Mechanism of Kaempferol in Anti-inflammation Based on Network Pharmacology

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Abstract. To explore the mechanism of kaempferol in treatment of anti-inflammation based on network pharmacology. The chemical ingredient targets of kaempferol were obtained from Traditional Chinese Medicine Systems Pharmacology Database (TCMSP). The predicted targets related to predicted targets related to inflammation were obtained from GeneCards database. The prediction target of kaempferol was mapped with the target of inflammation to get the prediction target of kaempferol to anti-inflammatory. Cytoscape 3.7.1 software was used to draw the kaempferol targeted-anti-inflammatory targets network. Protein interaction network was made through STRING database. GO and KEGG were analyzed by the “ClueGO” plug-in of Cytoscape 3.7.1 software. There were 61 targets for kaempferol, 3416 disease genes were obtained, and 50 same targets were found. Important targets were screened out, such as AKT1, TNF, PTGS2, GASP3, MAPK8, JUN and GASP3. KEGG signaling pathways was screened, and 20 signaling pathways were obtained, including TNF signaling pathway, IL-17 signaling pathway, Apoptosis, non-fatty liver disease (NAFLD), and so on. Kaempferol mainly acts on targets of AKT1, TNF, PTGS2, GASP3, MAPK8, JUN, GASP3 and other targets to inhibit inflammation through signaling pathways including TNF signaling pathway, IL-17 signaling pathway, Apoptosis, non-alcoholic fatty liver disease (NAFLD), etc.

1. Introduction

Inflammation is the defensive response of living tissues with vascular systems to injury factors. The symptoms include redness, swelling, heat and pain, leukocytosis, mononucleosis, and degeneration, necrosis and dysfunction of the heart, liver and kidney [1-2]. The persistence of inflammation is harmful to the body and plays an important role in the occurrence and development of many major diseases [3].

Kaempferol is a kind of flavonoids, also known as kaempferide, widely exists in fruits, vegetables and Chinese herbal medicine and other natural plants. Studies have shown that kaempferol has a very obvious anti-inflammatory effect [4-5]. Therefore, in order to further understand the role of this component in treating inflammation and thus provide theoretical support, this paper uses the network pharmacology method to visualize and analyze its target and mechanism of action, in the hope of explaining it.
2. Methods

2.1. Screening of component targets
TCMSP was used to retrieve the target of kaempferol, select the relevant target that meets the requirements, and query the corresponding gene name of the relevant target with the help of Universal protein.

2.2. Screening of disease targets
The key word “Anti inflammation” was searched in GeneCards database to obtain the related disease targets, and the common targets of components and diseases were obtained.

2.3. PPI network analysis
The integrated target information was imported into the STRING database, the species was limited to “Homo sapiens”, the protein protein interaction information was obtained, and the file was imported into the software of Cytoscape 3.7.1, and the “network analyzer” plug-in of the software was used to analyze the protein interaction network of the above network node values.

2.4. Acquisition of key targets
Through the network analyzer network analysis analysis network in the tools module of Cytoscape 3.7.1 software, the relevant topological parameters are obtained. The double median of node degree, the median of betweenness and closeness are selected as the screening basis to screen out the key targets.

2.5. Enrichment analysis of GO and KEGG pathways
The key drug-disease target genes were introduced into Cytoscape 3.7.1 software. The “ClueGO” plug-in of the software was used to map the signal pathways screened out in the enrichment analysis of the GO function and KEGG pathway, so as to illustrate the role of Kaempferol target proteins in gene function and signal pathway.

3. Results and discussions

3.1. Screening of component targets
The TCMSP database obtained 61 targets for kaempferol. The oral bioavailability of kaempferol was 41.88, and the drug likeness was 0.24.

3.2. Screening of disease targets
Through GeneCards database, 3416 disease genes was obtained, and 50 common genes of diseases and components were screened out. The common genes were introduced into the software of Cytoscape 3.7.1 to construct kaempferol targets inflammation targets network (Figure 1).

![Figure 1. The “component-target-disease” interaction network of the anti-inflammatory effects of kaempferol.](image-url)
3.3. PPI network analysis
The 50 targets were imported into STRING database, and the merge function in Cytoscape 3.7.1 was used to merge the active component targets network and the proteins interaction network. The node size is formed by size of the degree value. The larger the degree value, the larger the node (Figure 2).

Figure 2. PPI network of kaempferol against inflammation.

3.4. Acquisition of key targets
Selecting Degree double medians, Betweenness and Closeness median as the screening basis. The key targets were obtained by the software of Cytoscape 3.7.1, including AHR, HMOX1, MAPK8, JUN, AKT1, PTGS2, TNF and CASP3 (Figure 3).

Figure 3. Key targets network.

3.5. GO enrichment and KEGG analysis results
Go analysis and KEGG signal pathway analysis were performed by using ClueGO plug-in in Cytoscape 3.7.1. Two functional groups were obtained by Go analysis (Figure 4). The results were enriched in cellular response to calcium ion, positive regulation of smooth muscle cell promotion, external apoptotic
signaling pathway in absence of life, and positive regulation of nitric oxide biosynaptic process. KEGG pathway analysis results in 20 pathways (Figure 5). The enriched first 10 signaling pathways involving the TNF signaling pathway, IL-17 signaling pathway, typical Apoptosis, and other signaling pathways (Table 1).

Figure 4. Functional group diagram for GO enrichment analysis.

Figure 5. KEGG signaling pathways diagram.
Table 1. Top 10 KEGG signaling pathways.

| GOTerm                                      | Nr. Genes |
|---------------------------------------------|-----------|
| TNF signaling pathway                       | 6         |
| IL-17 signaling pathway                     | 5         |
| Apoptosis                                   | 5         |
| Non-alcoholic fatty liver disease (NAFLD)   | 5         |
| AGE-RAGE signaling pathway in diabetic      | 5         |
| complications                               |           |
| Hepatitis B                                 | 5         |
| Fluid shear stress and atherosclerosis      | 5         |
| Pertussis                                   | 4         |
| Osteoclast differentiation                  | 4         |
| Toll-like receptor signaling pathway        | 4         |

4. Discussion
Kaempferol is widely found in most traditional Chinese medicines. It has antioxidant, anti-inflammatory, anti-cancer and other biological functions, and is safe and non-toxic. It can be used as healthy food and medicine, with good development and application prospects [6]. MAPK signaling pathway is involved in regulating the expression of inflammatory mediators and promote inflammation by enhancing the expression of nuclear transcription factor (NF- B) and AP-1 through activation [7].

It was study found that kaempferol can significantly inhibit the expression of MAPK pathway of human monocyte THP-1 induced by LPS, and reduce the production of macrophage derived chemokine and interferon induced protein-10 inflammatory factors, thus effectively inhibiting the occurrence of inflammation[8]. Kaempferol can inhibit the activation of STAT3 by blocking the Tyk-STAT signaling pathway of airway epithelial cells in asthmatic mice, thus inhibiting the occurrence and development of inflammation [9].

With the use of network pharmacology, this study elaborated the specific mechanism of kaempferol anti-inflammation from multiple levels of components, proteins and pathways. The 61 targets of kaempferol were obtained through TCMSP database, and the values of oral bioavailability (41.88) and drug-like property (0.24) were both high.

The 50 targets related to inflammation were screened out. The protein level results showed that according to the screening of key targets, it was found that the targets mapped by kaempferol and inflammation included AKT1, TNF, PTGS2, GAS5P3, MAPK8, JUN and GAS5P3. Bi et al. [10] found that Catalpol inhibits the production of PTGS2 in the inflammatory response of astrocytes, making NF- B inactivated may be the main determinant of anti-inflammatory mechanism. The survival rate of endothelial cells induced by TNF was improved, and the activity of AP-1 and McP-1 was decreased, thereby inhibiting the inflammatory response of endothelial cells [11].

KEGG signal pathway analysis results show that the top channels are mainly TNF signaling pathway, IL-17 signaling pathway, Apoptosis, Non-alcoholic fatty liver disease (NAFLD) and so on. This study showed that kaempferol plays an anti-inflammatory role in inhibiting inflammatory response through multi-target and multi-signaling pathways.

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