloarthritis: an update,” Current Opinion in Rheumatology, vol. 30, no. 2, pp. 137–143, 2018.
[4] M. Bergman and A. Lundholm, “Managing morbidity and treatment-related toxicity in patients with ankylosing spondylitis,” Rheumatology, vol. 57, no. 3, pp. 419–428, 2018.
[5] W. F. Ye, J. Liu, L. Wan et al., “Effect of Xinfeng capsule on AS patients and their serum immunoglobulin subtypes and peripheral lymphocyte autophagy,” Chinese Journal of integrated traditional and Western medicine, vol. 36, no. 3, pp. 310–316, 2016.
[6] H. Yuan, Q. Ma, H. Cui et al., “How can synergism of traditional medicines benefit from network pharmacology,” Molecules, vol. 22, no. 7, p. 1135, 2017.
[7] L. Fang, Jian Liu, Fubing Zhu, Bing Tan, and Pingheng Zhang, “Impact of Xinfeng capsules on hypercoagulable state in active ankylosing spondylitis and its mechanism,” World Journal of integrated traditional Chinese and Western medicine, vol. 11, no. 7, pp. 949–955, 2016.
[8] Yanyan Fang, Jian Liu, Ling Xin et al., “Data mining research on improving spleen parameters and immune inflammation indexes in patients with ankylosing spondylitis by spleen unit therapy,” Chinese Journal of immunology, vol. 35, no. 10, pp. 1245–1250, 2019.
[9] Ying Wang, Wei Zheng, Xiaoping Liu et al., “Analysis on composition principles of prescriptions for rheumatoid arthritis using traditional Chinese medicine inheritance system,” Chinese Journal of experimental formulae, vol. 22, no. 23, pp. 181–186, 2016.
[10] C. V. Peng, S. V. Buldyrev, A. L. Goldberger et al., “Long-range correlations in nucleotide sequences,” Nature, vol. 356, no. 6365, pp. 168–170, 1992.
[11] J. Ru, P. Li, J. Wang et al., “TCMSP: a database of systems pharmacology for drug discovery from herbal medicines,” Journal of Cheminformatics, vol. 6, no. 1, p. 13, 2014.
[12] Y. Tang, M. Li, J. Wang, Y. Pan, and F. X. Wu, “CytoNCA: a cytoscape plugin for centrality analysis and evaluation of protein interaction networks,” Biosystems, vol. 127, pp. 67–72, 2015.
[13] L. Fang, J. Liu, F. B. Zhu, Pingheng Zhang, and Bing Tan, “Mechanism of ankylosing spondylitis patients with blood stagnation based on cytokines NF-κB signaling pathway,” *Chinese Journal of traditional Chinese medicine*, vol. 34, no. 12, p. 5, 2016.

[14] W. Z. Dong, J. Liu, L. Xin, Y. Y. Fang, and J. T. Wen, “Effect of Tripterygium Glycosides Tablets on immune-induced liver and kidney function in patients with rheumatoid arthritis based on data mining,” *China journal of Chinese materia medica*, vol. 44, no. 16, pp. 3526–3532, 2019.

[15] H. J. Wang, Y. G. Feng, and J. L. Wang, “Effect of integrated traditional Chinese and Western medicine on blood stagnation and obstruction type ankylosing spondylitis,” *Shenzhen Journal of integrated traditional Chinese and Western medicine*, vol. 30, no. 10, p. 2, 2020.

[16] J. Z. Li, “Observation on the efficacy of modified Daobi Decotion in the treatment of ankylosing spondylitis of qi stagnation and blood stagnation type,” *Asia Pacific traditional medicine*, vol. 16, no. 2, pp. 137–139, 2020.

[17] A. L. Hopkins, “Network pharmacology: the next paradigm in drug discovery,” *Nature Chemical Biology*, vol. 4, no. 11, pp. 682–690, 2008.

[18] X. F. Huang, W. B. Cheng, Y. Jiang et al., “A network pharmacology-based strategy for predicting anti-inflammatory targets of ephedra in treating asthma,” *International Immunopharmacology*, vol. 83, p. 106423, 2020.

[19] D. Fan, X. He, Y. Bian et al., “Triptolide modulates TREM-1 signal pathway to inhibit the inflammatory response in rheumatoid arthritis,” *International Journal of Molecular Sciences*, vol. 17, no. 4, p. 498, 2016.

[20] L. Li, W. Yan, X. Wang et al., “Formononetin attenuated allergic diseases through inhibition of epithelial-derived cytokines by regulating E-cadherin,” *Clinical Immunology*, vol. 195, pp. 67–76, 2018.

[21] J. M. Dutra, P. Espitia, and R. A. Batista, “Formononetin: biological effects and uses - a review,” *Food Chemistry*, vol. 359, no. 5, p. 129975, 2021.

[22] Q. Wang, L. J. Ying, B. Wei, Y. Ji, and Y. Xu, “Effects of quercetin on apoptosis and extracellular matrix degradation of chondrocytes induced by oxidative stress-mediated pyroptosis,” *Journal of Biochemical and Molecular Toxicology*, vol. 36, no. 2, p. e22951, 2022.

[23] B. C. Xie, Z. W. Zeng, S. Y. Liao, C. Zhou, L. Wu, and D. Xu, “Kaempferol ameliorates the inhibitory activity of dexamethasone in the osteogenesis of MC3T3-E1 cells by JNK and p38-MAPK pathways,” *Frontiers in pharmacology*, vol. 12, p. 739326, 2021.

[24] K. Yuko and T. Tsutomu, “An update on the pathogenic role of IL-6 in rheumatic diseases,” *Cytokine*, vol. 146, p. 155645, 2021.

[25] C. F. Ra Belo, T. Baptista, L. E. Petersen, M. E. Bauer, M. W. Keiserman, and H. L. Staub, “Serum IL-6 correlates with axial mobility index (Bath Ankylosing Spondylitis Metrology Index) in Brazilian patients with ankylosing spondylitis,” *Open Access Rheumatology: Research and Reviews*, vol. Volume 10, pp. 21–25, 2018.

[26] T. Shuai, Y. Yan, X. Qi, X. Li, and Z. Li, “Treatment of type II collagen-induced rat rheumatoid arthritis model by interleukin 10 (IL10)-mesenchymal stem cells (BMSCs),” *Medical science monitor: international medical journal of experimental and clinical research*, vol. 25, pp. 2923–2934, 2019.

[27] Q. Wei, F. Lv, H. Zhang et al., “MicroRNA-101-3p inhibits fibroblast-like synoviocyte proliferation and inflammation in rheumatoid arthritis by targeting PTGS2,” *Bioscience Reports*, vol. 40, no. 1, 2020.

[28] Y. Y. Fang, J. Liu, L. Wan, Wenzhe Dong, and Jianting Wen, “Xinfeng capsule-containing serum relieves platelet activation by inhibiting VEGFA/SDF-1/CXCR4 pathway in patients with ankylosing spondylitis,” *Journal of Immunology*, vol. 35, no. 8, pp. 691–696, 2019.

[29] L. Fang, J. Liu, and F. B. Zhu, “Effect of Xinfeng capsule on related factors of thrombus formation and inflammatory cytokines in active ankylosing spondylitis patients,” *Chinese Journal of integrated traditional and Western medicine*, vol. 36, no. 10, pp. 1202–1207, 2016.

[30] L. Fang, J. Liu, L. Wan, Fubing Zhu, Bing Tan, and Pingheng Zhang, “Xinfeng capsule inhibits miR-155 / NF-κB signal pathway improves hypercoagulability in patients with ankylosing spondylitis at active stage,” *Journal of cell and molecular immunology*, vol. 8, p. 6, 2016.