

Probing the Mechanism of Deed of Gegenqinlian Decoction in the Care of Pediatric Rotavirus Enteritis Based on Web Pharmacology

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Abstract: To probe the impression and machinery of traditional Chinese medication compound Gegen Qinlian Decoction on rotavirus enteritis in infants. Specific methods: Firstly, TCMSD database was used to search the main chemical components and functional targets of four medicinal materials, including Gegen Qinlian Decoction, and then drugs and diseases were selected. The intersection of target sites was obtained and a Venn diagram was drawn. The web structure chart was constructed using the Cytoscape computer program. Eventually, R computer program was used to total analysis of the improvement of GO and KEGG pathways. Results: The 140 effective compounds, 212 targets and 33 cross genes were obtained from Gegen Qinlian decoction in treating infantile rotavirus enteritis. The 1354 consequences of biological procedure, 3 results of cell component facts and 55 outcomes of molecular function get from GO analysis. The KEGG results showed that the active ingredients in Gegen Qinlian Decoction can regulate the information channels including IL-17 protein receptor information channels, tumor necrosis factor, toll-like receptors and so on by participating in the regulation of multi-molecular receptors, so as to play a therapeutic effect on RV enteritis. Discussion consequence: The research outcomes found the mechanism of action of Gegen Qinlian Decoction on the guard against RV with multi-component, multi-target and multi-channel, and furnishing a new clinical perspective basis and new therapeutic innovation ideas for succeeding clinical investigations.

1. Introduction

On the grounds of the worldwide investigation and numerical analysis[1], diarrhea leads to a high proportion of infant deaths, and rotavirus (RV) virus incidence is the principal cause of diarrhea in infants of all the years. RV virus infection is also one of the fundamental causes of infant

demise. Additionally, RV incidence is also the most commonplace bring about solemn gastroenteritis worldwide and infant diarrhea demise in developing countries[2]. Until a vaccine is developed, almost every infant and child is infected at least once. Relevant data show that RV causes 42.6% of hospital admissions for severe gastroenteritis, Relevant data represent that among infants under 5 years old in China, RV has led to 42.6% of hospital admissions for severe gastroenteritis, 32.5% of diarrhea outpatient calls on quoniam and 9.3% of association diarrhea attack quoniam[3]. Nevertheless, even if RV can vaccinal vaccinate, there is an indispensable venture of incidence, and the infection will also contribute to undernourishment and even expiry of infants. There are currently no effective antiviral chemicals for RV incidence, and symptomatic supportive care is mostly used in clinical therapeutic. Although there is a certain effect, the course of the disease has not been shortened, and clinical symptoms such as the weight loss, malnutrition, and decreased resistance appear after recovery. Gegen Qinlian Decoction is a classic formula for curing diarrhea. With the evolution of the clinical trials and basic investigation, it has been substantiated that it has good curative effect on diarrhea. Contemporary pharmacological studies have shown that Gegenqinlian Decoction is effective in the treatment of diarrhoea through different pathways, acting on relevant targets.

2. Gegen Qinlian Decoction is Made Up of Four Herbs, Including Pueraria Lobata, Coptidis Rhizoma, Scutellaria Baicalensis Georgi and Licorice Root

It has the function of relieving exterior syndrome and clearing interior, and is widely used to treat digestive system sicknesses in current clinical work. In the prescription, Pueraria lobata can not only remission emit heat, but also work up the Yang-Qi of spleen. Combine with Coptidis Radix Scutellariae to dry dampness to thicken the intestines and stop the benefit, and use licorice to reconcile the medicinal properties.

This study confirmed the scientific effectiveness and mechanism of Gegen Qinlian Decoction via network pharmacology. According to literature reports[4], network pharmacology is to comprehend the mechanism of illness and chemical interaction from the perspective of biology, which correspondence with the point of view of traditional Chinese medication. From the moment a drug is added to a living organism, many key biological steps take place at every moment, such as absorption, metabolism, interaction with specific target organs, and interaction with specific cellular receptors, all of which are achieved through the link between cellular receptor proteins and drug molecule interactions[5]. Based on the above foundation, to consummate the existing testimony of Gegen Qinlian Decoction in the remedy of youngsters with RV enteritis. The details are reported as follows:

2.1 Screening of Drug Components and Target Information

The TCMSP was used to index information of four Chinese herbal medications that is to scutellaria, coptis chinensis, kudzu root, and licorice. Subject to oral bioavailability ($OB \geq 30\%$) and drug like properties ($DL \geq 0.18$) were used as the filtration criteria for the chief competent constituents of medicines, and was supplemented with information on the major active substances and their targets that could not be predicted by previous literature studies. After data collection and aggregation, the Unipro database was used to retrieve the gene titles of the target proteins, and the data were de-consolidated and normalised.

2.2 Integration of RV Enteritis Disease-Associated Genes

In the name of “Rotavirus Enteritis, rotavirus gastroenteritis “for the antistop list. In virtue of

corresponding index of PharmGKB, DrugBank, OMIM, TTD, GeneCards databases, the information is wiped off the reiteration, classified and organized.

2.3 Drug Targets Intersect with Disease Targets

The drug target obtained in 1.2 was intersected with the complaint target obtained in 1.3 to obtain the direct target of Gegen Qinlian Decoction, a traditional Chinese medicine compound, in treating RV enteritis. Venn diagrams were plotted using the venn software in R language.

2.4 Build a Visual Network

Each node was identified by uedit with relevant attributes to obtain data on the medicine, active ingredient, the core target and source. Cytoscape 3.8.2 was imported to visualize the structure of the data network combining active compounds and core targets of complaint.

2.5 Construction of Protein Interaction Networks (Ppi)

The latent practical marks of TCM in 1.3 were brought in the STRING information center to choose the species as the humankind and put the score faith (the highest confidence) ≥ 0.7 , while removing the free nodes, leaving the remaining core target sites, thus obtaining the protein interaction network and stored as a TSV document. The TSV matters were imported into the Cytoscape3.8.2 software for network topology anatomy. The scores of each node were analyzed by the CytoNCA plug-in. In the study of this paper, the active active ingredients of compound herbal decoction were analyzed by degree value centering (degree), intermediary number centering (Betweenness Centrality) and shortest path centralization (Closeness Centrality). The PPI network was constructed again to obtain vital core objectives.

2.6 Go Enrichment Analysis and Kegg Pathway Analysis

R language was used to convert the active ingredients of medication and the symbols of common targets of RV enteritis into gene ID form. Several installation packages such as ggPlot2, DOSE and BiocManager can be downloaded from the R language to obtain histograms, bubble graphs, pathway maps and corrected P-value results for GO and KEGG. Only the top 10 options of the corrected P-values are displayed in the graphical settings.

3. Results

3.1 Screening Results of Active Ingredients of Prescriptions

A total of 274 active ingredients of 4 kinds of Chinese herbal medication were collected through TCMSP database search results, with OB value $\geq 30\%$, DL value $\geq 18\%$ as the standard, including 36 results of *Scutellaria baicalensis*, 15 results of *Coptis chinensis*, There are 4 results of *Pueraria lobata* and 92 results of licorice root, and there are 140 results after deletion of duplicates. In the aggregate, 2660 target genes were obtained from Gegen Qinlian Decoction, a traditional Chinese medication compound, and an amount of 212 target genes were obtained after duplicate values were deleted.

3.2 Prediction of Genes Associated with Paediatric Rv Enteritis and Prediction of Drug-Disease Targets

The 718 consequences of illness-associated genes were acquired from Genecards information center. Combined with OMIM, PharmGKb, TTD and DrugBank databases to supplement, after integration, de-duplication and correction, a whole of 656 gene data were obtained. Using R language, the drug targets and the illness genes are intersected, so 33 common targets are obtained, which are drawn into a Venn diagram, as shown in Figure 1.

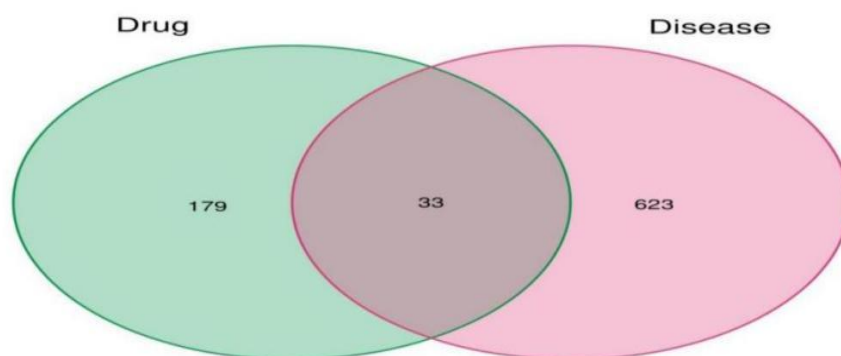


Figure 1: Venn Diagram of Intersection of Rv Enteritis Target and Gegenqinlian Decoction Target

3.3 Constructing the Network Graph

Each node is identified by attributes through uedit software, so as to obtain the data of chemicals, active ingredients and core targets (Figure 2). Import Cytoscape3.8.2 to make the drug components and targets of illness form a visual network. In the cutline, the tighter the concatenation at the nodule and the darker the nodule color, expressing the higher its consequence, the same is appropriate for the part of chemical, the big the nodule, the large the significance of the part as emerged in representation 2.

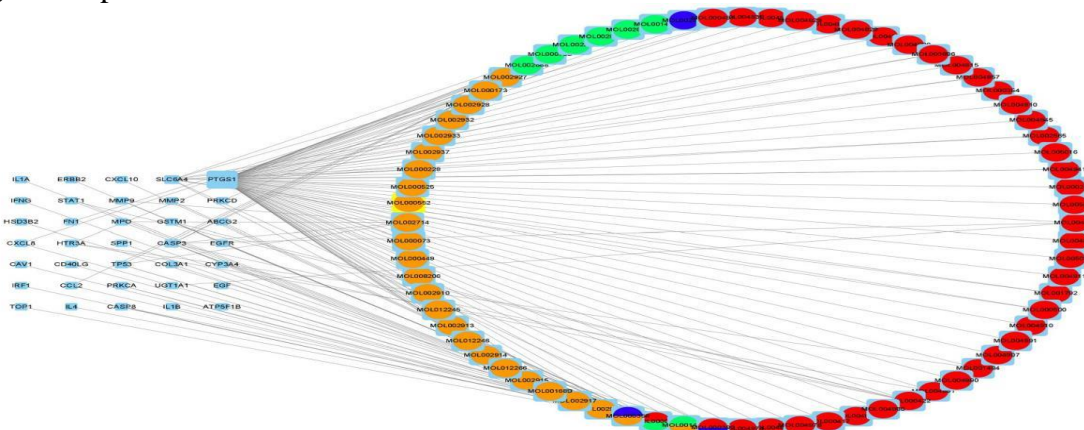


Figure 2: Visual Network Diagram of Gegenqinlian Decoction for RV Enteritis: Tcm-Active Component-Core Target

3.4 Constructing the Ppi Network

Feed in the mark message derived from the Venn plan in 2.2 into the STRING online information center to set up the mutual exclusion protein web, and select the confidence level of \geq

0.7. After removing the targets of free, screening out the targets that meet the conditions, the TSV files were exported and the PPI network was drawn with Cytoscape (Figure 3). The nodes were after that pologically resolved using plug-ins such as CytoNCA, and the median values of node neutrality, near-neutrality and intermediate centrality were filtered twice to obtain the four key interaction targets (Figure 4). Combining the values of each parameter with the recent literature, it was suggested that these targets might be the key genes in the treatment of RV enteritis with the Chinese medicine compound Ge Gen Scutellaria Tang.

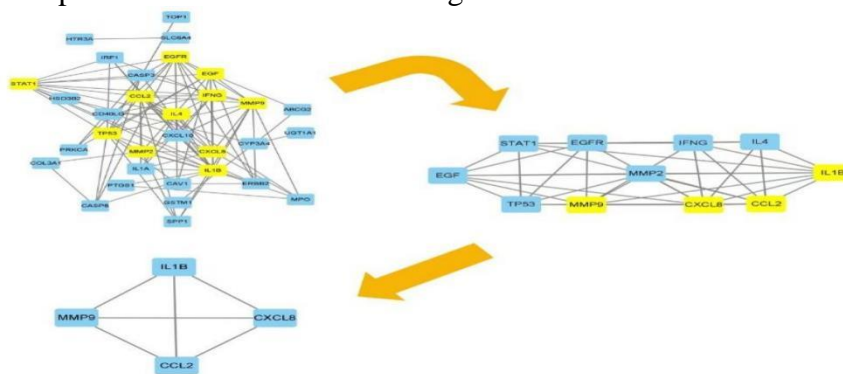


Figure 3: Ppi Network Topology Analysis of Core Genes

3.5 Go Process and Kegg Pathway Enrichment Analysis

The GO biological process provides a visual representation of the main functions performed by the network genes and the degree of gene enrichment. The method requires a P-value <0.05 and a corrected P-value <0.05. The analysis in R yields 1354 results for Biological process (BP), 3 results for Cellular Compont (CC) and 55 results for Molecular Function (MF). The cellular genes were sorted according to the number of enriched cellular genes, and the first 10 with the highest significance were selected and output in the form of bar graphs (see Figure 4), The ptimary functions include: response to glial apoptosis, response to drugs, tissue remodelling, monocyte growth, regulation of leukocyte differentiation, normal leukocyte growth, positive regulation of haematopoiesis, receptor ligand activity, activation of messenger receptor activators, binding to the tumour necrosis factor receptor superfamily and so on.

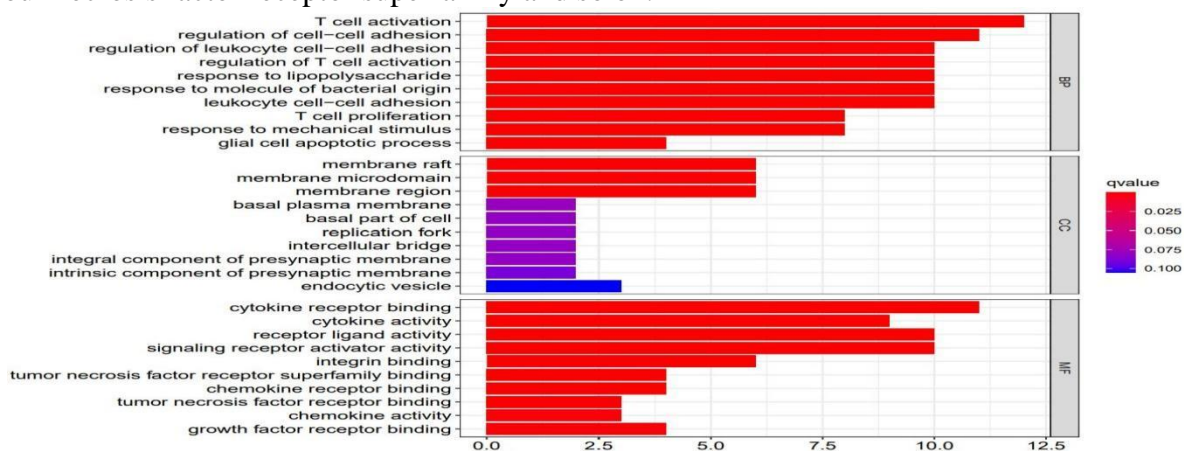


Figure 4: Histogram of Enrichment Analysis of Go Bioprocess of Gegenqinlian Decoction-Rv Enteritis Related Target Gene

Using the parallel filtrating criteria, 33 centre marks of Gegen Qinlian Decoction were analyzed for KEGG pathway improvement, and 167 enrichment results were obtained. The top 30 results

with the highest enrichment significance are presented as bubble plots (Figure.5). The primary channel results include: tumour necrosis factor, IL-17 protein receptor, malaria, toll-like receptors, amoebiasis, inflammatory bowel disease, MAPK signalling pathway, etc.

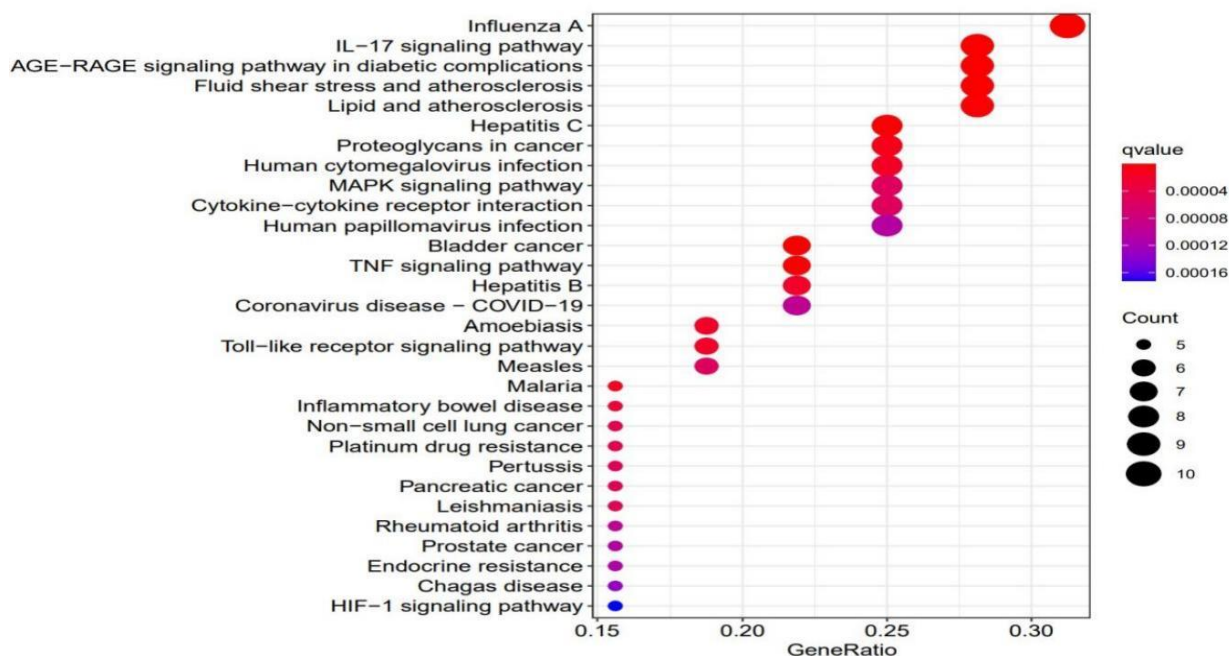


Figure 5: Bubble Analysis of Kegg Pathway Enrichment of Target Genes Associated to Gegenqinlian Decoction-Rv Enteritis

4. Discussion

Using the corresponding database, a total of 140 active ingredients, 212 drug target genes and 656 RV enteritis disease proteins were screened for Gegenqinlian Decoction. Through the network building diagram, it was revealed that the chemical components with high correlation with RV enteritis were primarily quercetin, wogon skullcap, baicalein and so on. Based on the above research results, it can be inferred that these components are the main active ingredients in Gegenqinlian Decoction for the prevention and treatment of RV enteritis. RV is extremely infectious in childhood, and there is the feasibility of repeated disease. The incubation course is in less than 48 hours, and the infection lasts about 10 days. Sickesses are either asymptomatic, self-confinement with diarrhoea, or else consequence in severe dehydration and/or fever, vomiting and mulligrubs. RV is principally transmitted through fecal-oral contact, surface of pollutants and hand, and can also be transmitted through the respiratory tract, and it can emerge all year round[6]. RV chiefly infects mature small intestinal epithelial cells and enteroendocrine cells, resulting in intestinal epithelial cells (IEC) due to villous atrophy, epithelial cell proliferation and necrosis, and the formation of grand vacuoles in intestinal epithelial cells, thereby disrupting IEC homeostasis[7,8]. IEC is the first physikalisch obstacle against RV complaint. In addition to acting as a physical barrier in the intestine, IEC also produces mucus and cytokines/chemokines, including toll-like receptor (TLR) expression and signaling, to reduce the risk of RV infection[9,10].

On the basis of contemporary age study and deduce, quercetin, a ubiquitous flavonoid, which is the most effective reactive oxygen species (ROS) scavenging agent. It can refrain the manufacture of a diversity of proinflammatory factors, reduce the activity of kinase MEK1, down regulate the cascade reaction of Raf and MAPK, inhibit the release of telomerase, and thus play an anti-inflammatory role[11]; Baicalin could directly bind to TLR4 receptor protein and interrupt the

formation of intermediate complex, thus inhibiting Baicalein can directly bind to TLR4 receptor protein and interrupt the formation of intermediate complexes, thus inhibiting TLR4 activity[12].

Therefore, it is hypothesized that Gegenqinlian Decoction can clear the development of RV infection by suppressing the intestinal inflammatory response and increasing the expression of the body's immunity. In conclusion, according to previous scientific studies, these important substances in Gegenqinlian Decoction have been shown to have virucidal as well as inflammatory functions, which may be a scientific explanation for the effectiveness of the traditional Chinese medicine formula Gegenqinlian Decoction in preventing and treating RV enteritis. In the PPI network, four central genes, including IL1B, CXCL8, CCL2 and MMP9, were identified as the capital central genes targeted by Radix Scutellariae Sinensis Tang to act. This may suggest a new reference direction for further in-depth study of the mechanism of action of RV enteritis.

The results of GO enrichment analysis represent that the genesis and development of RV are mainly relevant to inflammation and immune response, which is the same as the view of most previous researchers.

RV activates the immune reaction by inducing intestinal villus epithelial cells. The human immune system has two mechanisms: Th1/Th2 cells and Th17/Treg cells. Th17 cells take part in autoimmune sicknesses, infections and other pathological procedures by synthesizing and freeing cytokines for instance IL-17 and IL-6[13/14]. Treg cells participate in the progress of autoimmune illnesses via quantitative changes or inhibition of cytokine activity[15]. This indirectly verified that the imbalance of Th17/Treg cell expression may be one of the pathogenesis of RV.

The investigation of KEGG channel enrichment confirmed that the fundamental channel results included: tumour necrosis factor, IL-17 protein receptor, malaria, toll-like receptors, amoebiasis, inflammatory bowel disease, MAPK signalling pathway, etc. Cytokines bind to tyrosine kinase (tyrosine kinase) holding tanks and activate the transcription factor family, thereby regulating the body's immune response[16]; secondly, Toll-like receptors act as transcription factors related to the body's defence system by initiating the NF- κ B and MAPK cascades, which in turn contributes to the production of cytokines [17]. Matrix metalloproteinases (MMPs), as a kind of metal zinc dependent proteases, use cell lysis to regulate the activity of chemokines, and then participate in the process of bacterial invasion, the tissue destruction and repair [18, 19]. Kawamura et al. [20] Shown clearly that the dynamics of MMPs and TIMPs is the vital to RV illness through serum detection of RV enteritis patients, MMP-9 can give rise to tissue damage, and MMP-2 can alleviate IEC tissue remodeling. As a consequence, we speculate that Gegenqinlian Decoction may exert anti-inflammatory and antiviral therapeutic effects in the treatment of RV enteritis through the above signal pathways.

5. Conclusion

It is through the network pharmacology approach that this study has confirmed the exact efficacy of Gegenqinlian Decoction in the treatment of rotavirus infection and hypothesized that its mechanism of impact is relevant to the capability of Gegenqinlian Decoction to apply anti-inflammatory and antiviral roles via interrelated pathways. At present, network pharmacology has been increasingly applied in the research of Chinese medication, evidence and prescriptions, showing a trend of combining data, experiments and clinics, which provides a new way to interpret the principles of traditional Chinese medicine. In spite of our quite a few efforts, there are undeniably some limitations to our article. Nevertheless, it should be attended that, on the one hand, a pure focus on validated target genes may exclude potential targets that have not been experimentally validated. On the other hand, our study lacks the validation analysis. Hence, further unemotional and fundamental learn is indispensable to check it.

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