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Article

Exploring mechanism of Fuling Gancao decoction against functional dyspepsia using network pharmacology, molecular docking, and molecular dynamics simulation

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Abstract: Fuling Gancao Decoction (FGD) has been a typical formula for treating functional dyspepsia (FD) in China. Network pharmacology, molecular docking, and molecular dynamics simulation are applied to shed light on the comprehensive mechanisms of FGD against FD. The results showed that there were two core compounds (quercetin and kaempferol) and 16 crucial targets (KT1, SRC, EGFR, HRAS, and PIK3R1, etc.) of FGD against FD. Furthermore, 60 signaling pathways were modulated by the core targets, which contained estrogen signaling pathway, prolactin signaling pathway, cancer pathway, etc. The molecular docking analysis showed that quercetin and kaempferol had excellent binding affinity with the core targets. Molecular dynamic simulations indicated that quercetin-MAPK8 and kaempferol-AKT1 show favorable stability. The study successfully screened components, targets, and signaling pathways of FGD against FD, which provided a theoretical basis for further clinical application.

Keywords: Fuling Gancao decoction; functional dyspepsia; network pharmacology; molecular docking; molecular dynamics

1. Introduction

Functional dyspepsia (FD) is a relatively common digestive disorder with characteristics of recurrent and intractable. Despite the absence of obvious organic lesions in the stomach of FD patients, the symptoms, such as postprandial fullness, early satiation, epigastric pain or heartburn, nausea, etc., often are observed [1–3]. It was reported that FD attacked an estimated 15% of the world's adult population, which seriously diminished the quality of life of patients [4]. Notwithstanding the strong prevalence of FD, its pathogenesis remains complicated and poorly unexplained. Currently, emerging data increasingly pointed out that *helicobacter pylori* (*H. pylori*) infection and duodenal eosinophilia were recognized as strongly etiologically the development of FD [5–7]. To date, modern therapies for FD are somewhat restrictive and unsatisfactory. Clinicians administered acid suppression therapy, prokinetics, neuromodulators, and herbal medicines to treat FD [8]. Herbal medicines have multiple pharmacological activities, which could better target a broad range of pathophysiological mechanisms in FD [9]. Therefore, herb medicines were extremely attractive and promising as an adjunctive treatment against FD.

Fuling Gancao Decoction (FGD) was first prescribed in "Treatise on Febrile Diseases (Shang Han Lun)" and had become a typical formula for the treatment of FD in China. FGD comprised four herbs, namely, Fu ling (FL, *Poria cocos*), Gan Cao (GC, *Glycyrrhiza uralensis*, *Glycyrrhiza inflata*, and *Glycyrrhiza glabra*), Gui Zhi

(GZ, *Cinnamomum cassia*), and Sheng jiang (SJ, *Zingiber officinale*). It was reported that the extract of GC alleviated gastrointestinal symptoms of FD through prokinetic activity [10–12]. Experimental research has demonstrated that GZ exerted an anti-inflammatory effect on *H. pylori*-infected gastric cells [13]. In addition, SJ eradicated *H. pylori* in patients with *H. pylori*-positive FD and improved digestive symptoms [14]. Interestingly, FGD has achieved excellent curative effects on FD in Chinese medicine clinical applications. However, the pharmacological components and the therapeutic mechanism of FGD against FD were yet elusive. Consequently, based on following the clinical principles of traditional Chinese Medicine (TCM), the study adopted network pharmacology and molecular docking approach to initially elucidate the pharmacological components and mechanisms of FGD in treating FD, which could provide research to facilitate the development of this formula and the optimization of quality control standards. The specific flowchart is portrayed in **Figure 1**.

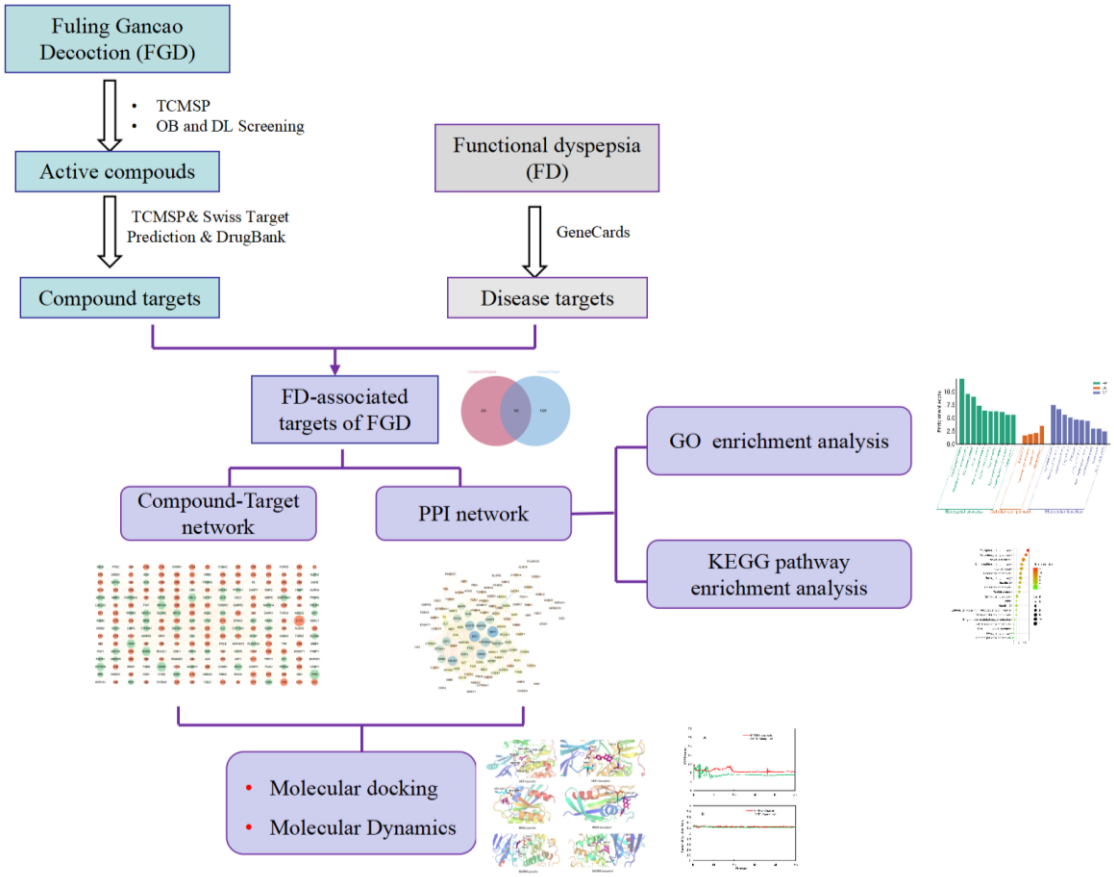

Figure 1. The flowchart for FGD against FD.

2. Materials and methods

2.1. Acquisition and selection of candidate components in FGD

The ingredients of each herb in FGD were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database [15]. Thereafter, we adopted oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 as the filtering criteria to screen the active ingredients in FGD. Afterward, the 3D structures (*.sdf) and the simplified molecular input line entry system (SMILES)

format of the active compounds were accessed from the PubChem [16] database for the next target prediction.

2.2. Prediction of potential FD-associated targets of FGD

Based on the inverse pharmacophore matching method and chemical similarity, the 3D structures and SMILES formats of the active ingredients in FGD were entered into PharmMapper [17] and Swiss Target Prediction [18] databases to predict their corresponding targets, respectively. With the filtering criteria of Probability and *Z*-score, respectively, Swiss Target Prediction and PhammMapper provide a score for every anticipated target to assess the probability of making an accurate prediction. Generally speaking, a better correlation between the component and the target was indicated by higher Probability and *Z*-score values for the target. Targets with probabilities greater than or equal to 0.5 were chosen by Swiss Target Prediction [19]. Simultaneously, the top 20 targets were chosen for additional PharmMapper analysis in descending order based on *Z*-score [20]. Lastly, the compound targets of FGD were identified by merging the targets from the two above-mentioned databases and excluding the overlapping targets.

The FD-related targets were captured from the GeneCards [21] database, which took "Functional dyspepsia" as the keyword. Then, both compound targets and disease targets were all normalized as "Gene Symbol" by the UniProt [22] database, of which species were set as "homo species". Immediately following, the Venn tool, one of the programs in OmicShare [23], was conducted to intersect compound targets and FD-related targets, and the overlapping targets were namely the FD-relevant targets of FGD.

2.3. Collection of protein-protein interactions

The FD-associated targets of FGD were loaded into the String [24] database to acquire protein-protein interactions (PPIs). To gain the accurate protein-protein interactions, the confidence level was defined as "high confidence (0.7)". In addition, the species was assigned to "homo species", and other settings were preserved as default values.

2.4. Network construction

The following two networks were visualized by Cytoscape (version 3.6.0) software: 1) Compound-target (C-T) network between compounds of FGD and their corresponding FD targets; 2) Protein-protein interaction (PPI) network of FD-associated targets from FGD. Degree, one of the network topological parameters, was calculated by the Cytoscape plug-in, NetworkAnalyzer. The degree value denoted the number of nodes directly connected to other nodes. Therefore, the higher the degree value, the greater the number of linkages with other ports the node was, implying that the node was located at a more central position in the network. Consequently, Degree was adopted to measure the significance of the nodes in the network. It was generally acknowledged that if the degree value of a node was twice the average degree value, the node could be assumed to be a hub node [25].

2.5. Gene ontology and KEGG pathway enrichment analysis

To clarify the biological functions and signaling pathways, the major FD-associated targets of FGD were imported into the Database for Annotation, Visualization, and Integrated Discovery (DAVID) [26] database for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. If the enrichment yielded a small *P*-value for GO entries and KEGG pathways, it indicated that the core target was associated with this particular process and not by chance. In general, a threshold of $P < 0.05$ is denoted statistically significant [27]. Therefore, the enriched GO terms and pathways with $P < 0.05$ were selected.

2.6. Molecular docking

The PDB [28] and PubChem databases were used to get the protein crystal structure of the primary targets and the 3D structures of the key components, respectively. Molecular docking was performed for validation of the reliability of the prediction results. The specific operation was as follows: 1) Protein pretreatment: Cocrystallized ligands and water molecules of target proteins were eliminated using Pymol (2.3) software. The Autodock tool was then used to further alter the target proteins by adding hydrogenation, figuring out point charges, and adding missing atoms to incomplete residues. The pdbqt format was used to store the final corrected proteins. 2) Ingredient pretreatment: By adding hydrogenation, charge, and atomic type, the Autodock tool also fixed the compound. 3) Docking parameters: To determine the size of the Grid box, repaired proteins in pdbqt format were submitted into the Autodock application. 4) Molecular docking: The modified target proteins and compounds were uploaded into Autodock Vina for molecular docking. Energy range, exhaustiveness, and num_mod set to 3, 50, and 10, respectively. Ultimately, binding energy was computed and conducted to assess the stability and effectiveness of molecular docking. It was generally assumed that the lower the docking energy, the more stable the docking conformation between molecular and target protein. The docked conformations with the strong affinity were visualized by Pymol 2.3.

2.7. Molecular dynamics simulation

The flexibility of the protein structure is currently not taken into account by semi-flexible docking, which is used in molecular docking. Using the Gromacs 2021.4 program, molecular dynamics simulations of the two molecule-protein complexes with the lowest binding energy were carried out in order to illustrate better the strength and stability of the binding between the ligand and the protein. The electrically neutral system was stabilized with Cl^- and Na^+ and the ligand-protein complexes were put in a solvent chamber with water molecules. A 50 ns molecular dynamics simulation was performed on the system after it had been adjusted by a constant number of particles, pressure, and temperature ensemble (NPT). The conformation was recorded every 10 ps throughout this simulation. Finally, the results were obtained by analyzing the root mean square deviation (RMSD) and radius of gyration (Rg) of the trajectories.

3. Results

3.1. Formation and analysis of C-T network

The chemical components of each herb from FGD (including FL, GZ, GC, and SJ) were retained from the TCMSP database, of which there were 34 for FL, 220 for GZ, 280 for GC, and 265 for SJ. A total of 704 compounds in FGD were derived after eliminating repeated entries. Notably, 118 FGD candidate compounds that met the selection criteria of OB ≥ 30% and DL ≥ 0.18 were subsequently made accessible. These included 15 from FL, 93 from GC, 7 from GZ, 5 from SJ, and 2 from the common compounds. The details of candidate ingredients are illustrated in Supplementary materials **Table S1**.

A total of 356 compound targets of FGD were retrieved from PharmMapper and Swiss TargetPrediction databases (**Table S2**). Furthermore, 1444 FD-associated targets were predicted from the GeneCards database (**Table S3**). Afterward, the compound targets were matched with the disease targets, and 123 intersecting targets were identified as the FD-associated targets of FGD. The Venn diagram and detailed information regarding FD-associated targets of FGD were highlighted in **Figure 2** and **Table S4**.

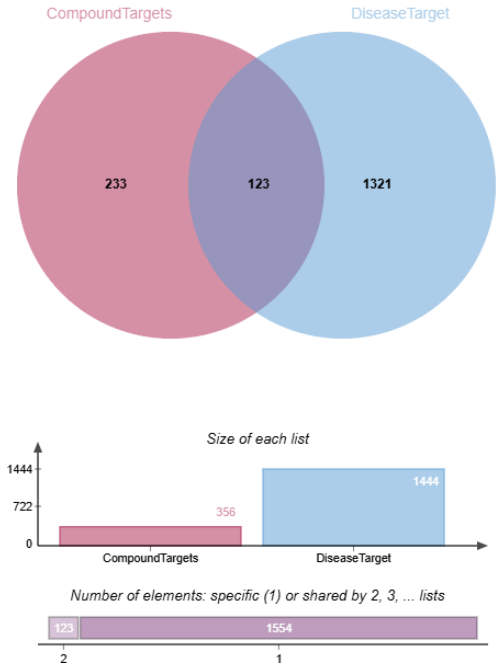

Figure 2. The Venn diagram of the potential target of FGD in the treatment of FD.

Cytoscape (3.6.0) software was used to construct the FGD network's components and their associated therapeutic FD targets. The network had 240 nodes (117 compounds and 123 FD-related targets of FGD) and 1043 edges (**Table S5**). In **Figure 3**, the light green trapezoidal nodes represented their relevant FD-related targets, while the tangerine yellow circular nodes represented the active ingredients of FGD. A larger node size meant that the node had a larger degree value. In addition, the edges indicated that the active constituents had a direct relationship with the targets.

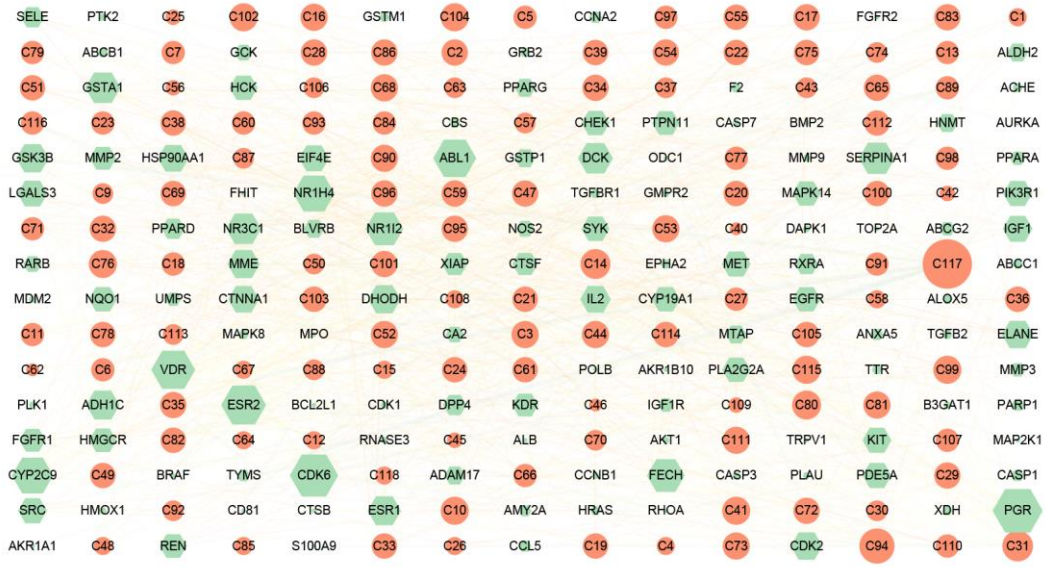

Figure 3. C-T Network.

From the network topology analysis, the median degree values of bio-active compounds and their corresponding FD-relevant targets of FGD were 8.9 and 8.5, respectively, which demonstrated that one target could correspond to 8.9 components on average, and conversely, one active ingredient hit 8.5 targets on average (**Table S6**). FGD was, therefore, thought to have synergistic effects on FD through a variety of targets and components. In particular, the degree values of quercetin (C117, degree 36) and kaempferol (C94, degree 20) were twice the median degree value of active compounds. Therefore, quercetin and kaempferol might be selected as crucial components of FGD for the treatment of FD.

3.2. PPI network construction and analysis

The PPI network of the FD-related targets of FGD is depicted in **Figure 4**. There were 112 nodes and 493 edges in the PPI network (**Table S7**). A larger circular node in the graph indicated a larger degree value for a node. According to network topological analysis, 16 targets had degree values that were twice as high as the mean (8.8) (**Table S8**). Therefore, 16 targets were chosen as the primary targets of FGD against FD, including serine/threonine-protein kinase AKT (AKT1), proto-oncogene tyrosine-protein kinase Src (SRC), epidermal growth factor receptor (EGFR), GTPase HRas (HRAS), phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1), heat shock protein HSP 90-alpha (HSP90AA1), mitogen-activated protein kinase 8 (MAPK8), insulin-like growth factor IA (IGF1), growth factor receptor-bound protein 2 (GRB2), caspase-3 (CASP3), transforming protein RhoA (RHOA), mitogen-activated protein kinase 14 (MAPK14), phosphatase non-receptor type 11 (PTPN11), estrogen receptor alpha (ESR1), serum albumin (ALB), and matrix metalloproteinase 9 (MMP9).

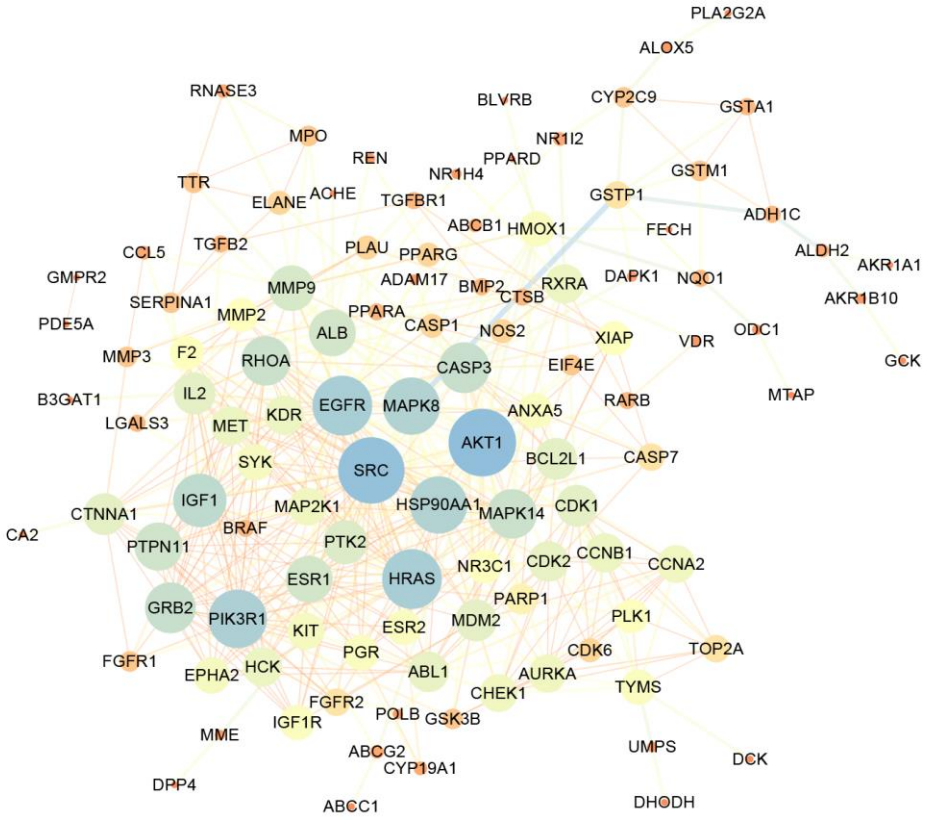

Figure 4. PPI network of FGD in treating FD.

3.3. Analysis of GO and pathway enrichment

For GO and pathway enrichment analysis, the UniProt IDs of the 16 core targets were input into the DAVID database. The findings showed that the 16 core targets were linked to 53 GO terms ($P < 0.05$), comprising 13 molecular function (MF) terms, 4 cellular component (CC) terms, and 36 biological process terms (**Table S9**). The specific BP terms involved the ERBB2 signaling pathway, phosphatidylinositol (PI)-mediated signaling, epidermal growth factor receptor (EGFR) signaling pathway, leukocyte migration, vascular endothelial growth factor (VEGF) receptor signaling pathway, etc. CC terms were closely associated with mitochondrion, perinuclear region of cytoplasm, cell-cell junction, and plasma membrane. MF included nitric-oxide synthase (NOS) regulator activity, protein phosphatase binding, insulin receptor binding, etc. The top 10 highly enriched BP and MF items, along with whole CC terms, are highlighted in **Figure 5** based on the descending ranking of *P*-value.

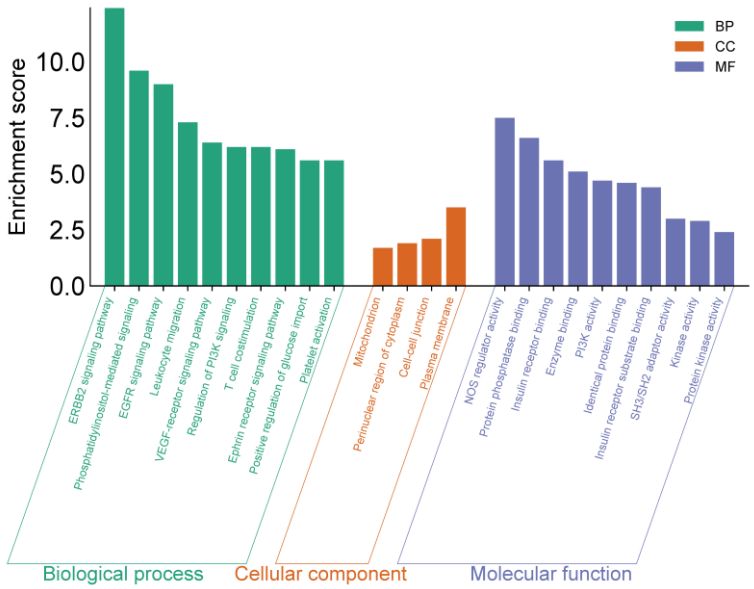

Figure 5. The GO terms.

The core FD-associated targets of FGD were enriched to 60 signaling pathways with $P < 0.05$, which principal modulated estrogen signaling pathway, prolactin signaling pathway, pathways in cancer, neurotrophin signaling pathway, focal adhesion, FoxO signaling pathway, Ras signaling pathway, etc (**Table S10**). The top 20 signaling pathways were screened in descending order according to *P* value, as portrayed in **Figure 6**.

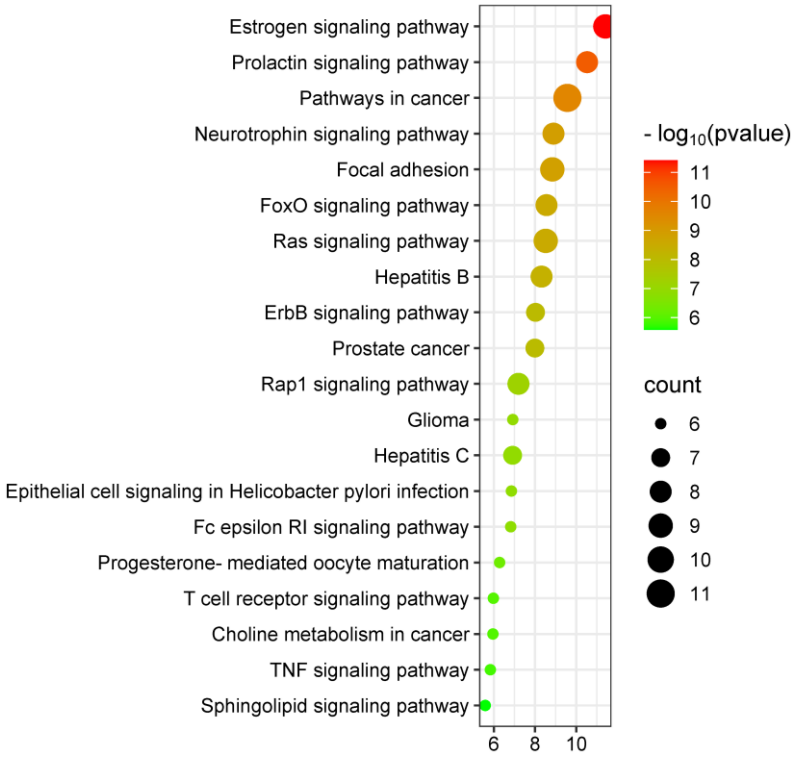

Figure 6. The top 20 KEGG signaling pathways.

3.4. Molecular docking validation

The top 10 target proteins in the PPI network (AKT1, SRC, EGFR, HRAS, PIK3R1, HSP90AA1, MAPK8, IGF1, GRB2, and CASP3) were docked with kaempferol and quercetin, which are the two principal active constituents of FGD in treating FD. The results of molecular docking are illustrated in **Table 1**. In general, strong binding affinity was defined as binding energy ≤−5.0 kcal/mol [29]. Both quercetin and kaempferol were successfully docked with AKT1, SRC, EGFR, HRAS, PIK3R1, HSP90AA1, MAPK8, IGF1, GRB2, and CASP3, according to the molecular docking data. It was crucial to note that MAPK8, AKT1, and HRAS all showed substantial binding affinities, as seen by their binding energies, with quercetin and kaempferol being less than −9.0 kcal/mol, respectively. The number of hydrogen bonds reflected the ability of the compound to bind to the target. As illustrated in **Figure 7**, quercetin interacted with amino acid residues ASN54, GLN79, THR211, VAL271, TYR272, and ASP292 in AKT1 via six H bonds. Similarly, kaempferol and amino acid residues ASN54, GLN79, SER205, and THR211 in AKT1 were linked by four H bonds. Quercetin could form two H bonds with amino acid residues ALA146 and LYS147 in HRSA. Kaempferol interacted with amino acid residues SER145, ALA146 and LYS147 via three H bonds. Furthermore, quercetin was bound to MET111, ASN114, and GLN117 in MAPK8 by the formation of three H bonds. Kaempferol had three H bonds with SER34, MET111, and ASP112 in MAPK8.

Table 1. The result of molecular docking with active compound-target.

Target protein	PDBID	Binding energy (kcal/mol)	
		Quercetin	Kaempferol
AKT1	4ejn	−9.4	−9.5
SRC	4f5b	−6.1	−6.1
EGFR	4lqm	−8.4	−8.0
HRAS	4dlt	−9.4	−9.2
PIK3R1	3i5r	−6.4	−6.2
HSP90AA1	4cwp	−9.0	−8.8
MAPK8	4i7f	−9.5	−9.1
IGF1	1tgr	−7.2	−7.1
GRB2	2vvk	−6.0	−5.7
CASP3	3h0e	−7.0	−7.2

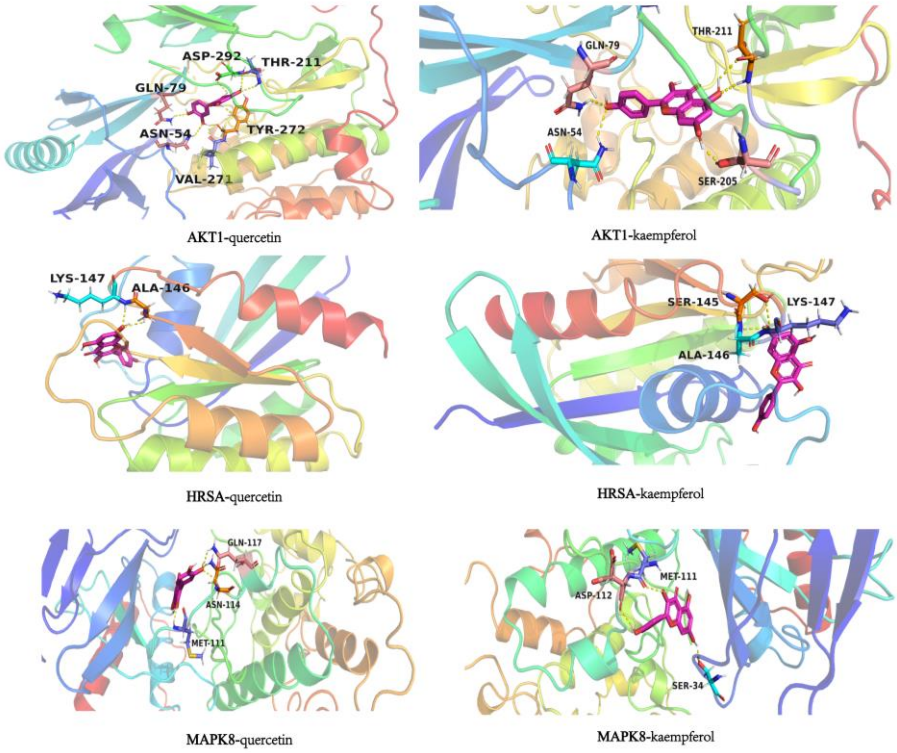

Figure 7. Molecular docking pattern of partial active ingredients with targets.

3.5. Molecular dynamics simulation

Molecular dynamics simulation is a crucial technique to analyze the stability and conformational variation of ligand-protein complexes following docking. RMSD curves and Rg were computed for the binding stability of kaempferol with AKT1 and quercetin with MAPK8. The position difference between the conformation and the initial conformation during the simulation may be observed through the RMSD. A smaller RMSD can detect the more stable structure, while a larger fluctuation may indicate an excessive or unstable state of the system. Rg is a measure of the molecule's mean rotating radius in space, which reflects its size and shape. In general, a molecule is tight if its Rg value is higher and looser if its Rg value is lower. **Figure 8** shows that the trajectories of all molecules and energy levels stabilize after 20 ns. Both the Rg and the RMSD curves exhibit strong stability.

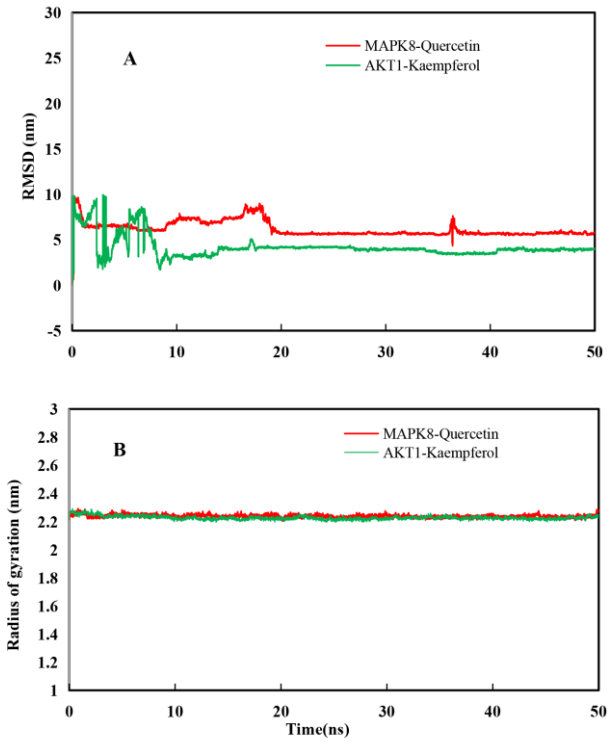

Figure 8. The molecular dynamic simulations results of quercetin-MAPK8 and kaempferol-AKT1. **(A)** RMSD; **(B)** Rg variation diagram.

4. Discussion

The pathogenic mechanism of FD, a prevalent chronic recurrent functional disorder of the digestive system, has not yet been fully understood. Nonetheless, research has indicated that FD has a complex etiology. Its pathophysiology may be intimately associated with gastrointestinal dysfunction, inflammation, *H. pylori* infection, visceral hypersensitivity, etc, according to modern medicine [30–34]. In the post-infectious irritable bowel syndrome rat model, quercetin was found to reduce intestinal chromophores' proliferation and 5-hydroxytryptamine (5-HT) utilization, thereby attenuating visceral hypersensitivity [35].

Quercetin improved gastrointestinal motility disorders and prompted human stomach smooth muscle to relax [36]. The pathophysiology and progression of FD are linked to stomach epithelial cell damage brought on by oxidative stress [37]. The study demonstrated that quercetin decreased oxidative stress damage in gastric mucosal epithelial (GES-1) cells by enhancing mucosal barrier and mitochondrial function and reducing inflammation by controlling the PI3K/AKT signaling pathway. It suggested that quercetin had therapeutic benefits for FD [38]. Besides, kaempferol and quercetin both had comparatively high antioxidant activity and showed protective benefits against indomethacin- or ethanol-induced gastric ulcers in mice [39,40]. In summary, it could be seen that quercetin and kaempferol were considered major components of FGD in treating FD.

From the PPI network, we identified 16 critical FD-targets of FGD, including AKT1, SRC, EGFR, HRAS, PIK3R1, HSP90AA1, MAPK8, IGF1, GRB2, CASP3, and others. It was noteworthy that both targets and core components showed strong

docking affinities, demonstrating the reliability of the predictions. Recent data demonstrated a correlation between gastric hypersensitivity and increased expression of nerve growth factor (NGF) in the stomach [41,42]. It was documented that in the gastric fundus of gastric hypersensitive rats, overexpression of PIK3R1 has enhanced the production of NGF. Furthermore, MMP9 was the predominant protease in NGF degradation, and NGF degradation was suppressed by downregulating MMP9 expression [43]. Consequently, PIK3R1 and MMP9 were thought to be promising therapeutic targets for treating stomach hypersensitivity. CASP3, MAPK8/14, RHOA, and ALB were closely relevant to gastrointestinal dysfunction [44–46]. Inflammation was associated with AKT1, SRC, EGFR, HRAS, and IGF1 [47–51]. In addition, PTPN11, GRB2, HSP90AA1, and ESR1 were linked to the development of gastric cancer [52–55]. Interestingly, both gastric cancer and FD experienced indigestion symptoms such as upper abdominal pain and fullness [56]. Consequently, PTPN11, GRB2, HSP90AA1, and ESR1 might be indirect targets of FGD in the treatment of FD. Overall, FGD treated FD either directly or indirectly by achieving the aforementioned targets.

FGD might have an impact on the ERBB2 signaling pathway, PI-mediated signaling, EGFR signaling route, leukocyte migration, VEGFR signaling pathway, regulation of PI3K signaling, and other biological processes, according to the enrichment analysis of GO biological processes. The EGFR family's targetable transmembrane glycoprotein receptor, ERBB2, is crucial for cell division, survival, and proliferation. Aberrant HER2 signaling is implicated in gastric cancers [57]. The gene encoding variation of ERBB2 is closely associated with gastrointestinal motility disorders [58]. PI3K signaling pathway is an important branch of PI-mediated signaling. The PI3K signaling pathway regulates inflammatory processes in the intestinal mucosa [59]. Leukocyte migration to the affected sites is a critical process in inflammation [60]. Elevated VEGFA expression could weaken intestinal epithelial cells' tight connection and impair their barrier function, making it easier for germs to infiltrate and escalating inflammation [61]. In summary, FD in treating FGD may mainly focus on the regulation of gastrointestinal motility disorders and intestinal inflammation.

KEGG pathway enrichment analysis displayed that the estrogen signaling pathway was the most remarkable. Estrogen, a steroid hormone, can access the cytoplasmic membrane to interact with intracellular ERα and ERβ and exert a multitude of physiological and pathological effects by binding to DNA sequences [62]. By encouraging the release of duodenal bicarbonate, estrogen has been shown to protect the duodenal mucosa from gastric acid injury and lower the risk of duodenal ulcers [63]. ERα and ERβ in the estrogen signaling pathway could differentially manipulate gene expression by triggering different transcriptional responses, while differences in ERα and ERβ might enable estrogen to exert anti-inflammatory and pro-inflammatory effects in intestinal inflammation [64]. Furthermore, estrogen plays a critical role in triggering gastrointestinal disorders and visceral hypersensitivity [65]. Taken together, FGD could further alleviate FD syndrome by regulating intestinal inflammation, gastric hypersensitivity, and gastrointestinal dysfunction through its action on the estrogen signaling system.

5. Conclusion

The study stated that FGD may have a synergistic effect on treating FD through multi-component, multi-target, and multi-pathway approaches. It gave traditional Chinese medicine research a fresh viewpoint and gave researchers a theoretical foundation for clinical application and drug development. The lack of an in vivo experiment, which will be planned for the follow-up study to support our current conclusion, is the study's limitation.

Author contributions: Conceptualization, BL and NW; methodology, BL and NW; data analysis, BL and NW; validation, HQ, YC and YL; supervision, HQ, YC and YL; funding acquisition, HQ; writing—original draft, BL and HQ; review and editing, HQ. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest: The authors declare no conflict of interest.

References

1. Ford AC, Mahadeva S, Carbone MF, et al. Functional dyspepsia. Functional Gastrointestinal Disorders. 2020; 396(10263):1689-1702. doi: 10.1016/S0140-6736(20)30469-4
2. Mounsey A, Barzin A, Rietz A. Functional Dyspepsia: Evaluation and Management. Am Fam Physician. 2020; 101(2): 84-88.
3. Talley NJ. Functional Dyspepsia: Advances in Diagnosis and Therapy. Gut and Liver. 2017; 11(3): 349-357. doi: 10.5009/gnl16055
4. Ford AC. Aetiopathogenesis of functional dyspepsia. Gut. 2015; 64(7): 1182-1183. doi: 10.1136/gutjnl-2014-308959
5. Ronkainen J, Aro P, Walker MM, et al. Duodenal eosinophilia is associated with functional dyspepsia and new onset gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. 2019; 50(1): 24-32. doi: 10.1111/apt.15308
6. Talley NJ, Walker MM, Holtmann G. Functional dyspepsia. Current Opinion in Gastroenterology. 2016; 32(6): 467-473. doi: 10.1097/mog.0000000000000306
7. Talley NJ. Functional dyspepsia: new insights into pathogenesis and therapy. The Korean Journal of Internal Medicine. 2016; 31(3): 444-456. doi: 10.3904/kjim.2016.091
8. Vandenberghe A, Schol J, Van den Houte K, et al. Current and emerging therapeutic options for the management of functional dyspepsia. Expert Opinion on Pharmacotherapy. 2020; 21(3): 365-376. doi: 10.1080/14656566.2019.1707805
9. Gwee K, Holtmann G, Tack J, et al. Herbal medicines in functional dyspepsia—Untapped opportunities not without risks. Neurogastroenterology & Motility. 2020; 33(2). doi: 10.1111/nmo.14044
10. Asha MK, Debraj D, Dethe S, et al. Effect of Flavonoid-Rich Extract of Glycyrrhiza glabraon Gut-Friendly Microorganisms, Commercial Probiotic Preparations, and Digestive Enzymes. Journal of Dietary Supplements. 2016; 14(3): 323-333. doi: 10.1080/19390211.2016.1223257
11. Azimi M, Zahedi MJ. Persian Herbal Medicine in Functional Dyspepsia: A Systematic Review. Current Drug Discovery Technologies. 2021; 18(2): 272-281. doi: 10.2174/1570163817666200611132831
12. Murugan S, Velusami CC, Bethapudi B, et al. Effect of Flavonoid Rich Root Extract of Glycyrrhizaglabra on Gastric Emptying and Gastrointestinal Transit in Albino Wistar Rats. SOJ Pharmacy & Pharmaceutical Sciences. 2017; 4(2): 1-4. doi: 10.15226/2374-6866/4/2/00159

13. Muhammad JS, Zaidi SF, Shaharyar S, et al. Anti-inflammatory Effect of Cinnamaldehyde in Helicobacter pylori Induced Gastric Inflammation. Biological and Pharmaceutical Bulletin. 2015; 38(1): 109-115. doi: 10.1248/bpb.b14-00609
14. Ebrahimzadeh Attari V, Somi MH, Asghari Jafarabadi M, et al. The Gastro-protective Effect of Ginger (Zingiber officinale Roscoe) in Helicobacter pylori Positive Functional Dyspepsia. Advanced Pharmaceutical Bulletin. 2019; 9(2): 321-324. doi: 10.15171/apb.2019.038
15. Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform database. https://old.tcmsp-e.com/tcmsp.php
16. PubChem. https://pubchem.ncbi.nlm.nih.gov/
17. PharmMapper. https://www.lilab-ecust.cn/pharmmapper/
18. Swiss Target Prediction. http://www.swisstargetprediction.ch/
19. Shi R, Chen D, Ji M, et al. Network pharmacology-based screening of the active ingredients and mechanisms of Cymbaria daurica against diabetes mellitus. Food Science and Human Wellness. 2023; 12(6): 2001-2013. doi: 10.1016/j.fshw.2023.03.022
20. Li T, Li Y, Chen J, et al. Hyperibone J exerts antidepressant effects by targeting ADK to inhibit microglial P2X7R/TLR4-mediated neuroinflammation. Journal of Advanced Research; 2024. doi: 10.1016/j.jare.2024.07.015
21. GeneCards. https://www.genecards.org/
22. UniProt. https://www.uniprot.org/
23. OmicShare. https://www.omicshare.com/
24. String. https://cn.string-db.org/
25. Guo MF, Dai YJ, Gao JR, et al. Uncovering the Mechanism of Astragalus membranaceus in the Treatment of Diabetic Nephropathy Based on Network Pharmacology. Journal of Diabetes Research. 2020; 2020: 1-13. doi: 10.1155/2020/5947304
26. Database for Annotation, Visualization, and Integrated Discovery. https://davidbioinformatics.nih.gov/
27. Zhao H, Shan Y, Ma Z, et al. A network pharmacology approach to explore active compounds and pharmacological mechanisms of epimedium for treatment of premature ovarian insufficiency. Drug Design, Development and Therapy. 2019; 13: 2997-3007. doi: 10.2147/dddt.s207823
28. PDB. https://www.rcsb.org/
29. Chen Z, Lin T, Liao X, et al. Network pharmacology based research into the effect and mechanism of Yinchenhao Decoction against Cholangiocarcinoma. Chinese Medicine. 2021; 16(1): 13-32. doi: 10.1186/s13020-021-00423-4
30. Rosen JM. Visceral hypersensitivity and electromechanical dysfunction as therapeutic targets in pediatric functional dyspepsia. World Journal of Gastrointestinal Pharmacology and Therapeutics. 2014; 5(3): 122. doi: 10.4292/wjgpt.v5.i3.122
31. Tack J, Carbone F. Functional dyspepsia and gastroparesis. Current Opinion in Gastroenterology. 2017; 33(6): 446-454. doi: 10.1097/mog.0000000000000393
32. Wauters L, Talley NJ, Walker MM, et al. Novel concepts in the pathophysiology and treatment of functional dyspepsia. Gut. 2019; 69(3): 591-600. doi: 10.1136/gutjnl-2019-318536
33. Smith ML. Functional dyspepsia pathogenesis and therapeutic options—Implications for management. Digestive and Liver Disease. 2005; 37(8): 547-558. doi: 10.1016/j.dld.2005.04.001
34. Schäppi MG, Borrelli O, Knafelz D, et al. Mast Cell–Nerve Interactions in Children With Functional Dyspepsia. Journal of Pediatric Gastroenterology and Nutrition. 2008; 47(4): 472-480. doi: 10.1097/mpg.0b013e318186008e
35. Qin HY, Zang KH, Zuo X, et al. Quercetin Attenuates Visceral Hypersensitivity and 5-Hydroxytryptamine Availability in Postinflammatory Irritable Bowel Syndrome Rats: Role of Enterochromaffin Cells in the Colon. Journal of Medicinal Food. 2019; 22(7): 663-671. doi: 10.1089/jmf.2018.4264
36. Modzelewska B, Drygalski K, Kleszczewski T, et al. Quercetin relaxes human gastric smooth muscles directly through ATP-sensitive potassium channels and not depending on the nitric oxide pathway. Neurogastroenterology & Motility. 2021; 33(7): 1-13. doi: 10.1111/nmo.14093
37. Chang Y, Wei W, Tong L, et al. Weikangning therapy in functional dyspepsia and the protective role of Nrf2. Experimental and Therapeutic Medicine. 2017; 14(4): 2885-2894. doi: 10.3892/etm.2017.4892
38. Yao X, Mei Y, Mao W. Quercetin Improves Mitochondrial Function and Inflammation in H2O2-Induced Oxidative Stress Damage in the Gastric Mucosal Epithelial Cell by Regulating the PI3K/AKT Signaling Pathway. Yong YK, ed. Evidence-Based Complementary and Alternative Medicine. 2021; 2021: 1-10. doi: 10.1155/2021/1386078

39. Alkushi AGR, Elsawy NAM. Quercetin attenuates, indomethacin-induced acute gastric ulcer in rats. Folia Morphologica. 2017; 76(2): 252-261. doi: 10.5603/fm.a2016.0067
40. Li Q, Hu X, Xuan Y, et al. Kaempferol protects ethanol-induced gastric ulcers in mice via pro-inflammatory cytokines and NO. Acta Biochimica et Biophysica Sinica. 2018; 50(3): 246-253. doi: 10.1093/abbs/gmy002
41. Shi H, Zhu S, Qin B, et al. Nerve growth factor and Tropomyosin receptor kinase A are increased in the gastric mucosa of patients with functional dyspepsia. BMC Gastroenterology. 2019; 19(1): 221-228. doi: 10.1186/s12876-019-1133-7
42. Winston JH, Sarna SK. Developmental Origins of Functional Dyspepsia-Like Gastric Hypersensitivity in Rats. Gastroenterology. 2013; 144(3): 570-579.e3. doi: 10.1053/j.gastro.2012.11.001
43. Li Q, Winston JH, Sarna SK. Noninflammatory upregulation of nerve growth factor underlies gastric hypersensitivity induced by neonatal colon inflammation. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2016; 310(3): R235-R242. doi: 10.1152/ajpregu.00342.2015
44. Chang MJ, Xiao JH, Wang Y, et al. 2, 3, 5, 4′-Tetrahydroxystilbene-2-O-Beta-D-Glucoside Improves Gastrointestinal Motility Disorders in STZ-Induced Diabetic Mice. Tache Y, ed. PLoS ONE. 2012; 7(12): e50291. doi: 10.1371/journal.pone.0050291
45. Song MH, Zhu GJ, Ma L, et al. Comparative analysis of bilirubin in correlation to albumin between nephrotic syndrome patients and postoperative gastroparesis syndrome patients. Genetics and Molecular Research. 2014; 13(4): 9403-9411. doi: 10.4238/2014.february.14.13
46. Wu XF, Chen XL, Zheng XN, et al. Effects of electroacupuncture with different stimulation intensities on gastrointestinal motor function and expression of sinus smooth muscle Ras homologue genome member A/associated coiled-coil protein kinase signaling in diabetic gastroparesis rats (Chinese). Zhen Ci Yan Jiu. 2018; 43(3):169-174. doi: 10.13702/j.1000-0607.170299.
47. Burns M, Muthupalani S, Ge Z, et al. Helicobacter pylori Infection Induces Anemia, Depletes Serum Iron Storage, and Alters Local Iron-Related and Adult Brain Gene Expression in Male INS-GAS Mice. Boneca IG, ed. PLOS ONE. 2015; 10(11): e0142630. doi: 10.1371/journal.pone.0142630
48. Kinoshita H, Hayakawa Y, Konishi M, et al. Three types of metaplasia model through Kras activation, Pten deletion, or Cdh1 deletion in the gastric epithelium. The Journal of Pathology. 2018; 247(1): 35-47. doi: 10.1002/path.5163
49. Mansouri V, Tavirani SR, Zadeh-Esmaeel MM, et al. Comparative study of gastric cancer and chronic gastritis via network analysis. Gastroenterol Hepatol Bed Bench. 2018; 11(4):343-351.
50. Shin KK, Park JG, Hong YH, et al. Anti-Inflammatory Effects of Licania macrocarpa Cuatrec Methanol Extract Target Src- and TAK1-Mediated Pathways. Evidence-Based Complementary and Alternative Medicine. 2019; 2019: 1-13. doi: 10.1155/2019/4873870
51. Tafreshi M, Guan J, Gorrell RJ, et al. Helicobacter pylori Type IV Secretion System and Its Adhesin Subunit, CagL, Mediate Potent Inflammatory Responses in Primary Human Endothelial Cells. Frontiers in Cellular and Infection Microbiology. 2018; 8: 1-15. doi: 10.3389/fcimb.2018.00022
52. Meng X, Zhao Y, Liu J, et al. Comprehensive analysis of histone modification-associated genes on differential gene expression and prognosis in gastric cancer. Experimental and Therapeutic Medicine. 2019; 18(3):2219-2230. doi: 10.3892/etm.2019.7808.
53. Wang J, Cui S, Zhang X, et al. High Expression of Heat Shock Protein 90 Is Associated with Tumor Aggressiveness and Poor Prognosis in Patients with Advanced Gastric Cancer. PLOS ONE. 2013; 8(4): e62876. doi: 10.1371/journal.pone.0062876
54. Xu L, Zhou C, Pan R, et al. PTPN11 hypomethylation is associated with gastric cancer progression. Oncology Letters. 2020; 19(3): 1693-1700. doi: 10.3892/ol.2020.11250.
55. Ye B, Duan B, Deng W, et al. EGF Stimulates Rab35 Activation and Gastric Cancer Cell Migration by Regulating DENND1A-Grb2 Complex Formation. Frontiers in Pharmacology. 2018; 9: 1-12. doi: 10.3389/fphar.2018.01343
56. Yu QX. Clinical presentations of gastric small gastrointestinal stromal tumors mimics functional dyspepsia symptoms. World Journal of Gastroenterology. 2014; 20(33): 11800-11807. doi: 10.3748/wjg.v20.i33.11800
57. Cheng X. A Comprehensive Review of HER2 in Cancer Biology and Therapeutics. Genes. 2024; 15(7): 903. doi: 10.3390/genes15070903

58. Chanpong A, Alves MM, Bonora E, et al. Evaluating the molecular and genetic mechanisms underlying gut motility disorders. Expert Review of Gastroenterology & Hepatology. 2023; 17(12): 1301-1312. doi: 10.1080/17474124.2023.2296558
59. Weaver SA, Ward SG. Phosphoinositide 3-kinases in the gut: a link between inflammation and cancer?. Trends Mol Med. 2001; 7(10): 455-462. doi: 10.1016/S1471-4914(01)02107-4
60. Nourshargh S, Alon R. Leukocyte Migration into Inflamed Tissues. Immunity. 2014; 41(5): 694-707. doi: 10.1016/j.immuni.2014.10.008
61. Frysz-Naglak D, Fryc B, Klimacka-Nawrot E, et al. Expression, localization and systemic concentration of vascular endothelial growth factor (VEGF) and its receptors in patients with ulcerative colitis. International Immunopharmacology. 2011; 11(2): 220-225. doi: 10.1016/j.intimp.2010.11.023
62. Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. Advances in Protein Chemistry and Structural Biology. 2019; 116:135-170. doi: 10.1016/bs.apcsb.2019.01.001.
63. Tuo B, Wen G, Wei J, et al. Estrogen Regulation of Duodenal Bicarbonate Secretion and Sex-Specific Protection of Human Duodenum. Gastroenterology. 2011; 141(3): 854-863. doi: 10.1053/j.gastro.2011.05.044
64. Nie X, Xie R, Tuo B. Effects of Estrogen on the Gastrointestinal Tract. Digestive Diseases and Sciences. 2018; 63(3): 583-596. doi: 10.1007/s10620-018-4939-1
65. Accarie A, Toth J, Wauters L, et al. Estrogens Play a Critical Role in Stress-Related Gastrointestinal Dysfunction in a Spontaneous Model of Disorders of Gut–Brain Interaction. Cells. 2022; 11(7): 1214. doi: 10.3390/cells11071214