Mechanism of Xuanhuang Ointments for the Acute Soft Tissue Injury Based on Network Pharmacology

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Abstract: Screen the therapeutic target of XuanHuang Ointment on acute soft tissue injury by network pharmacology method, and to clarify its mechanism. The main chemical constituents and their targets of XuanHuang Ointment were obtained by using TCMSP database. The disease targets of acute soft tissue injury were searched by GeneCards. A compound-target-disease network was constructed using Cytoscape3.8.2 software. The targets were analyzed by GO analysis and KEGG enrichment analysis based on Metascape database. The core active components of XuanHuang Ointment were Quercetin, beta-sitosterol, Stigmasterol. The core target spots are: NCOA2, PTGS2, PTGS1, PGR and NR3C2. Pathways in cancer, Lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications may play a potential role in XuanHuang Ointment in the treatment of acute soft tissue injury Signaling pathway. Conclusion XuanHuang Ointment has the characteristics of multiple components, multiple targets and overall regulation in the treatment of acute soft tissue injury.

Keywords: XuanHuang Ointment; Acute soft tissue injury; Network pharmacology

1. Introduction

Acute soft tissue injury refers to a kind of trauma syndrome caused by a variety of acute direct or indirect violent injury factors, which is a common orthopedic disease[1], most present with local edema of soft tissue, muscle fiber rupture, pain and dysfunction[2]. Acute soft tissue injury Traditional Chinese medicine belongs to the category of "acute tendon injury", which is due to external external and internal damage to qi and blood, qi stagnation and blood stasis, meridians obstruction, resulting in pain, swelling, subcutaneous bleeding, movement obstruction[3]. With the continuous development of medicine, the Chinese and western medicine treatment methods for acute soft tissue injury are numerous. Conservative treatment of western medicine and the treatment of acute soft tissue injury is based on the basic principles of internal and external treatment, both internal and external treatment, and the treatment methods of internal and external treatment, acupuncture and manipulation[4].

Xuanhuang ointment is the effect of the long-term experience of treating acute tendon injury, namely acute soft tissue injury, in Shaanxi Provincial Hospital of Traditional Chinese Medicine. Xuanhuang ointment consists of rhubarb, gardenia, frankincense, myrrh, dandelion, and turtle insects. Rhubarb bitter, cold, working in clearing away heat and detoxification, cooling blood and removing blood stasis, external use can detoxify, reduce swelling and relieve pain[5]. Gardenia is bitter and cold; it is "the main medicine to relieve heat and cool blood", with the effect of clearing heat and detoxification, promoting blood circulation and dispersing knot, external use of swelling and pain, treating contusion and pain[6]. Frankincense and myrrh belong to the drugs of promoting blood circulation and removing blood stasis, frankincense, bitter, warm, activating blood circulation, swelling, no muscle, pain, flat, swelling, pain, Zhang Sichun believes that frankincense is good at measure the body and qi; Myrrh is good at regulating blood stasis, the effect of promoting viscera and meridians[7]. Dandelion bitter, sweet, cold, heat detoxification, swelling and knot. Ground turtle insect into the blood, good walk channeling, can promote the blood swelling and pain, continuous bone healing, especially for fracture injury, hematoma and pain[8]. Prescription drug bitter cold, co-treatment of early qi stagnation and blood stasis type of acute soft tissue injury[9].

Network pharmacology is a discipline that integrates the relationship between drugs and diseases from the perspective of system and whole, and shows the systemic pharmacological mechanism of drugs[10]. Network pharmacology studies TCM from the perspective of "multi-component, multi-target and multi-channel", which is consistent with the overall concept of TCM and the treatment concept of
syndrome differentiation and treatment\footnote{11}. Many studies have found that xuanhuang ointment has a significant effect in the treatment of acute soft tissue injury. The author uses network pharmacology to identify the main active components and core targets of xuanhuang ointment and acute soft tissue injury, and further analyzes the molecular mechanism of the treatment of acute soft tissue injury.

2. Method

2.1 Search and screening of the active ingredients of Xuanhuang ointment

Using the TCMSP database (http://tcmsp.com/tcmsp. Search php) for the prescription ingredient: rhubarb, gardenia, frankincense, no medicine, dandelion, all the active ingredients of the turtle worm. All the active ingredients of the searched drug were selected as oral availability (OB) 30%, drug-like (DL) 0.18 for the active ingredients and their protein targets. Then in the Uniprot Protein Data Bank (https://www.uniprot.org/) to normalize the protein targets.

2.2 GO pathway enrichment analysis and KEGG pathway enrichment analysis

In order to explore the role of the target protein of Xuanhuang ointment in gene function and to find the core pathway of its action on acute soft tissue injury, this study used the Metascape database (https://metascape.org/) conducted GO pathway enrichment analysis and KEGG pathway enrichment analysis on core targets, and used microxin cloud platform (http://www.bioinformatics.com.cn/) to alizee the results.

2.3 Construction of the component-target-disease network map

The drug active ingredients and the screened core targets were uploaded to the Cytoscape 3.8.2 software to generate the "component-target-pathway network map". The built-in tools of CytoScape3.8.2 is used to analyze the active components and the network topological parameters of the targets, and to judge the core targets and the main active components according to the relevant parameters.

2.4 Molecular docking

Selecting the PDB database (https://www.rcsb.org/packages/search_features) download the PDB structure of key targets, and the MOL 2 structure of the active components of Xuanhuang ointment in the TCMSP database to docking the molecules and targets with AutoDock Vina 1.1.2. If the binding energy is less than 0, then there is a binding activity between the ligand and the receptor, which is less than-5 kcal / mol\footnote{Good docking. Finally, the results were visualized using Pymol 2.2.0.

<table>
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<th>number</th>
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<th>DL</th>
<th>source</th>
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<td>tricarcol</td>
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<td>0.15</td>
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<td>RX2</td>
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<td>And O-acetyl- α -lactocentic acid</td>
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<td>0.7</td>
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3.1 Acquisition of active ingredients and targets of xuanhuang ointment

The active ingredients of rhubarb, gardenia, frankincense and myrrh can be directly collected through TCMSP, including 92 kinds of rhubarb, 98 kinds of gardenia, 127 kinds of frankincense and 276 kinds of medicine. The active components of dandelion and turtle worm cannot be found directly by the TCMSP database; retrieve the database and find the relevant components of dandelion and turtle worm[12-13].

Combined with the TCMSP database, after ADME, set the threshold and select the effective components of dandelion and turtle worm. The effective ingredients of all the prescriptions of Xuanhuang ointment were summarized, and the effective ingredients of xuanhuang ointment were obtained, including 62 kinds, 7 kinds of rhubarb, 14 kinds of gardenia, 5 kinds of frankincense, 31 kinds of myrrh, 37 kinds of dandelion and 2 kinds of turtle worm, among which there were 3 kinds of repeated effective ingredients between drugs, see Table 1. After the merger, 201 active components of xuanhuang ointment were obtained.

3.2 Acquisition of targets associated to acute soft tissue injury

The search results for disease-related targets of acute soft tissue injury was: 4448 GeneCards...
database, 207 OMIM database, removing duplicate targets, and totaling 4600 targets related to acute soft tissue injury.

3.3 Results of GO pathway enrichment and KEGG pathway enrichment analysis

GO pathway enrichment analysis and KEGG pathway enrichment analysis were performed on 148 targets using the Metascape gene annotation and analysis resource platform, and the enrichment analysis results were visualized using the microcloud platform. The results show that multiple target functions are closely related to the treatment of acute soft tissue injury. Among them, Xuanhuang ointment mainly involved in biological processes includes: hormone response, response to inorganic substances, cell response to lipids, response to external stimuli; cell component analysis results mainly include: membrane raft, transcriptional regulatory complex, dendrites, etc.; molecular function analysis results mainly include: DNA transcription binding factor, nuclear receptor activity, protein domain specific binding, kinase binding bond, protein kinase activity, etc. The results of KEGG pathway enrichment analysis were 203 pathways, which showed that the main pathways of xuanhuang ointment for acute soft tissue injury were: cancer pathway, lipid and atherosclerosis pathway, AGE-RAGE signaling pathway in diabetic complications, and PI3K-Akt signaling pathway.

3.4 Construction of the component-target-pathway network map

The 62 active ingredients of Xuanhuang ointment and 167 common targets of acute soft tissue injury were uploaded to Cytoscape3.8.2 software to construct a "component-target-pathway network map". Through CytoScape3.8.2 built-in NetworkAnalyzer tool, analyze the network topological parameters for acute soft tissue injury, and obtain the core components and core targets. CytoScape3.8.2 Analysis results showed that the main component of acute soft tissue injury was quercetin with 372, resolution is 0.2176, tightness is 0.5995; β-sitosterol has 108, resolution is 0.0160, 0.3982; stigmasterol was 66, 0.0121, tightness is 0.3912; predicted that β-sitosterol and prosterol also play an important role in the treatment of acute soft tissue injury. In the target analysis results, NCOA2 was the first target with connectivity 38, resolution of 0.0504, and tightness of 0.5068. NCOA2 was predicted to be the core target of acute soft tissue injury. In addition, PTGS 2, PTGS 1, PG, GR, and NR 3 C 2 were predicted to play an important role in the treatment of acute soft tissue injury.

3.5 Molecular docking results

Docking of the active ingredients: quercetin, β-sitosterol and core targets: PGR, NCOA2 and PTGS 2. The results showed that the binding energy between the active components and the core target sites was less than -5kcal / mol -1, all have strong binding activity, as shown in Table 2,3,4. Finally, the molecular docking results.

<table>
<thead>
<tr>
<th>MOLID</th>
<th>name</th>
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<th>intermittivity</th>
<th>compactedness</th>
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<td>0.217589532</td>
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<td>MOL000358</td>
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<td>66</td>
<td>0.01210298</td>
<td>0.39122807</td>
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<tr>
<td>MOL000006</td>
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<td>0.041353099</td>
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<td>aloe-emodin</td>
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<td>0.387152778</td>
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<td>69</td>
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<td>MOL001002</td>
<td>ellagic acid</td>
<td>16</td>
<td>0.006337286</td>
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<tr>
<td>MOL001004</td>
<td>pelargonin</td>
<td>14</td>
<td>0.003996555</td>
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<td>MOL001126</td>
<td>[(5 AS, 8R, 9R)-8-oxo-9-(3,4,5-trimethoxyphenyl]-6,9-tetrahydroxydienzofuran[6,5-c] [1,3[benza jodioxol-8a-based] acetate</td>
<td>12</td>
<td>0.00342738</td>
<td>0.377966102</td>
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</table>

Table 3: Characteristic parameters of the core target network nodes of Xuanhuang ointment

<table>
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<td>38</td>
<td>0.0503666534</td>
<td>0.5068188182</td>
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<td>PTGS2</td>
<td>37</td>
<td>0.040694183</td>
<td>0.504524887</td>
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<td>PTGS1</td>
<td>28</td>
<td>0.021359745</td>
<td>0.484782609</td>
</tr>
<tr>
<td>PGR</td>
<td>27</td>
<td>0.028106676</td>
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<td>NR3C2</td>
<td>19</td>
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</table>
Table 4: Molecular docking of core components and targets of XuanHuang Ointment

<table>
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<tr>
<th>Ingredient</th>
<th>NCOA2 Binding energy / kcal · mol⁻¹</th>
<th>PTGS2 Binding energy / kcal · mol⁻¹</th>
<th>PTGS1 Binding energy / kcal · mol⁻¹</th>
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<td>Melatonin</td>
<td>-7.3</td>
<td>-7.9</td>
<td>-9.7</td>
</tr>
<tr>
<td>β-sitosterin</td>
<td>-7.4</td>
<td>-8.0</td>
<td>-8.9</td>
</tr>
</tbody>
</table>

4. Conclusions

At present, with the development of society, acute soft tissue injury has become more and more frequent in the fast pace of life and work, and the influence on people's work and life is increasing year by year. With the continuous progress of medical technology and more attention to their own health, the treatment of acute soft tissue injury is increasing in traditional Chinese and western medicine. Internal and external treatment of traditional Chinese medicine, acupuncture and massage, modern Chinese medicine, oral medicine, western medicine, physical therapy, regenerative medicine, all achieve acute soft tissue injury local detumescence, analgesia, anti-inflammatory and even the whole body under the action of various principles.

Xuanhuang ointment is used in the treatment of acute soft tissue injury such as flash tendons, falling and injury for a long time. It is an important compatibility of seven li powder, nine dispersion, and activating blood circulation and removing blood stasis. This paper analyzed the molecular mechanism of xuanhuang ointment, and analyzed the molecular mechanism of acute soft tissue injury. After analysis, the main effective component of acute soft tissue injury is quercetin. Various studies have shown that quercetin has the effects of antioxidant, tumor suppressor, hypoglycemic, anti-inflammatory, anti-inflammatory, antiviral, antioxidant, lipid regulation, cardiovascular protection and bone protection. NCOA2 is the core target of Xuanhuang ointment for the treatment of acute soft tissue injury. The pathway prediction of xuanhuang ointment for acute soft tissue injury may be related to cancer pathway, lipid and atherosclerosis pathway, AGE-RAGE signaling pathway in diabetic complications, PI3K-Akt signaling pathway, etc.

The results show that the compound regulatory targets are complex, and the target intervention in biological processes and signaling pathways are diverse, which fully reflects the characteristics of multi-target and multi-pathway interaction of Xuanhuang ointment. It suggests that the possibility and feasibility of important targets in the regulatory network can regulate the whole network, which provides a scientific basis for the clinical use of xuanhuang ointment to treat acute soft tissue injury, and also provides a new direction for exploring the potential mechanism of xuanhuang ointment. However, this paper only predicts the effective components, targets and pathway information of xuanhuang ointment in the treatment of acute soft tissue injury from the perspective of network pharmacology, without the support of relevant clinical trials. Follow-up studies should complete the relevant research content of the treatment of acute soft tissue injury from basic and clinical aspects.

References


