Exploring the Mechanism of Action of Xinfeng Capsule in Treating Hypercoagulable State of Rheumatoid Arthritis Based on Data Mining and Network Pharmacology

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Abstract

Objective: To explore the effect of Xinfeng Capsule (XFC) on hypercoagulable state in patients with rheumatoid arthritis (RA) using data mining and network pharmacology. Methods: The data were collected of 524 inpatients with RA who were treated with XFC in the Department of Rheumatology and Immunology of the First Affiliated Hospital of Anhui University of traditional Chinese medicine (TCM) before October 2021. The changes of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), complement component 3 (C3), C4, platelet (PLT), fibrinogen (FBG), thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (APTT) were observed before and after the treatment. By implementing the Apriori module, the association rules between XFC and immune-inflammation indexes and coagulation indexes were analyzed. XFC and disease targets were obtained through traditional chinese medicine systems pharmacology database and analysis platform, Genecards, OMIM, and other databases. The cross targets and core targets were screened, and the network diagram of TCM—active ingredients—potential targets was constructed using Cytoscape3.7.2 software. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed through Database for Annotation, Visualization and Integrated Discovery (DAVID) database. AutoDock Vina software was used for molecular docking between active ingredients and core targets. The docking results were visualized using PyMOL2.3.0 software. Results: (1) Data mining results showed that the inflammation and coagulation indexes of RA patients were significantly improved after XFC treatment, and there was a strong correlation between XFC and the improvement of CRP, ESR, RF, C3, C4, PLT, FBG, TT, PT, and APTT. (2) Network pharmacology results showed that prostaglandin-endoperoxide synthase 2 (PTGS2), CASP3, tumor necrosis factor (TNF), AKT1, and JUN, the main targets of XFC in the treatment of RA, were closely related to apoptosis and were mainly involved in interleukin 17 (IL-17), TNF, and nuclear factor-κB (NF-κb), and other apoptotic and inflammatory signaling pathways. (3) Molecular docking results showed that the active components of XFC, β-sitosterol, and stigmasterol, had good docking with TNF and PTGS2, which might be the key active components of XFC in the treatment of RA-related hypercoagulable state. Conclusion: XFC can improve the hypercoagulable state of patients with RA by promoting cell apoptosis and improving immune inflammatory response.

Keywords
rheumatoid arthritis, Xinfeng capsule, hypercoagulable state, data mining, network pharmacology

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the presence of aggressive arthritis. The basic pathological changes in RA involve chronic inflammation of joint synovia, formation of pannus, and destruction of cartilage caused by inflammatory cytokines and mediators. Clinically, RA patients often suffer from joint stiffness, swelling, pain, and other symptoms, which may lead to joint deformity and loss of function in severe cases. At present, RA is mainly
treated with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs, and biological agents in the field of Western medicine. Although these drugs can alleviate the clinical symptoms of RA to a certain extent, they are prone to adverse reactions when taken in large quantities for a long time, resulting in intolerance and unsatisfactory long-term effect.\(^4\)

Previous studies have proved that there are pathological changes in blood coagulation and fibrinolysis indexes of RA patients, which are clinically manifested as a hypercoagulable state.\(^3,9\) Coagulation and fibrinolysis indexes mainly include D-dimer (D-D), fibrinogen (FBG), and platelet (PLT) count. The coagulation and fibrinolysis indexes FBG and D-D in RA patients were significantly higher than those in the healthy control group.\(^8,9\) The abnormal changes in diabetes, inflammation in RA patients.

Therefore, the abnormality of the coagulation and fibrinolysis system may be closely related to the occurrence and development of inflammation in RA patients.

Xinfeng capsule (XFC; Patent No.: Z20050062), a traditional Chinese medicine (TMC) compound, is composed of Radix Astragali Mongoli, Yiyiren (Semen Coicis), Wugong (Scutellariae), and Leigongteng (Radix et Rhizoma Tripterygi). It has been applied in clinical practice for 30 years with remarkable curative effects.\(^12\) In the early stages, our research team conducted systematic studies on the fingerprint and pharmacokinetics of XFC. Relatively complete chromatographic information was obtained, and the relative peak area ratio of each substance was within a certain range, which was the unique rule of XFC. In terms of the fingerprint, it could not only reflect the type and quantity of chemical components in XFC, but also describe and evaluate XFC to control its quality in an all-round way. Therefore, it can be used as one of the quality control methods of XFC.\(^13\)

Apriori algorithm is a popular approach used in data mining and association rule analysis.\(^14\) Network pharmacology has been applied to reveal the network characteristics of drugs, indicating that multiple drugs and targets may have better clinical efficacy and less toxic side effects compared to single-target drugs. Based on Hospital Information System (HIS) and data mining, this study focused on the changes of immune-inflammation indexes and coagulation indexes of RA patients who received TCM combined with XFC treatment, and explored the potential targets, main active ingredients and core targets of XFC in the treatment of RA through network pharmacology and molecular docking technology. This study opens up new ideas for the follow-up experimental study of XFC in the treatment of RA and provides a scientific basis for its clinical application.

Materials and Methods

Materials

Hospitalization data were collated from RA inpatients with blood stasis syndrome before October 2021 in the Department of Rheumatology and Immunology of The First Affiliated Hospital of Anhui University of Chinese Medicine. The dataset contained records of the use of TCM, formulations of XFC, and disease-related laboratory indicators, including immune-inflammation indexes, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), complement component 3 (C3), and C4, and coagulation indexes, such as PLT, FBG, thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (APTT). This study was approved by the Ethics Research Committee of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine. A total of 524 patients were enrolled and treated with XFC.

Methods

Cluster Analysis. The designation for the use of Chinese herbal medicine was 1 while that for nonuse was 0. Systematic clustering in SPSS v. 21.0 (IBM Corp.) was employed to investigate the compatibility of the Chinese herbal medicine. In the clustering analysis algorithm, each herb was regarded as a cluster. According to the similarity between objects, N clusters were combined to form a new class. Euclidean metric was used to calculate the similarity between herbs\(^14\):

$$d(x, y) = \sqrt{\sum_{k=1}^{n} (x_k - y_k)^2}$$

Association Rules. Apriori algorithm: The designation for the use of Chinese herbal medicine was 1 while that for nonuse was 0. The Apriori module in SPSS Clementine v. 11.1 (IBM Corp.) was employed to identify the correlations among Chinese herbal medicines. The minimum support and confidence were set to 80% and the degree of improvement to >1. The Apriori algorithm was implemented to establish the relationships among items within a dataset. It is also known as a shopping blue analysis. In this dataset, each drug was treated as a variable. The formulae applied were as follows\(^15\):

$$\text{support}(X \rightarrow Y) = \frac{\sigma(X \cup Y)}{N}$$

$$\text{confidence}(X \rightarrow Y) = \frac{\sigma(X \cup Y)}{N}$$

$$\text{lift}(X \rightarrow Y) = \frac{\text{confidence}(X \rightarrow Y)}{\text{support}(X \rightarrow Y)} = \frac{\sigma(X \cup Y)}{N}$$

where X → Y is an association rule, X (left-hand side [LHS]) and Y (right-hand side [RHS]) represent the set of herb items, \(\sigma(X)\) is the frequency of itemset X, X \cup Y is the union of itemsets X and Y, \(\sigma(X \cup Y)\) refers to the frequency with which itemsets X and Y appear together, support(X → Y) is the frequency with which X and Y appear together, and confidence (X → Y) is the probability that itemset Y appears in the presence of X. Expected confidence (X → Y) is the probability that
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Acquisition of XFC Active Components

The OB screening threshold was set to oral bioavailability (OB), druglikeness (DL), and half-life (HL), pounds of each herb in XFC was conducted using 3 parameters, utilized to screen the active ingredients of XFC more efficiently and economically. Virtual screening of potent active compounds of each herb in XFC was conducted using 3 parameters, oral bioavailability (OB), druglikeness (DL), and half-life (HL), in which the OB screening threshold was set to ≥30% and the DI ≥ 0.18.

Acquisition of XFC Active Components—RA Common Targets. With “rheumatoid arthritis” as the keyword, we searched GeneCards, Online Mendelian Inheritance in Man (OMIM), DrugBank, and other databases to obtain all known targets related to RA. In addition, relevant target names were standardized through UniProt database. FunRich software was used to conduct Venn analysis on the main targets of XFC and RA-related targets to obtain the potential targets of XFC in the treatment of RA.

Correlation of XFC in Immune-Inflammation and Coagulation Indexes

The latter item was set as the indicator and the former as XFC. The minimum support was set to 60% and the minimum confidence to 70%. The following results were obtained in the Apriori module analysis of the association rules between XFC and improvement of RF, Hs-CRP, ESR, C3 and C4, and coagulation indexes, including FBG, PLT, TT, PT, and APPT, were decreased significantly after treatment compared with those before treatment (P < .01) (Table 1), indicating that the inflammatory response and hypercoagulable state of RA patients were effectively improved.

Results

Changes of Immune-Inflammatory Indexes before and after the Treatment

The immune inflammatory reaction in RA patients can activate the coagulation and fibrinolysis system, increase the levels of FBG and PLT, and lead to a hypercoagulable state. Our results demonstrated that the immune-inflammatory indexes of RA patients, including high-sensitivity (Hs)-CRP, ESR, RF, C3 and C4, and coagulation indexes, including FBG, PLT, TT, PT, and APPT, were decreased significantly after treatment compared with those before treatment (P < .01) (Table 1), indicating that the inflammatory response and hypercoagulable state of RA patients were effectively improved.

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Table 1. Changes of Immune-Inflammatory Indexes and Coagulation Indexes Before and After the Treatment.

| Indicators | Before treatment | After treatment |
|------------|------------------|-----------------|
| RF (IU/mL) | 203.5 ± 315.2    | 177.7 ± 260.8   |
| ESR (mm/h) | 45.0 ± 28.8      | 31.8 ± 22.1     |
| Hs-CRP (mg/L) | 30.1 ± 37.8 | 9.6 ± 19.3      |
| C3 (mg/dL) | 105.4 ± 38.7     | 98.4 ± 37.6     |
| C4 (mg/dL) | 23.7 ± 11.8      | 21.0 ± 10.3     |
| FBG (g/L)  | 4.0 ± 1.1        | 3.9 ± 1.1       |
| PLT (10^9/1 L) | 257.3 ± 102.0 | 253.2 ± 90.3   |
| Coagulation indicators |         |                  |
| TT (sec)   | 17.6 ± 2.1       | 17.7 ± 2.0      |
| PT (sec)   | 11.3 ± 1.8       | 11.2 ± 1.7      |
| APTT (sec) | 30.6 ± 5.5       | 30.2 ± 5.2      |

Table 2. Correlation of Xinfeng Capsule (XFC) in Immune-Inflammatory Indicators.

| Items (LHS⇒RHS) | Support | Confidence | Lift |
|-----------------|---------|------------|------|
| {XFC}⇒{FBG}    | 82.6%   | 89.3%      | 1.03 |
| {XFC}⇒{Hs-CRP} | 80.4%   | 86.8%      | 1.19 |
| {XFC}⇒{ESR}    | 79.4%   | 79.3%      | 1.99 |
| {XFC}⇒{RF}     | 75.6%   | 78.8%      | 1.12 |
| {XFC}⇒{PLT}    | 72.6%   | 78.1%      | 1.08 |
| {XFC}⇒{C3}     | 70.4%   | 74.2%      | 1.04 |
| {XFC}⇒{C4}     | 70.4%   | 70.2%      | 1.04 |

Abbreviations: APTT, activated partial thromboplastin time; CRP, C-reactive protein; C3, complete component 3; ESR, erythrocyte sedimentation rate; FBG, fibrinogen; Hs, high sensitivity; PT, prothrombin time; PLT, platelet; RF, rheumatoid factor; TT, thrombin time.

Active Components of XFC

By searching the traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP) database and reviewing relevant literature, 92 chemically active components in XFC formula were obtained. Among them, there were 20 effective components of *Huangqi* (*Radix Astragali Mongolic*), 12 of *Yiynen* (*Semen Caicii*), 51 of *Leigongteng* (*Radix et Rhizoma Tripterygii*), and 9 of *Wugong* (*Scrophularia*).

Action Targets of XFC and RA and Their Common Targets

A total of 197 targets corresponding to XFC active ingredients were retrieved from the TCMSP database. Moreover, 2810, 27, 571, and 169 RA-related targets were collected, respectively, by searching GeneCards, OMIM, DrugBank, and TTD databases. A total of 152 RA-related targets were eventually obtained after the removal of duplicate genes. Venn analysis was performed on 197 targets corresponding to XFC active ingredients and 152 RA-related targets using RData software. Thirty intersected genes were found which were the potential targets of XFC in the treatment of RA (Figure 2).

Target Prediction of Active Ingredients of XFC

Cytoscape3.7.2 software was used to construct a network diagram of “Chinese Medicine – Active Ingredient – Potential Target”, in which pink represents the drugs in XFC, yellow represents an active ingredient of Chinese medicine, and purple represents the potential target (Figure 3).
Construction of PPI Network

The intersection genes were imported into the STRING database to draw the PPI network diagram, as shown in Figure 4. The downloaded PPI network files were imported into Cytoscape, and 5 core targets were obtained using the MCC algorithm in the cytoHubba plug-in (Figure 5).

GO Functional Analysis and KEGG Pathway Enrichment Analysis

In this study, the enrichment analysis of the abovementioned PPI protein interaction network targets was completed through the DAVID database, suggesting that the overall treatment process had multiple signaling pathways that took part in the regulation of various BPs. The results of GO functional enrichment analysis showed that the key targets of XFC in the treatment of RA were mainly enriched in biological reactions, such as inflammation, apoptosis, I-kappaB phosphorylation, and immune reaction. KEGG signaling pathway enrichment analysis manifested that the related targets were significantly enriched in interleukin-17 (IL-17), tumor necrosis factor (TNF), nuclear factor-κB (NF-κB), and other signaling pathways (Figures 6 and 7).

Table 3. Random Walking Model of Immune-Inflammatory and Coagulation Indicators.

| Index | Maximum random fluctuation | Walking positive growth rate | Random fluctuation power law value | Improvement coefficient | Comprehensive evaluation records | Ratio |
|-------|-----------------------------|-----------------------------|-----------------------------------|-------------------------|----------------------------------|-------|
| RF    | 223                         | 0.195                       | 0.407 ± 0.170                     | 0.330                   | 675                              | 5.130 |
| ESR   | 280                         | 0.212                       | 0.392 ± 0.125                     | 0.353                   | 794                              | 4.710 |
| Hs-CRP| 305                         | 0.220                       | 0.453 ± 0.143                     | 0.354                   | 862                              | 4.540 |
| C3    | 119                         | 0.110                       | 0.349 ± 0.106                     | 0.215                   | 553                              | 9.050 |
| C4    | 148                         | 0.137                       | 0.399 ± 0.113                     | 0.268                   | 553                              | 7.280 |
| FBG   | 20                          | 0.030                       | 0.352 ± 0.161                     | 0.133                   | 151                              | 33.750|
| PLT   | 68                          | 0.052                       | 0.390 ± 0.143                     | 0.088                   | 775                              | 19.100|
| TT    | 21                          | 0.031                       | 0.267 ± 0.175                     | 0.138                   | 152                              | 32.190|
| PT    | 18                          | 0.027                       | 0.238 ± 0.100                     | 0.118                   | 152                              | 37.560|
| APTT  | 31                          | 0.046                       | 0.310 ± 0.161                     | 0.205                   | 151                              | 21.770|

Abbreviations: APTT, activated partial thromboplastin time; CRP, C-reactive protein; C3, complete component 3; ESR, erythrocyte sedimentation rate; FBG, fibrinogen; Hs, high sensitivity; PT, prothrombin time; PLT, platelet; RF, rheumatoid factor; TT, thrombin time.

Figure 1. Random walking model of immune-inflammatory indices in rheumatoid arthritis (RA) patients. Note: The length of the horizontal line increases with the number of walking steps. The height of the vertical line increases with intervention efficacy and response.
Molecular Docking of key Targets

To conduct an in-depth investigation into the key molecular mechanism of XFC in the treatment of RA, we selected 10 active components as ligands and 5 core targets as receptors. The docking results are shown in Figure 8. The abscissa represents the active component of XFC, and the ordinate represents the core target. The color depth indicates the binding energy. A binding energy $< -7.0 \text{ kcal mol}^{-1}$ indicated a strong binding activity and a negative correlation between the docking effect and binding energy. The results unveiled that the minimum binding energy obtained by $\beta$-sitosterol and stigmasterol docking with TNF and prostaglandin-endoperoxide synthase 2 (PTGS2) was less than $-8.0 \text{ kJ mol}^{-1}$, and $\beta$-sitosterol had a better binding ability to TNF. In addition, PyMOL was used to visualize the docking results of $\beta$-sitosterol and TNF, as...
shown in Figure 9. Therefore, these 2 compounds and 2 proteins may be the key compounds and core targets in the treatment of RA by XFC, which may also provide a molecular biological basis for further experimental verification.

Discussion

Synovial vasculitis is regarded as the major pathological change in RA patients. In vivo inflammation can activate the body’s coagulation and fibrinolysis system and increase the levels of FBG and PLT, leading to hypercoagulability. Therefore, it is of great value to clarify the hypercoagulability of patients for the treatment of RA. FBG is a protein synthesized by the liver, which can result in PLT aggregation in the body and induce red blood cell adhesion and thrombosis when it plays a role. The increase of this index indicates that the human body is in a hypercoagulable state. According to the study carried out by Lu Xuedan, RA patients had high serum D-D activity and their FBG levels were higher compared to the normal group due to the high activity group joint inflammation. Joint inflammation can induce prothrombin and FBG, such as plasma components, into the joint cavity, while the joint cavity inflammation factor could lead to the activation of
blood coagulation responses. Moreover, the higher the RA activity is, the more severe is the inflammatory response. Meanwhile, the inflammatory response can stimulate the synthesis of large amounts of FBG in the liver, which further participates in the formation of a microthrombus and activation of the coagulation-fibrinolytic system, resulting in a vicious cycle.

As one of the tangible components in blood, PLTs play an important role in physiological and pathological processes, such as coagulation, inflammatory reaction, and thrombosis. Modern studies have shown that an elevated PLT count is one of the main characteristics of RA, and RA patients have a significantly higher PLT count than that of normal subjects.

In this study, laboratory indicators of clinical RA patients were observed before and after the treatment based on the HIS system. According to our results, after the treatment, the inflammatory indicators, including RF, ESR, C3, C4, and Hs-CRP, improved significantly, while the coagulation indicators, including PLT, FBG, TT, PT, and APTT, improved notably. Association rule analysis results showed that XFC was strongly correlated with the improvement of RF, Hs-CRP, ESR, C3, C4, FBG, and PLT indexes, with Support > 70%, Confidence > 70%, and Lift > 1, as shown in Table 2. According to the data mining results, XFC had the effect of improving immune-inflammatory and coagulation indicators in RA patients and regulate the immune-inflammatory response.

XFC is a TCM compound. Our team’s previous research results show that XFC accelerates the apoptosis of synovial fibroblasts by regulating long noncoding RNA MAPKAPK5-AS1, thus repressing the response of RA. XFC can improve the symptoms of RA patients, improve cardiopulmonary function, and reduce the parameters of anemia and PLT factor. XFC can reduce the immune inflammatory response to improve the extra-articular lesions in RA patients. XFC can regulate the level of B cell activating factor and its receptor in active RA and increase the level of immunoglobulin in RA patients. XFC can regulate the level of B cell activating factor and its receptor in active RA and increase the level of immunoglobulin in RA patients. XFC can regulate the level of B cell activating factor and its receptor in active RA and increase the level of immunoglobulin in RA patients. XFC can regulate the level of B cell activating factor and its receptor in active RA and increase the level of immunoglobulin in RA patients. XFC can regulate the level of B cell activating factor and its receptor in active RA and increase the level of immunoglobulin in RA patients.

According to the results of network pharmacology analysis, the main target proteins involved in the treatment of RA by
Figure 7. Kyoto Encyclopedia of Genes and Genomes (KEGG) signal pathway bubble map (top10).

Figure 8. Heat map of the minimum binding energy of docking of active compounds with core targets.
XFC, such as PTGS2, CASP3, TNF, AKT1, and JUN, were closely related to inflammation, tumor, and immunity. Among them, PTGS2 and TNF were the active target proteins with optimal binding in molecular docking. Moreover, AKT1 is involved in the regulation of cell proliferation, invasion, and differentiation, as well as tissue fibrosis. The transforming growth factor-β1 (TGFβ1) can bind to the fibroblast membrane receptors to activate the PI3K/Akt pathway, leading to phosphorylation and activation of the AKT factor.30 As an important cytokine, TNF has multiple biological functions, which can be involved in inducing inflammatory and immune responses, cell survival and apoptosis.31

Through screening the effective compounds of XFC in the treatment of RA in the early stage and verifying by molecular docking technology, our study found that β-sitosterol and stigmasterol, the active ingredients of XFC, had the strongest binding with TNF and PTGS2 in molecular docking, suggesting that XFC may play a critical role in the treatment of RA. Research shows that β-sitosterol has neuroprotective, antimutagenic, anti-diabetes, and antifungal effects.32 Its effect is especially related to the reduction of oxidative stress in cardiovascular diseases, aging, and cancer.33 Stigmasterol can also remarkably reduce the mRNA expressions of cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS), which are inflammatory factors stimulated by lipopolysaccharide (LPS), and has an anti-inflammatory effect by reducing PGE2 and NO release.34

**Conclusion**

This study elucidated that the immune-inflammatory indicators and coagulation indicators in RA patients were effectively improved after XFC treatment, suggesting the critical role of XFC in the improvement of immune inflammatory response. In addition, the molecular mechanism of XFC in the treatment of RA was preliminarily discussed by adopting the network pharmacology method, which demonstrated that the key active components of XFC, such as β-sitosterol and stigmasterol, mainly acted on TNF, PTGS2, CASP3, AKT1, JUN, and other targets. Through IL-17, TNF, NF-κB, and other signaling pathways, the drug participated in the activity of transcription factors and immune response, thus contributing to anti-PLT aggregation, inhibition of inflammatory response, and anti-myocardial ischemia. Overall, the research results can comprehensively reflect the synergistic characteristics of Chinese medicinal compounds with multiple components, targets, and pathways. However, due to the limitations of network pharmacology analysis, this study only studied the mechanism of action of XFC in treating RA from the theoretical level. Therefore, relevant pharmacological experiments are needed for verification so as to further clarify the pharmacological mechanism of XFC in treating RA and provide new research ideas for the prevention and treatment of RA in clinical practice.
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