

Gut microbiota-derived metabolites in prostate cancer: a network pharmacology-based identification

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Short Report

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Abstract

Recent studies have indicated that microbial metabolites produced by the gut microbiota can influence the progression of prostate cancer (PCa). To identify metabolites with therapeutic potential for PCa and to further clarify the mechanisms by which gut microbial metabolites regulate PCa progression, a novel and comprehensive perspective is required. Here, network pharmacology was used to screen 277 metabolites recorded in the gutMGene database. Through the combined application of metabolite target databases and disease target databases, we ultimately identified 34 core targets mediating the impact of gut microbial metabolites on PCa. Enrichment analyses showed that these metabolites may affect PCa progression by modulating the PI3K-AKT and MAPK pathways. Molecular docking results showed that quercimeritrin bound well to IL-6, whereas quercetin, indole-3-lactic acid, and 3-indolepropionic acid bound well to AKT1. These findings offer new perspectives on how gut microbial metabolites may regulate PCa and suggest novel avenues for drug discovery against this disease.

1. Introduction

Prostate cancer (PCa) is the second most common malignancy in men, accounting for approximately 15% of all male cancers, with an estimated 1.5 million men diagnosed globally each year[1, 2]. Although significant advancements have been made in the screening, diagnosis, and treatment of PCa, the management of certain PCa subtypes, such as recurrent, metastatic, and castration-resistant prostate cancer (CRPC), continues to pose challenges at various levels[3, 4]. According to 2022 World Health Organization (WHO) data, PCa ranks as the fifth leading cause of cancer-related mortality among men[5]. Therefore, further in-depth research on PCa is particularly imperative.

The gut bacterial flora serves as the foundation for maintaining intestinal microecological stability and plays a crucial role in human health and disease[6, 7]. Disruption of the normal equilibrium between the gut microbiota and the host, termed dysbiosis, is implicated in the onset and progression of various metabolic diseases, inflammatory diseases, and malignant tumors[6, 8] [9–12]. The gut microbiota can metabolize substrates in the gut into a variety of bioactive substances, and these metabolites act as core hubs and regulatory factors, profoundly influencing the host's physiological and pathological processes[13, 14].

Research suggests that the gut microbiota can affect the initiation and progression of PCa. Specific microbial taxa, such as *Phocaeicola massiliensis*, *Bacteroides* spp., *Streptococcus* spp., and members of the Akkermansiaceae family, have been found to be dysregulated in the gut environment of individuals with PCa[15–17]. Similarly, microbial metabolites, including folate and arginine, exhibit differential levels in PCa patients[15]. Furthermore, supplementation with gut microbiota derived from CRPC patients and short-chain fatty acids (SCFAs) can significantly accelerate the progression of PCa in murine models[18]. Other gut microbial metabolites, such as urolithins, equol, and trimethylamine N-oxide, have also demonstrated varying degrees of therapeutic potential against PCa in research studies[19–21]. These findings confirm the therapeutic potential of gut microbiota metabolites in PCa. However, current studies

have largely focused on individual or a few known metabolites, and a global perspective that can systematically reveal the complex interaction network between the two remains lacking. Network pharmacology is an interdisciplinary approach that can bridge pharmacology and biology. This approach provides a powerful tool for panoramic screening from metabolites to targets and pathways, as well as for discovering novel metabolite–target relationships. Recent studies have identified gut microbial metabolites targeting various diseases, including benign prostatic hyperplasia, through network pharmacology approaches[22–24]. This has inspired our research, prompting us to employ network pharmacology methodologies to identify gut microbial metabolites with therapeutic potential for PCa, thereby complementing the mechanistic understanding of the gut–prostate axis. All supplementary figures are provided in Additional file 1. The overall workflow of this study is shown in Figure S1.

2. Materials and Methods

2.1 Acquisition of Gut Microbiota and Metabolite Targets

Metabolites and their associated targets were obtained from the gutMGene v2.0 database[25, 26]. We employed the Similarity Ensemble Approach (SEA)[27, 28] and SwissTargetPrediction (STP)[29, 30] to acquire potential targets of the microbial metabolites. For the retrieval of PCa-related targets, we used the following databases: GeneCards v5.24[31, 32], DisGeNET v25.1[33, 34], the Therapeutic Target Database [35, 36] and the Online Mendelian Inheritance in Man[37, 38].

2.2 Construction of the Core Target Protein-Protein Interaction (PPI) Network

PPI analysis was performed using the STRING database v12.0[39]. Hub targets were identified using the cytoHubba plugin in Cytoscape v3.10.3.

2.3 Gene Ontology (GO) analyses and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway

GO pathway and KEGG analyses were performed using RStudio v4.3.1. Pathway interaction networks were constructed using OmicShare Tools, an open-access analysis platform [40, 41].

2.4 Microbiota-Substrate-Metabolite-Target-Pathway (M-S-M-T-P) Network construction

After screening through the SEA and STP databases and molecular docking, only those metabolites that were documented in the gutMGene database as being producible by relevant microorganisms through the metabolism of specific substrates were retained. A network model was constructed using Cytoscape v3.10.3 to generate the M-S-M-T-P network.

2.5 Molecular Docking and Visualization

Metabolite structure files were obtained from the PubChem database[42] and protein 3D structure files were obtained from the PDB databas[43]. Ligands were energy-minimized using Chem3D v22.0.0.22. Prior to docking, proteins were preprocessed with PyMOL software. Molecular docking of the metabolites and target proteins was performed using AutoDock Vina v1.1.2, and the results were subsequently visualized using AutoDock Tools.

2.6 Drug-Likeness and Toxicity Evaluation

The drug-like properties of gut microbial metabolites targeting the core targets were evaluated using SwissADME[44, 45], and the toxicity of these metabolites was assessed using ADMETlab 3.0[46, 47].

3. Results

3.1. Acquisition of Targets for PCa-Related Microbial Metabolites

A total of 277 metabolites were retrieved from the gutMGene database. Targets associated with these metabolites were identified through the SEA and STP databases, yielding 989 overlapping metabolite targets (Figure S2A) (Additional file 2). Among these metabolite targets and 1,523 PCa-related targets, 196 overlapping targets were identified (Figure S2B). Finally, the intersection between these 196 overlapping targets and 238 targets obtained from the gutMGene database resulted in 34 core targets (Figure S2C) (Additional file 3).

3.2 Core Target PPI Network and GO Enrichment Analysis

The PPI network of the 34 core targets was constructed using the STRING database, generating a network comprising 34 nodes and 319 edges (Figure S3A). Subsequently, GO enrichment classification analysis was performed on the core targets. Among the significantly enriched Biological Process (BP) terms, entries related to response to biotic stimulus were identified. Furthermore, cellular response to reactive oxygen species and cellular response to metal ion were also significantly enriched in the results (Figure S3B). In the Cellular Component (CC) category, core targets were significantly enriched in entries such as ruffle, the NF- κ B complex, and the AP-1 transcription factor complex. (Figure S3C). Molecular Function (MF) enrichment analysis revealed that two significantly enriched terms were RNA polymerase II-specific DNA-binding transcription factor binding and DNA-binding transcription factor binding (Figure S3D) (Additional file 4).

3.3 KEGG Pathway Analysis

KEGG pathway analysis was performed on the 34 core targets, and the top 30 entries ranked by p-value are displayed. Several key pathways identified in the KEGG enrichment analysis, such as the MAPK signaling pathway, Toll-like receptor signaling pathway, TNF signaling pathway and IL-17 signaling pathway, play a critical role in the initiation and advancement of PCa[48-51] (Figure 1A). Subsequently, we performed KEGG pathway classification analysis[52] (Figure 1B). Among them, the category Environmental Information Processing represents signal perception/transduction at the cellular level,

providing a critical framework for precisely identifying the key bridging pathways through which gut microbial metabolites influence PCa development and progression. In the Environmental Information Processing category, as a central signaling axis, the PI3K-Akt pathway plays a key role in driving tumor proliferation and resistance to apoptosis. Blocking this pathway together with AR inhibition now represents a key strategy for combating drug resistance in PCa[53-56]. A pathway interaction analysis was subsequently performed on the top 30 KEGG-enriched pathways. Among them, the MAPK signaling pathway (21) had the highest degree value (Figure 1C) (Additional file 5). Acting as a modulator of AR signaling, the MAPK cascade also represents a major promoter of PCa advancement[57, 58]. Therefore, we identified two key signaling pathways, PI3K-Akt and MAPK, as collective mediators of the effects of gut microbial metabolites on PCa.

3.4 PPI network analysis

Four topological algorithms—Degree, Closeness, Maximum Neighborhood Component (MNC), and Maximal Clique Centrality (MCC)—were applied, and the 10 highest-ranked genes from each were designated as hub targets (Figure S4) (Additional file 6).

Through four topological algorithms, both AKT1 and IL6 achieved the top scores across all analyses, consistently occupying the first or tied-first position in Degree, Closeness, MNC, and MCC rankings (Table 1).

Table 1. Top 10 hub targets identified by four topological algorithms (Degree, Closeness, MNC, and MCC) from the PPI network.

Degree (score)	Closeness (score)	MNC (score)	MCC (order)*
IL6(62)	IL6(32)	IL6(31)	IL6(1)
AKT1(62)	AKT1(32)	AKT1(31)	AKT1(2)
JUN(56)	JUN(30.5)	IL1B(28)	IL1B(3)
CASP3(54)	CASP3(30)	NFKB1(27)	NFKB1(4)
PPARG(54)	PPARG(30)	CASP3(27)	CASP3(5)
EGFR(54)	EGFR(30)	JUN(27)	JUN(6)
IL1B(54)	IL1B(30)	PPARG(27)	PPARG(7)
NFKB1(52)	NFKB1(29.5)	FOS(26)	FOS(8)
PTGS2(50)	PTGS2(29)	PTGS2(25)	PTGS2(9)
FOS(48)	FOS(28.5)	EGFR(24)	EGFR(10)

*For MCC algorithm, raw scores were extremely large (all > 6.6×10¹³); only the descending gene order is shown. Numbers in parentheses in this column indicate the rank. Ranks are strict (no ties).

As the central kinase of the PI3K-Akt signaling pathway[54], AKT1 operates in concert with the MAPK cascade in PCa to promote cell proliferation and survival [59]. For IL6, on the one hand, activation of p38 MAPK promotes androgen-independent proliferation of PCa cells by regulating IL6 secretion[60], on the other hand, IL6 can activate the PI3K/Akt pathway and upregulate cyclin A1, thereby enhancing PCa cell survival[61]. Collectively, these findings led us to pinpoint AKT1 and IL6 as the core targets mediating the influence of gut microbial metabolites on PCa.

3.5 Molecular Docking Binding Energy Acquisition and M-S-M-T-P Network

Since ligand–receptor association at the active pocket leads to a change in binding energy, a value lower than -5 kcal/mol typically indicates a strong binding tendency. Guided by the SEA and STP database predictions, after screening for metabolites with binding potential to the core targets based on molecular docking binding energy results (Additional file 7), we retrieved information on these metabolites and their corresponding microorganisms from the gutMGene database. Then, based on the KEGG categorization, the top five pathways ranked by adjusted p-value in the Environmental Information Processing and Organismal Systems categories were selected from the KEGG pathway analysis to jointly construct the M-S-M-T-P network (Figure 2).

The final network contained 192 interactions in total, distributed among 43 microbes, 29 substrates, 27 microbial metabolites, 10 core targets, and 10 mechanistic pathways. AKT1 is the primary target of various indole compounds derived from tryptophan metabolism, while the flavonoid quercetin exhibits the strongest binding affinity for AKT1 (-9.8 kcal/mol). Quercetin can be further biotransformed by *Bacillus* sp. 46 into quercimeritrin, which has a predicted binding affinity of -5.8 kcal/mol for IL6 (Additional file 8).

3.6 Visualization of Molecular Docking

Molecular docking visualization was subsequently performed for the screened metabolites and their targets. (Figure 3). Notably, 3-(1H-indol-3-yl)propanoate represents the predominant form of 3-indolepropionic acid at physiological pH, which further supports the potential of 3-indolepropionic acid to target AKT1. Therefore, in the subsequent discussion, we will collectively refer to both as 3-indolepropionic acid. Based on the above results, we identified these metabolites as gut microbial metabolites with therapeutic potential against PCa, representing promising candidates for further development.

3.7 Drug-Likeness Evaluation

Lipinski's rule of five is a critically important empirical guideline in medicinal chemistry and drug discovery. It is primarily used to predict the potential oral bioavailability of small-molecule compounds[62, 63]. We evaluated the drug-likeness of the 27 microbial metabolites present in the network. Based on ADME parameters, Quercimeritrin, which showed binding potential toward IL6, was noted for having an overabundance of hydrogen bond donor and acceptor groups (Additional file 9).

3.8 Toxicity Evaluation

In addition to physicochemical properties, adverse effects impacting safety must also be considered in drug development. Using ADMETlab 3.0, we assessed multiple toxicological endpoints. The results indicated that quercetin received relatively high probability scores for DILI, approximately 0.78. Although the severity and reversibility of this potential toxicity require further validation (Additional file 10).

4. Discussion

Although significant progress has been made in the treatment of PCa, it remains a major threat to men's health. Recent studies have shown that the gut microbiota influences the progression of PCa through various mechanisms, including remote transmission of pathogens[64], actions of microbial metabolites[64], and alterations in androgen levels[65]. Among these, gut microbial metabolites serve as a crucial focal point for investigating the impact of the gut microbiota on various diseases. These metabolites not only play a vital role in maintaining intestinal homeostasis but can also be transported to distant sites, such as the prostate, where they exert diverse biological functions.

GO enrichment analysis systematically elucidated the potential molecular mechanisms of the core targets in PCa from multiple functional dimensions. At the BP level, the core targets were significantly enriched in the response to lipopolysaccharide[66, 67], cellular response to reactive oxygen species, and response to metal ions[68–70], indicating that these targets are deeply involved in the aforementioned biological processes and play critical regulatory roles in the initiation and progression of PCa. Furthermore, the enrichment of multiple terms in the CC and MF categories further revealed that the core targets can influence the pathological process of PCa at multiple levels through diverse subcellular localizations and transcription regulator activities.[71–76].

In the KEGG classification analysis, multiple pathways were significantly enriched in the Environmental Information Processing category. Considering that the PI3K-Akt pathway constitutes a central driver of tumor proliferation, apoptotic evasion, and castration-resistant progression in PCa, and that the MAPK pathway can enhance AR transcriptional activity by phosphorylating co-regulators and cooperatively drive PCa progression together with PI3K-Akt signaling[53, 57, 77], exhibiting the highest connectivity within the PCa pathway interaction network, we identified both pathways as key bridging routes through which gut microbial metabolites influence PCa and focused our discussion on them. Notably, the other enriched pathways are also implicated, to varying degrees, in the initiation and progression of PCa, and the mechanisms involving their associated targets and metabolites warrant further investigation in future studies[78–84].

AKT1 is the core downstream effector kinase of the PI3K/AKT signaling pathway. The regulation of cell proliferation, invasion, and autophagy, together with this pathway-mediated metabolism, plays a key role in promoting the formation and progressive deterioration of PCa. As one of the most frequently occurring molecular events in PCa, this pathway is considered a key factor contributing to tumor drug resistance and therapeutic resistance[53, 85–87]. IL-6, a pro-inflammatory cytokine, can lead to the

simultaneous activation of both the PI3K-AKT and MAPK pathways, serving as a key downstream effector and signal convergence node in PCa[61, 88–91]. These tightly intertwined and mutually influential mechanisms highlight the central role of these two targets in coordinating proliferative and survival signals within the PCa microenvironment.

Our results showed that two indole metabolites—indole-3-lactic acid and 3-indolepropionic acid—can tightly bind to AKT1. These two indole metabolites are dependent on the gut microbiota-mediated metabolism of tryptophan[92]. Evidence indicates that indole-3-lactic acid exhibits diverse therapeutic and pro-tumorigenic potentials across multiple cancer types. In colorectal cancer, indole-3-lactic acid suppresses tumor cell proliferation by inhibiting the STAT3–HK2 pathway to impair glycolysis[93]. In esophageal cancer, indole-3-lactic acid triggers the aryl hydrocarbon receptor (AhR) and suppresses NF- κ B signaling within CD8⁺ T_H1 cells, leading to impaired T cell activity and resistance to immunotherapy[94]. In contrast, the role and underlying mechanisms of indole-3-lactic acid in PCa remain largely unexplored. A previous study indicated a potential inverse association between indole-3-lactic acid and advanced PCa risk[95]; however, given the tissue specificity and strain dependence of indole-3-lactic acid observed in other malignancies, its precise function in PCa awaits further elucidation. 3-Indolepropionic acid exerts a direct inhibitory effect on PCa cells, attenuating their proliferation, migration, and invasion while forcing cell cycle arrest and apoptosis via activation of the p53–p21–RB pathway[96]. We employed network pharmacology for the first time to uncover an additional potential mechanism of 3-indolepropionic acid in PCa. The stable binding of 3-indolepropionic acid to the core target AKT1 indicates that it may exert anti-tumor effects not through a single linear pathway, thereby providing fresh network pharmacology-based insights into its role in the initiation and progression of PCa.

As a flavonol aglycone, quercetin is widely distributed in fruits, vegetables, and tea, and can exert multiple biological effects such as antioxidant, anti-inflammatory, and cardiovascular protective activities[97]. Previous studies have demonstrated that quercetin can inhibit the progression of PCa by directly binding to AKT1, which is consistent with our findings[98, 99]. As another flavonoid compound, quercimeritrin can be produced from quercetin via biotransformation by *Bacillus* sp. 46. Comparative studies have demonstrated that an isomer of quercimeritrin, isoquercitrin, can hinder the migration of pancreatic cancer cells[100]. However, quercimeritrin's role in PCa has not been reported in the literature to date. The molecular docking identified, for the first time, the interaction potential between quercimeritrin and IL-6, providing a preliminary direction based on network pharmacology for exploring its potential anti-tumor activity in PCa. Although ADMET analysis predicted poor drug-likeness for quercimeritrin, a previous study has confirmed that it exhibits significant oral hypoglycemic effects in a diabetic mouse model[101], this indicates that it can still be effectively absorbed and exert pharmacological effects in vivo, providing a feasibility basis for its oral administration, and it may serve as a candidate precursor compound for further in-depth validation of anti-PCa activity in cell-based and animal models.

Previous studies on PCa and gut microbial metabolites have demonstrated that metabolites such as SCFAs, urolithins, equol, and trimethylamine N-oxide play critical roles in the initiation and advancement of PCa[18–21, 102]. However, these relationships were not displayed in our study, which arises from methodological differences rather than any contradiction. In constructing the M-S-M-T-P network, we did not directly use the interactions recorded in gutMGene; instead, we adopted a dual criterion combining evidence from target prediction databases and qualified molecular docking binding energies. Directly employing the relationships recorded in gutMGene can clearly present interactions already supported by existing research data, providing a comprehensive approach to delineate the known functional links of gut microbial metabolites[24, 103]. In contrast, using target prediction database evidence helps identify previously uncharacterized metabolites and offers a new perspective on the modes of action of related metabolites[23]. Building on this, we further applied molecular docking binding energy filtering and incorporated interaction elements with clearly established relationships among specific microbes, substrates, and metabolites documented in gutMGene into the network, thereby achieving a comprehensive perspective that simultaneously encompasses the discovery of novel metabolites and the microbial action modes relevant to PCa targets.

5. Limitations

The public databases used in this network pharmacology analysis are continuously updated; therefore, some target information may have changed since our initial search. Re-checking the main databases revealed only minor changes that did not alter the core targets or overall conclusions. However, this database variability may affect reproducibility, and updated validation is warranted. Although the network pharmacology analysis in this study has revealed critical roles in the initiation and advancement of PCa, the findings are constrained by limited database coverage and the predictive nature of computational methods. Therefore, we plan to experimentally validate the biological functions and therapeutic potential of these metabolites to definitively establish their clinical value.

6. Conclusions

Through molecular docking simulations, we identified two indole metabolites—indole-3-lactic acid and 3-indolepropionic acid—both of which bind tightly to AKT1. Additionally, two flavonoids, quercetin and quercimeritrin, were found to target AKT1 and IL6, respectively. These four metabolites may exert therapeutic potential against PCa by targeting the PI3K-AKT and MAPK signaling axes.

Declarations

Acknowledgment

Not applicable.

Author contributions

Y.-D.W. conceived and designed the study, performed the software analysis, and supervised the project. L.C. developed the methodology, performed the formal analysis and investigation, and curated the data. Y.-D.W. and L.C. jointly validated the results, wrote the original draft, reviewed and edited the manuscript, and managed the project. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The datasets supporting the conclusions of this article are included within the article and its additional files.

Declaration

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Figures

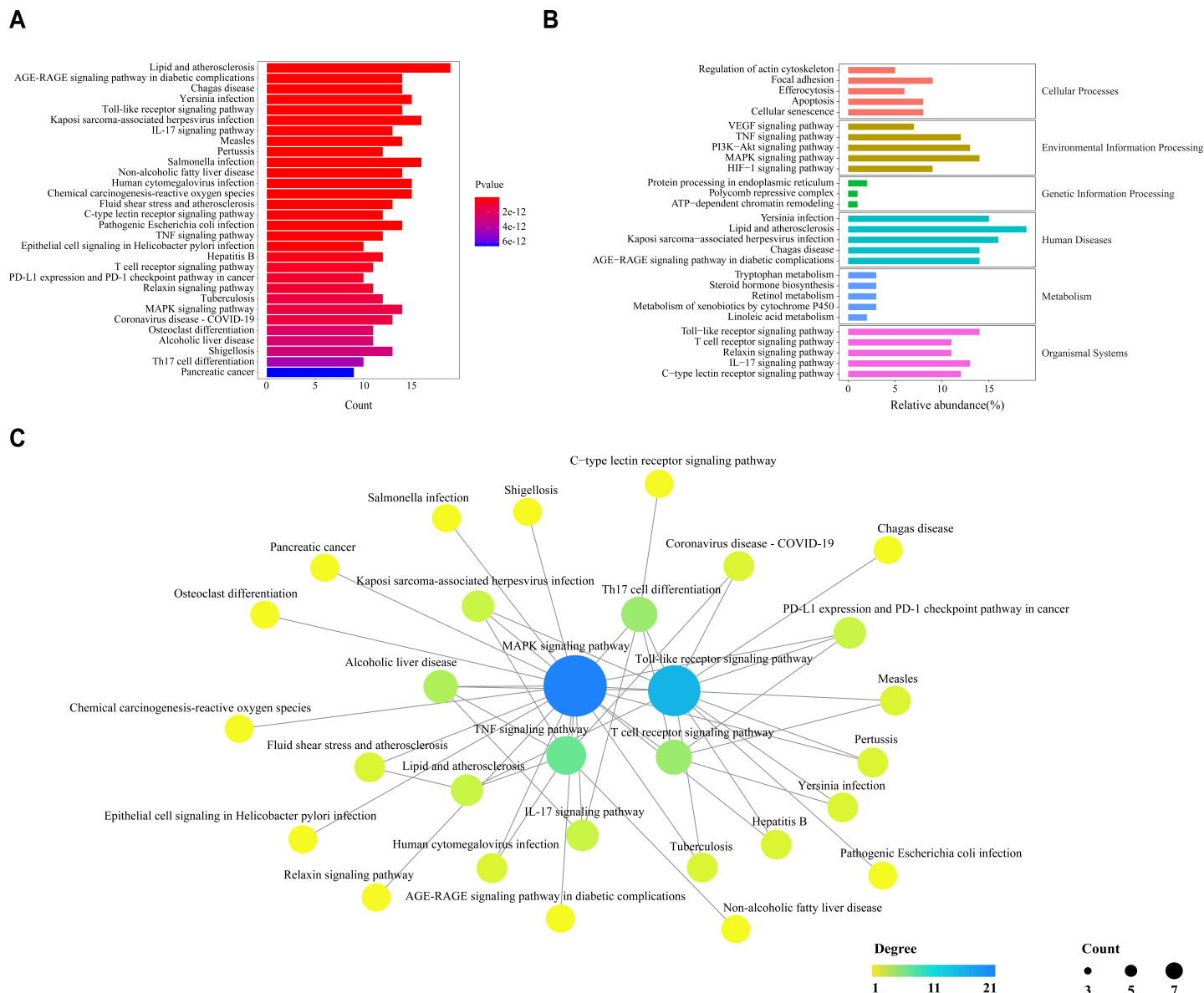


Figure 1

(A) Bar plot of KEGG pathway analysis.(B) Bar plot of categorized KEGG pathway analysis.(C) Interaction network of KEGG pathways for the 34 core targets. Nodes are arranged from the center outward according to their degree value.

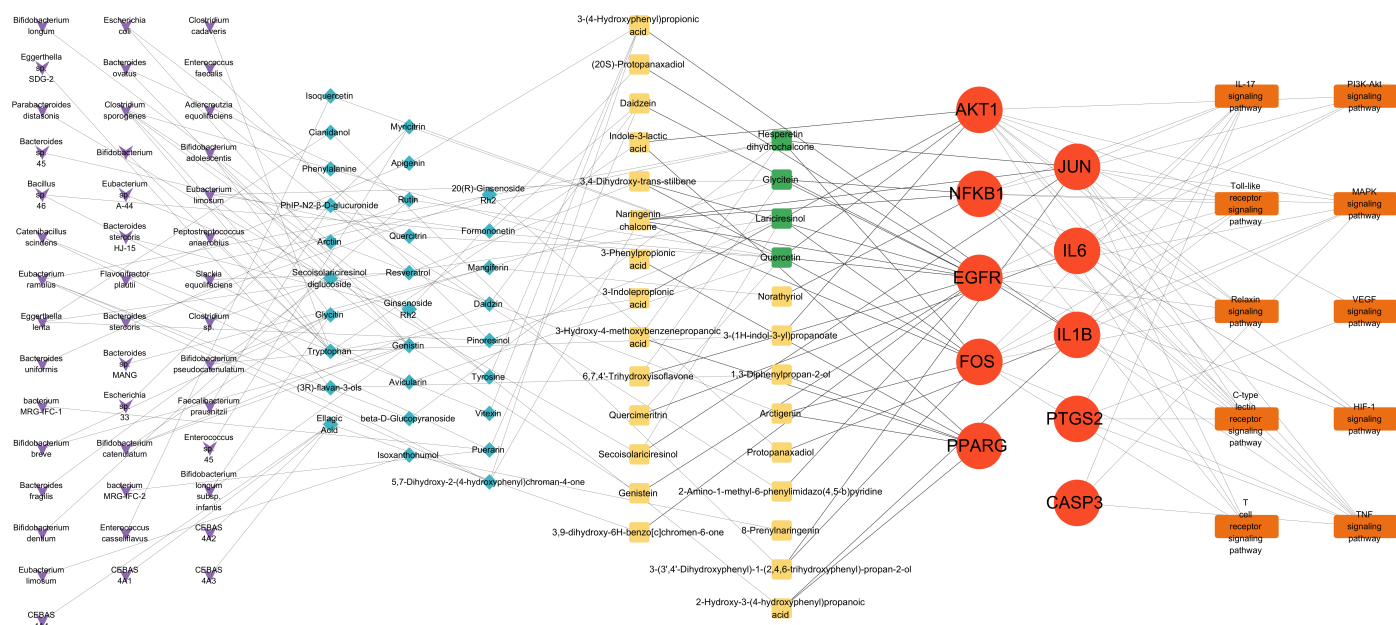
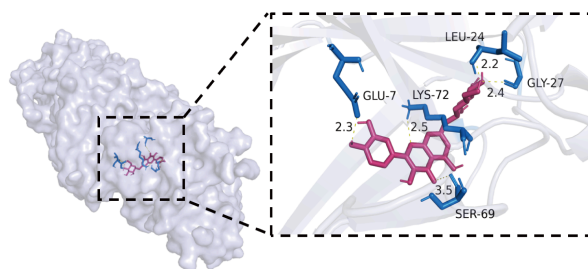
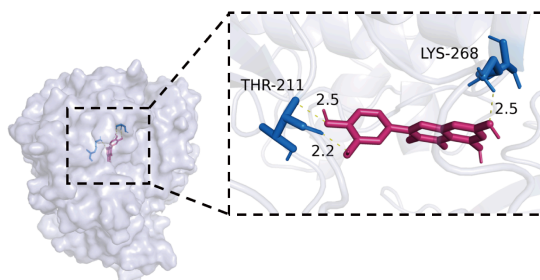
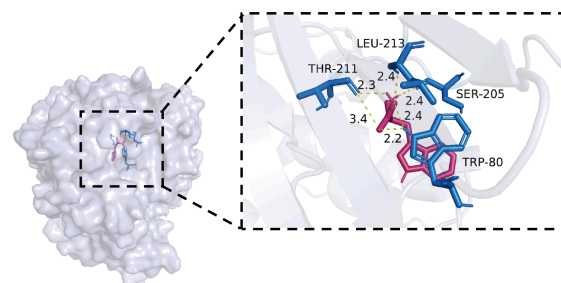
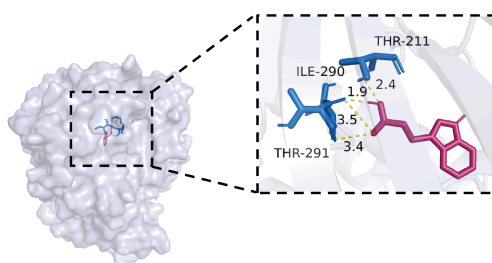
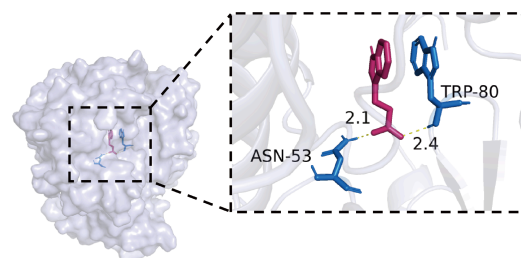


Figure 2

The microbiota–substrate–metabolite–target–pathway network. Note: Purple represents gut microbiota, blue represents substrates, yellow represents microbial metabolites, green represents ligands that function as both substrates and metabolites, red represents targets, and orange represents pathways.

A**B****C****D****E****Figure 3**

Molecular docking visualization of target-metabolite pairs. (A) Quercimeritrin-IL6. (B) Quercetin-AKT1. (C) Indole-3-lactic acid-AKT1. (D) 3-Indolepropionic acid-AKT1. (E) 3-(1H-indol-3-yl)propanoate-AKT1.

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