ORIGINAL RESEARCH

Identification of active components and functional mechanisms of BAIMA oil against acute soft-tissue injury using network pharmacology

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Abstract

Objective

Acute soft-tissue injury (STI), a common exercise-related clinical injury, significantly affects patients' health and work capacity. This study aimed to analyze the main components and underlying therapeutic targets of BAIMA oil in the treatment of acute STI using network pharmacology.

Methods

The major components and potential targets of BAIMA oil were identified using the TCMSP, PubChem, and SwissTargetPrediction databases. Disease-related targets of acute STI were obtained from the GeneCards and OMIM databases and intersected with the predicted targets of BAIMA oil. Subsequently, a herb–component–target–disease network was constructed using Cytoscape to identify key active components. A protein–protein interaction (PPI) network of the shared targets was then established, and hub genes were identified based on topological and cluster analyses. In addition, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed on the selected disease–component targets.

Results

A total of 46 active components and 680 potential targets of BAIMA oil were identified. Overall, 261 disease–component targets were screened using a Venn diagram. In the herb–component–target–disease network, the top five active components were naringenin, Sennoside E_qt, 5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone, acacetin, and quercetin. In the PPI network, TP53, EGFR, and STAT3 were identified as the top three core targets based on topological analysis. GO and KEGG enrichment analyses indicated that the disease–component target genes were mainly associated with ATP binding, protein kinase activity, regulation of cell proliferation and apoptosis, protein phosphorylation, and were involved in signaling pathways such as the PI3K/Akt and MAPK pathways.

Conclusion

This study systematically analyzed the active components and molecular targets of BAIMA oil in the treatment of acute soft-tissue injury, providing scientific evidence to support the potential application of BAIMA oil as an alternative therapeutic strategy for patients with acute STI.

Keywords: BAIMA oil, active components, acute soft-tissue injury, network pharmacology

Introduction

Chronic or acute soft-tissue injury (STI) is a common condition among athletes as well as the general population and typically involves sprain, strain, or contusion of joints, ligaments, tendons, or muscles[1]. STI patients often present with symptoms such as localized pain, swelling, stasis, and functional impairment of the affected tissues[2]. In the UK, acute STI is estimated to account for 5%–10% of emergency department visits[3]. Patients with acute STI may be treated with injectable therapies such as corticosteroids and platelet-rich plasma (PRP), oral analgesics, physiotherapy, or surgical intervention. However, some pain-relieving treatments are associated with adverse effects, including nausea, vomiting, and dizziness, and long-term use of corticosteroids may be harmful, whereas PRP, although safe and effective, is limited by high cost and delayed therapeutic effects[4,5]. Moreover, improper treatment or insufficient healing may result in lifelong pain, thereby significantly impairing patients' quality of life. Therefore, it is essential to explore safe and effective alternative therapeutic strategies for patients with acute STI.

Traditional Chinese Medicine (TCM) has demonstrated beneficial effects in the treatment of various diseases based on thousands of years of clinical experience. In TCM theory, acute STI is considered a type of tendon injury characterized

by qi stagnation and blood stasis. An increasing number of studies have reported favorable clinical outcomes of TCM interventions for the treatment of acute STI[2,6,7]. For example, Wuhu oral liquid has been shown to be a safe and effective therapeutic option for alleviating symptoms such as swelling, ecchymosis, and dysfunction in patients with acute STI[8]. Medicinal oil is an ideal form of external therapy that is widely used for pain relief and injury healing, and transdermal drug delivery offers the advantage of reduced systemic toxicity by avoiding the first-pass effect[9, 10]. BAIMA oil is a modified prescription derived from Arcane essentials from the imperial library, a classic collection of medical prescriptions from the Tang Dynasty. It consists of four ingredients, including Menthae Herba (Bohe), Gardeniae Fructus (Zhizi), Chebulae Fructus (Hezi) and Camellia oil (Shanchayou). Bohe is widely used in medicinal preparations and exhibits anti-inflammatory and antioxidant activities. Zhizi, a member of the Rubiaceae family, is commonly used in TCM for the treatment of mental disorders such as anxiety, depression, insomnia, and psychosis. Previous studies have also reported that Zhizi possesses antithrombotic and anti-inflammatory properties[11,12]. Bohe and Zhizi are the main components of the Shang-Ke-Huang-Shui lotion, which is used to treat soft tissue injuries with high safety and minimal toxicity or side effects[12-14]. Hezi, known as the "king of medicine" in Tibet, belongs to the Combretaceae family and is commonly used to reduce toxicity and relieve diarrhea, cough, and sore throat due to its anti-inflammatory, antioxidant, and detoxifying properties[15-17]. Shanchayou exhibits antioxidant, anti-inflammatory, and immunomodulatory activities and is commonly consumed as an edible oil in China. Studies have shown that Shanchayou is effective in the treatment of obesity, liver injury, and neurodegenerative diseases such as Alzheimer's disease[18-21]. However, the specific active components and molecular targets of BAIMA oil in the treatment of acute STI remain largely unclear.

Network pharmacology provides an effective strategy for understanding traditional medicines and facilitating drug discovery by shifting disease treatment from a "single-disease, single-target, single-drug" paradigm to a multi-target, system-level regulatory approach[22,23]. In the present study, we investigated the active components and potential therapeutic targets of BAIMA oil in the treatment of acute STI using network pharmacology, aiming to provide novel insights into STI therapy.

Materials and Methods

Screening of effective components and related targets of BAIMA oil

The active components of BAIMA oil ingredients (Menthae Herba, Gardeniae Fructus, and Chebulae Fructus) were retrieved from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database using the screening criteria of drug-likeness (DL) ≥ 0.18 and oral bioavailability (OB) ≥ 30% 24. The components of Camellia oil were collected from previously published literature 25, 26. The SMILES structures of all identified components were obtained from the PubChem database and subsequently imported into the SwissTargetPrediction platform to predict potential molecular targets. Targets with a prediction probability of 0 were excluded from further analysis.

Identification of the disease targets of acute STI

OMIM (https://omim.org/) and Genecards (https://www.genecards.org/) databases were used to search the disease targets using the "acute soft-tissue injury" as the keyword. The duplicates were eliminated.

Herb-component-target-disease network

The target genes of BAIMA oil and acute STI were imported into the Venny 2.1 online platform to visualize the candidate targets of BAIMA oil involved in acute STI. The component–target data were integrated to construct an herb–component–target–disease network using Cytoscape software (version 3.9.1), and the degree value of each node was calculated using the Network Analysis function.

PPI network and analysis

The STRING database (https://cn.string-db.org/) was used to analyze protein–protein interaction (PPI) relationships among the candidate component targets associated with acute STI under a high-confidence threshold (confidence score ≥ 0.7) (0.7) 27. The interaction data were downloaded and imported into Cytoscape software for visualization and analysis. To identify hub genes, the CentiScaPe plug-in was used to calculate the degree, betweenness, and closeness centrality of the network. The top ten target genes ranked by degree were selected and visualized. The MCODE plug-in was then applied for cluster analysis, and the top three clusters of the network were identified and visualized using the following parameters: node score cutoff = 0.2, K-core = 2, and maximum depth from seed = 100.

GO function and KEGG pathway enrichment analysis

For Gene Ontology (GO) functional and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses, the target genes of BAIMA oil related to acute STI were uploaded to the DAVID database (https://david.ncifcrf.gov/). The top ten enriched GO terms across biological processes, cellular components, and molecular functions, as well as the top twenty significantly enriched KEGG pathways, were screened based on P values and visualized using the ggplot package in R software (version 4.2.1).

Results

Identification of targets of BAIMA oil in acute STI

The disease-related gene set of acute STI was obtained from the GeneCards and OMIM databases. A total of 1,911 acute STI–related targets were collected after removing duplicate entries. As shown in the Venn diagram, 261 overlapping targets were identified as potential therapeutic targets of BAIMA oil in the treatment of acute STI (Figure 1A). Subsequently, a herb–component–target–disease network was constructed using Cytoscape software, as illustrated in Figure 1B. The top ten components ranked by degree were naringenin (B9), Sennoside E_qt (H8), 5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone (Z3), acacetin (B1), quercetin (Z12), genkwanin (B6), diosmetin (B3), kaempferol (Z10), luteolin (B8), and cheilanthifoline (H4), which were suggested to be the most effective components against acute STI (Figure 1B).

Construction of the PPI network

The candidate target genes of BAIMA oil involved in the treatment of acute STI were analyzed using the STRING database with a minimum required interaction score of 0.7, and disconnected nodes were excluded. The interaction

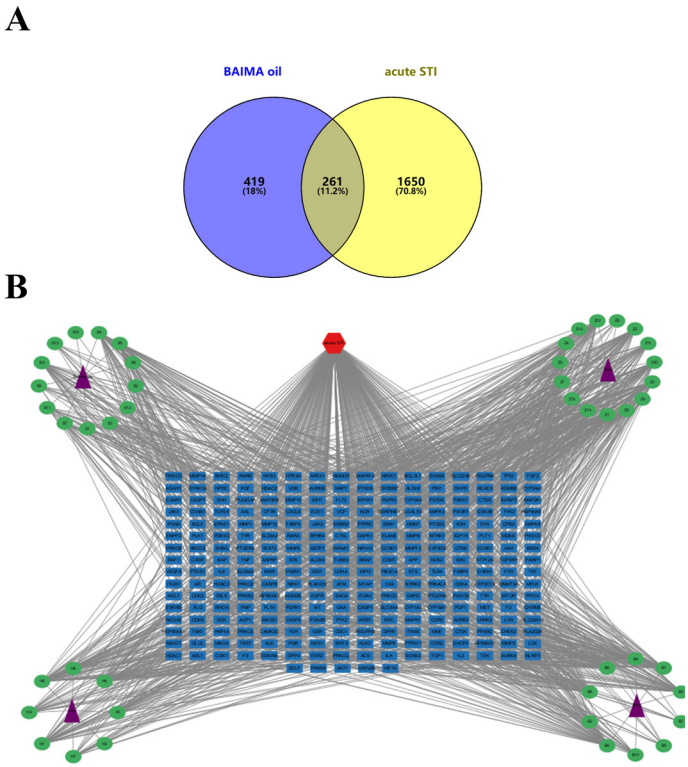

Figure 1. Potential targets of BAIMA oil in acute STI. (A) The venn diagram showed the shared targets between BAIMA oil and acute STI. (B) The herb-component-target-disease network for 46 candidate bioactive ingredients and 261 potential targets of BAIMA oil in acute STI.

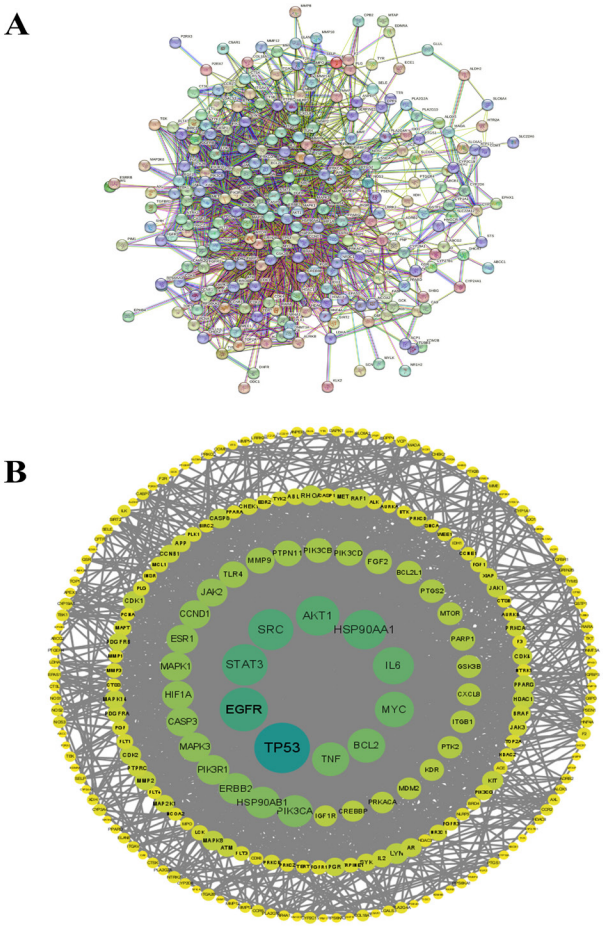

Figure 2. Construction of the PPI network of the target genes. (A) STRING database constructed the PPI network of the 261 target genes of BAIMA oil in acute STI. (B) The herb-component-target-disease network was constructed using the Cytoscape software.

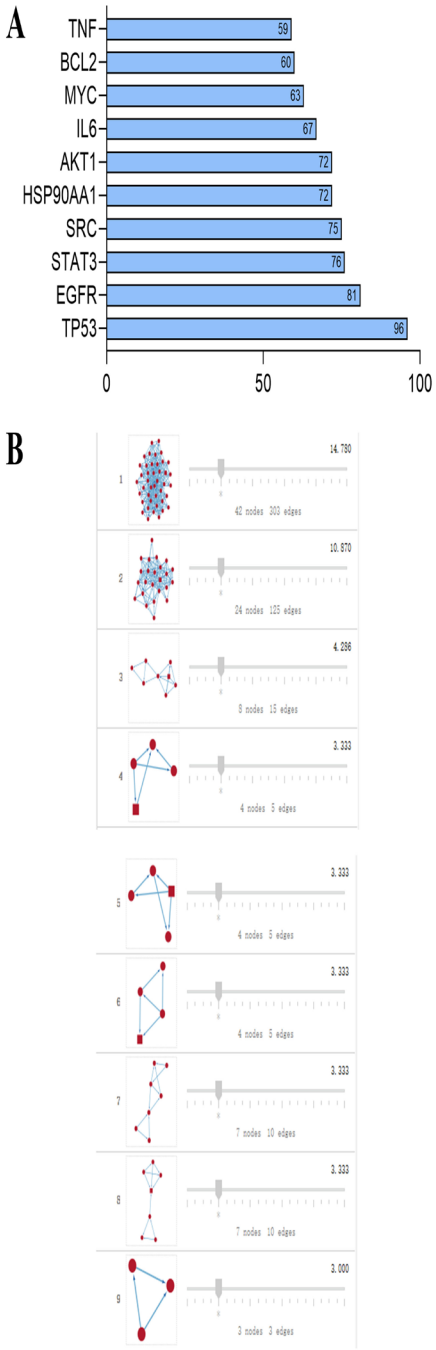

Figure 3. Analysis of the PPI network for hub genes. (A) The centiscape plug-in was used to select the hub genes among the 261 candidate targets. The top 10 genes ranked by degree were screened and visualized. (B) The MCODE plug-in was used to select the hub genes among the 261 candidate targets based on clustering analysis.

data downloaded from the STRING database were then imported into Cytoscape software, and the PPI network was constructed, as shown in Figure 2B. The resulting network consisted of 249 nodes and 2,098 edges. The interaction degree of each node was represented by node size and color.

Discovery of hub genes

The PPI network was further analyzed using the CentiScaPe plug-in in Cytoscape software. The top ten genes ranked by degree were identified as hub genes, including TP53, EGFR, STAT3, SRC, HSP90AA1, AKT1, IL6, MYC, BCL2, and TNF (Figure 3A). Subsequently, the MCODE plug-in was applied for cluster analysis, resulting in the identification of nine gene clusters (Figure 3B). Genes within cluster 1 were considered core targets, including ERBB2, TYK2, STAT3, and others.

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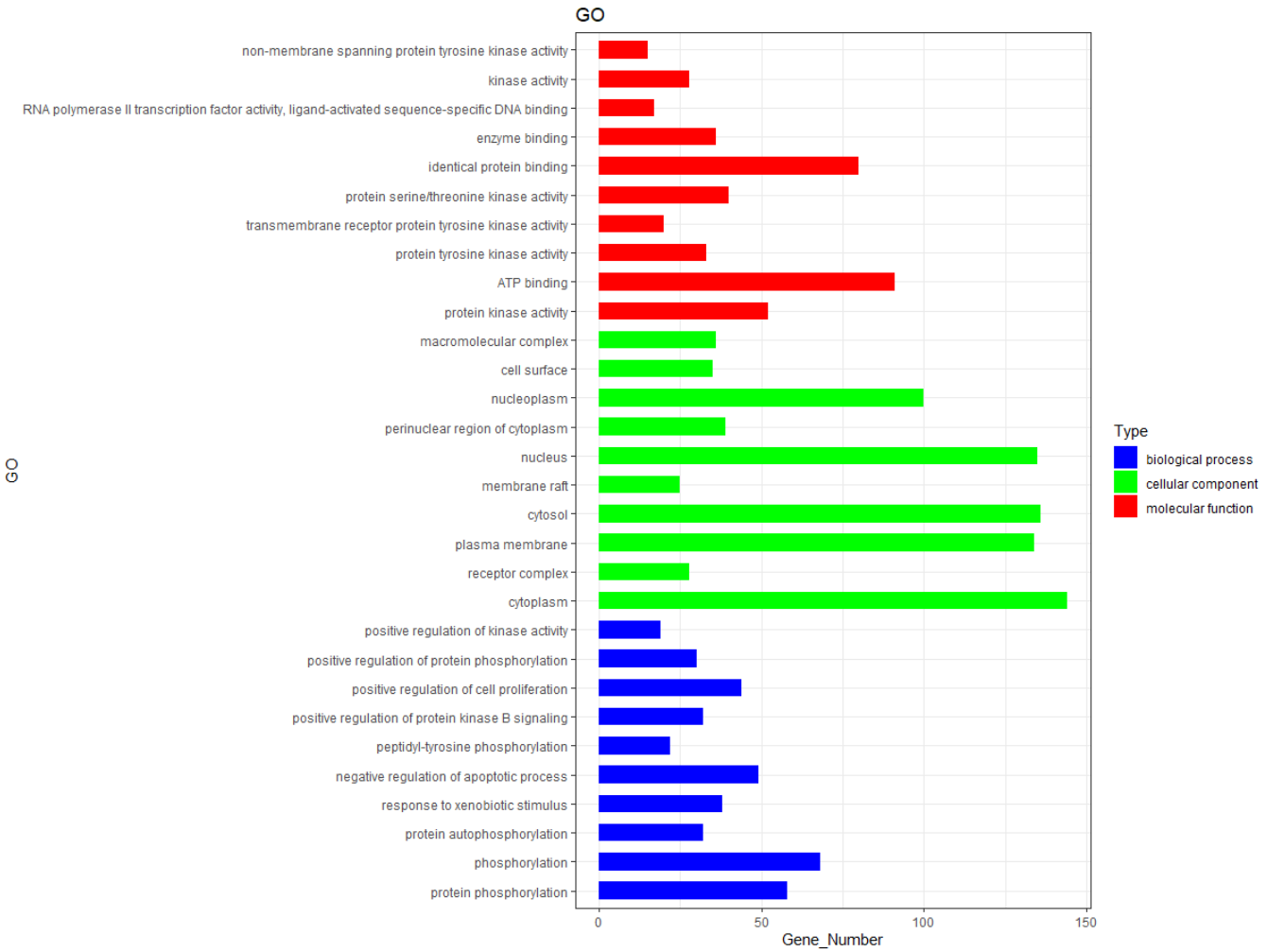

Figure 4. GO Enrichment analysis of the target genes

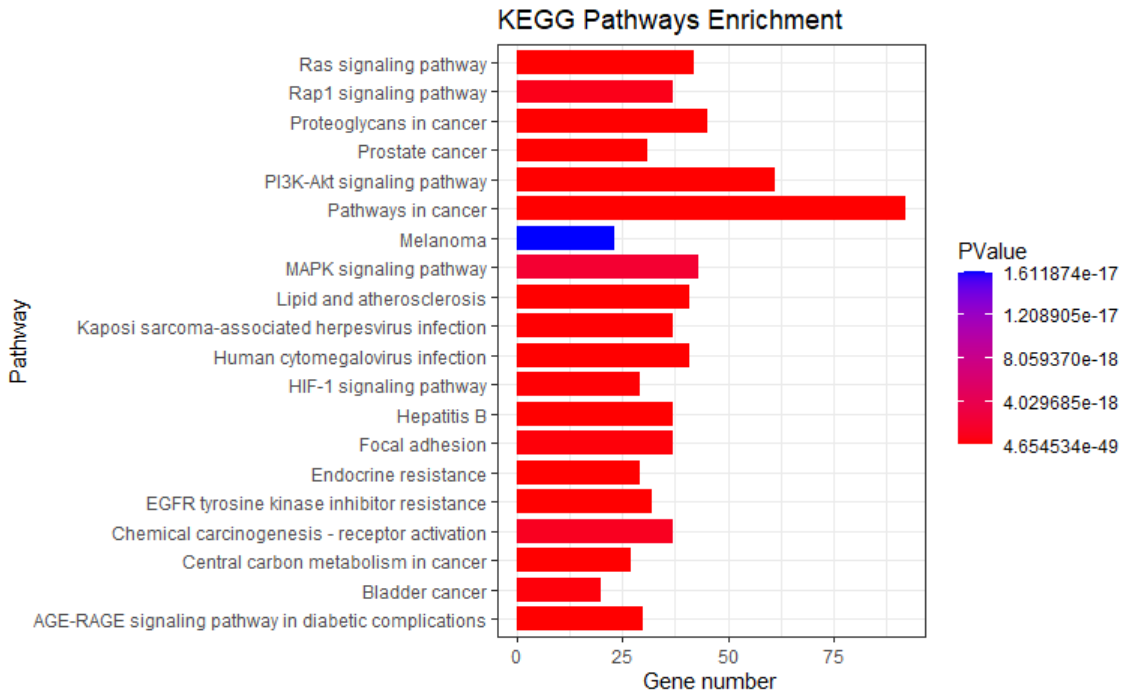

Figure 5. KEGG enrichment analyses of the target genes.

Enrichment analysis of the target genes

The DAVID database was used to perform GO functional and KEGG pathway enrichment analyses of the 261 candidate target genes. The top ten enriched terms for biological processes, cellular components, and molecular functions were visualized, as shown in Figure 4. The results indicated that these targets were mainly enriched in biological processes such as phosphorylation, response to xenobiotic stimulus, negative regulation of apoptotic processes, and positive regulation of kinase activity and cell proliferation. In terms of cellular components, the target genes were predominantly enriched in the cytoplasm, nucleus, cytosol, plasma membrane, and nucleoplasm. Regarding molecular function, the targets were mainly associated with ATP binding, identical protein binding, protein kinase activity, protein serine/threonine kinase activity, and enzyme binding. KEGG pathway enrichment analysis revealed that these target genes were primarily involved in signaling pathways related to cancer, the PI3K-Akt signaling pathway, the MAPK signaling pathway, and other related pathways (Figure 5).

Discussion

STI, a common exercise-related injury, is characterized by symptoms such as pain, edema, bruising, and impaired limb function[28]. It is usually caused by external mechanical stress exceeding the tolerance threshold of soft tissues. A better understanding of the mechanisms involved in acute STI treatment is expected to provide clinical benefits for affected patients. In the present study, a network pharmacology approach was applied, through which 46 active components and 261 potential therapeutic target genes of BAIMA oil against acute STI were identified. Subsequently, a PPI network was constructed to identify hub genes, and functional enrichment analyses were performed to explore the biological functions and signaling pathways associated with the candidate targets.

Acute soft-tissue injury is characterized by aseptic inflammation, and Traditional Chinese Medicine has demonstrated beneficial effects in the management of acute STI. For instance, Huanglian-Jie-Du-Tang decoction has been reported to suppress inflammation and alleviate acute STI in rodent models[2]. Taohong Siwu Decoction (THSWD), which exhibits anti-inflammatory and antioxidant properties, has also been shown to promote recovery from acute STI 7 In this study, 46 major active components of BAIMA oil were identified, with a total of 680 predicted targets based on network pharmacology analysis. After intersecting these targets with acute STI–related disease targets, 261 overlapping targets were obtained. Within the herb–component–disease network, the top ten active components ranked by degree included naringenin (B9), Sennoside E_qt (H8), 5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone (Z3), acacetin (B1), quercetin (Z12), genkwanin (B6), diosmetin (B3), kaempferol (Z10), luteolin (B8), and cheilanthifoline (H4). Previous studies have demonstrated that acacetin, a flavone component of Bohe, possesses antimicrobial, anti-inflammatory, antioxidant, and vasorelaxant activities and can attenuate inflammatory damage by reducing TNF-α and IL-1β levels or inhibiting inflammation-related signaling pathways[29, 30]. Quercetin, a naturally occurring dietary polyhydroxy flavonoid, has been reported to exert anti-inflammatory effects, alleviate osteoarthritis symptoms, and promote wound healing[31-33]. In addition, other identified components have also been documented to exhibit anti-inflammatory pharmacological activities. For example, ellagic acid, an active constituent of Hezi, has been reported to prevent collagen degradation, suppress inflammatory responses, and reduce blood stasis[34,35]. Stigmasterol, derived from Zhizi, has been shown to attenuate inflammation and relieve pain in various disease models[36,37]. Linolenic acid and oleic acid, the major components of Shanchayou, have been demonstrated to promote wound healing through anti-inflammatory effects and are widely used in the development of wound dressings for tissue repair[38,39].

Furthermore, a PPI network was constructed based on the 261 potential targets of BAIMA oil in acute STI. Topology analysis revealed that TP53, EGFR, and STAT3 were the top three hub genes in the network. Previous research has shown that TP53 expression is downregulated in rat models of STI, and treatment with increasing concentrations of Taohong Siwu Decoction can gradually restore TP53 expression in injured tissues[7]. EGFR has been reported to play a crucial role in regulating fibroblast migration and proliferation during wound healing 40. STAT3 is critically involved in scar formation and tendon injury repair[41], and modulation of STAT3 signaling to regulate tendon cell proliferation has been proposed as a promising therapeutic strategy for tendon injury[42,43].

In addition, enrichment analyses were conducted to further elucidate the biological functions of the potential BAIMA oil targets in acute STI. The results revealed a close association between these targets and the regulation of cell proliferation and apoptosis. KEGG pathway enrichment analysis indicated that these genes were involved in signaling pathways such as PI3K–Akt signaling, MAPK signaling, and other cancer-related pathways. Previous studies have shown that inhibition of the PI3K–Akt signaling pathway can prevent ectopic ossification and promote tendon healing[44]. Aspirin has been reported to downregulate the PTEN/PI3K/AKT pathway, thereby inhibiting adipogenic differentiation of tendon stem cells and improving the biomechanical properties of injured tendons[45]. MAPK signaling is also indicated to be associated with tendon remodeling[46]. It can be activated in response to the mechanical loading in fibroblast of various tissues, and can regulate the proliferation of tendon fibroblasts and extracellular matrix synthesis[47,48]. Elucidating these biological functions and signaling pathways may further enhance our understanding of the molecular mechanisms underlying the therapeutic effects of BAIMA oil in acute STI.

In conclusion, this study systematically identified the major active components and corresponding molecular targets of BAIMA oil in the treatment of acute soft-tissue injury using a network pharmacology approach. Naringenin, Sennoside E_qt, 5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl) chromone, acacetin, and quercetin were identified as key active components of BAIMA oil in acute STI treatment. Moreover, BAIMA oil may exert therapeutic effects by modulating the expression of TP53, EGFR, STAT3, and other proteins involved in the PI3K/AKT and MAPK signaling pathways. These findings are expected to deepen the understanding of the pharmacological basis of BAIMA oil in the treatment of acute STI.

Declarations

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Conflicts of interest/ Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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