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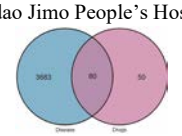
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RESEARCH ARTICLE

Title: Network Pharmacology Reveals Mechanisms of Yang Jin Hua in Alleviating Osteosarcoma Pain

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ARTICLE HISTORY

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Abstract: Background: Yang Jin Hua (YJH), a traditional Chinese herbal formula, has demonstrated potential in pain management, particularly in alleviating pain associated with malignant tumors such as osteosarcoma. It has been recommended for clinical use in pain relief.Objective: This study aimed to explore the mechanisms of action and interactions of YJH compounds in alleviating osteosarcoma pain using network pharmacology and molecular docking techniques.Methods: The active compounds in YJH were identified based on oral bioavailability and drug-likeness using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database. Potential target genes for these compounds were predicted via TCMSP and Swiss Target Prediction databases, and relevant target genes related to osteosarcoma pain relief were identified using the GeneCards database. Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation were performed using the Matescape database. A composition-target-pathway (C-T-P) network and protein-protein interaction (PPI) network were constructed using Cytoscape 3.8.2 software.Results: Molecular docking confirmed the interactions between key active components of YJH and their targets. Key targets, including Ache, IL-6, IL1B, EGFR, and TNF, were identified as playing crucial roles in the pain mechanism of osteosarcoma. The primary active components—Quercetin, Kaempferol, Datuemine, and Apohyoscine—were found to bind with the protein structures 5KIR and 6LB4.Conclusion: This study provides an in-depth understanding of the molecular mechanisms underlying the pain-relieving effects of YJH in osteosarcoma, offering a theoretical basis for its application in osteosarcoma pain management and contributing to the development of alternative pain relief strategies based on traditional Chinese medicine.

Keywords: Osteosarcoma pain, Network Pharmacology, Yang Jin Hua, Molecular Docking, Bioinformatics

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1. INTRODUCTION

Traditional Chinese Medicine (TCM) has been used for centuries to treat a wide range of ailments, including pain and inflammation. Yang Jin Hua (YJH) is a traditional Chinese medicine known for its analgesic and anesthetic properties [1]. Anesthesia refers to a reversible loss of sensation and consciousness, allowing for pain-free surgical procedures. Anesthesia can be induced using various drugs, including general anesthetics, local anesthetics, and regional anesthetics. However, these drugs can have side effects, particularly with prolonged use, and may be associated with toxicity. Therefore, there is a pressing need to develop new, safe, and effective anesthetic agents.

Yang Jin Hua is derived from the dried flower buds of Daphne genkwa Sieb, a plant known for its analgesic and anesthetic effects. It has been used for centuries in China to treat pain and inflammation [2]. In recent years, there has been growing interest in the potential of Yang Jin Hua as an alternative to conventional anesthetics, especially due to its potential for fewer side effects and lower toxicity, making it a promising option for pain management, including in conditions like osteosarcoma.

Osteosarcoma is a common malignant bone tumor that often causes severe pain, significantly affecting the quality of life of patients. Traditional pain management for osteosarcoma typically relies on opioids and other potent

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analgesics. However, prolonged use of these drugs can lead to issues such as tolerance and dependence, underscoring the need for alternative pain management strategies with fewer side effects. Yang Jin Hua, with its analgesic and anesthetic properties, offers a potential new avenue for alleviating pain, including pain associated with osteosarcoma.

Studies have shown that Yang Jin Hua has a dose-dependent analgesic effect and can induce anesthesia in animal models. The anesthetic effect of Yang Jin Hua is believed to result from its ability to block sodium channels in neurons, thereby inhibiting the transmission of pain signals. This unique mechanism of action makes Yang Jin Hua an interesting candidate for both anesthetic use and the management of osteosarcoma-related pain.

With the rise of bioinformatics and network pharmacology, these modern approaches have been widely applied to the study of traditional Chinese medicines. These methods help identify active ingredients and molecular targets, leading to the discovery of new therapeutic targets and the development of novel drugs based on traditional Chinese medicine [3][4]. Bioinformatics uses computational methods to analyze and interpret biological data, while network pharmacology integrates data from genomics, proteomics, and metabolomics to analyze drug-target interactions and identify new therapeutic targets.

The application of bioinformatics and network pharmacology has provided a new approach for studying the mechanism of action of Yang Jin Hua in anesthesia and pain management. These methods have identified potential targets and pathways involved in the anesthetic effects of Yang Jin Hua and revealed possible interactions between Yang Jin Hua and anesthesia-related targets. However, further experimental studies are needed to validate the predictions and fully understand the mechanism of action of Yang Jin Hua. In our study, we used Gene Ontology (GO) functional enrichment analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation, and constructed Composition-Target-Pathway (C-T-P) and Protein-Protein Interaction (PPI) networks using Cytoscape 3.8.2 [6][7][8][9]. These analyses provide valuable insights into the molecular mechanisms underlying the therapeutic effects of YJH in anesthesia and pain management, particularly for osteosarcoma. By analyzing biological functions and pathways, we aim to develop a comprehensive understanding of how YJH exerts its therapeutic effects, which could lead to the development of new pain management strategies. Additionally, identifying potential drug targets or pathways for further investigation could have important implications for developing new therapies for osteosarcoma-related pain.

2. MATERIALS AND METHODS

In order to analyze the potential mechanisms of action of active components in anesthetic, various databases and software were utilized. The TCMSP database was used to screen active components based on specific criteria, while information on the chemical structure of these components was obtained from PubChem. To obtain data on the three-dimensional structure of proteins, the RCSB PDB was used. Gene Cards and OMIM databases were used to gather information on target genes related to anesthetic. Venn diagrams were generated using the Venny 2.1.0 software to identify common targets of the active components. The STRING database was used to construct protein-protein interaction networks, and the Cytoscape software was utilized to build the composition-target-pathway (C-T-P) network and protein-protein interaction (PPI) network. By utilizing these databases and software platforms, a comprehensive understanding of the potential mechanisms of action of the active components and their target genes in anesthetic was obtained.

We searched the TCMSP database to obtain target information for each active component and then searched the UniProt database to obtain corresponding gene symbols of the targets. This method helped us to identify potential target genes of the active components and the possible roles in anesthetic. By using these databases and software platforms, we gained a comprehensive understanding of the potential mechanisms of action of the active components and their target genes in anesthetic.

TCMSP database amd active components were screened based on their oral bioavailability (OB) and drug-likeness (DL) parameters. OB $\geq$ 30% indicates that the active component has good oral absorption, while DL $\geq$ 0.18 suggests that the compound has favorable drug-like properties.

The target information for each active component was obtained from the TCMSP database, and the corresponding gene symbols were retrieved from Uniprot. The molecular structures of the active components were obtained from PubChem, and docking studies were performed using the RCSB PDB database to predict their potential binding to the target proteins. GeneCards and OMIM were used to obtain the related target genes of anesthetics, which served as a validation step to ensure the relevance of the identified targets. Venn diagrams were generated using the Venny2.1.0 online tool to show the overlap between the active components and target genes. The STRING database was used to construct PPI networks to identify potential functional relationships between the target genes. Finally, a compound-target-pathway (C-T-P) network was constructed and visualized using Cytoscape software, which integrates the active components, target genes, and related pathways to provide insights into the mode of action of TCM.

3. EXPERIMENTAL

3.1 Identification Compounds with Potential Bioactivity

The chemical constituents of YJH were obtained from two databases, namely the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform

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(http://lsp.nwu.edu.cn/tcmsp.php) and the Encyclopedia of Traditional Chinese Medicine (ETCM) (https://pubchem.ncbi.nlm.nih.gov/). The chemical components database of YJH was established by retrieving the common name and PubChem CID from the PubChem database. To ensure that the active components were suitable for further analysis, they were screened based on the ADME principle using the criteria of oral bioavailability (OB) index ≥30% and drug likeness (DL) index ≥0.18.

3.2 Identification of Target Proteins for Active Components

The gene targets associated with the chemical components were obtained from two databases, namely the SwissTargetPredict database (http://www.swisstargetprediction.ch/index.php) and TCMSP database. To obtain the Gene Official Symbol formats of the corresponding genes of active components, the Retrieve/ID mapping tool was used with "human" set as the species in UniProt. Disease-related gene targets were obtained by searching GeneCards (https://www.genecards.org/) using the keywords "anesthetic." The intersection of target genes of the active components in YJH with disease-related genes was obtained using Microsoft Excel, and the results were visualized using a Venn diagram (Fig.1).

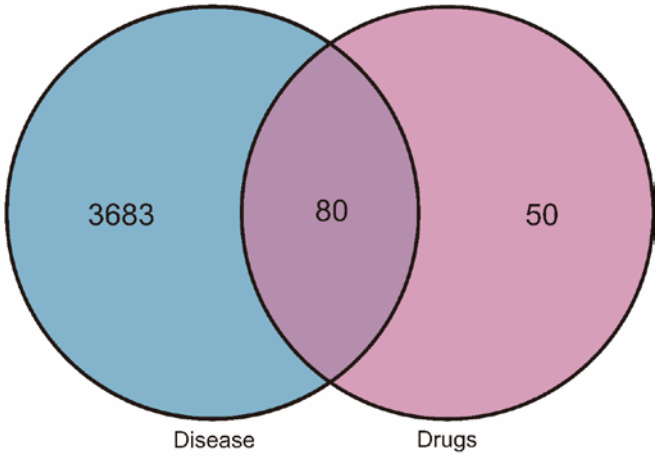


Fig. (1). Venn Common targets of diseases and drugs.

3.3 Enrichment Analysis of Gene Ontology and KEGG Pathways

GO enrichment and KEGG analysis were performed using the Metascape database (http://metascape.org/). The potential target genes were analyzed with "H. sapiens" set as the species. A significance threshold of $P < 0.01$ was used, and the top 20 pathways and GO enrichment results were visualized using an R bubble plot.

3.4 Construction of "C-T-P" Network

Modular network and bioscience network diagrams were finished by using the Cytoscape 3.8.2 software. The analysis involves importing 15 active components, 66 gene targets, and the top 10 KEGG pathways into the Cytoscape 3.8.2 database. The active components, gene targets, and enrichment pathways are represented by different nodes, while the correlation between the nodes is represented by edges. The components-targets network and targets pathways network are merged to obtain the "C-T-P" network. To identify important active components in the study, the analysis involved screening components with high degree values in the topographic parameters, with the degree value greater than twice the median serving as the standard. This approach allows for the identification of key active components in the network that may be important for further analysis or investigation.

Table 1. The composition of YJH.

Herbs Name	Content
codonopsis pilosula	12g
cstragalus membranaceus	12g
atractylodes macrocephala	9g
aucklandia odora	6g
dipsacus aspera	15g
rhizoma menisci	12g
sangsheng	12g
salvia mitiorrhiza	15g
angelica sinensis	9g

3.5 Constructing Protein-Protein Interaction Network

The ELIXIR infrastructure's Core Data Resource, the STRING database (https://string-db.org/), comprises 5090 species, 24,584,628 proteins, and 3,123,056,667 interactions. To conduct the analysis, the Cytoscape 3.8.2 software plug-in was utilized to examine the topological parameters, and 35 targets with the highest degree value were chosen. The study focused on the human species within the STRING database. The interaction between gene targets was assessed, and the protein-protein interaction (PPI) network diagram was downloaded after ranking. The PPI network diagram was optimized and subsequently imported into Cytoscape 3.8.2 for visualization.

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Table 2. The details of 80 potential ingredients for the treatment of anesthetic

potential targets						
EGFR	IL6	TNF	RB1	GSTM1	MMP13	NR3C2
CYP3A4	NR3C1	AR	EGF	PRSS1	IFNG	EDNRA
ESR2	MMP1	F3	MMP2	MET	KCNMA1	CYP1A2
PTGS1	PGR	CALCR	IL1B	GJA1	ITGB3	ODC1
BCL2	MMP3	PPARG	TP53	VEGFA	DPP4	TOP1
MPO	INSR	MAPK8	NCOA2	MAPK14	KDR	CA2
IL2	HMOX1	PLAU	FASN	NCOA1	PDE3A	PTGER3
RXRA	PLAT	NOS2	CCL2	JUN	MMP8	AHR
CASP7	CTSD	ESR1	CHEK1	PTGS2	VCAM1	THBD
CCNA2	ADRA1B	PIK3CG	MAPK1	GSK3B	KCNH2	ADRA2B
ACHE	TUBB1	GSTP1	RXRB	ACP3	PON1	POR
ADRB2	CHRM3	F7				

3.6 Molecular Docking

To conduct molecular docking, the Sybyl 2.1.1 software was employed. The 3D structures of the gene targets, 5KIR and 6LB4, were obtained from the RSCB PDB database (https://www.rcsb.org/), while the 3D structures of the active components were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Using Sybyl 2.1.1 software, the downloaded protein structures were prepared by eliminating non-protein molecules like water molecules and ligands. The software was also used to optimize, hydrogenate and charge the structures of the active components. Molecular docking was performed to predict the potential interactions between the active components and the target proteins. Subsequently, the docking results were analyzed and visualized using PyMol software to identify the binding sites and key residues involved in the interactions.

4. RESULTS

4.1 Potential Active Ingredients

By searching for herb names in YJH and applying filters for OB ⩾30% and DL ⩾0.18 using the TCMSP database, a total of 15 chemical compositions were discovered, along with 279 YJH targets. After comparing and analyzing the chemical components, 27 potential effective components were identified by removing repetitive and non-corresponding target components. The details for these components are provided in Table 1, while Table 2 outlines the 27 potential ingredients identified for the treatment of YJH by comparing the active ingredients of drugs with YJH. The results of this analysis are presented in Figure 2.

4.2 Analysis of Biological Function Targets

The Matescape analysis was conducted to assess the potential targets' roles in different biological pathways. By utilizing KEGG pathway annotation, the top 10 pathways were determined, which encompassed fluid shear stress and atherosclerosis, IL-17 signaling pathway, pathways in cancer, and neuroactive ligand-receptor interaction. It was observed that these pathways were associated directly or indirectly with anesthesia, as depicted in Figure 2A. Additionally, GO enrichment analysis was conducted to identify biological processes (BP), cell composition (CC), and molecular function (MF) associated with the potential targets. The top 20 BP enrichments were cellular response to nitrogen compound, response to hormone, and cellular response to cellular response to organic cyclic compound, inflammatory response and response to xenobiotic stimulus, as shown in the green bar graph in Figure 2B. The top 20 CC enrichments included membrane raft as shown in the blue bar chart in Figure 2B. The top 20 MF enrichments was protein homodimerization activity as shown in the orange bar graph in Figure 2B.

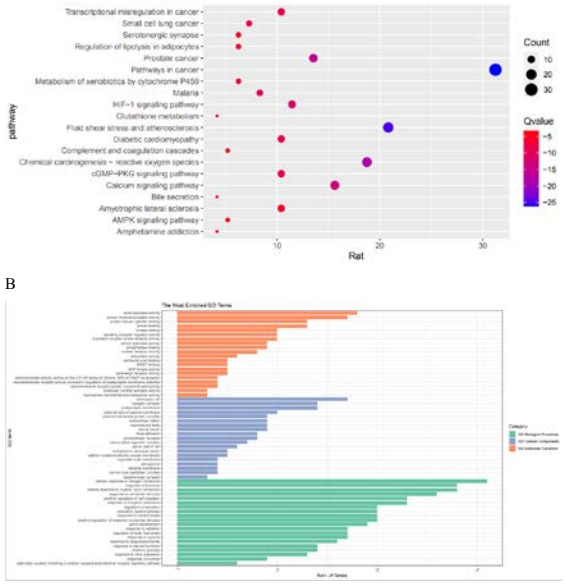


Fig. (2). (2A) KEGG pathways annotation; (2B) GO BP enrichment; GO CC enrichment; and GO MF enrichment. BP, biological process; CC, cell composition; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular function.

4.3 Construction of PPI Network

The intersection targets of the active components and anesthetic-related genes were analyzed using the STRING database to construct a protein-protein interaction network. The generated network diagram was optimized and adjusted in Cytoscape. The nodes in the network were sized based on their degree values, and the larger node size indicates a higher degree value. Notably, IL6, TP53, VEGFA, EGFR, JUN, and TNF exhibited larger node sizes, suggesting that they are

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closely related to anesthetic. The network diagram is presented in Figure 3.

4.4 Construction of "C-T-P" Network

The study imported the 43 active components, 36 gene targets, and top 20 pathways into Cytoscape 3.8.2 software to obtain the "C-T-P" network, as shown in Figure 4. The network is color-coded to represent the active components in green, potential targets in orange, and pathways in blue. The nodes were visualized based on the degree value, and their size is proportional to the degree value. The study then determined the key nodes with degree values greater than twice the median to identify potential active components for molecular docking tests. Based on these parameters, quercetin and luteolin were selected as the key active components for the docking study.

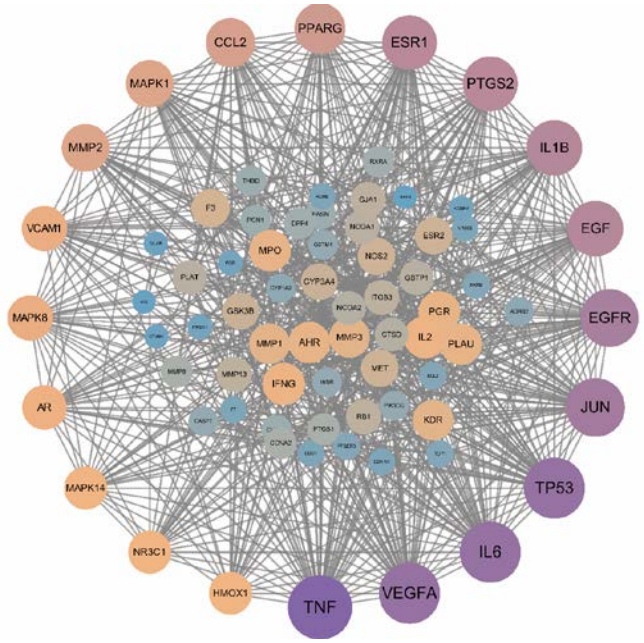


Fig. (3). Protein-protein interaction network diagram.

4.5 Molecular Docking and Analysis

The central ingredients of YJH are Quercetin and Iuteolin, and they are the key compounds in the molecular docking analysis. 5KIR and 6LB4 are the essential receptors that interact with these compounds. Based on the docking analysis, the results indicate that Quercetin and Iuteolin possess a strong binding affinity with 5KIR and 6LB4, as illustrated in Figure 5 and summarized in Table 3.

5. DISCUSSION

The results presented here reflect an in-depth pharmacological analysis of YJH through the TCMSP database, which was crucial for identifying the bioactive compounds and potential therapeutic pain targets associated with its clinical efficacy. The 27 effective components identified represent promising candidates for further investigation into their molecular mechanisms in alleviating osteosarcoma pain. Their OB and DL values indicate that they possess both oral bioavailability and drug-likeness, suggesting they are suitable for clinical application. From the pathway analysis, we observed several key biological pathways such as the regulation of lipids, cancer-related pathways, and metabolic pathways that could potentially be influenced by the active ingredients in YJH [10]. These findings imply that the active components of YJH may exert their effects via multiple mechanisms, possibly including anti-inflammatory, anticancer, and metabolic regulation effects, as suggested by the enriched GO terms in Figure 2. Furthermore, by comparing the active ingredients of YJH with those of other drugs, it is evident that these components may share common therapeutic properties. The next steps should involve further validation of these compounds through in vitro and in vivo experiments to confirm their therapeutic potential and refine the understanding of their molecular targets and interactions. Additionally, the use of more advanced computational techniques such as molecular docking could help elucidate the binding affinities between the identified components and their respective targets, paving the way for future clinical applications.

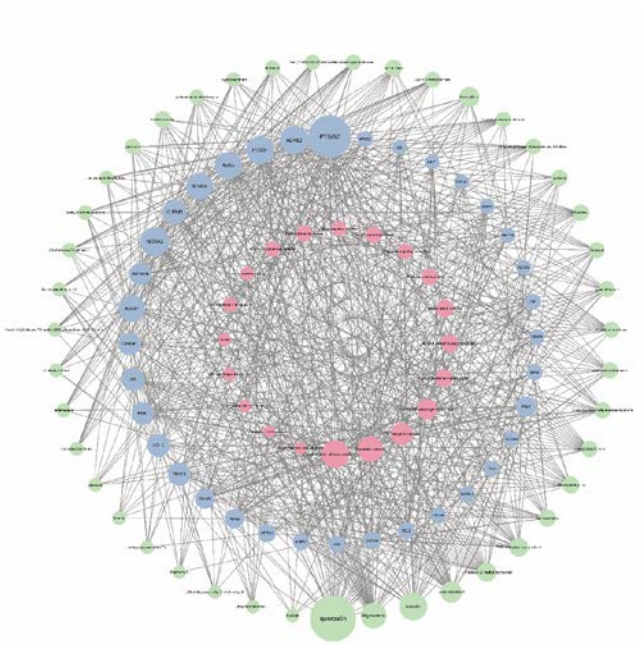


Fig. (4). Active components-targets-Kyoto Encyclopedia of Genes and Genome pathways networks.

An in-depth analysis of the active components, targets, and related pathways of Yang Jin Hua (YJH) was conducted to explore its application in alleviating osteosarcoma pain. Figures 3 and 4 provide compelling insights into the potential molecular mechanisms involved, which could offer novel therapeutic strategies for osteosarcoma pain management. In

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Figure 3, the PPI network was constructed to identify key targets within the YJH treatment processes. The network revealed that genes such as IL6, TP53, VEGFA, EGFR, JUN, and TNF exhibited prominent node sizes [12], indicating their strong association with pathways related to osteosarcoma pain relief. These genes are known to play pivotal roles in inflammation, cell survival, and tissue repair, all of which are critical in pain modulation and response to surgery in osteosarcoma patients [13]. The significant connectivity of these genes highlights their potential as central players in the pharmacological action of YJH. Furthermore, Figure 4 presents the "C-T-P" network, integrating 43 active components, 36 gene targets, and the top 20 pathways involved in alleviating osteosarcoma pain. This network not only underscores the complexity of YJH's action but also demonstrates how its active ingredients can influence various biological processes. The color-coded representation of active components (green), targets (orange), and pathways (blue) provides a clear visual of how the components interact with the targets and pathways. The size of the nodes, indicative of their degree values, further emphasizes the importance of key components and targets. These compounds are known for their anti-inflammatory, antioxidative, and neuroprotective effects [14], which are particularly relevant for alleviating osteosarcoma pain. By targeting critical pathways related to inflammation and cell survival, these components could enhance pain management and recovery in osteosarcoma patients undergoing surgery. This comprehensive network analysis has provided valuable insights into the complex molecular mechanisms through which YJH exerts its therapeutic effects. The identification of key active components and their associated targets opens new avenues for further research and clinical application, particularly in pain management during osteosarcoma surgery. The use of molecular docking studies to validate these findings will be a crucial step toward understanding how these active compounds interact with their targets, ultimately leading to more effective osteosarcoma pain relief strategies in clinical settings.

Fig.5A 5kir with Luteolin

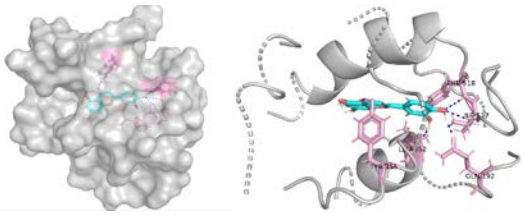


Fig.5B 5kir with Quercetin

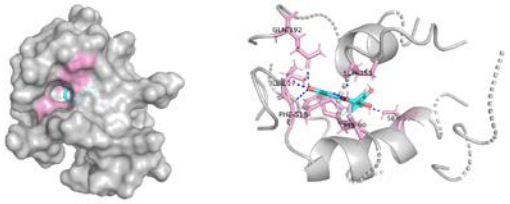


Fig.5C 6lb4 with Luteolin

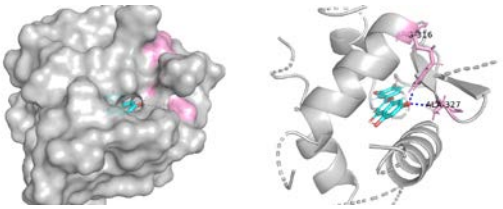


Fig.5D 6lb4 with Quercetin

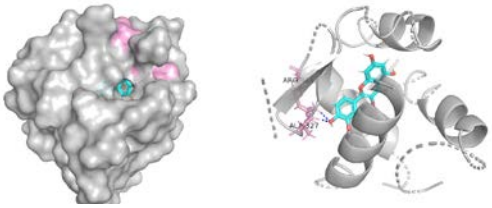


Fig. (5A-D). Three-dimensional docking mode diagram of Quercetin and Iuteolin with 5KIR and 6LB4.

The molecular docking analysis highlights the significant binding affinity of Quercetin and Luteolin, the key ingredients of YJH, with two key receptors, 5KIR and 6LB4. As indicated in Figure 5 and summarized in Table 3, both compounds demonstrate strong interactions with these receptors, which is important for understanding their pharmacological effects. Specifically, the binding affinity of Luteolin with 5KIR (total score of 6.8422) and 6LB4 (total score of 7.0230) is notable, suggesting a robust interaction with these receptors. Similarly, Quercetin also shows a significant affinity for both receptors, with a slightly lower total score for 5KIR (6.6884) but maintaining a reasonable affinity with 6LB4 (6.2332). The polar and similarity values further illustrate the nature of these interactions, with Luteolin exhibiting higher polar values, which may contribute to a more stable and favorable binding conformation [15]. These results are crucial for understanding how Quercetin and Luteolin may modulate biological processes via 5KIR and 6LB4, reinforcing their potential therapeutic roles in alleviating osteosarcoma pain and promoting recovery.The docking data suggests that these active ingredients of YJH have a promising interaction profile, supporting further studies to elucidate their exact molecular mechanisms and potential clinical applications in osteosarcoma pain management.

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Table 3. binding affinity of core components of quercetin and iuteolin with 5kir and 6lb4

Molecule		Total Score	Polor	Sinilarity
5KIR	with	6.8422	3.0184	0.480
Luteolin				
5KIR	with	6.6884	3.6790	0.523
Quercetin				
6LB4	with	7.0230	1.1700	0.461
Luteolin				
6LB4	with	6.2332	1.0327	0.455
Quercetin				

6. CONCLUSION

Our study utilized network pharmacology and molecular docking methods to comprehensively investigate the therapeutic mechanisms of YJH, a Yang Jin Hua (YJH) is a traditional Chinese herbal formula recommended for alleviating pain. By identifying the active components and predicting their potential target genes, this research highlighted key targets such as Ache, IL-6, IL1B, EGFR, and TNF, which are involved in the therapeutic effects of YJH. Molecular docking analysis confirmed strong interactions between the key active components, including Quercetin and Kaempferol, with receptors 5KIR and 6LB4, indicating their potential roles in modulating osteosarcoma pain. The findings from GO enrichment and KEGG pathway annotation provided additional insights into the complex biological pathways influenced by YJH, further elucidating its potential as a pain-relief agent. This study not only enhances our understanding of the molecular mechanisms underlying YJH's therapeutic effects but also opens new avenues for the development of innovative pain-relief strategies utilizing traditional herbal formulas like YJH in osteosarcoma treatment.

ETHIC APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not Applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The source of data has been given in the Tables.

FUNDING

None.

CONFLICT OF INTEREST

In this study, there are no financial conflicts of interest or otherwise.

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