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Research Article

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Food and Medicine Homology Substance in Cancer Treatment: Mechanism of *Astragalus* against Pancreatic Cancer

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Abstract
This work explores the mechanism of food and medicine homology substance—*astragalus*—against pancreatic cancer (PC). PC is a notably lethal solid tumor, often presenting with a poor clinical prognosis and typically diagnosed at an advanced stage. Food and medicine homology herbs possess dual attributes as both functional foods and therapeutic agents, which showed promise as a treatment strategy demonstrating substantial inhibitory effects with reduced side effects and toxicity about PC. *Astragalus* (HQ, also known as Huang-Qi in Chinese), a herb that falls under the category of food and medicine homology, shows potential in combating PC. To explore its underlying mechanism, we utilized network pharmacology to identify potential compounds and their related targets of PC and molecular docking techniques to assess the binding affinity between the identified compound ds and targets. The presence of quercetin, kaempferol, isorhamnetin, and formononetin in HQ provides compelling evidence for their pivotal role as key constituents in combating PC. Our findings suggest that HQ potentially regulated MMP-9 through TNF/TGF, thereby exerting its inhibitory effects on PC. This study elucidates a novel mechanism by which a natural herb exhibits anti-PC capacity.

Keywords:
pancreatic cancer; *Astragalus*; food and medicine homology; TGF/TNF/MMP9 axis; Traditional Chinese Medicine

1. Introduction

Pancreatic cancer (PC) is a condition associated with a poor clinical prognosis, resulting in high mortality rates among patients [1–3]. The primary treatment methods currently utilized encompass surgery, chemotherapy [4], and radiotherapy [5]. Although targeted therapy [6,7] and immunotherapy [8–10] hold potential promise for PC patients, their benefits are still limited [11]. Therefore, there is an urgent need to develop alternative therapeutic strategies that can reduce adverse effects and enhance overall patient survival [12–18].

Traditional Chinese Medicine (TCM) has emerged as a valuable supplementary therapy, offering promising potential for the development of drugs through its multi-compound, multi-target, and multi-pathway approach [19–21]. TCM has shown significant anti-cancer effects and has been extensively researched for its potential in cancer treatment. Herbal medicines are typically cost-effective, widely accessible, and exhibit minimal toxicity or adverse

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effects in clinical settings [22,23]. However, despite the substantial interest and growing demand, the lack of robust evidence-based research and the absence of standardized herbal product formulations pose significant challenges to the global dissemination of TCM. In recent years, advancements in analytical technologies and methodologies have significantly propelled research in TCM [24–27].

Food and medicine homology (FMH) has been a cornerstone in TCM since ancient times, underscoring the inherent link and mutual transformation between food and drugs [28]. FMH substances are characterized by their dual functionality; they serve as nutritional sources and medicinal agents [29]. These substances not only alleviate hunger but also demonstrate pharmacological effects when preventing and treating disease [30,31]. There is a growing trend where individuals are turning to dietary practices for health regulation, often preferring "food therapy" over "medication therapy". [32–34] Individuals tend to prefer functional foods [35] or beverages [36] as a method of bolstering their immune system against diseases, rather than depending on nutritional supplements [37]. Long-term ingestion of these substances is associated with beneficial health outcomes, disease prevention, and minimal adverse effects due to their nutritional and therapeutic properties, as well as their negligible toxicity [38,39].

Astragalus (also known as Huang-Qi in Chinese and *Hedysarum Multijugum Maxim* in Latin, HQ) is a potential anti-tumor herb. It is also renowned for its anti-aging and immunomodulating properties [40–42]. Previous studies have reported the antitumor effect of HQ on hepatocellular carcinoma (HCC). The combination with *Atractylodes* (also known as Bai-Zhu in Chinese and *Atractylodes Macrocephala Koidz* in Latin, BZ) has demonstrated potential in the treatment of HCC, specifically through targeting IL-6/STAT3 and modulating immune cell activity [43]. Additionally, HQ has demonstrated potential in treating breast cancer [44], colorectal cancer [45], and prostate cancer. However, further research is needed to explore the potential antitumor effects of HQ as a standalone component, as existing studies have primarily focused on medicinal formulations containing two or more ingredients. The single specific mechanism of HQ has been shown to exhibit anti-cancer effects on cell proliferation [46], apoptosis [47], and metastasis [48]. In this regard, HQ may offer potential therapeutic options for patients with PC, and further investigation is warranted to explore its efficacy and related mechanisms.

Network pharmacology could be considered an invaluable tool, leveraging bioinformatics data to explore biological systems and pinpoint potential targets of TCMs [49]. As the comprehension of cancer's intricate nature expands, the constraints of singularly targeted therapies are increasingly evident. Network pharmacology, emerging as a pioneering research methodology, provides insights into the underlying mechanisms of TCM in cancer therapy by adopting a multi-target and multi-pathway lens. Furthermore, this method illuminates the synergistic impacts of TCM compounds through the construction of drug-target-disease networks. This not only offers a novel perspective on the application of TCM in cancer management but also catalyzes the modernization of TCM and propels the evolution of precision medicine.

In this study, network pharmacology was employed to utilize public databases for identifying shared targets between HQ and PC, validating their potential targets and compounds. Subsequently, molecular docking analysis was conducted to confirm their affinity further. This study provides a fundamental basis for investigating the potential use of FMH herbs in cancer treatment.

2. Materials and Methods

2.1. Collecting HQ Potential Targets

HQ putative targets were obtained from TCMSP databases "https://old.tcmsp-e.com/tcmsp.php (accessed on 20 November 2024)". The UniProt database "https://www.uniprot.org/ (accessed on 20 November 2024)" was used to translate the protein names into corresponding gene symbols.

2.2. Identification of PC-Related Therapeutic Genes

In order to screen for potential therapeutic targets for PC, the keyword "pancreatic cancer" was utilized in two public databases: MalaCards "https://www.malacards.org (accessed on 12 November 2024)" and GeneCards "https://www.genecards.org/ (accessed on 12 November 2024)". Subsequently, common targets within these databases were identified using Venn diagrams.

2.3. Potential Targets Identification

The overlapping targets were identified using Venn diagrams, which compared the HQ potential targets with PC-related therapeutic genes.

2.4. protein-Protein Interaction (PPI) Analysis

First, the targets were input into the STRING database "https://string-db.org/cgi/input.pl (accessed on 12 Nove-

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mber 2024)", and the species was set as Homo sapiens. Then, the interaction analysis results were exported, and the protein interaction degree was used for subsequent analysis.

2.5. Enrichment Analyses

Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were conducted. The visualization of signaling pathway diagrams was facilitated by the KEGG "https://www.kegg.jp/ (accessed on 12 November 2024)".

2.6. Network Construction

The network of herb-compound targets was meticulously constructed utilizing the advanced capabilities of Cytoscape. After this construction, a comprehensive degree analysis was conducted to facilitate an in-depth examination and elucidation of the intricate relationships within the network.

2.7. Molecular Docking Analysis

Four hub genes, which may play crucial roles in mediating the effects of HQ on PC, were identified based on their degree of centrality in the PPI network and selected for molecular docking simulations with HQ constituents. The HQ constituents were selected through the herb-compound-targets network based on their highest degree values. These simulations were carried out using AutoDock Tools version 1.5.6, as previously described [50]. The protein structures were sourced from the Protein Data Bank [PDB, "http://www.rcsb.org/ (accessed on 24/11/2024)"] and were pre-processed using PyMOL software to eliminate water molecules, co-crystallized ligands, and ions. The docking results were saved as protein files in PDBQT format. [51].

2.8. Prognostic Analyses of Potential Therapeutic Target Genes

Survival analyses of potential therapeutic target genes MMP-9 were conducted on the Cancer Genome Atlas (TCGA) database. Kaplan-Meier survival analyses, utilizing the "surv_cutpoint" function from the survminer package, were conducted to determine the risk scores' cutoff value.

3. Results

3.1. Target Genes of HQ

The potential target genes associated with HQ were sourced from the TCMSP databases, yielding 16 compounds and 211 therapeutic targets.

3.2. PC-Related Target Genes

Initially, we performed an exhaustive search in two databases using the keyword "Pancreatic cancer," which yielded 777 targets in MalaCards and 12,652 targets in GeneCards. Moreover, we identified overlapping targets and converted protein names into gene symbols, resulting in a total of 568 putative targets associated with PC (Figure 1).

3.3. Construction and Topological Analysis of the PPI Network

The 24 genes linked with HQ-PC were scrutinized utilizing the STRING database (Figure 2), which led to the creation of a PPI network with a minimum interaction score threshold set at 0.9. Following this, ten potential gene targets were singled out for additional examination, based on their protein degree. TNF, TGF, and MMP-9 were confirmed as the central target genes for further analysis (Figure 3).

3.4. GO Enrichment and KEGG Analysis

GO enrichment analysis was performed to explore the potential targets, including biological processes (BP), cellular components (CC), and molecular functions (MF). A total of 158 GO terms were obtained, among which 134 BP, 7 CC, and 17 MF. The bubble diagram (Figure 4) showed the top ten significantly enriched entries for BP, CC, and MF with the smallest p-value. The redder color of the dot indicated the smaller p-value and more significant enrichment of the corresponding term. The bigger dot represented the higher gene count in each entry.

The analysis results revealed that the commonly targeted genes of HQ and PC are primarily enriched in several biological processes. These include positive regulation of mononuclear cell migration (GO: 0071677), vascular-associated smooth muscle cell proliferation (GO: 1904707), cytokine production (GO: 0001819), MHC class II biosynthetic process (GO: 0045348), DNA-templated transcription (GO: 0045893), myoblast differentiation (GO: 0045662), microglial cell activation (GO: 0001774), liver regeneration (GO: 0097421), response to hypoxia (GO: 0001666), and cellular response to

lipopolysaccharide (GO: 0071222). Additionally, these genes are associated with various cell components such as the CC extracellular space (GO: 0005615), extracellular region (GO: 0005576), collagen-containing extracellular matrix (GO: 0062023), extracellular matrix (GO: 0031012), external side of the plasma membrane (GO: 0009897), platelet alpha granule lumen (GO: 0031093), and cell surface (GO: 0009986). Furthermore, they are involved in molecular functions like cytokine activity (GO: 0005125), growth factor activity (GO: 0008083), demethylase activity (GO: 0032451), protein binding (GO: 0005515), hydroperoxy icosatetraenoate dehydratase activity (GO: 0106256), steroid 17-alpha-monooxygenase activity (GO: 0004508), estrogen 16-alpha-hydroxylase activity (GO: 0101020), aromatase activity (GO: 0070330), and enzyme binding (GO: 0019899).

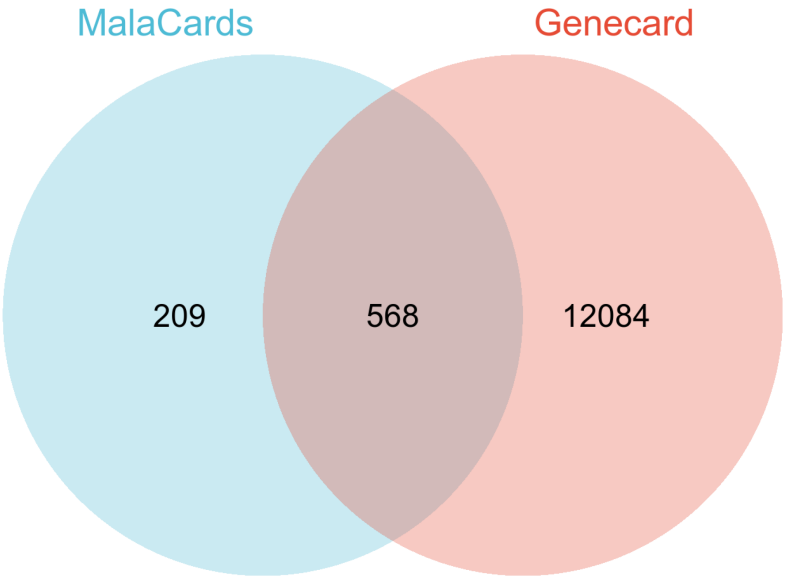

Figure 1: The common targets retrieved from MalaCards and Genecard database.

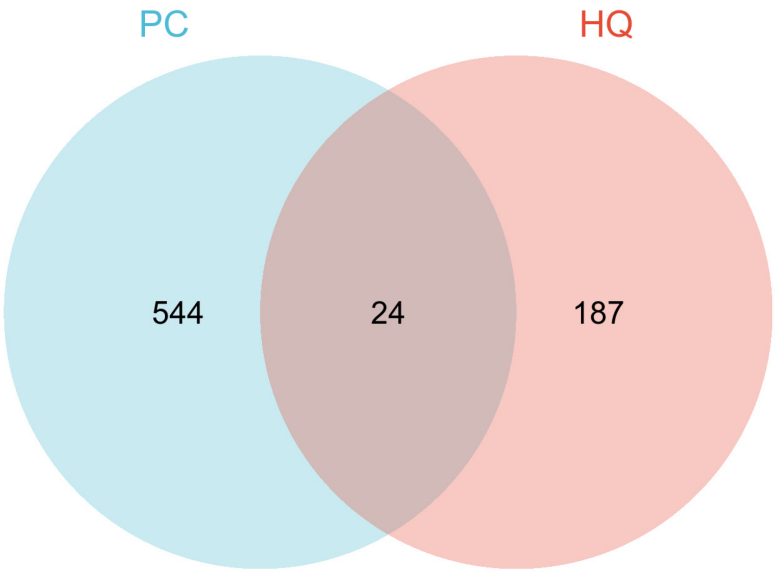

Figure 2: The common targets obtained between the HQ potential targets and PC related genes.

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3.5. KEGG Enrichment Analysis of Co-Targeted Genes of HQ and PC

The KEGG analysis was utilized to explore the potential functions and signaling pathways of the identified anti-PC targets associated with HQ. The results from the KEGG pathway analysis indicated that 10 target genes were notably enriched, leading to a total of 54 statistically significant pathways.

The top five pathways with the highest gene counts selected are: Cytokine-cytokine receptor interaction (hsa04060, n = 6), Pathways in cancer (hsa05200, n = 6), IL-17 signaling pathway (hsa0465, n = 5), TNF signaling pathway (hsa04668, n = 5), and Fluid shear stress and atherosclerosis (hsa05418, n = 5).

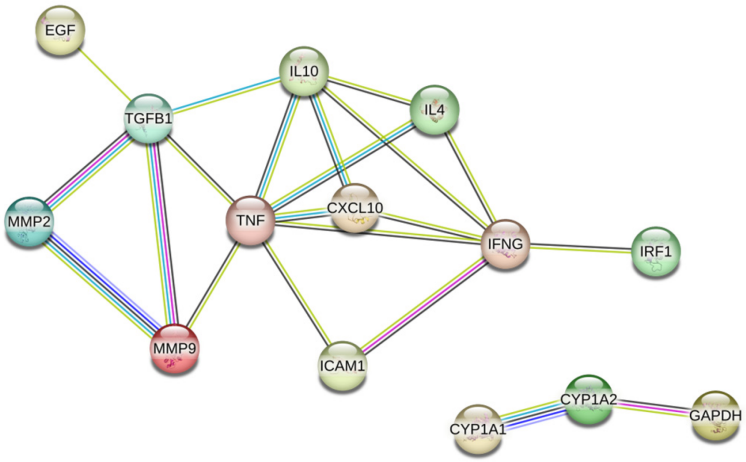

Figure 3: The PPI of the core target genes.

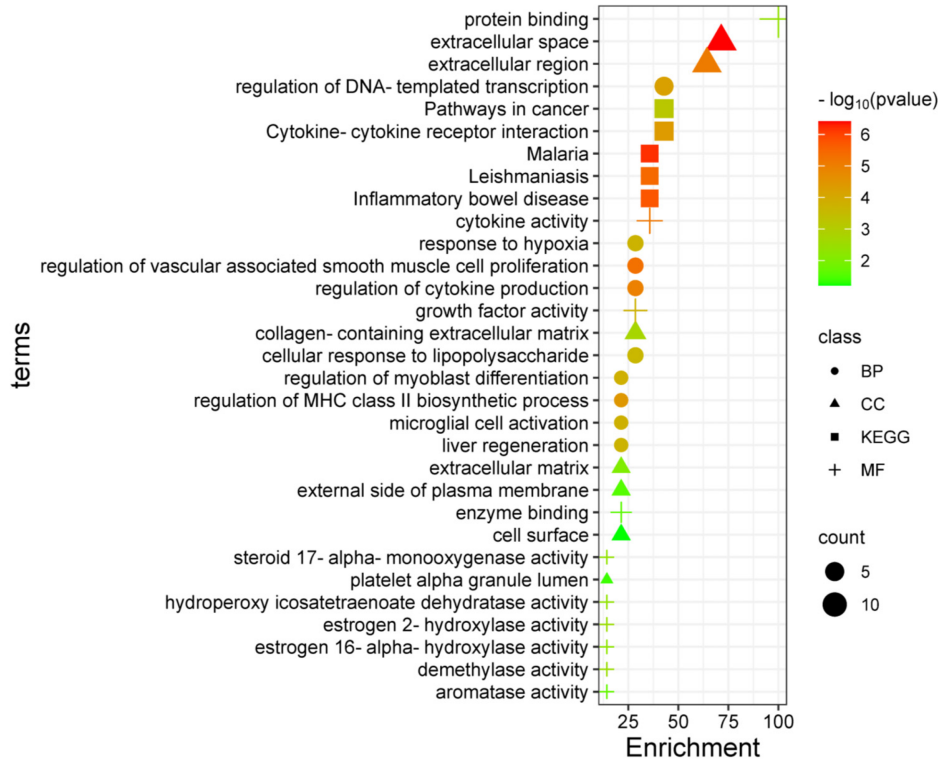

Figure 4: GO and KEGG enrichment.

3.6. Construction of Compound-Targets Network

To elucidate the interplay among targets, compounds, and HQ, a network encompassing HQ-compounds-targets was meticulously constructed utilizing Cytoscape. Through an in-depth degree analysis, it was unequivocally confirmed that quercetin assumes the role of the principal compound within HQ during the anti-PC process. Furthermore, kaempferol, isorhamnetin, and formononetin were identified as the most promising compounds within HQ (Figure 5).

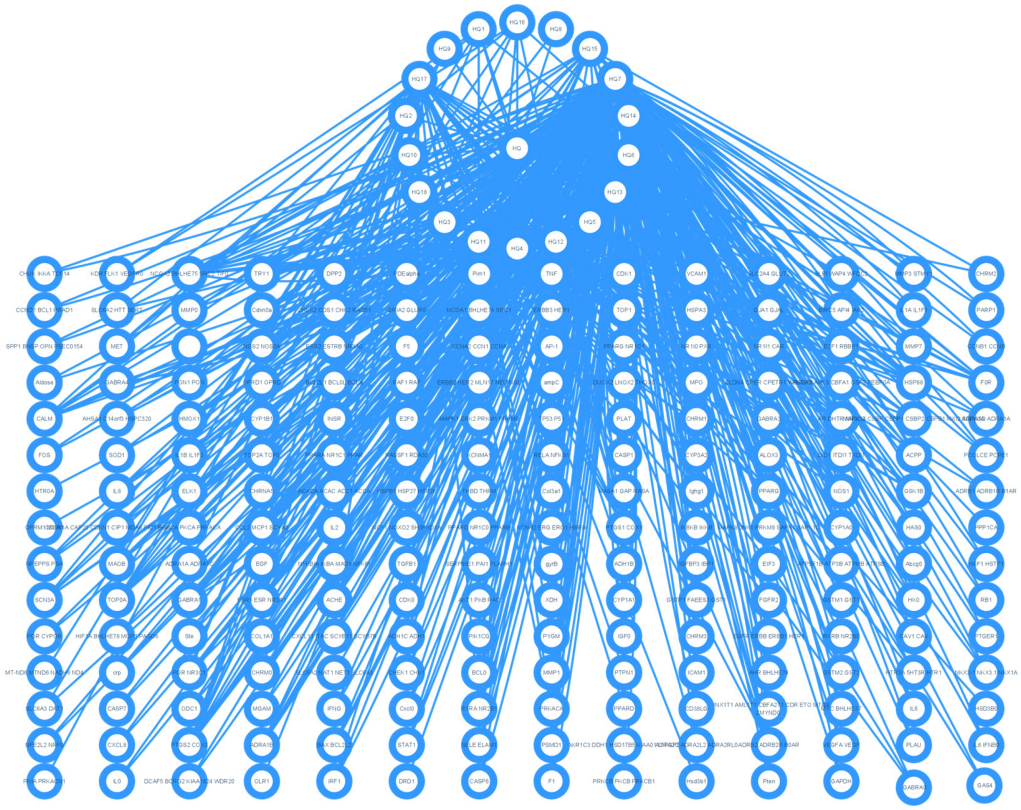

Figure 5: The herb-compounds-targets network.

3.7. Molecular Docking

Based on the PPI and the network degree analysis, the molecular docking analysis of the compound's quercetin, kaempferol, isorhamnetin, and formononetin with TNF, TGF, and MMP-9 was conducted to ascertain their affinity (Figure 6). The most significant combination was observed between formononetin and MMP-9, exhibiting an affinity of -10.11 kcal/mol. Conversely, the least binding energy was noted between kaempferol and TGF, registering an affinity of -6.1 kcal/mol (Table 1). The binding affinity of MMP-9 to the four small molecules was significantly higher compared to their affinity towards TNF and TGF, suggesting a potential direct interaction between these molecules and MMP-9 protein, subsequently leading to indirect regulation of TNF and TGF (Figure 7). These results were validated through the previous study [52], formononetin showed decreased regulation of MMP-9 in breast cancer, which was confirmed associated with metastatic PC [53]. Quercetin was shown to improve the disease prognosis by inhibiting MMP-9 [54]. Isorhamnetin was reported to potentially inhibit the proliferation and metastasis of cancer cells [55]. Kaempferol was investigated and found to inhibit cancer cells' migration and invasion [56,57].

3.8. Prognostic Analyses of Potential Therapeutic Target Genes

Based on the TCGA database, which contains various available comprehensive cancer types data, the prognosis of PC patients expressing MMP-9 was investigated. This analysis revealed that MMP-9 downregulation was correlated with improved survival in PC patients. (Figure 8).

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Table 1: Molecule docking data results.

Targets	Compounds	Binding Site	Affinity (kcal/mol)	Estimated Ki	Ligand Efficiency
TNF	Quercetin	2	−6.9	8.76 μM	−0.31
	Kaempferol	9	−7.3	4.46 μM	−0.35
	Isorhamnetin	9	−7.4	3.77 μM	−0.22
	Formononetin	7	−6.2	28.53 μM	−0.31
TGF	Quercetin	2	−6.2	28.53 μM	−0.28
	Kaempferol	5	−6.1	33.78 μM	−0.29
	Isorhamnetin	6	−6.6	14.53 μM	−0.19
	Formononetin	4	−6.2	28.53 μM	−0.31
MMP-9	Quercetin	8	−8.67	0.44 μM	−0.39
	Kaempferol	8	−8.88	0.31 μM	−0.42
	Isorhamnetin	2	−9.36	0.14 μM	−0.28
	Formononetin	1	−10.11	38.84 nM	−0.51

4. Discussion

PC is a lethal disease that presents significant challenges in the development of effective therapeutic strategies [58, 59]. This study employed a combination of network pharmacology and molecular docking to explore the potential therapeutic benefits of HQ in treating PC. The bioactive components of HQ and their potential PC-targeted genes were thoroughly analyzed, underscoring the multifaceted therapeutic effects of various compounds.

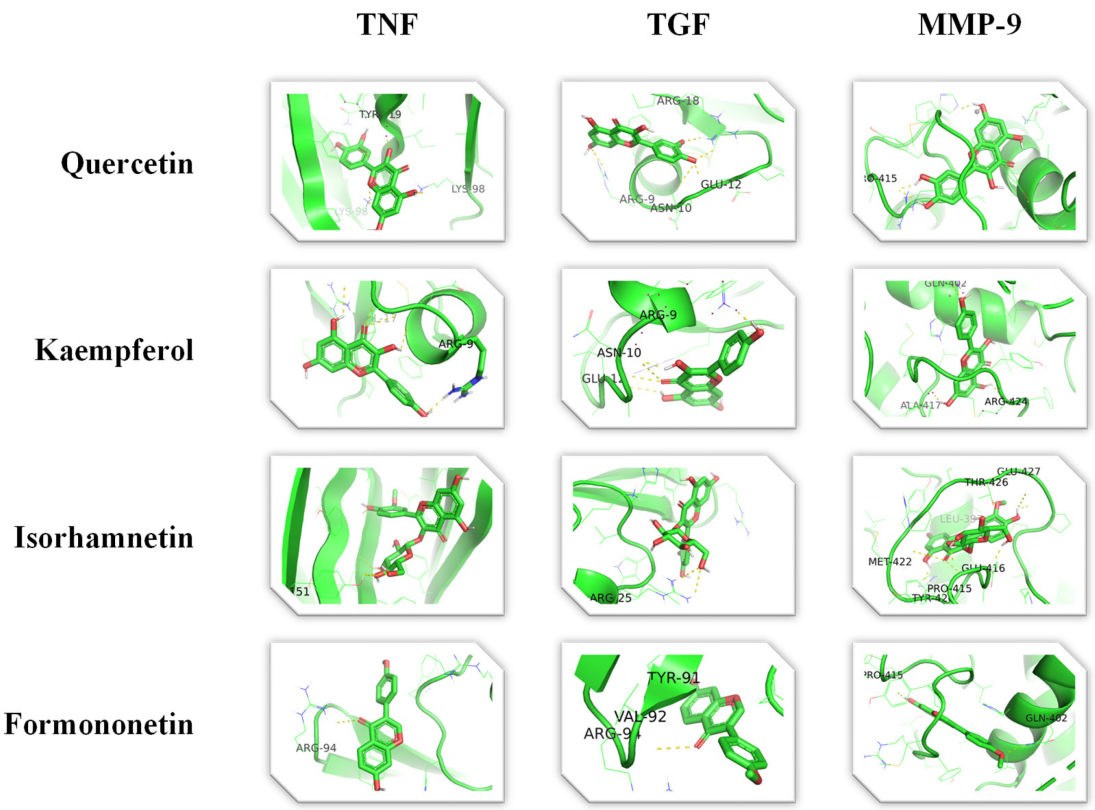

Figure 6: Molecule docking.

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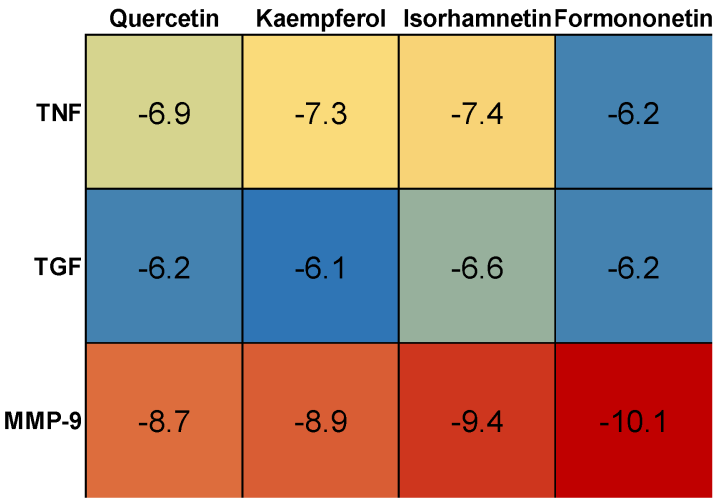

Figure 7: Binding energies between the small molecules and these three target proteins.

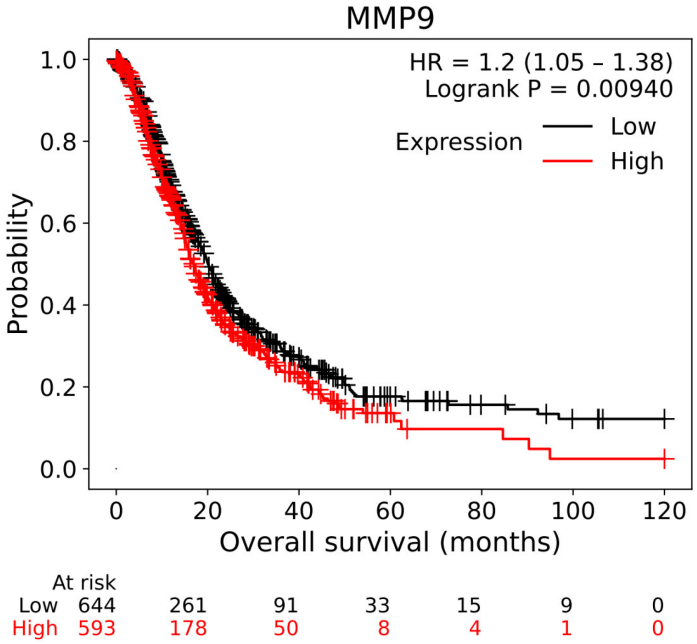

Figure 8: Survival analysis of PC patients expressed MMP-9.

Utilizing the TCMSP database, we identified 16 active compounds and 211 therapeutic targets that demonstrated favorable oral bioavailability (OB) and drug-likeness (DL). Upon further analysis of these 211 genes to discern common targets, we found 24 overlapping targets within the MalaCards and GeneCards database, encompassing a total of 568 PC genes. This suggests that the therapeutic efficacy of HQ may be attributed to its multi-component nature and its involvement in multiple molecular pathways, underscoring a key characteristic of TCMs.

The PPI network analysis, constructed using a stringent confidence threshold, was employed to examine the top ten-degree core target genes. Subsequently, these selected core targets underwent GO and KEGG analysis, yielding 158 GO terms and 54 KEGG terms. The observed complexity suggests that the active compounds in HQ concurrently influence multiple biological processes, offering a potential strategy for addressing the heterogeneity of PC. GO enrichment highlighted the biological processes, cell components, and molecular functions of these gene targets when engaged and absorbed by cancer cells. These include regulation of mononuclear cell migration, response to hypoxia, and protein binding, which align with the current understanding of PC progression. This con-

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forms to its anti-PC mechanism and enhances understanding at the molecular level [60].

The enriched KEGG terms from the selected proteins suggest that the potential compounds of HQ are likely to exert an anti-tumor effect through multiple signaling pathways. These are particularly associated with Cytokine-cytokine receptor interaction, Pathways in cancer, IL-17 signaling pathway, and TNF signaling pathway. Chronic systemic and localized inflammation may heighten the risk of PC. The inflammatory infiltrate linked with PC within the tumor microenvironment contributes to the promotion of tumor growth and metastasis. Inflammation is intricately intertwined with the immune system, with the same immune cell populations playing roles in both inflammatory processes and immune responses [61]. The results of the KEGG analysis reveal that HQ may exert its therapeutic effects by targeting the inflammatory process associated with PC progression. This suggests an alternative treatment strategy focused on modulating inflammation-related target genes [62].

The herb-compound-targets network analysis was utilized to pinpoint the most efficacious compound for anti-PC applications. The compounds quercetin, kaempferol, isorhamnetin, and formononetin were identified as possessing the highest potential. These compounds are all flavonoids, exhibiting significant anti-tumor and antioxidant properties [63–66]. They have the ability to neutralize active oxygen by inhibiting free radical generation and can potentially mitigate inflammation [67].

A plethora of studies have shown that quercetin can impede the growth and migration of pancreatic cancer cells through various mechanisms. Upon treatment with quercetin, the cell cycle of pancreatic cancer cells is arrested in the S phase, achieved by downregulating cyclin A expression [68]. Furthermore, quercetin can reduce the invasiveness of PC cells by suppressing the expression of MMP genes [69]. Additionally, it can trigger mitochondrial-dependent apoptosis in pancreatic cancer cells by inhibiting the PI3K/Akt signaling pathway [70]. Studies revealed that kaempferol can suppress the Akt/mTOR signaling pathway, thereby augmenting its anti-PC properties [71]. Furthermore, it has been demonstrated to induce cell cycle arrest, specifically in the G0/G1 phase, thus inhibiting the proliferation of cancer cells [72]. Isorhamnetin, an *O*-methylated derivative of quercetin, exhibits properties analogous to quercetin in the context of pancreatic cancer treatment [73]. Formononetin has been shown to increase the efficacy of chemotherapeutic agents, which can enhance the antiproliferative activity of gemcitabine, a standard treatment for pancreatic cancer, by downregulating key survival pathways [74,75]. This synergistic effect suggests that formononetin may be useful as an adjunct therapy in the treatment of pancreatic cancer.

The molecular docking analysis indicated that the most promising binding pair was formononetin and MMP-9, exhibiting a binding affinity of -10.12 kcal/mol. Kaempferol and MMP-9 demonstrated a binding affinity of -8.88 kcal/mol, while quercetin and MMP-9 showed a slightly lower affinity of -8.67 kcal/mol. Notably, isorhamnetin displayed the highest binding affinity among all tested compounds, with an impressive value of -9.36 kcal/mol against MMP-9. These results collectively underscore the pivotal role of MMP-9 in mediating the anti-PC effects of HQ. MMP-9 has been correlated with PC cell invasion [76], migration [77], and growth [78]. The increased expression of MMPs in pancreatic cancer, combined with the universally poor survival rates associated with even relatively early-stage disease, complicates the establishment of clinicopathologic correlations [79]. TNF /TGF was found to be associated with poor prognosis of PC [80], and inhibiting the TNF/TGF can inhibit the epithelial-to-mesenchymal transition of PC [81]. Therefore, by downregulating the TNF/TGF and MMP-9, we may find patients with a better prognosis. There is substantial evidence demonstrating the regulatory role of TGF and TNF interaction in modulating MMP-9, thereby influencing breast cancer progression [82]. This suggests that HQ may modulate the progression of pancreatic cancer through the TGF/TNF pathway to regulate MMP-9 signaling. However, some limitations still exist in this study. The investigation of the potential compounds still lies in the *in-silico* aspect, further validation based on the in vitro and in vivo models is needed. The exploration of anti-tumor compounds is built upon previous studies, yet there may be undiscovered effective compounds that remain to be identified, necessitating further research. Future research should focus on enhancing clinical relevance, which requires validation through patient-derived models that best preserve the structural and mutational characteristics of patients' tumors [83].

5. Conclusions

In conclusion, this study utilizes a network pharmacology analysis and molecular docking to reveal the potential therapeutic mechanisms of HQ in treating PC. The identification of active compounds and their associated targets provides a robust foundation for subsequent in vitro and in vivo experiments. A wealth of evidence suggests that quercetin, kaempferol, isorhamnetin, and formononetin are effective anti-pancreatic cancer ingredients present

in HQ. These compounds have the potential to regulate MMP-9 through the TNF/TGF axis. This pioneering study illuminates the unprecedented potential effect and mechanism of HQ against pancreatic cancer, offering a fresh perspective on the exploration of food and medicine homology herbs for tumor therapy. Future research should focus on validating these potential mechanisms using preclinical models while investigating their clinical translational potential. However, further validation is necessary, and patient-derived models should serve as a robust platform to evaluate their clinical potentials.

Abbreviations

PC	Pancreatic cancer
TCM	Traditional Chinese medicine
MFH	medicine and food homology
GO	Gene ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
PPI	protein-protein interaction
BP	biological processes
CC	cellular components
MF	molecular functions

Author Contributions

M.-Y.L. and G.Z. conceived the work; A.G. designed and conducted the experiments; A.G. wrote the manuscript. A.G., J.L., N.T., G.Z., and M.-Y.L. revised the manuscript. All authors analyzed the results and commented on the manuscript.

Availability of Data and Materials

Data supporting the results of this study are available upon request from the corresponding author.

Ethics Committee Approval and Consent to Participate

The study has no ethical implications.

Human Rights Statement

The research didn't involve any human subjects.

Consent for Publication

Not Applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

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