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The molecular mechanism of Gegen Qinlian Decoction in the treatment of radiation enteritis based on network pharmacology

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Abstract: PrObjective This study aimed to explore the potential mechanism of Gegen Qinlian Decoction in the treatment of radiation enteritis by means of network pharmacology. Methods The Chinese Medicine System Pharmacology Database and Analysis Platform was used to search the active ingredients and targets of Gegen Qinlian Decoction, and the relevant targets of radiation enteritis were searched online through the GeneCards and OMIM databases. Cytoscape 3.7.0 software was used to construct the interaction network of "Gegen Qinlian Decoction-active ingredient-radiation enteritis-target," and the PPI visualization network diagram of the interaction between target and protein was drawn through STRING database analysis. R language was used to analyze the intersection of drug targets and disease targets to enrich the GO and KEGG pathways of core target genes. Results The search results obtained 146 effective active ingredients of Gegen Qinlian Decoction, including formononetin, □-sitosterol, 3'-methoxydaidzein, acacetin, 5,8,2'-trihydroxy-7-methoxyflavone, berberine, epiberberine, isorhamnetin, formononetin, kaempferol, and naringenin. The PPI network contained 101 nodes and 399 edges. The biological functions involved in GO enrichment analysis included nuclear receptor activity, ligand-activated transcription factor activity, ubiquitin-like protein ligase binding, DNA binding transcription activator activity, RNA polymerase II specific signaling, steroid hormone receptor activity, ubiquitin protein ligase binding, and activation transcription factor binding. The biological pathways and processes involved in KEGG included lipids and atherosclerosis, chemical carcinogenesis-receptor activation, fluid shear stress and atherosclerosis, Kaposi's sarcoma-associated herpes virus infection, and apoptosis, TNF signaling pathway, and IL-17 signaling pathway. Conclusion The effective active ingredients in Gegen Qinlian Decoction treat radiation enteritis through multiple targets and pathways. This work provides a theoretical basis for further research on the effect and mechanism of Gegen Qinlian Decoction on radiation enteritis.

Keywords: PGegen Qinlian decoction; radiation enteritis; network pharmacology; target; signaling pathway

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1. Introduction

Radiotherapy is an important method for the clinical treatment of tumors, which has a significant effect on many kinds of malignant tumors; however, the radionuclides used in treatment have serious side effects, which can damage adjacent tissues and organs, or cause inflammatory reaction or immune disorder-related complications [1]. Radiation enteritis (RE) is a common intestinal complication of abdominal and pelvic

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tumors after radiotherapy. It damages intestinal mucosa and causes inflammatory changes in intestinal mucosa and submucosal arteries. The main clinical manifestations are abdominal pain, diarrhea, nausea, and vomiting. The incidence of RE is about 5% – 20% [3 – 5]. Intestinal lesions deteriorate over time; in severe cases, they can cause intestinal obstruction, intestinal perforation, sepsis, systemic multiple organ failure, and death [6]. At present, Western medicine protects intestinal mucosa, provides off-site nutritional support and endoscopic hemostasis, and improves intestinal flora imbalance [7,8], but the results are unsatisfactory, so more effective treatment ideas and methods are urgently needed.

Traditional Chinese medicine has a unique effect on relieving and eliminating complications and adverse reactions in the treatment of tumors by Western medicine. RE belongs to the category of "diarrhea" and "abdominal pain" in traditional Chinese medicine. Radiation burns Jin, damages intestinal choriolipid membrane, patients with abdominal pain, acute and severe anus, diarrhea, smelly smell, mucus, purulent and bloody stool, or both hot and thirsty, short and yellow urine, red tongue, yellow fur, pulse slippery or osmosis. It is identified as the syndrome of internal accumulation of dampness and heat, and Gegen Qinlian decoction is added or removed. Gegen Qinlian decoction comes from the Treatise on Febrile Diseases, which mainly treats body heat, anal burning, lower heart pain, dry mouth and thirst, chest heat, wheezing, and sweating as the main manifestations of unsolved exterior malaise. The syndrome of "evil heat" entering inside, both exterior and interior, focuses on Qingli heat. At present, some studies have examined the active components of Gegen Qinlian decoction, but the molecular mechanism of Gegen Qinlian decoction in the treatment of RE remains unclear. Therefore, this study used the method of network pharmacology to identify the active components of Gegen Qinlian decoction in the treatment of RE and determine the active components and pathways to provide a theoretical basis for the in-depth development and clinical application of the prescription in the treatment of RE.

2.Method

2.1Extraction of active components from Gegen Qinlian decoction

The drug composition of Gegen Qinlian decoction is Pueraria, Scutellaria, Coptis, and licorice. All the active components of the four traditional Chinese medicine were searched in the TCMSP database, and the active components were selected based on the conditions of bioavailability (OB) > 30% and drug-like property (DL) > 0.18. All the drug-related targets were downloaded, the targets related to the above active components in all targets with Perl software were screened, and the selected target names were converted into target symbols through the Uniprot database for standardized processing for follow-up operation.

2.2Acquisition of RE target

Using "Radiation enteritis" as the keyword in the GeneCards database (https://www.genecards.org/), all the targets related to RE were derived, and the targets with high correlation with RE were obtained by screening under the relevance score > 1. In the OMIM database (https://www.omim.org/), GeneMap was searched with "radiation enteritis" as the keyword, and all RE-related targets were derived. The targets retrieved from the two databases were summarized, and the symbol was extracted for standby.

2.3Common target of Gegen Qinlian decoction-RE

The Wayne diagram online tool was used to draw the Wayne diagram. The common target of Gegen Qinlian decoction and RE was obtained by intersecting the Gegen Qinlian decoction obtained from 1.1 and 1.2 with the target symbols of RE. The Wayne diagram was then drawn and saved (https://bioinfogp.cnb.csic.es/tools/venny/index.html).

2.4Gegen Qinlian decoction-active ingredient-RE-target relationship network

The relationship network diagram of Gegen Qinlian decoction in the treatment of RE was constructed by Cytoscape3.7.0 software (pre-installed Javaversion8). Cytoscape was opened to import the relevant files prepared before, draw the network diagram, adjust the color format and size of the picture, export the picture, and determine the relationship network of "Gegen Qinlian decoction-active ingredient-RE-target."

2.5Construction of protein–protein interaction (PPI) network and histogram drawing

STRING (https://string-db.org/) online analysis software was used to find multiple proteins, input the intersection file of Gegen Qinlian decoction and RE target symbol in List Of Names, and select species (i.e., Homo sapiens). After clicking search, the default minimum score was 0.7, and the PPI protein interaction network map was obtained. R language was used to calculate the number of node connections and connected genes, and the first 30 genes with the largest number were selected to draw a histogram.

2.6GO Functional enrichment analysis and KEGG pathway enrichment analysis

Go biological process enrichment analysis and KEGG pathway enrichment analysis of the target genes of the active ingredients in Gegen Qinlian Decoction for RE were performed in R language with the settings of $P < 0.05$ and $Q < 0.05$. The species was human (HSA), and the analysis results were presented in the form of column and bubble plots

Table 1 Active ingredients of Gegen Qinlian Decoction (top 20 OB) Table 1 Active components of GeGen QinLian decoction

Mol ID	Molecule Name	OB(%)	DL
MOL002907	Corchoroside A_qt	104.9542429	0.77599
MOL002934	Neobaicalein	104.3446052	0.43917
MOL002311	Glycyrol	90.77578223	0.66819
MOL008647	Moupinamide	86.71215907	0.26454
MOL004990	7,2',4'-trihydroxy — 5-methoxy-3 — arylcoumarin	83.71436744	0.27136
MOL004904	licopyranocoumarin	80.36001331	0.6535
MOL004891	shinpterocarpin	80.29527688	0.72746
MOL005017	Phaseol	78.76621925	0.57867
MOL004841	Licochalcone B	76.75735485	0.1935
MOL002932	Panicolin	76.25704989	0.2915
MOL004810	glyasperin F	75.83680013	0.53514
MOL001484	Endless	75.18306038	0.53754
MOL000500	Vestitol	74.65518912	0.20935
MOL012246	5,7,4'-trihydroxy-8-methoxyflavanone	74.23522001	0.26479
MOL005007	Glyasperins M	72.67080984	0.59274
MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	71.12298901	0.18303
MOL004959	1-Methoxyphaseollidin	69.98097678	0.63739
MOL000392	formononetin	69.67388061	0.21202
MOL000392	formononetin	69.67388061	0.21202
MOL002907	Corchoroside A_qt	104.9542429	0.77599

3.Result

3.1 Active ingredients and targets of Gegen Qinlian decoction

On the basis of the conditions of bioavailability (OB) > 30% and drug-like property (DL) > 0.18, 146 active components of Gegen Qinlian decoction (Pueraria, Scutellaria, Coptis, and licorice) were selected (Table 1). A total of 4681 therapeutic targets of all active components in Gegen Qinlian decoction were found by perl, and 2649 targets were found by perl. These target names were transformed into symbols in the Uniprot database, and 1172 target symbols were obtained.

3.2 Gegen Qinlian decoction target of RE

After deletion of duplicates from 1172 targets of active ingredients in Gegen Qinlian decoction, 124 remained. A total of 5398 integrated RE targets were retrieved by the GeneCard and OMIM databases, and 5112 duplicated targets were removed. The intersection of the active ingredient action targets of Gegen Qinlian decoction and the RE target sets yielded 101 targets of Gegen Qinlian Decoction RE, and the spe

3.3 Gegen Qinlian Decoction - active ingredient- RE - target relationship network construction

The "Gegen Qinlian decoction-active ingredient-RE-target" relationship network diagram of Gegen Qinlian decoction in the treatment of RE was constructed by Cytoscape3.7.0 software (Figure 2). The red oval represents RE, the yellow oval represents Gegen Qinlian decoction, the blue triangle represents the disease target, and the green quadrilateral represents the drug active ingredient. The network consists of 124 active components and 101 nodes, with 1108 interactions between component targets. Through the visualization of the relationship network of Gegen Qinlian decoction in the treatment of RE, an effective ingredient in Gegen Qinlian decoction could act on multiple targets of RE. The target of the same RE could also be regulated by multiple active components.

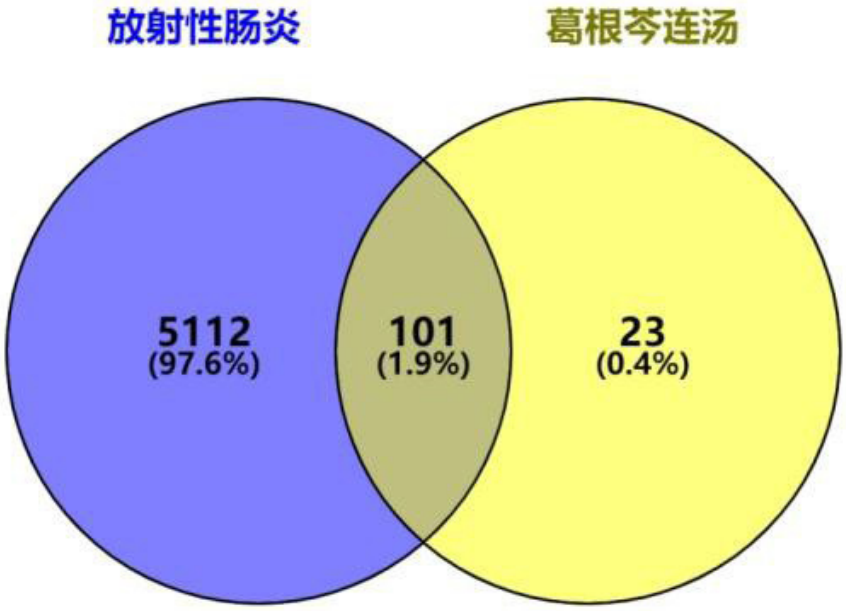

Fig. 1 Wayne diagram of Gegen Qinlian Decoction target and radiation enteritis target
Figure 1 Venn diagram of GeGen QinLian decoction target and Radiation enteritiscific information is shown in Figure 1.

3.4 PPI protein interaction network and histogram

The PPI network consisted of 101 nodes and 399 edges. The average node degree was 7.9, and the average local clustering coefficient was 0.389 p < 1.0e-16. The network node represented the protein, and the depth of its size and color represented the value. The larger the node value was, the more the node was in the core position in the network, and the edge thickness represented the score size. Here, the default minimum score was 0.7.

The top 30 factors with the largest number of node connections and connection factors are shown in Figure 3. The more factors adjacent to the node factor, the more

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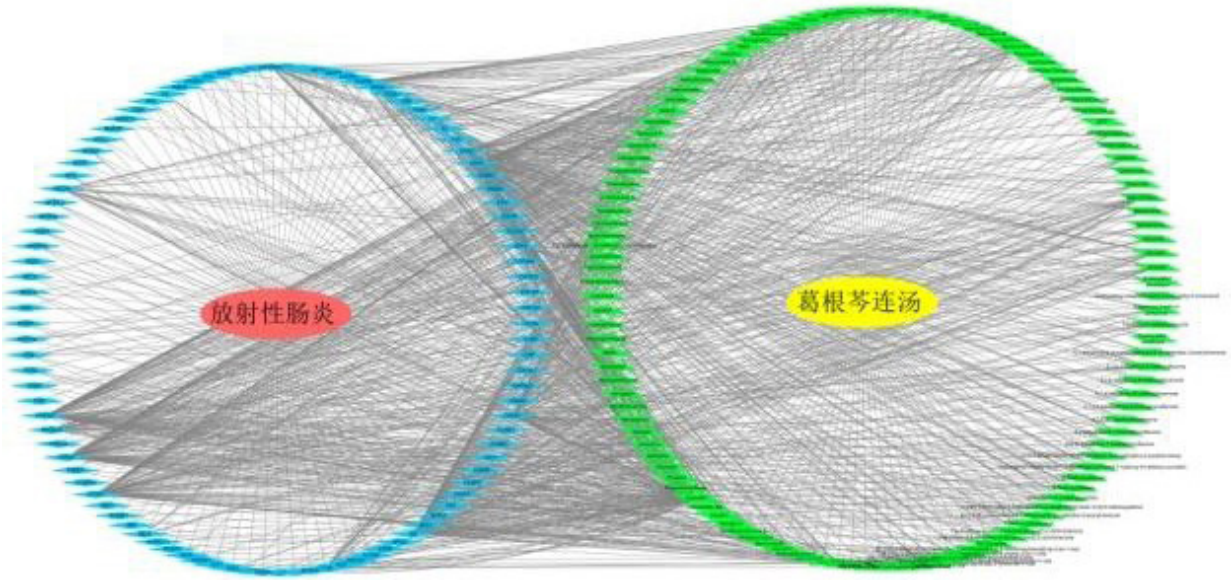

Fig. 2 The network diagram of Gegen Qinlian Decoction-active ingredient-radiation enteritis-target. Figure 2 GeGen QinLian decoction Ingredient- Radiation enteritis-Target Network diagram

central the factor was in the network. Among them, there are 32 connections between MAPK8 and surrounding factors; 26 connections between IL6 and HSP90AA1; and 25 connections between CCND1, EGFR, ESR1, and VEGFR. These results indicated that Gegen Qinlian decoction was closely related to these factors in the treatment of RE.

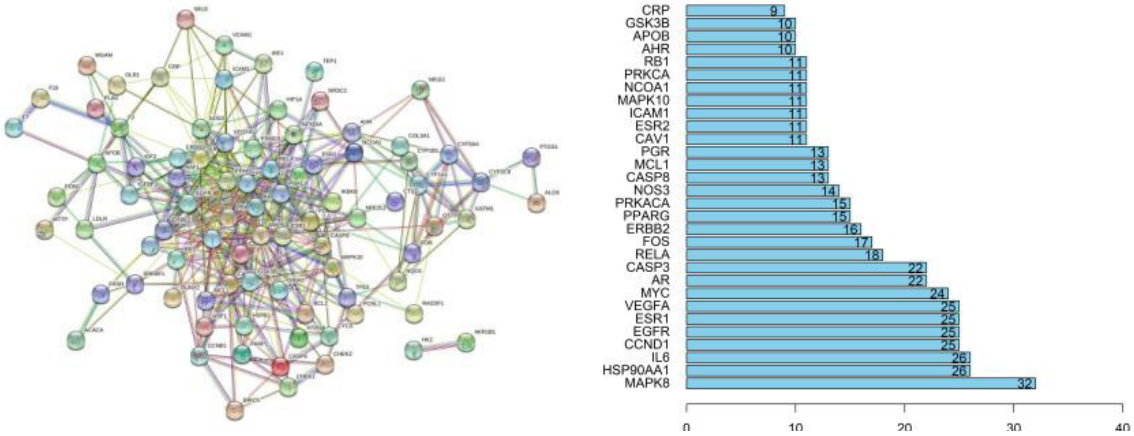

Fig. 3 The network diagram and histogram of Gegen Qinlian Decoction-PPI protein interaction of radiation enteritis target. Figure 3 GeGen QinLian decoction-Radiation enteritis target PPI protein interaction network and histogram

3.5 Functional enrichment analysis of GO

Figure 4 shows the bar chart of the first 20 results of GO analysis. The ordinate represents the biological function of genes, and the abscissa represents the number of enriched genes. Figure 5 shows the bubble chart of the first 20 results of GO analysis. The ordinate represents the biological function of genes, the abscissa represents the proportion of enriched genes, and the size of bubbles represents the number of enriched genes. The biological functions involved include nuclear receptor activity, ligand-activated transcrip-

tion factor activity, ubiquitin-like protein ligase binding, DNA binding transcriptional activator activity, RNA polymerase II specificity, steroid receptor activity, ubiquitin protein ligase binding, and activating transcription factor binding. chart of the first 20 results of KEGG analysis. The biological pathways involved included lipid and atherosclerosis, chemical carcinogenesis-receptor activation, fluid shear stress and atherosclerosis, Kaposi's sarcoma-associated herpesvirus infec-

Fig. 4 histogram of go function enrichment analysis. Figure 4 Histogram of go functional enrichment analysis

Fig. 5 Bubble diagram of GO function enrichment analysis Figure 5 Bubble chart of GO function enrichment analysis

Gegen Qinlian decoction may play a role in the treatment of RE by affecting these key biological functions.

3.6 KEGG pathway enrichment analysis

Figure 6 shows the bar chart of the first 20 results of KEGG analysis, and Figure 7 shows the bubble

tion, apoptosis, TNF signaling pathway, and IL-17 signaling pathway. These signaling pathways were highly enriched with biological processes, indicating that they were closely related to the therapeutic effect of Gegen Qinlian decoction on RE.

4.Discuss

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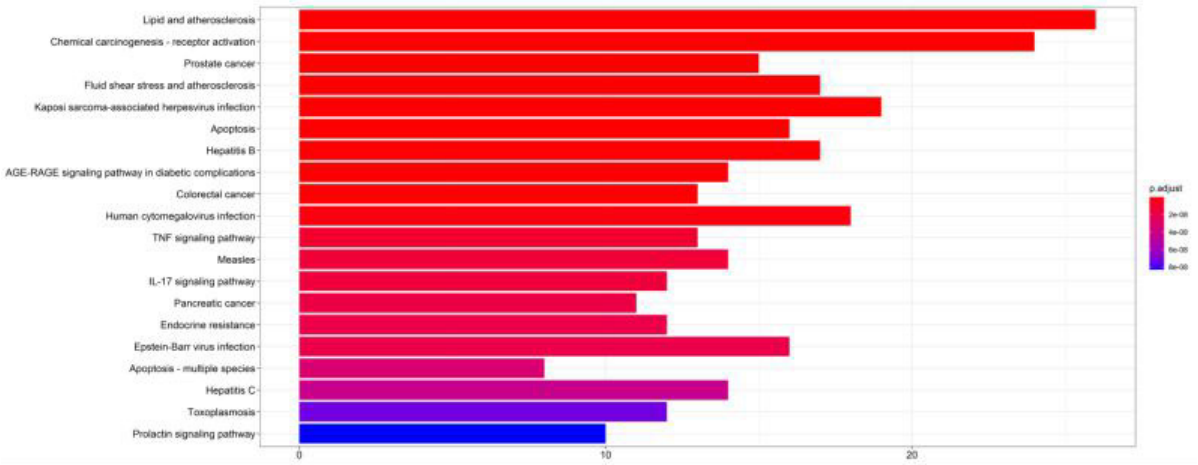

Fig. 6 histogram of Kegg pathway enrichment analysis. Figure 6 Histogram of enrichment analysis of KEGG pathway

Gegen Qinlian decoction of the king medicine Pueraria (Radix Puerariae) is the leguminous plant Pueraria lobata or Pueraria lobata dry root, taste sweet, pungent, flat; into the spleen, stomach meridian, with muscle antipyretic, Shengjin thirst, rash, rising yang diarrhea, channel activating collaterals and other effects [9]. It can be used for the treatment of exogenous fever, headache, measles, fever, diarrhea, diarrhea, dysentery, and other diseases. Kudzu root enters the Yangming meridian, alleviates muscle surface, clears the internal heat of Yangming, and increase yang and stop diarrhea, treat injury of vital qi, and heal conduction of the large intestine. RE can injure vital qi and damage viscera. Scutellaria baicalensis and Huanglian bitter cold clear heat and dampness to stop diarrhea. With adjuvant medicine licorice, these medicines can be used for the care of the spleen and stomach. Gegen Qinlian decoction is often used to treat many kinds of enteritis clinically, and the curative effect is significant [10, 11], but its mechanism has not been clarified. In view of the complexity of the research on compound prescription of traditional Chinese medicine, we can apply network pharmacology to construct the model of the relationship between drugs and diseases, determine the mechanism of its synergistic effect, and better guide further research.

In this study, we obtained the active components of Gegen Qinlian decoction, such as formononetin, β -sitosterol, 3-methoxy daidzein, farnesin, 5meme 8-trihydroxy-7-methoxyflavone, berberine, epiberberine, isorhamnetin, formononetin, kaempferol, and naringenin, through the construction and analysis of a drug disease – target interaction network. These active components may act on key target genes such as MAPK8, HSP90AA1, IL6, CCND1, EGFR, ESR1, VEGFA, MYC, AR, and CASP3. Through GO functional enrichment analysis, we found that they were involved in nuclear receptor activity, ligand activated transcription factor activity, ubiquitin-like protein ligase binding, and DNA binding transcriptional activator activity. Biological processes such as RNA polymerase II specificity, steroid hormone receptor activity, ubiquitin protein ligase binding, and activating transcription factor binding suggested that Gegen Qinlian decoction could inhibit inflammatory changes and repair cell membrane in the treatment of RE by regulating these target molecules.

Through KEGG pathway enrichment analysis, the main pathways involved were determined to be TNF signaling pathway, IL-17 signaling pathway, and AGE-RAGE signaling pathway in

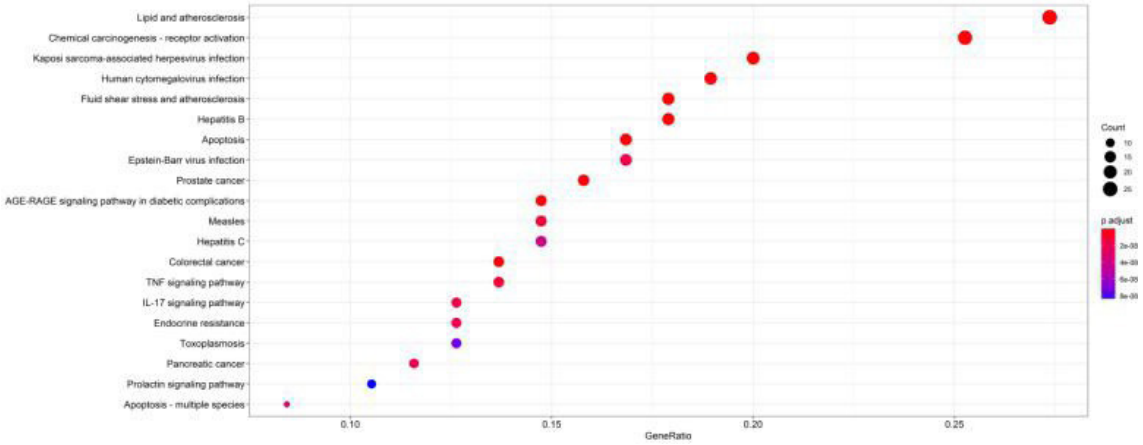

Fig. 7 Bubble diagram of Kegg pathway enrichment analysis. Figure 7 Bubble chart of enrichment analysis of KEGG pathway

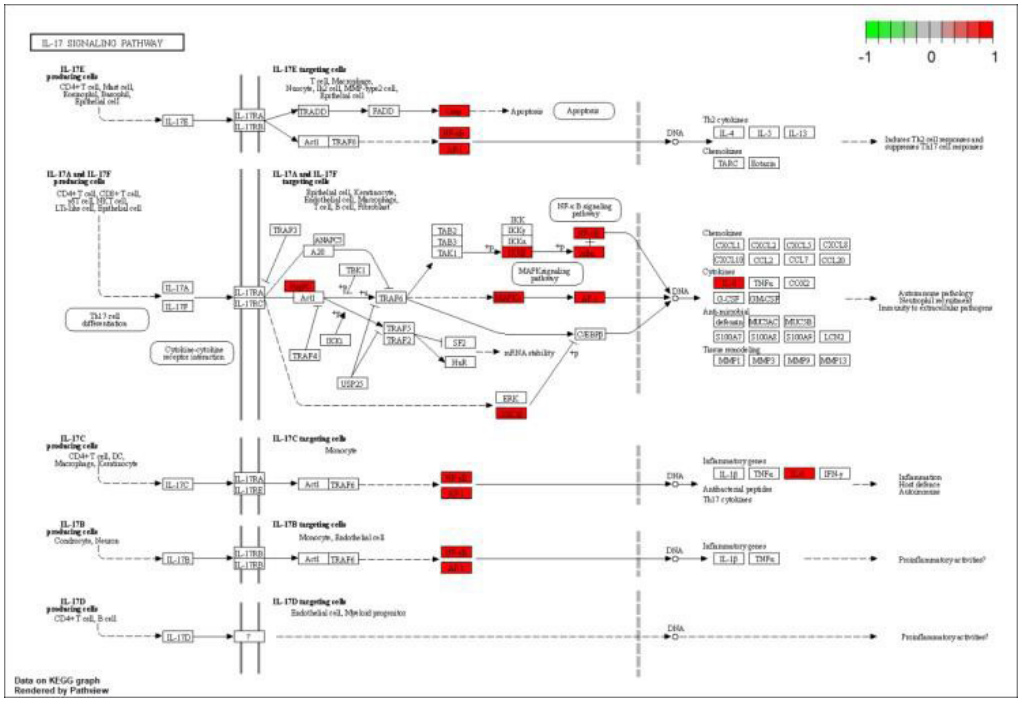

Fig. 8 IL-17 signaling pathway . Figure 8 IL-17 signaling pathway. Fig. 8 shows the IL-17 signal pathway obtained by KEGG pathway analysis, and the red color indicates the factors or molecules related to the active ingredients of Gegen Qinlian Decoction in treating radiation enteritis.
Fig. 8 shows the IL-17 signal pathway obtained by KEGG pathway analysis, and the red color indicates the factors or molecules related to the active ingredients of Gegen Qinlian Decoction in treating radiation enteritis.

diabetic complications. The main biological pro- cesses involved included lipid and atherosclero-

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sis, chemical carcinogenesis-receptor activation, fluid shear stress, atherosclerosis, hepatitis B virus infection, Kaposi sarcoma-associated herpesvirus infection, and apoptosis.

IL-17 is mainly produced by Th17/Thil-17 cells [12]. Radiation can upregulate the expression of IL-17 and activate the IL-17 signaling pathway [13]. The activation of the IL-17 pathway can further activate the NF- κ B pathway, initiate the cascade of inflammation, cause the death of proliferative intestinal epithelial cells, result in intestinal mucosal barrier damage, and lead to RE [14]. IL-17 can act on intestinal epithelial cells, endothelial cells, and fibroblasts. Our analysis showed that IL-17 could upregulate the expression of heat shock proteins, such as Hsp90 and Actl, and then act on tumor necrosis factor-related receptor factor (TRAF), activate the classical MAPK signaling pathway, activate MAPKs, act on activator protein-1 (AP-1) to participate in DNA transcription, and induce the synthesis and release of IL-6. IL-6 is one of the most important inflammatory cytokines, which is highly expressed in RRE and promotes the occurrence and development of RE [17]. Reducing the expression of IL-17 can inhibit the inflammatory response [18]. Our analysis suggested that Gegen Qinlian decoction may inhibit the activation of the NF- κ B signaling pathway and downregulate the synthesis and release of IL-6 through the IL-17 pathway to inhibit the changes in colitis induced by radiotherapy and repair the intestinal mucosal barrier.

Fluid shear stress is the shear force on vascular endothelial cells when blood flows continuously in blood vessels. Fluid shear stress can regulate the gene expression of vascular endothelial cells and affect the function of vascular endothelial cells by activating membrane receptors and intracellular signal transduction (such as NF- κ B, MAPK, and platelet endothelial adhesion molecules). It can also regulate vascular tension, vascular wall permeability, and the balance between coagulation and fibrinolysis [19]. After the stimulation of radiation, fluid shear stress in the colon of patients increased abnormally, destroying the blood vessels of the intestinal wall and dilating and increasing permeability. Thus, the patients showed symptoms of purulent stool. This study suggested that Gegen Qinlian decoction could reduce intestinal bleeding by reducing fluid shear stress and reducing vascular wall injury. In summary, Gegen Qinlian decoction may improve the symptoms of diarrhea, abdominal pain, and hematochezia through multi-target and multi-pathway inhibition of inflammation and reduction of vascular wall injury. Thus, Gegen Qinlian decoction has high application value in the clinical treatment of RE.

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