Role of Granati Pericarpium in the Treatment of Ulcerative Colitis: Insights from Network Pharmacology and Molecular Docking

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Introduction. To investigate the mechanism underlying the therapeutic effects of Granati Pericarpium(GP) in treating ulcerative colitis(UC).
Methods. The TCMSP database and SymMap database were utilized to acquire information regarding the active constituents and potential targets of GP, respectively. Disease-associated targets of ulcerative colitis were identified from the GeneCards database based on relevance scores. Protein interaction networks were constructed using the String database and Cytoscape software to identify key targets. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis and Gene Ontology (GO) enrichment analysis were conducted using the DAVID database. Subsequently, molecular docking verification was performed using AutoDock software, and the results were visualized using Pymol software.
Results. Seven primary chemical constituents of GP were identified, and a total of 195 common targets shared between GP and UC were determined. Protein-protein interaction analysis revealed that Cellular tumor antigen p53 (TP53), RAC-alpha serine/threonine-protein kinase (AKT1), Signal transducer and activator of transcription 3 (STAT3), Tumor necrosis factor (TNF), and Interleukin-6 (IL6) may serve as key targets for treatment. KEGG pathway analysis suggested that GP may exert its therapeutic effects on UC through signaling pathways such as Pathways in cancer, Lipid and atherosclerosis, and AGE-RAGE signaling pathway in diabetic complications. Molecular docking simulations demonstrated the effective interaction of both the key active components and the core targets.
Conclusion. Utilizing network pharmacology and molecular docking technology, it has been elucidated that GP possesses the potential to treat UC through a multifaceted approach involving multiple components, targets, and pathways. These findings lay a solid theoretical foundation for subsequent research endeavors.
Keywords. Ulcerative colitis; Punica granatum peel; Network pharmacology; Molecular Docking

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory disorder that occurs in the colorectum, and its incidence and prevalence are increasing globally.[1] Until now, its cause has not been fully defined. The main clinical features are abdominal colic, severe defecation, and diarrhea (often bloody), and it can greatly affect the lives of patients and lead to long-term complications. At present, although there are many anti-UC drugs, the treatment effect on patients is still not good, and because of safety and availability, WTO still encourages the search for traditional herbs against UC.[2, 3] In recent years, with the in-depth study of traditional Chinese medicine (TCM) in experimental and clinical aspects, it has been found that TCM has a unique effect in the treatment of UC. Some TCM has a better therapeutic effect on UC than Western medicine and has fewer side effects and obvious advantages. [4]

Shiliupi (Punica granatum L.) has been used for medicinal purposes for a long time. Its juice, seeds, peels, flowers, leaves, and bark have medicinal value.[5, 6] Granati Pericarpium (GP) has an astringent effect on the intestines and can stop diarrhea. It is commonly used to treat chronic diarrhea, chronic dysentery, hematochezia, and rectal prolapse.[7] Studies have shown that the active ingredients of GP primarily include polyphenols, flavonoids, alkaloids, etc. These components have various benefits, including anti-oxidation, anti-cancer, anti-inflammatory, anti-bacterial, and cardiovascular protection effects.[8-10] Additionally, numerous studies have shown that GP is effective in the treatment of UC.[11-13] However, the mechanism is not clear.

Network pharmacology is a discipline that utilizes a disease-phenotype-gene-drug multi-layer network, integrating computer software, systems biology theory, and other technologies to predict and identify the core biological targets of drug active ingredients and diseases. This approach demonstrates significant potential as the next drug discovery paradigm.[14, 15] Network pharmacology is a valuable tool for identifying the main biological processes and signaling pathways involved in the relationship between drugs and diseases. By taking an overall perspective, it can predict drug targets and improve the success rate of clinical trials for new drugs. Additionally, it provides new methods for researching traditional Chinese medicine. Currently, network pharmacology is a popular method for predicting the basis and mechanism of pharmacodynamic substances in traditional Chinese medicine.[16, 17]

Molecular docking is a theoretical simulation method based on the principles of structural biology. It uses computer technology to study the binding sites and affinity of target protein receptors and small molecule drug ligands.[18] This method can complement the study of traditional Chinese medicine in treating diseases and provide new insights for screening and exploring the mechanisms of active compounds.

The objective of this study is to investigate the potential targets and pathways of GP in preventing and treating UC through protein-protein interaction (PPI) and signaling pathways. Network pharmacology and molecular docking were utilized to confirm the binding affinity of active components to key targets. This process further validates the mechanism of action of GP in preventing and treating UC, as well as the accuracy of predicted targets. The aim is to establish a theoretical basis for future research on GP.

MATERIALS AND METHODS

Screening of Active Components and Targets of GP

The primary constituents of pomegranate peel were identified by querying the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://old.tcmsp-e.com/tcmsp.php) using 'Granati Pericarpium' as the keyword. Based on traditional Chinese medicine component pharmacokinetic parameters, screening criteria were set with a bioavailability (OB) threshold of ≥30% and a drug-likeness (DL) threshold of ≥0.18.[19, 20] The active constituents of pomegranate peel meeting these criteria were then determined. Subsequently, the active constituents of pomegranate peel were inputted into the traditional Chinese medicine comprehensive database SymMap (http://www.symmap.org/) to explore the potential targets of each component. Components without identified targets were excluded, and the targets of each component were further analyzed to compile a list of GP targets.

Target Screening of GP in the Treatment of UC

Disease targets related to UC were retrieved from the human disease database GeneCards (https://www.genecards.org/) using 'Ulcerative colitis' as the keyword. Close disease targets associated with ulcerative colitis were filtered based on the relevance score. A Venn diagram illustrating the intersection of GP targets and UC-related targets was generated using the VENNY2.1 platform (https://bioinfogp.cnb.csic.es/tools/venny/). These common targets were considered

potential key targets of GP in UC treatment. The 'GP-common target-UC' network diagram was constructed using Cytoscape 3.8.0 software (https://cytoscape.org/).

Construction and Analysis of the PPI Network

The common target genes of GP and UC were uploaded into the STRING database (https://cn.string-db.org/) to construct a PPI network, with a confidence threshold set to > 0.900. Free nodes were eliminated, and the resulting network was imported into Cytoscape 3.8.0 for visual analysis. Core targets of GP in UC treatment were identified based on their degree of centrality within the network.

Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis and Gene Ontology (GO) Functional Enrichment Analysis Were Performed

The common targets of GP and UC were submitted to the DAVID database (https://david-d.ncifcrf.gov/tools.jsp) for KEGG and GO signaling pathway analysis. The top 20 P-values of the KEGG signaling pathway were selected, while the top 10 P-values of biological process (BP), cellular component (CC), and molecular function (MF) categories of GO enrichment analysis were ranked. The results were then subjected to visual analysis using the online tool (http://www.bioinformatics.com.cn/).

Molecular Docking Verification

In the PPI network, the top five key targets with the highest degree of centrality were selected for molecular docking with active components of GP. The 2D structure files of the key compounds screened from GP in the UC regulatory network were exported from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format. These files were then converted into 3D structures in PDB format using Chem3D software (https://library.bath.ac.uk/chemistry-software/chem3d). AutoDock Tools software was employed to prepare the active components and save them as pdbqt format files for subsequent molecular docking as ligands. The PDB ID of the key target proteins was obtained from the UniProt database (https://www.uniprot.org/), and their 3D structures were downloaded from the PDB database. The protein receptors were processed using Pymol and AutoDock Tools software and saved as pdbqt format files for use as receptors in subsequent molecular docking. AutoDock Vina software was utilized for virtual docking, and the model with the lowest binding energy score was selected for further analysis. The results were visualized using Pymol software.

RESULTS

Screening of Active Ingredients and Targets of GP

A total of 26 main components of GP were retrieved from the TCMSP database, including tannins and flavonoids. With OB ≥ 30 % and DL ≥ 0.18 as the screening indexes, 7 main active components were obtained, and only 6 components had corresponding targets after searching in the SymMap database, they are (+)-catechin, Quercetin, Ellagic acid, Kaempferol, β-sitosterol, Luteolin (Table 1). Their structures are shown in Figure 1. The pharmacokinetic parameters of the six components are shown in the radar plot (Figure 2). After removing duplicates, we obtained 342 GP targets out of the initial 617 targets.

Table 1: Active components of Granati Pericarpium

Mol ID	Component	OB (%)	DL	Category	Molecular Formula
MOL000492	(+)-catechin	54.83	0.24	Tea polyphenols	C15H14O6
MOL000098	Quercetin	46.43	0.28	Flavonoids	C15H10O7
MOL001002	Ellagic acid	43.06	0.43	Tannins	C14H6O8
MOL000422	Kaempferol	41.88	0.24	Flavonoids	C15H10O6
MOL000358	β-sitosterol	36.91	0.75	Phytosterol	C29H50O
MOL000006	Luteolin	36.16	0.25	Flavonoids	C15H10O6

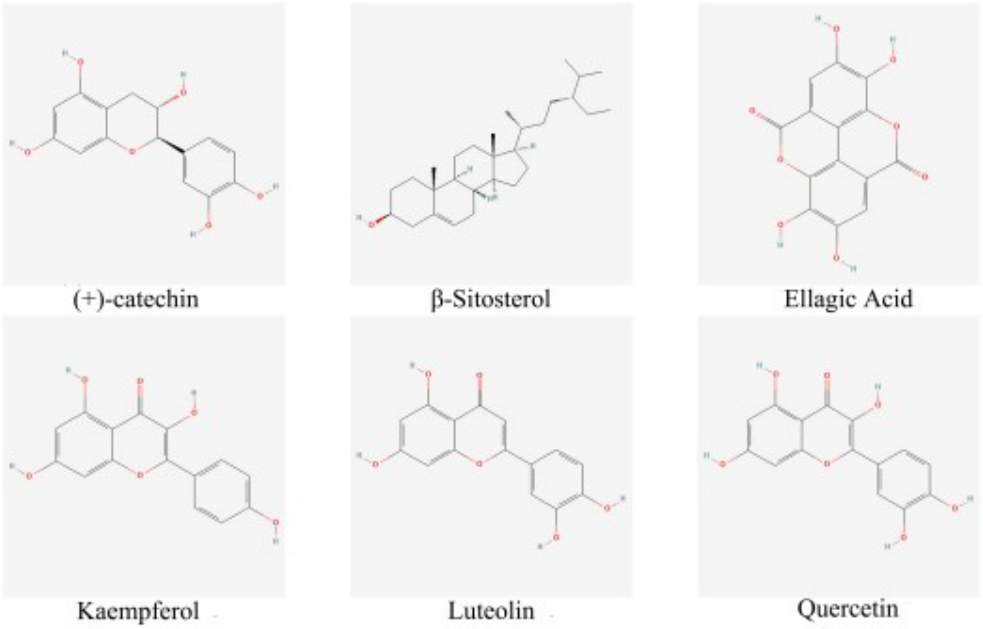

Figure 1: Structure of active components in Granati Pericarpium

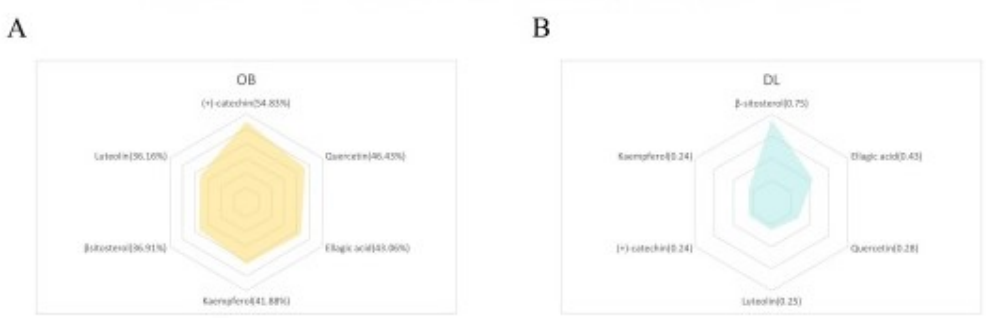

Figure 2: Pharmacokinetic parameters of traditional Chinese medicine components of active ingredients in Granati Pericarpium

Potential Targets of GP for the Prevention and Treatment of UC

The GeneCards database was searched for potential disease targets of UC, resulting in 5332 targets. A total of 2065 targets with a Relevance score ≥ 2.0 were selected as closely related disease targets of UC. By visualizing the drug targets and disease targets (Figure 3), we identified 195 common intersection targets. By visualizing the drug targets and disease targets in Figure 3, we identified 195 common intersection targets that could potentially be used for GP to prevent and treat UC. A 'GP-common target-UC' relationship network was constructed, which had 197 nodes and 390 edges (Figure 4).

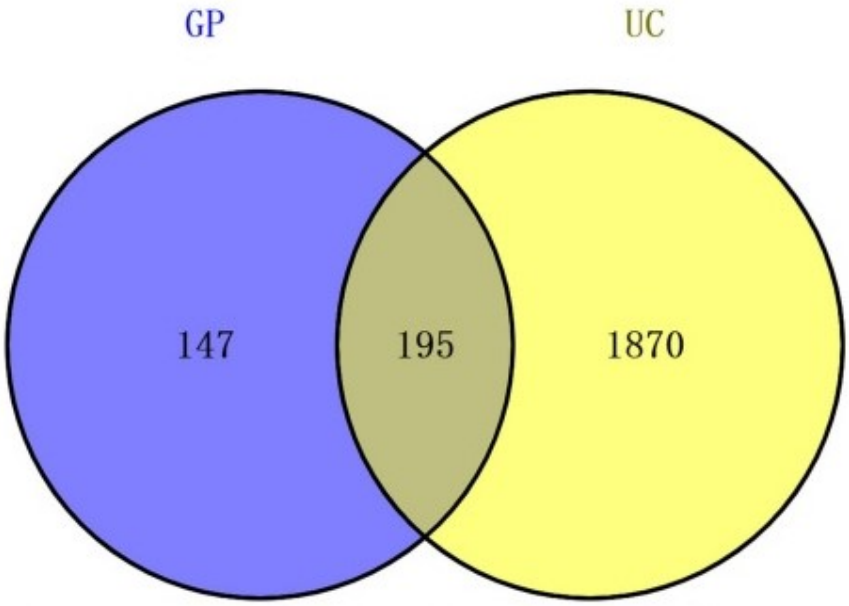

Figure 3: Venn plot of intersection targets between Granati Pericarpium and Ulcerative Colitis

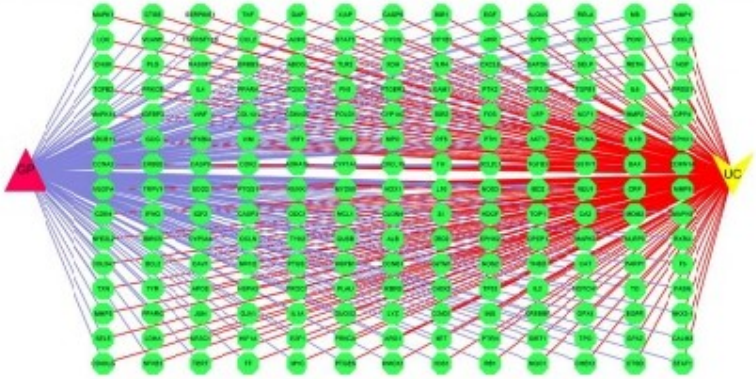

Figure 4: Network diagram of intersection targets between Granati Pericarpium and Ulcerative Colitis

Construction and Analysis of the PPI Network

The intersection targets are uploaded to the STRING database, with the High Confidence parameter set to 0.900 and the irrelevant targets hidden. Figure 5 shows the PPI network diagram, which includes 195 nodes and 784 edges. The average node degree is 8.04, and the average local clustering coefficient is 0.465. The expected number of edges is 171. The PPI enrichment p-value was found to be less than 1.0e-16. The core targets of GP in the treatment of UC were analyzed and screened using the 'Analysis Network' function in Cytoscape 3.8 software. According to the “Degree”, the top five targets were screened, including Cellular tumor antigen p53 (TP53), RAC-alpha serine/threonine-protein kinase (AKT1), Signal transducer and

activator of transcription 3 (STAT3), Tumor necrosis factor (TNF), and Interleukin-6 (IL6) (Table 2).

Table 2: The key targets of Granati Pericarpium in the treatment of Ulcerative Colitis

UniProt ID	PDB ID	Gene	Target	Degree
P04637	1AIE	TP53	Cellular tumor antigen p53	54
P31749	1UNP	AKT1	RAC-alpha serine/threonine-protein kinase	37
P40763	5AX3	STAT3	Signal transducer and activator of transcription 3	37
P01375	3WD5	TNF	Tumor necrosis factor	35
P05231	1IL6	IL6	Interleukin-6	35

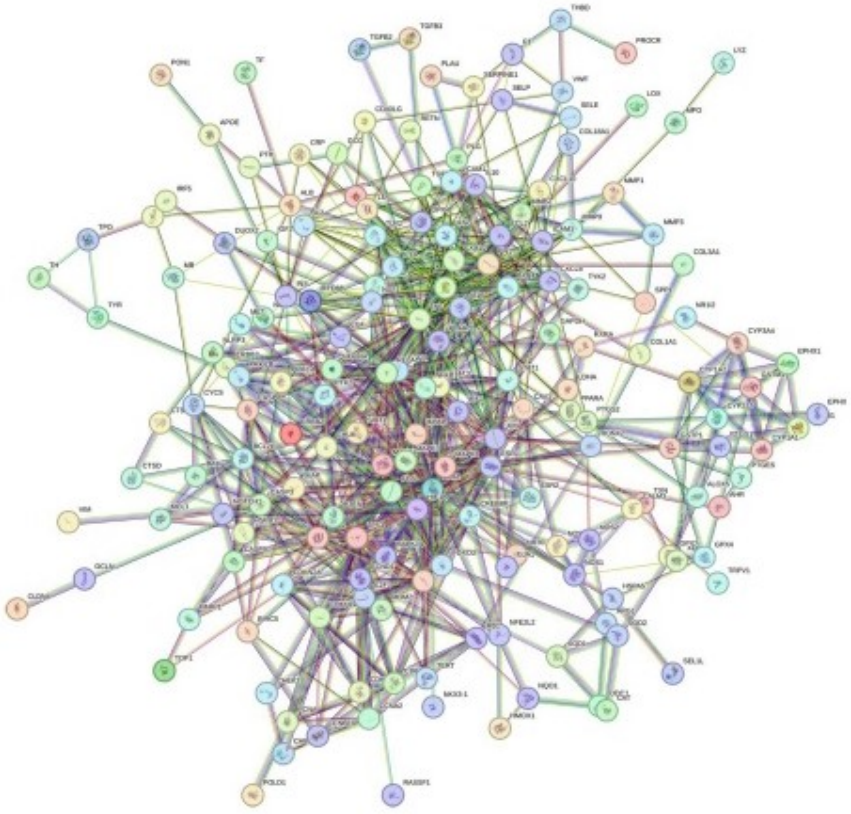

Figure 5: PPI network diagram of potential targets for Granati Pericarpium treatment of Ulcerative Colitis

KEGG Pathway Analysis and GO Functional Enrichment Analysis

The DAVID database was used to analyze the intersection targets, and the KEGG pathway and GO function enrichment analysis data were obtained. According to the results of KEGG enrichment analysis screened by P-value < 0.05, a total of 182 pathways were obtained. According to the P value, the top 20 pathways were selected for visualization, and the bar chart shown in Figure 6 was obtained. The KEGG enrichment data showed the important factors of GP in the treatment of UC. The main related pathways include Pathways in cancer, Lipid, and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, etc. A total of 1194 items related to GO functional enrichment analysis were obtained, comprising 928 BP items, 104 CC items, and 162 MF items. Based on the P value, the top 10 items were selected for visual display (Figure 7). Figure 8 displays the KEGG-enriched signaling pathways and BP enrichment items related to the five core targets.

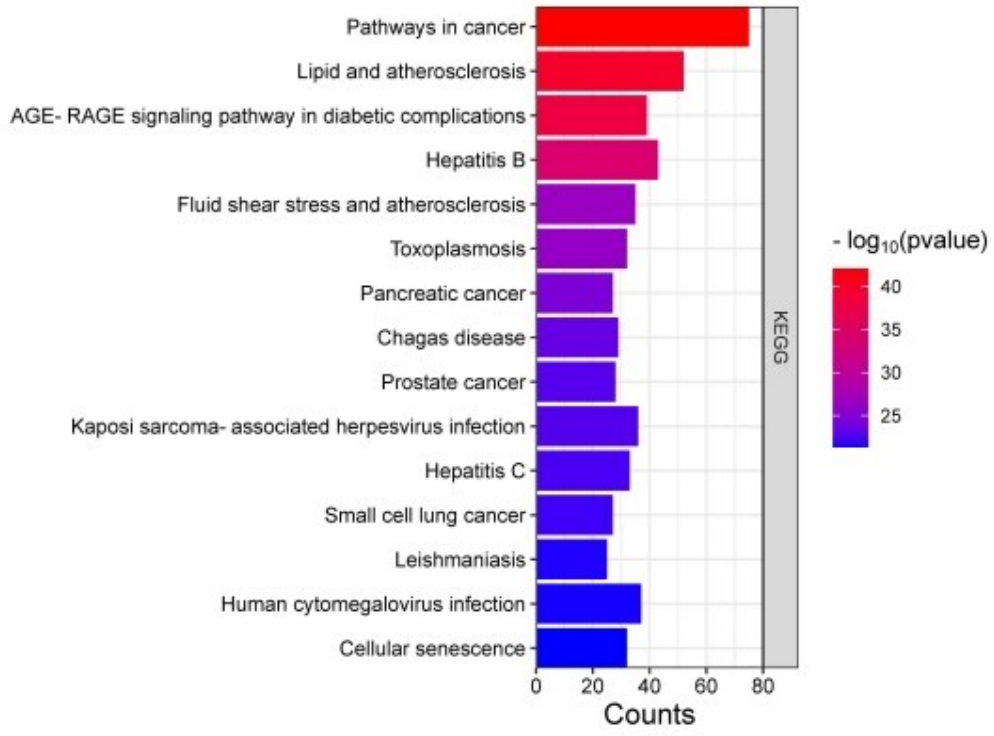

Figure 6: KEGG enrichment analysis

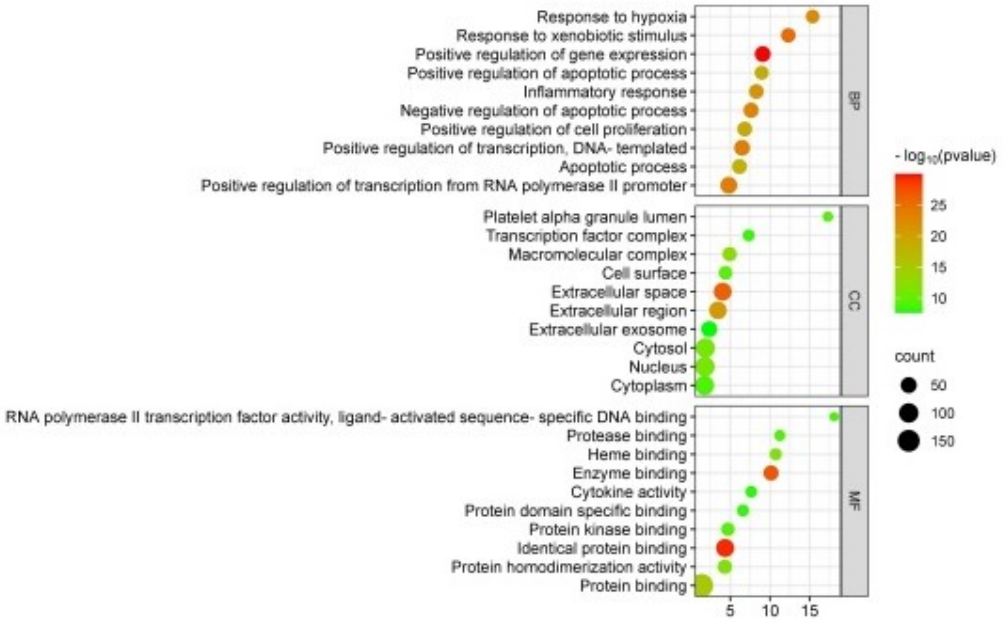

Figure 7: GO enrichment analysis diagram

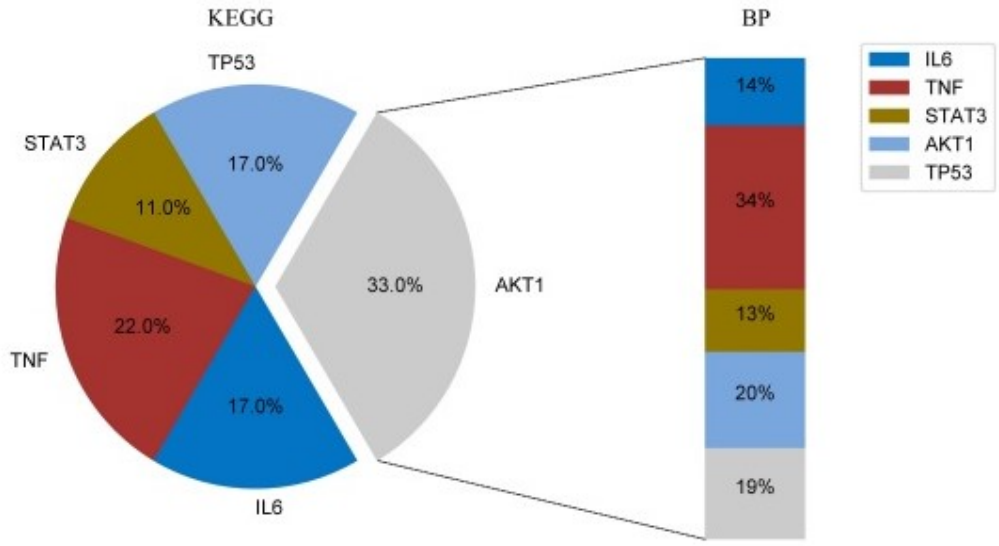

Figure 8: The number of KEGG signaling pathways and biological processes involved in the core targets

Molecular Docking Results

To demonstrate the binding activity between the target protein and the GP active ingredient, we utilized Auto Dock to perform molecular docking between the six key components and the core target. According to Auto Dock Vina, a lower binding

energy score indicates a higher affinity between the receptor and ligand, resulting in greater docking activity and a better binding effect. It is commonly believed that small molecules with a binding energy score of less than 0 can bind spontaneously to docking proteins under natural conditions.

The study found that the key components of GP have good binding ability with the core targets of UC, as evidenced by their spontaneous binding under natural conditions and the binding scores of the five targets to all the key components being less than −5.0 kcal/mol (Figure 9). This suggests that the key components of GP could potentially improve or treat UC. Among them, ellagic acid exhibits better binding performance with TNF (the lowest binding energy being -9.0 kcal/mol). The treatment using PyMol software is shown in Figure 10.

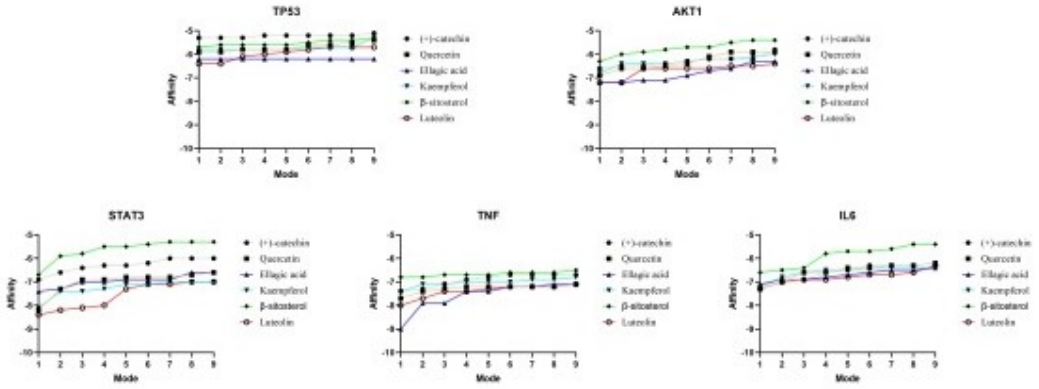

Figure 9: Molecular docking binding energy diagram

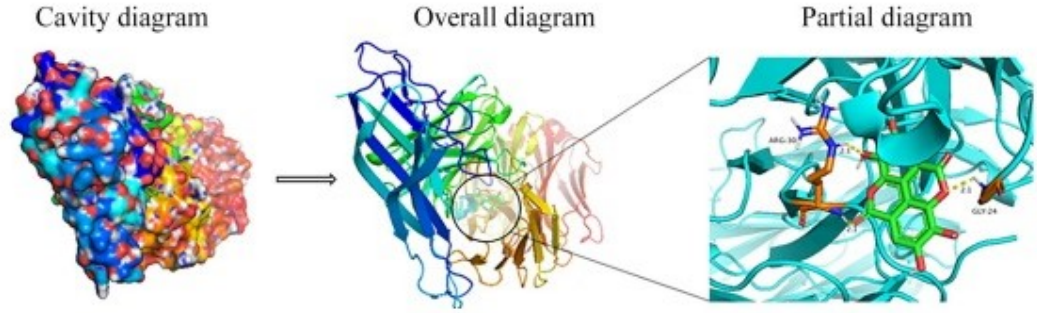

Figure 10: Molecular docking display of TNF and Ellagic acid

DISCUSSION

Ulcerative colitis (UC) is a chronic, non-specific, non-infectious inflammatory bowel disease that affects the mucosa and submucosa of the colon and rectum. It is a complex immune-mediated inflammatory condition characterized by continuous and diffuse inflammation. UC manifests as mucosal ulcers that extend continuously from the rectum and may progress to involve varying extents of the colon, with the potential to reach the cecum.

Ulcerative colitis (UC) is a chronic, non-specific, non-infectious inflammatory bowel disease that affects the mucosa and submucosa of the colon and rectum.[21] It is a complex immune-mediated inflammatory condition characterized by continuous and diffuse inflammation.[22] UC manifests as mucosal ulcers that extend continuously from the rectum and may progress to involve varying extents of the colon, with the potential to reach the cecum.[23] Severe cases of UC can lead to the development of colorectal cancer. While the exact cause of UC remains incompletely understood, it is widely acknowledged that the initiation of UC involves an abnormal inflammatory response triggered by factors that disrupt the mucosal barrier, alter the normal composition of intestinal microflora, and aberrantly activate the intestinal immune system.[24]

Pomegranate has a rich history in traditional medicine, with its juice, seeds, peel, flowers, leaves, and bark all exhibiting pharmacological activity, forming a diverse phytochemical repository with significant medicinal potential.[25] GP is frequently employed in the treatment of UC. Ganjiang decoction, which has demonstrated efficacy in UC treatment, contains GP among its constituents.[26] Ou developed a functional Chinese medicine screening model for treating active UC by constructing an herb-compound-target network and conducting immune infiltration analysis. They discovered that GP could alleviate abdominal pain and hematochezia in active UC.[27]

In this study, we employed a network pharmacology approach to investigate the molecular mechanism of GP in UC treatment, focusing on the concept of a 'disease-gene-target-drug' relationship. Preliminary analysis revealed that (+)-catechin, Quercetin, Ellagic acid, Kaempferol, β-sitosterol, and Luteolin were the primary active components of GP. These active ingredients act on core targets such as TP53, AKT1, STAT3, TNF, and IL6 to play a role in the treatment of UC.

TP53 is a widely recognized tumor suppressor gene, and its encoded P53 tumor

suppressor protein serves as a key regulator of genomic integrity, cell cycle, and apoptosis. Alterations in the TP53 phenotype have been closely linked to the progression of UC to colorectal cancer.[28] This association was confirmed by Yan.[29] The most extensively studied single nucleotide polymorphism (SNP) of p53 involves an Arg>Pro substitution at codon 72 (R72P), with the TP53 codon 72 Arg/Arg genotype associated with an increased risk of UC development.[30] In UC, the Pro/Pro genotype was significantly associated with a family history of IBD.[31] Arai conducted a microarray analysis of cancer-related gene expression in rectal mucosal biopsy specimens obtained from randomly selected pediatric cases. Through RT-PCR and immunohistochemical techniques, they validated significant down-regulation of TP53 in UC patients.[32] These findings suggest that TP53 is implicated in the onset and progression of UC and is associated with its progression to cancer, consistent with the findings of our KEGG signaling pathway enrichment analysis, particularly Pathways in cancer.

AKT1 is activated by various growth and survival factors and plays a crucial role in regulating cell growth, division, and apoptosis inhibition. The post-translational modification pathway of AKT1 is associated with inflammatory signal transduction in UC epithelium.[33] AKT1 is a crucial component of the PI3K-AKT-MTORC1 signal transduction axis, which can suppress autophagy, thereby exacerbating endoplasmic reticulum stress and promoting UC development.[34] Modulating this signaling pathway to enhance autophagy has been proposed as a therapeutic approach for UC.[35] Wu utilized the Dextran Sulfate Sodium Salt (DSS)-induced C57BL/6 mouse model for metabolomics and other experimental investigations, demonstrating that inhibition of PI3K/ AKT/mTOR pathway protein expression reduces colon inflammation and ameliorates UC, consistent with the findings of Kang.[36, 37] Additionally, Jiang conducted in vivo experiments confirming that MiR-223 up-regulates the PI3K/Akt/mTOR signaling pathway, leading to UC cell apoptosis and inflammation.[38] Bisdemethoxycurcumin emerges as a potentially therapeutic agent for UC treatment.

In vitro studies by Wu demonstrated that Bisdemethoxycurcumin can mitigate LPS-induced proinflammatory factor levels in RAW264.7 cells by inhibiting the PI3K/Akt pathway, thus exhibiting therapeutic potential for UC.[39] Zhang, utilizing tandem mass tag-based quantitative proteomics, observed increased expression of

fibrinogen and activation of AKT, along with subsequent microfilament depolymerization in colon tissue of the DSS-induced UC mouse model, exacerbating UC development.[40] Furthermore, bioinformatics analysis identified AKT1 as one of the key genes involved in biological processes related to both UC and Colon Adenocarcinoma.[41] STAT3-mediated ferroptosis has been implicated in UC. Inhibition of STAT3 expression exacerbates UC inflammation by augmenting the degree of ferroptosis.[42] Conversely, STAT3 overexpression can diminish the expression of pro-inflammatory cytokines in UC and restore epithelial barrier function.[43] The disruption of intestinal flora homeostasis is strongly associated with the onset of UC. Lactobacillus johnsonii, an anti-inflammatory bacterium, functions as a probiotic by activating macrophage immunity and inducing the release of IL10 through the TLR1/2-STAT3 pathway. This mechanism contributes to the alleviation of DSS-induced colitis in mice.[44] Nevertheless, the involvement of STAT3 in the pathogenesis of UC remains contentious. Some reports suggest that STAT3 activation exacerbates the inflammatory response in UC.[45]

Chen investigated the use of ginsenosides to treat DSS-induced UC in mice. Through Western blotting and other experiments, they observed that ginsenosides effectively suppressed STAT3 phosphorylation and miR-214 expression in colonic epithelial cells of the diseased group, thereby impeding the progression of UC.[46] Overexpression of sphingosine kinase 1 enhances the secretion of pro-inflammatory cytokines in RAW264.7 cells and triggers the activation of the JAK2/STAT3 signaling pathway, thereby promoting the inflammatory progression of UC.[47] Additionally, STAT3 is closely associated with UC complicated by colorectal cancer. The marked elevation of phosphorylated STAT3 (pSTAT3) in the colon of UC patients is linked to colorectal cancer mutagenesis.[48] TNF inhibitors have shown significant progress in the treatment of UC.[49, 50] S.boulardii has been shown to effectively mitigate UC carcinogenesis by lowering the levels of TNFα and IL6.[51] IL6 is a multifunctional cytokine regulated by NF-κB that acts on both epithelial and immune cells.[52] Activation of the IL-6/STAT3 pathway exacerbates intestinal mucosal barrier damage in UC.[53] Increased expression and activation of IL6 and STAT3 have been observed in UC-associated carcinogenesis, with expression levels correlating with disease severity.[54] Elevated IL6 expression in intestinal tissue of UC patients suggests its role in inflammation, and reducing IL6 expression can benefit UC treatment by

attenuating the inflammatory response.[55-57] This is supported by GO enrichment analysis, which highlights the involvement of inflammatory response in UC pathogenesis. Core targets associated with UC indicate that GP may mitigate inflammation, enhance intestinal barrier function, regulate intestinal flora, and improve immunity by modulating cell inflammation, proliferation, apoptosis, and oxidative stress.

Among the six active components of GP identified in the previous study, it is evident from Figure 9 that, aside from STAT3, Ellagic acid exhibits the lowest binding energy with other targets and the strongest binding capability. Molecular docking results of Ellagic acid with the target TNF showed the most promising outcomes. Ellagic acid, a polyphenolic compound naturally present in various plant taxa, particularly in GP, possesses antioxidant, anti-inflammatory, anti-mutagenic, and anti-proliferative properties. Marta demonstrated that Ellagic acid from pomegranate exhibits anti-inflammatory effects by modulating IL6, TNFα, and other mediators, thus offering the potential for UC treatment.[58] These targets align with the core target findings from our previous PPI analysis. Ellagic acid inhibits oxidative and inflammatory processes and regulates intestinal barrier function and microbiota composition.[12] Peng confirmed that Ellagic acid alleviates TNBS-induced intestinal barrier dysfunction by modulating mucin secretion and maintaining tight junction integrity in SD rats,[59] with implications for the miR-145/p70S6K1/HIF1α axis.[60] Leveraging the therapeutic potential of Ellagic acid, Chen developed a polyphenol-assisted delivery system combining IL10 mRNA and Ellagic acid to treat UC, effectively suppressing inflammatory factor expression, promoting mucosal repair, and safeguarding colonic epithelial cells from apoptosis.[61]

CONCLUSION

GP has the potential to interact with proteins such as TP53, AKT1, STAT3, TNF, IL6, and others through its tannins and flavonoid constituents. This interaction allows GP to modulate signaling pathways such as Pathways in cancer, Lipid and atherosclerosis, and AGE-RAGE signaling pathways in diabetic complications. Furthermore, GP participation in cell inflammation, proliferation, apoptosis, oxidative stress, and other processes contributes to its ability to reduce inflammation, enhance intestinal barrier function, regulate intestinal flora, and improve immunity, thereby offering therapeutic benefits for ulcerative colitis.

ACKNOWLEDGEMENT

Conflict of Interest

The authors have no conflicts of interest to disclose.

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