Based on the Transcriptome Study of the Effect of Sanyeqing Active Ingredients on Liver Cancer and the Impact of Resveratrol on MAPK3 and PRKCD

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Abstract: Tetrastigmatis hemsleyani (Sanyeqing) has pharmacological effects such as clearing away heat and detoxifying, anti-tumor, and regulating immunity. This research is dedicated to discovering and verifying the impact of Sanyeqing on liver cancer. Download the practical components and corresponding targets in Sanyeqing and liver cancer-related genes, and take the intersection of the two. Perform enrichment analysis and related gene interaction network analysis on the intersection genes. Subsequently, the core genes and pivot genes were screened out by Cytoscape to select different indicators for the intersection genes. Carry out survival analysis, tumor differential expression analysis, and cancer cell visual summary of core genes and pivot genes, and screen out the two most critical genes for molecular docking with corresponding active ingredients. The KEGG analysis results enriched the final two genes with the highest-ranking pathways and TIMER data tumor immune assessment. After the gene and the target were crossed, 131 crossed genes were obtained. The subsequent screening got 38 core genes and 20 pivot genes, and finally, the two most critical genes of MAPK3 and PRKCD were comprehensively screened through survival analysis. Resveratrol, the main chemical component, affects MAPK3 and PRKCD, and the docking results show that there is an effect between the two. The tumor immune assessment results also indicate that MAPK3 and PRKCD are expressed differently in normal tissues. Resveratrol has a particular effect on MAPK3 and PRKCD, which may have new thinking for treating liver cancer in the future.

1 INTRODUCTION

Tetrastigmatis hemsleyani (Sanyeqing) is the root tuber of Tetrastigrna hemsleyanum Diels et Gilg in the grape family. San Ye Qing is used as medicine with tuber roots to clear away heat, detoxify, expel wind and phlegm, promote blood circulation, and relieve pain (Liu et al. 2021, Liu et al. 2019, Liu et al. 2018). Modern pharmacological research shows that Tetrastigmatis hemsleyani has anti-inflammatory, analgesic and antipyretic, anti-tumor, anti-virus, and immune-regulating effects (Pu et al. 2021, Wu et al. 2018, Zhong et al. 2016). Since cancer is a worldwide health problem, it has brought huge safety risks to people worldwide. In the latest report on the national cancer burden released by IARC, newly diagnosed cases of liver cancer accounted for 4.7% of the newly diagnosed patients and deaths. The rate has reached 8.3%. This is enough to show that liver cancer is a disease that cannot be ignored. In this paper, by studying the relationship between Sanyeqing and

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liver cancer, we are committed to discovering and verifying the effect of Sanyeqing on liver cancer. We hope that it will be helpful in the treatment of liver cancer (Zhong et al. 2013, Zhong et al. 2014).

2 MATERIALS AND METHODS

2.1 Data Source

Use the Computational Systems Biology Laboratory (https://tcmspw.com/) to query and download the active ingredients in San Ye Qing, and screen the effective ingredients with OB greater than or equal to 30%, DL greater than or equal to 0.18, and the targets of San Ye Qing.

We download human liver cancer genes in gene banks (GeneCards, OMIM, PharmGKB, TTD, DurgBank), use R (4.0.3) and (Venn) packages to make a Venn diagram, and merge all liver cancer genes.

2.2 Associated Tetrastigmatis Hemsleyani Components, Targets, and Human Liver Cancer Genes

It intersects the target genes of Sanyeqing and human liver cancer genes to obtain shared genes, using R (4.0.3) and (venn) program packages to screen out the corresponding practical components and the intersection genes and make a Venn diagram. Use Cytoscape (3.8.0) to make a tri-leaf green-liver cancer gene regulatory network to see the relationship between the effective ingredients in tri-leaf green and human liver cancer genes.

2.3 Related Gene Enrichment Analysis

The intersection genes were analyzed for GO analysis using R (4.0.3) and clusterProfiler, org.Hs.eg.db, enrichplot, and ggplot2 packages. In addition, cluster profile, org.Hs.eg.db, enrichplot, ggplot2, pathview packages are used to perform KEGG analysis to predict the enrichment of these components in each pathway.

2.4 Protein Protein Interaction Network (PPI) and Enrichment Analysis

Metascape analyzed the intersection genes for protein interaction network enrichment analysis. Show the relationship between the enriched terms (paths) in a network diagram, and use String to calculate the similarity between the enriched pathways.

2.5 Screening of Core Genes

Use Cytoscape (3.8.0) to import the protein interaction relationship of the intersection gene, and use R (4.0.3) to get the part of each item whose score is greater than the average through 6 scoring methods (Betweenness, Closeness, Degree, Eigenvector, LAC, Network). Survival analysis was performed using e Kaplan Meier plotter database.

2.6 Screening of Pivot Genes

Use Cytoscape (3.8.0) to introduce the interaction relationship of the intersection gene and protein, calculate the score by Degree, and use the Kaplan Meier plotter database for survival analysis of the top 20 parts.

2.7 Comprehensive Screening of Intersection Genes for Prognostic Analysis

Firstly, Combines the two screening methods of 1.5 and 1.6 to obtain effective genes, select the two with the smallest log-rank P (MAPK3, PRKCD), and find the corresponding effective ingredient Resveratrol from the previous correspondence. Secondly, download MAPK3 and PRKCD models in PubChem, then use ChemOffice to build 3D models and optimize them. Thirdly, download the 3D model of Resveratrol in UniProt and use PyMOL to remove water molecules. Fourthly, use AutoDock to hydrogenate Resveratrol and use its center as the center of the active pocket. The size of the functional bag is 40, 40, and 40. Finally, PyMOL was used to dock the active ingredients with MAPK3 and PRKCD, respectively molecularly.

2.8 MAPK3, PRKCD Enrichment Pathway Analysis

R (4.0.3) was used to analyze the pathway with the highest enrichment ranking of MAPK3 and PRKCD.

2.9 TIMER Data Tumor Immunity Assessment

Use the TIMER algorithm to evaluate the abundance of six immune infiltration fluids (B cells, CD4 + T cells, CD8 + T cells, neutrophils, macrophages, and

dendritic cells), and explore the presence of MAPK3 and PRKCD in tumors and Differential gene expression between normal tissues.

3 RESULTS

3.1 Screening of Genes Related to the Role of Sanyeqing and Human Liver Cancer

Downloaded the active ingredients (Chlorogenic acid, caffeic acid, quercetin, Resveratrol, orientin, rutin) and targets of Sanyeqing from the Computational Systems Biology Laboratory downloaded the union of human liver cancer genes from five gene libraries (Fig1.a). The intersection of component targets and liver cancer genes was used to screen out related genes (Fig.1.b), 177 trifoliate targets and 3024 liver cancer genes, and 131 common genes were obtained. We used Cytoscape (3.8.0) to create a trifoliate-human liver cancer gene regulatory network (Fig1.c). Resveratrol and quercetin have the most connections with genes and have the best correlation.

3.2 Shared Gene Enrichment Analysis

The top 5 essential pathways from the GO enrichment analysis diagram (Fig. 2Aa) show that in BP, CC, MF, KEGG pathway analysis, the critical pathways of intersection genes include Lipid and atherosclerosis, Fluid shear stress, and atherosclerosis (Fig. 2Ab).

3.3 Enrichment Analysis of Related Gene Protein Interaction Network

We constructed a PPI network using intersection genes. Metascape uses the protein interaction relationships in BioGrid, InWeb_IM, and OminPath databases and uses the MCODE algorithm to cluster the PPI (protein interaction) network to identify the subnetworks.

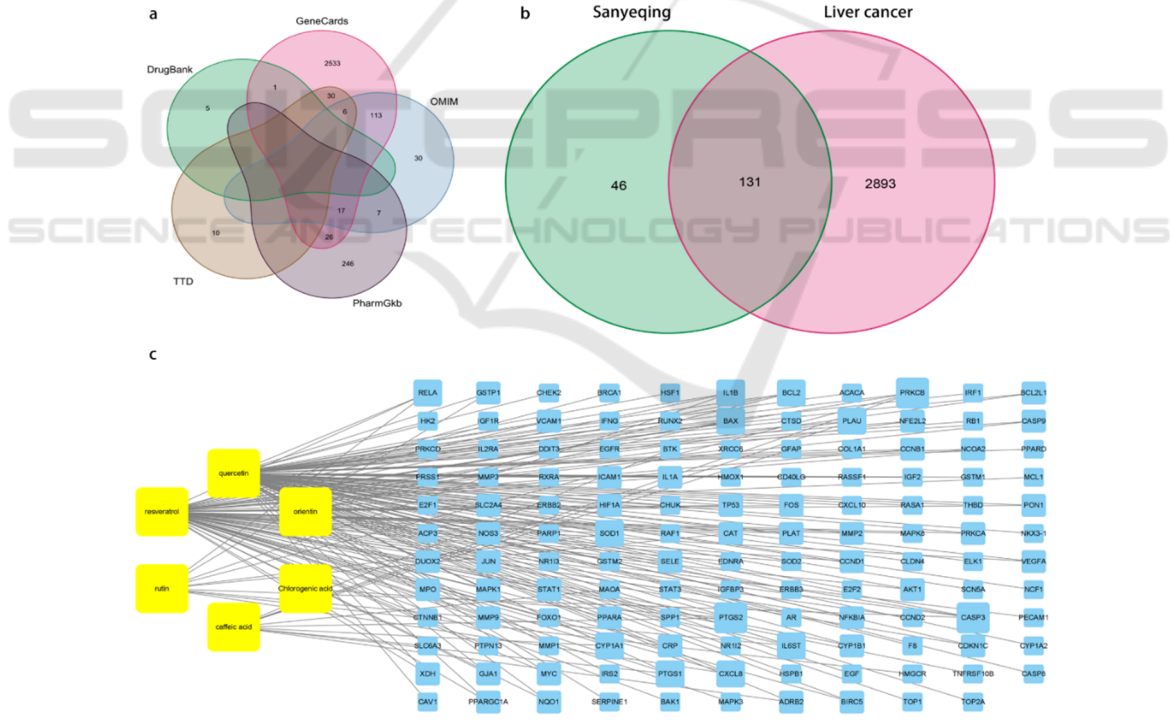

Figure 1: Screening of trifoliate green-hepatocarcinoma genes. a. There are 131 intersecting targets of Sanyeqing and human liver cancer genes (There are 3024 human liver cancer genes.). b. Trefoil green-human liver cancer gene regulatory network, in which yellow is the main component of Trefoil green, blue is the intersection gene, and the size of blue indicates the strength of the effect.

3.4 Screening Core Genes

We used Cytoscape (3.8.0) and R (4.0.3) to obtain 38 genes with scores above the average (Fig. 3A). We analyzed the prognostic information of these 38 core genes at different stages for the liver cancer group and the normal group by using the Kaplan Meier plotter database. The part with log-rank P<0.05 was screened out, and the ten core genes with the smallest log-rank value (AR, EGFR, EGF, IGF2, MAPK3, MMP9, PPARA, PRKCD, STAT3, VEGFA) were obtained. The results show that in patients with early LIHC, EGFR, IGF2, PPARA, STAT3 expressed higher. (Fig.3B)

In addition, the GEPIA database is used to verify the expression levels of 10 core genes in tumors and normal tissues (Fig.4Ba-j). Results LIHC patients based on the GEPIA database had higher expressions of MAPK3, MMP9, and PRKCD than healthy people.

3.5 Screening for Pivot Genes

Using CytoHubba plug-in in Cytoscape (3.8.0), we calculated Degree to determine the 20 highest-scoring genes (Fig.5A).

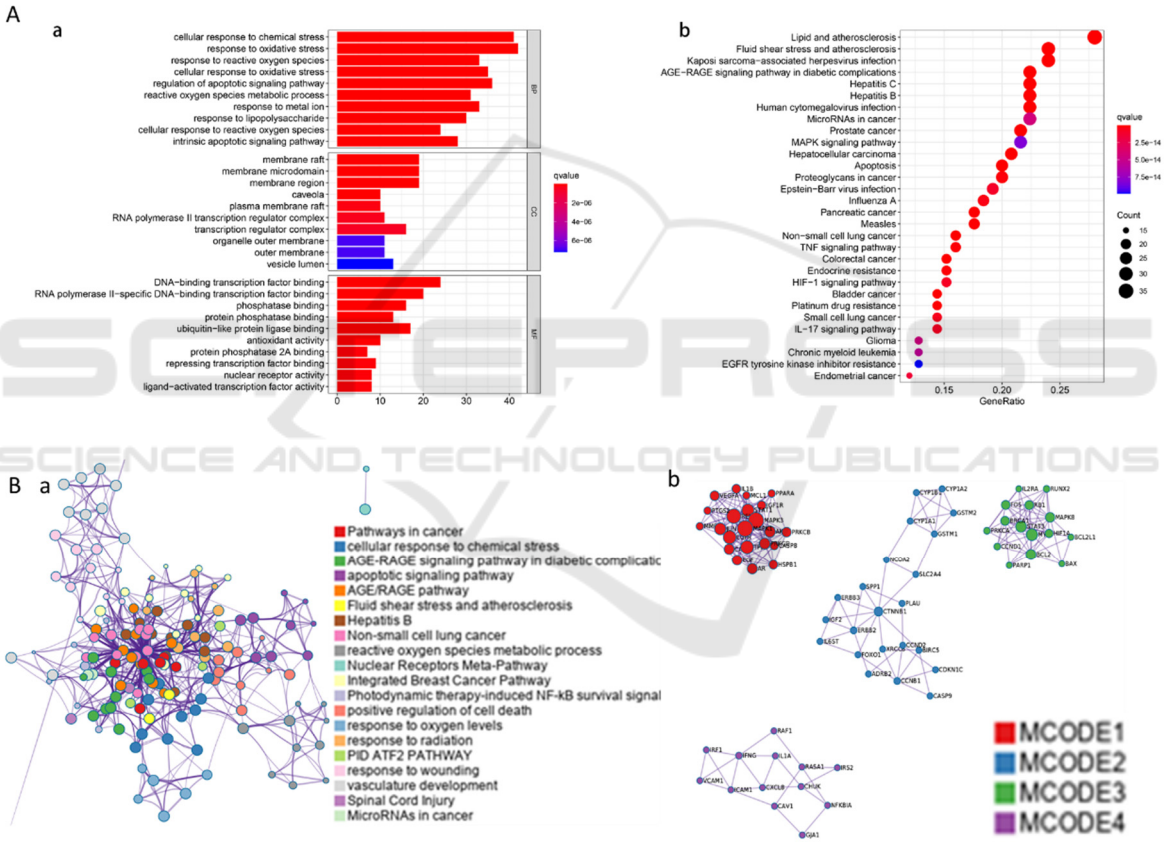

Figure 2: A. Enrichment analysis of related genes. (a. Gene Ontology (GO), Biological Process (BP), Cell Component (CC), and Molecular Function (MF). b is the KEGG analysis of related genes.) B. Enrichment network diagram and PPI protein interaction network diagram (a. In the enrichment network Figure. The same color nodes are enriched as a label. b. Identify densely connected regions of proteins through MCODE.)

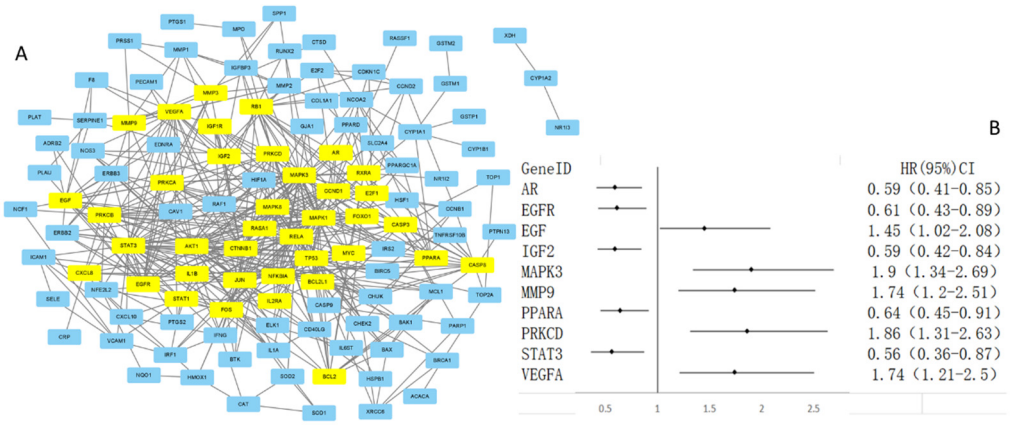

Figure 3: A. Screening of core genes, the picture shows the intersection genes, and the yellow ones are the core genes screened out. B. Survival analysis and forest map of core genes. (log-rank P<0.05).

Subsequently, we used cBioPortal to determine the genetic change information of 10 core genes, as shown in the figure (Fig. 4A). VEGFA and AR have the most frequent mutations (8% and 2.7%, respectively).

The prognostic information of these 20 pivot genes on the liver cancer group and the normal group at different stages was analyzed by using the Kaplan Meier plotter database. The part with logrank P<0.05 was screened out, and the 10 pivot genes with the smallest logrank value (CCND1, EGFR, EGF, MAPK3, PRKCD, RXRA, STAT1, STAT3, TP53, VEGFA) were selected. Early-stage LIHC patients CCND1, EGFR, RXRA, STAT1, STAT3, TP53have higher expressions (Fig.5B). Subsequently, cBioPortal was used to determine the genetic change information of the ten pivot genes, as shown in the figure (Fig.6A). TP53, CCND1, and VEGFA were most frequently mutated (33%, 8%, and 8%, respectively).

In addition, we also used the GEPIA database to verify the expression levels of 10 pivot genes in tumors and normal tissues. According to the gene expression profiles of Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) projects (Fig6a-k). Results The LIHC patients based on the GEPIA database had higher expressions of CCND1, MAPK3, PRKCD, STAT1, TP53 than healthy people (P <0.01).

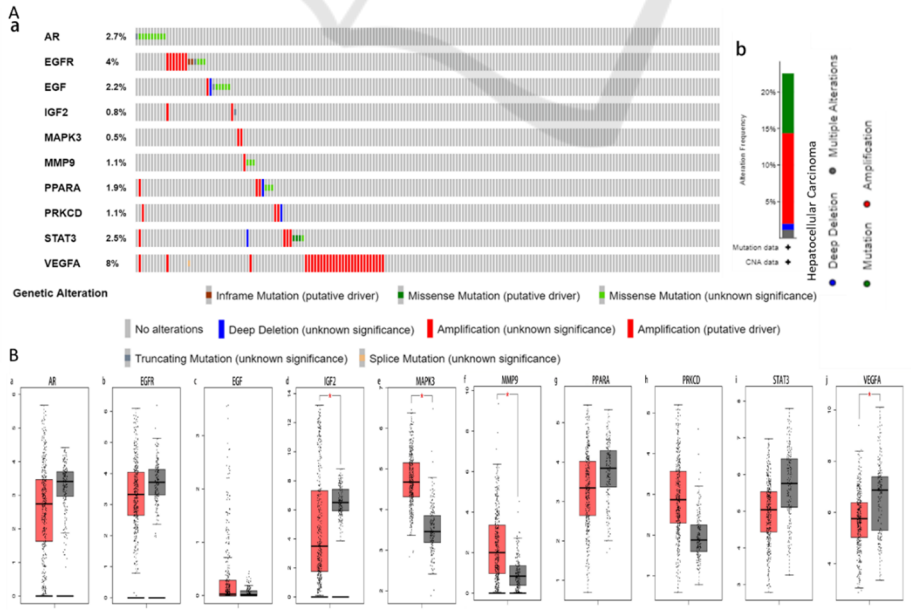

Figure 4: A. Visual summary of cancer cells for core analysis. B. Tissue expression analysis of core genes. (a-j) are the gene expression status in LIHC tissues and normal tissues (LIHC num(T)=369, num(N)=160).

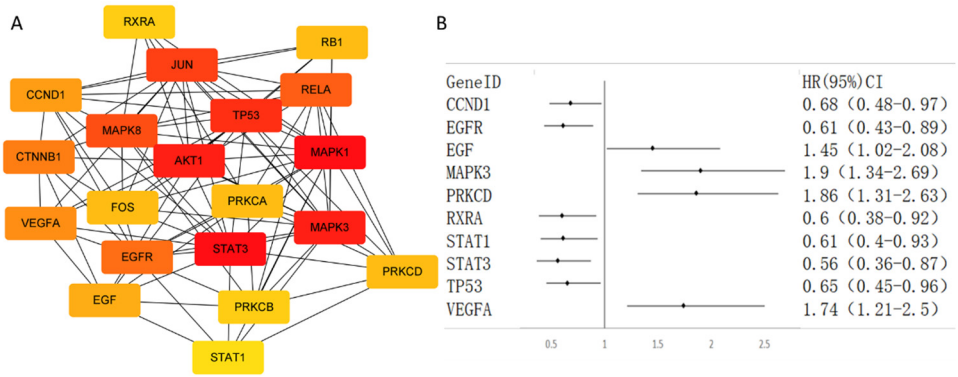

Figure 5: A. Screen the pivot genes. The darker the color, the higher the Degree. B. Hub gene survival analysis forest map. (log-rank P<0.05)

3.6 Comprehensive Screening of Genes for Prognostic Analysis

According to the 2.4 2.5 screening method results, the shared genes are EGFR, EGF, MAPK3, PRKCD, STAT3, VEGFA, and the two genes with the smallest log-rank value (MAPK3, PRKCD) are molecularly docked with their corresponding active ingredients.

We use AutoDock to hydrogenate MAPK3 and PRKCD and use their center as the center of the active pocket, the size is 40, 40, and 40. Then, use Vina and PyMOL for molecular docking to select the conformation with the lowest Grid Score (Fig.7A). The optimal conformation Grid Score of the docking results of MAPK3 and Resveratrol is -8.5, indicating a good combination between the two. The optimal conformational Grid Score score of PRKCD and resveratrol docking results is -6.2, showing a good mix between the two.

3.7 MAPK3 and PRKCD Pathway

Both MAPK3 and PRKCD are enriched in the AGE-RAGE signaling pathway (Fig. 7B).

3.8 Immune Microenvironment

The correlation analysis between MAPK3, PRKCD gene expression and a large number of immune infiltration (fig.8a). P<0.05 has statistical significance. The differential expression of MAPK3 and PRKCD in other tumor tissues compared with normal tissues (fig.8b).

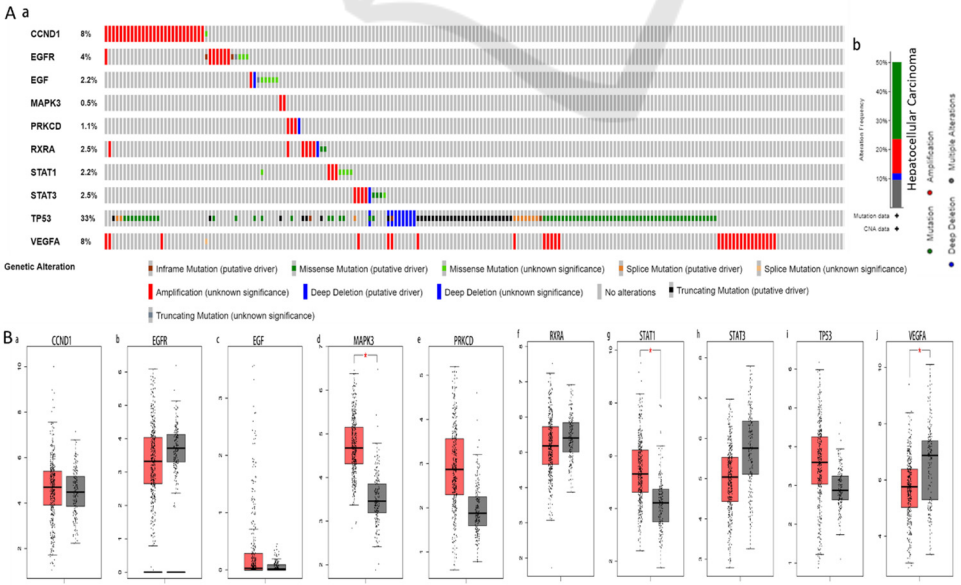

Figure 6: A. Visual summary of hub gene cancer cells. B. Hub gene tissue expression analysis (a-j) The gene expression status of patients in LIHC tissues and normal tissues (LIHC num(T)=369, num(N)=160).

4 DISCUSS

Sanyeqing is often used to clear heat and detoxify in Chinese medicine and can be used for anticancer in western medicine. Internet pharmacology ended the research model of "one component, one target" in traditional Chinese medicine and opened a new "multi-component, multi-target" model (Medvedev et al. 1997, Salkovic-Petrisic et al. 2001). Due to the numerous chemical components in Trifolium repens, we explored the interaction network between the six elements of Resveratrol (Bailey et al. 2021, Najafi et al. 2019, Pandey et al. 2014, Tabibiazar et al. 2019), quercetin (Bui Van et al., 2022 , Oh et al., 2021 , Ozkok et al. 2021, Safi et al. 2021, Zhang et al. 2021), orientin (Jiang et al. 2021), chlorogenic acid (Le-Bail et al. 2015, Wu et al. 2010, Xing et al. 2015), caffeic acid(Akyol et al., 2016 , Celli et al., 2007 , Petelinc et al. 2017, Schaller and Holler, 1976), and rutin (Cao et al. 2019, Ojha et al. 2016, Park et al. 2014) in the liver cancer gene library. We screened that Resveratrol and quercetin are the most critical anticancer effects of Resveratrol and quercetin Element.

Firstly, continue the GO and KEGG enrichment analysis through the component target interaction network. In the BP category, the intersection genes are mainly involved in cellular response to chemical stress (Kultz 2003, Szewczyk et al. 2020), oxidative stress, response to reactive oxygen species (Molassiotis and Fotopoulos 2011), cellular response to oxidative stress, regulation of apoptotic signaling pathway. The intersection genes are related to membrane raft (Levental et al. 2014), membrane microdomain, membrane region, caveola, and plasma membrane raft for class CC. For MF, the molecular functions of the intersection genes are mainly DNA-binding transcription factor binding, RNA polymerase II-specific DNA-binding transcription factor binding, phosphatase binding, protein phosphatase binding, and ubiquitin-like protein ligase binding. For KEGG pathway analysis, the top five essential KEGG pathways of intersection genes include Lipid and atherosclerosis (Feng et al. 2021, Ni et al. 2021), Fluid shear stress and atherosclerosis, Kaposi sarcoma-associated herpesvirus infection, AGE-RAGE signaling pathway in diabetic complications, and Hepatitis C.

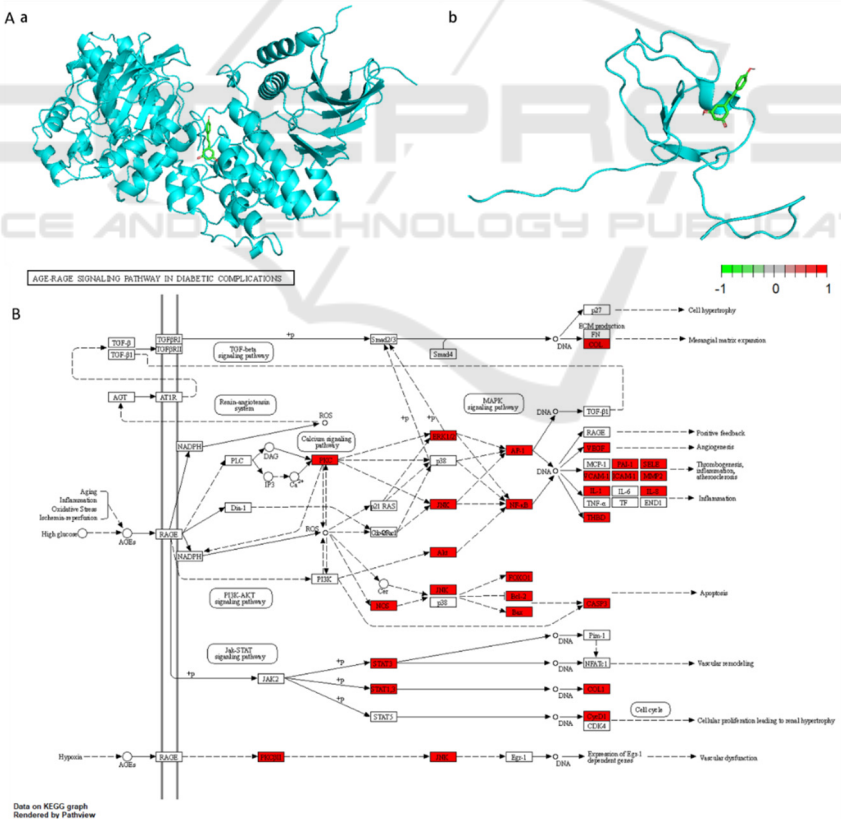

Figure 7: A. Intersection genes for predictive analysis. a . the docking of MAPK3 and resveratrol molecules. b . the molecular docking of PRKCD and Resveratrol. B. MAPK3, PRKCD enrichment pathway analysis. The enrichment pathway is the AGE-RAGE signaling pathway in diabetic complications.

Secondly, we calculated ten core genes AR, EGFR, EGF, IGF2, MAPK3, MMP9, PPARA, PRKCD, STAT3, VEGFA through Cytoscape. We calculated 20 hub genes through CytoHubba (Chen et al. 2021, Chin et al. 2014, Sang et al. 2018, You et al. 2020). We conducted survival rate analysis and differential expression analysis and finally determined that EGFR, EGF, MAPK3, PRKCD, STAT3, VEGFA have significant effects on liver cancer.

Finally, let Resveratrol and PRKCD, and MAPK3 be analyzed and docked. The results show that Resveratrol has a particular therapeutic effect on liver cancer's differentially expressed PRKCD and MAPK3. In addition, the enrichment results show that MAPK3 and PRKCD have a more significant impact on the AGE-RAGE signal pathway, indicating that the trifoliate component resveratrol has a particular effect on liver cancer through the AGE-RAGE signal pathway (Kay et al. 2016, Ren and Yan, 2021, Waghela et al. 2021, Zong et al. 2011).

During the analysis of the immune microenvironment (Cui et al. 2021, Liu 2019, Zhang et al. 2020), we found that MAPK3 and PRKCD are significantly correlated with B cell, CD8+ T Cell, CD4+ T Cell, Macrophage, Neuropil, and Dendritic Cell in the tumor environment. And MAPK3 and PRKCD not only have significant differential expression in liver cancer but also in BLCA, BRCA, CHOL, COAD, ESCA, HNSC, HVCE-HPVpos, KICH, KIRP, LUAD, LUSC, PRAD, READ, SKCM, STAD, THCA, UCEC, and other cancer tissues also have significant differential expression. In the future, we can continue to explore the effect of Sanyeqing on other cancer tissues.

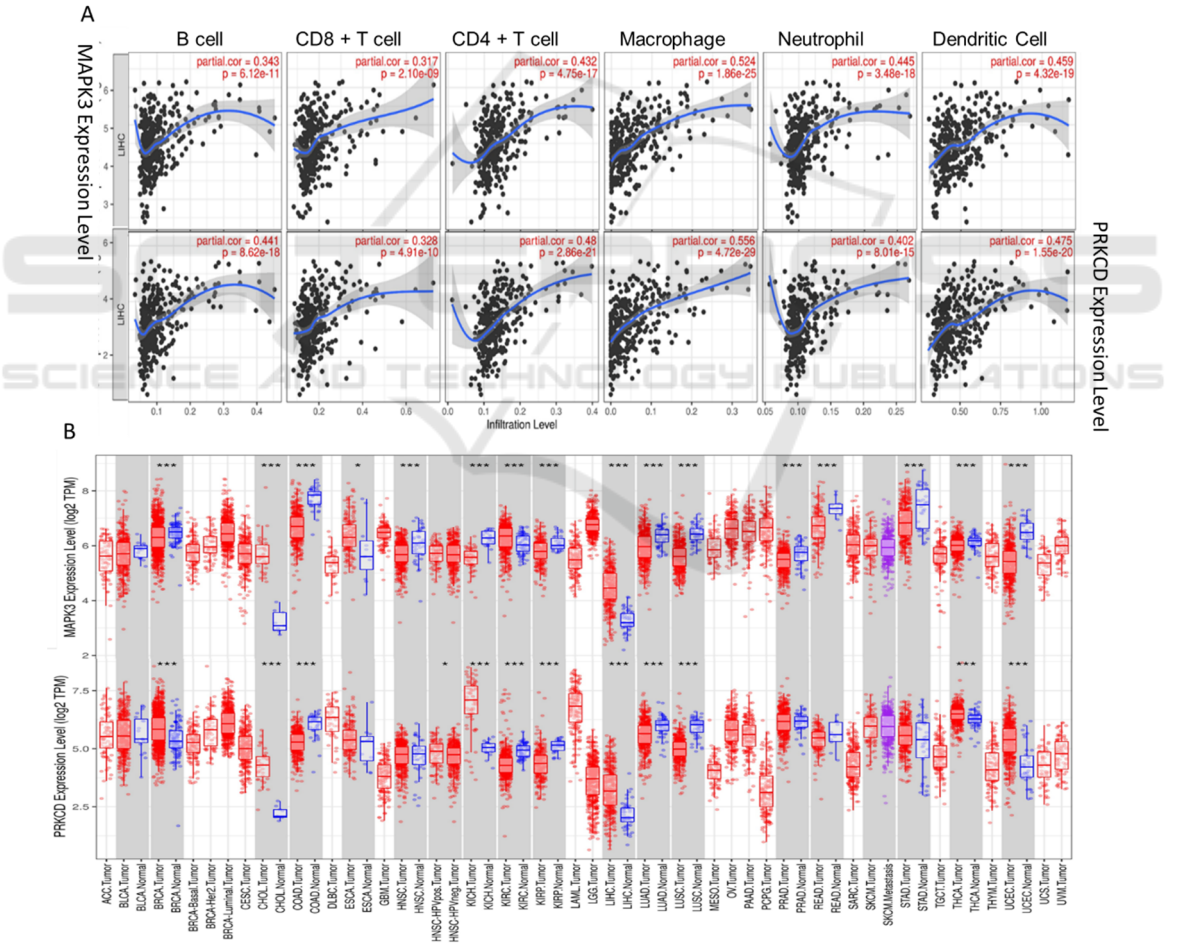

Figure 8: Correlation analysis between MAPK3, PRKCD gene expression, and a large number of immune infiltrations (A. Estimate six resistant infiltration fluids (B cells, CD4 + T cells, CD8 + T cells, neutrophils, macrophages, Dendritic CellS) through the TIMER algorithm (And dendritic cells), B. MAPK3, PRKCD differential gene expression between tumor and normal tissue, the shaded area indicates that the cancer is significantly different from normal tissue) (https://cistrome.shinyapps.io/timer/).

5 CONCLUSIONS

(1) Resveratrol and quercetin were screened for anticancer pharmacological components Resveratrol and quercetin through the chemical constituents of the Sanyeqing-liver cancer target network.

(2) Through the screening of liver cancer core genes and pivot genes, and survival verification and differential expression, it is verified that MAPK3 and PRKCD are the most critical to the occurrence and development of liver cancer, and the active ingredients Sanyeqing have a specific binding effect on them.

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