Tropical Journal of Pharmaceutical Research December 2022; 21 (12): 2591-2599
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i12.13

Original Research Article

Anti-cancer molecular mechanism of *Actinidia chinensis* Planch in gastric cancer based on network pharmacology and molecular docking

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Sent for review: 17 August 2022 *Revised accepted: 26 November 2022*

Abstract

Purpose: *To determine the anti-tumor effects of Actinidia chinensis Planch (ACP) root extract as well as its mechanism of action against gastric cancer (GC) using network pharmacology.*
Methods: *The bioactive compounds and targets of ACP, as well as GC-related genes were identified from a series of public databases. Functional enrichment analysis was conducted to find relevant biological processes and pathways. The survival analysis was conducted using GEPIA tool. Autodock was used to carry out molecular docking between the ingredients and their targets.*
Results: *A total of 20 bioactive compounds with 209 corresponding targets were identified for ACP, and a total of 871 GC-related genes were obtained. Forty-nine (49) targets of ACP were identified as candidate genes for the prevention of GC, and the PPI network with 584 interactions among these genes was constructed. The data demonstrated that the candidate targets were involved in multiple biological processes such as oxidative stress response, apoptosis, and proliferation. Moreover, these candidate targets were significantly associated with cancer-related pathways and signal transduction pathways. The compound-target-pathway network containing 16 bioactive compounds, 49 targets and 10 pathways was constructed and visualized, and the top 3 targets with a higher degree value were AKT1, MYC, and JUN, respectively. Survival analysis revealed significant associations between GC prognosis and several targets (PREP, PTGS1, AR, and PTGS2). Molecular docking further revealed good binding affinities between bioactive compounds and the prognosis-related targets, indicating the potential roles of these ingredient-target interactions in GC protection.*
Conclusion: *Taken together, this study has provided novel clues for the determination of the anti-gastric cancer mechanism of ACP.*

Keywords: *Actinidia chinensis Planch, Gastric cancer, Network pharmacology, Enrichment analysis, Molecular docking*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Gastric cancer (GC) is one of the most widespread malignant tumors worldwide, with the mortality rate ranked fourth among all malignant cancers, thereby posing a serious threat to life and health. It is a highly aggressive tumor and is usually diagnosed at an advanced stage due to

the asymptomatic status at the early-stage. Despite progress in preliminary screening, surgical resection, and chemotherapy of GC, the average 5-year survival rate of patients with GC remain below 40 % owing to tumor recurrence and metastasis [1]. Although chemotherapy being helpful to improve the prognosis of GC patients, chemotherapy resistance and adverse effects limit its application. Patients with GC can face serious financial challenges due to the high cost of treatment. Hence, it is necessary to develop novel anti-GC drugs with effective anticancer activities, lower toxicity profiles, and less adverse effects.

Recently, the traditional Chinese herbal medicine has gained great attention because of its low toxicity, broad-spectrum, and high efficiency in the treatment of cancers. *Actinidia chinensis* Planch (ACP) is a traditional Chinese herbal medicine with multiple pharmacological actions such as anti-tumor, anti-oxidative, anti-inflammatory, and antibacterial activities[2]. Growing evidence has demonstrated that ACP inhibited proliferation and migration in several types of cancer, such as GC, colon carcinoma, hepatic cancer, and lung cancer. Moreover, ACP is one of the main components of “Weikang Keli”, a traditional Chinese medicine formula that can effectively prolong the survival of mice transplanted with gastric cancer[3]. A recent study has demonstrated that ACP could prevent GC cell proliferation and migration via apoptosis, ferroptosis activation, and mesenchymal phenotype suppression[4]. Although clinical and experimental studies revealed the therapeutic effects of ACP on GC, the underlying molecular mechanism of its actions on GC remains poorly understood.

Network pharmacology is an effective way to discover the pharmacological mechanism of TCM against diseases [5,6], and has also been applied in anti-cancer research. In this study, the underlying mechanism of ACP against GC was investigated using network pharmacology and molecular docking. The bioactive compounds of ACP were identified from database and literature retrieval, and their targets were also collected and predicted. Gastric cancer related genes were identified from public databases. The candidate targets of ACP against GC were obtained through intersect of the GC targets and ACP targets, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were also performed. The expressions and prognostic significance of candidate targets were analyzed, and molecular docking was carried out to assess the binding affinities between bioactive compounds and target proteins.

EXPERIMENTAL

Identification of bioactive compounds and targets of ACP

The chemical compounds of ACP were downloaded from the TCMSP (https://lsp.nwu.edu.cn/tcmsp.php). The active compounds were identified using oral bioavailability (OB) ≥ 30 % and drug-likeness (DL) ≥ 0.18, and the corresponding targets were also obtained from the TCMSP database. Other bioactive compounds were obtained through relevant literature retrieval, and 14 active anti-cancer compounds were finally included. The targets of ursolic acid were obtained from the PubChem, while the targets of other compounds were identified by merging the predicted results of Swiss Target Prediction (http://www.swisstargetprediction.ch/) and TargetNet (http://targetnet.scbdd.com/). Targets that do not belong to human proteins are eliminated. **Figure 1** illustrated the protocol of the research.

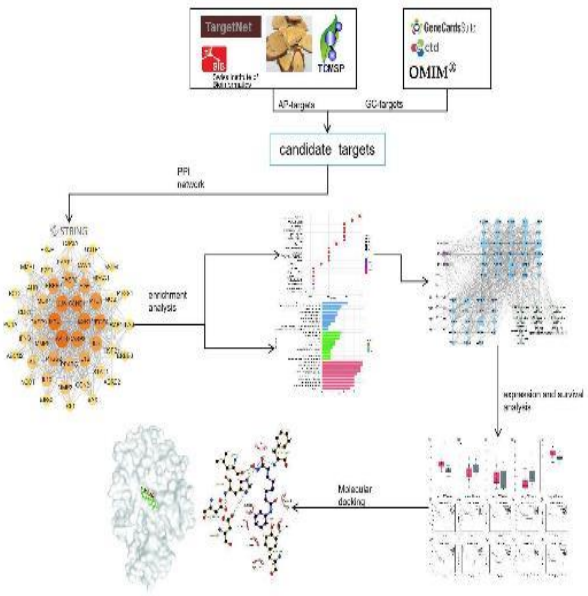

Figure 1: Flowchart of experimental designs

Identification of GC-related targets

The targets of GC were retrieved from the OMIM Database (http://omim.org/), CTD (http://ctdbase.org/), and GeneCards Database (https://www.genecards.org/). The seaching keyword was set as “breast cancer”.

Identification of candidate targets and construction of a protein-protein interaction (PPI) network

The overlapping genes were identified as candidate targets of ACP against GC and were submitted to the STRING database (https://string-db.org/) so as to obtain information on PPI. The PPI network was visualized using Cytoscape 3.7.2.

Functional enrichment analyses

The "clusterprofiler" package were employed for GO and KEGG pathway enrichment analyses. The functional categories were finally identified and ranked based on P value, and P value ≤ 0.05 denotes significant GO terms and KEGG pathways.

Construction of target-component-pathway network and survival analysis

The top 10 enriched pathways associated with signal transduction were selected for target-component-pathway network construction. The PPI network was also merged into the target-component-pathway network.

Survival analysis was performed using the Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/) platform.

Molecular docking

Molecular docking analysis was performed to assess the binding affinities between the bioactive compounds and the predicted targets. The 3D structure files of the human proteins were downloaded from the RCSB PDB database (https://www.rcsb.org/), and the structures files of the bioactive compounds were downloaded from the TCMSP database.

SmilesDrawer was applied to construct the 3D structures for those compounds with no 3D structures[7]. The protein structures were prepared by removing water molecules, adding nonpolar hydrogen, and computing charge. Grid box containing the active pocket sites were set for each receptor protein. Autodock Vina was used for the docking of the receptor protein with bioactive compounds, and the binding affinities were calculated accordingly.

The best conformations with the lowest binding energy were exported, and LigPlus and PyMOL were used to generate the 2D and 3D diagrams of the ligand-protein complexes, respectively.

RESULTS

Identified targets of ACP against GC

Six bioactive compounds of ACP including beta-sitosterol, sitosterol, aloe-emodin, (+)-catechin, ent-epicatechin, and quercetin, were identified from the database. In addition, 14 anti-cancer compounds (x1 - x14) were determined through literature review of relevant published studies[8-13] (**Table 1)**. After removal of 6 constituents without targets, 209 targets of 14 bioactive compounds were finally included for further analysis. We retrieved 310, 535 and 162 GC-related genes from CTD, GeneCards and OMIM databases, respectively. After removing duplications, 871 GC-related genes were retained. As shown in Figure 2 A, the 49 overlapped genes were regarded as candidate targets of ACP against GC. There were 584 interactions among the candidate targets, out of which AKT1 was the most interactive protein (Figure 2 B), indicating its pivotal role in the action of ACP on GC.

To further determine the biological functions and pathways of these potential genes, functional enrichment analyses were performed *(Supplementary material: Table S1 and Table S2).* The results demonstrated that the 1489 GO terms comprising 1380 biological processes, 24 cellular components, and 85 molecular functions, were significantly associated with the candidate targets. The top 10 terms in each categories are illustrated in Figure 2 C, and they were shown to be primarily related to stress response, apoptosis, and proliferation. Pathway enrichment analysis demonstrated that the candidate targets were significantly associated with 128 KEGG pathways. The top 20 pathways with a lower p-value were shown in Figure 2D, which mainly included pathways associated with cancer, signal transduction, or drug resistance.

Constructed compound-target-pathway network

A compound-target-pathway network was constructed based on the significantly enriched signal transduction pathways, gene-regulating pathways, as well as the relevant compounds. After that, the network was merged with the PPI network to integrate the interactions of compound-target, target-target, target-pathway (Figure 3). Topological characteristics of the network were analyzed, and the size and color of the nodes were reset according to the degrees.

Table 1: Bioactive compounds of *Actinidia chinensis* Planch

S/no.	ID	Name	Source
1	MOL000073	Ent-Epicatechin	TCMSP (OB≥30, DL≥0.18)
2	MOL000098	Quercetin	TCMSP (OB≥30, DL≥0.18)
3	MOL000358	Beta-sitosterol	TCMSP (OB≥30, DL≥0.18)
4	MOL000359	Sitosterol	TCMSP (OB≥30, DL≥0.18)
5	MOL000471	Aloe-emodin	TCMSP (OB≥30, DL≥0.18)
6	MOL000492	(+)-catechin	TCMSP (OB≥30, DL≥0.18)
7	X1	Ursolic acid; 3β-Hydroxyurs-12-en-28-oic acid	[16, 17]
8	X10	2α,3β,19α, 23-Tetrahydroxyurs-12-en-28-oic acid	[18]
9	X11	Pseudotaraxasterol	[18]
10	X12	Corosolic acid	[18, 19]
11	X13	2β,3α,23-Trihydroxyurs-12-en-28-oic acid	[17]
12	X14	2β,3β,23-Trihydroxyurs-12-en-28-oic acid	[17]
13	X2	2α,3α,24-Trihydroxyolean-12-en-28-oic acid	[16]
14	X3	2α,3α,23-Trihydroxyurs-12-en-28-oic acid	[16, 18]
15	X4	(2α,3α)-2,3,23,24-Tetrahydroxyurs-12-en-28-oic acid; 2α,3α,23,24-Tetrahydroxy ursan-12-en-28-acid	[16, 20]
16	X5	Ursonic acid; 3-oxo-urs-12-en-28-oic acid	[16]
17	X6	Oleanolic acid; 3β-Hydroxyolean-12-en-28-oic acid	[17]
18	X7	Maslinic acid	[16, 21]
19	X8	Asiatic acid; 2α,3β,23-Trihydroxyurs-12-en-28-oic acid	[17]
20	X9	Oleanan-28-oic acid, 12-chloro-2,3,13,23-tetrahydroxy-, γ-lactone, (2α,3β,4α,12α)-	[20]

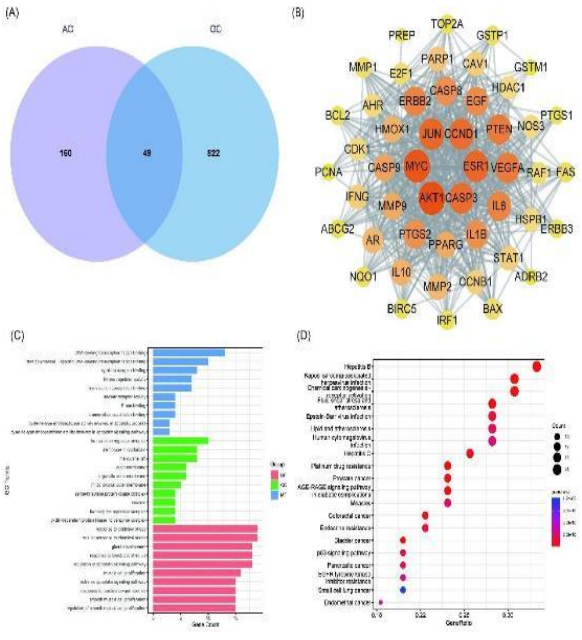

Figure 2: Analysis of anti-GC candidate targets in ACP. (A) Venn plot of ACP targets and GC-related genes. (B) The PPI network of the candidate targets of ACP against GC. The larger the circle and the darker the color, the more interactive the proteins of the target. (C) The top 10 terms with a higher gene count of the biological processes, cellular components, and molecular functions. (D) The top 20 pathways with a lower P value obtained from the enrichment analysis of candidate targets

The results revealed that the top three targets with higher degrees were AKT1, MYC, and JUN, indicating the crucial roles of these targets in the effects of ACP against GC. Quercetin (MOL000098) was a compound with the highest degree, whose anticancer activity has been confirmed.

Constructed compound-target-pathway network

A compound-target-pathway network was constructed based on the significantly enriched signal transduction pathways, gene-regulating pathways, as well as the relevant compounds. After that, the network was merged with the PPI network to integrate the interactions of compound-target, target-target, target-pathway (Figure 3). Topological characteristics of the network were analyzed, and the size and color of the nodes were reset according to the degrees. The results revealed that the top three targets with higher degrees were AKT1, MYC, and JUN, indicating the crucial roles of these targets in the effects of ACP against GC. Quercetin (MOL000098) was a compound with the highest degree, whose anticancer activity has been confirmed.

Expression and prognosis of candidate targets

In the compound-target-pathway network, 5 targets (HDAC1, PTGS1, PTGS2, AR, and PREP) linked to x1-x5 were selected for

subsequent analyses. To confirm their ability as bioactive compound targets against GC, their gene expressions in GC and their effects on GC prognosis were first analyzed, as shown in Figure 4A. The overexpression of PREP was found in GC tissues when compared with that of the normal tissues ($p < 0.05$), while no significant differences were found for other genes. Furthermore, in terms of the overall or disease-free survival, or taking both into account, genes excluding HDAC1 were significantly associated with GC prognosis (Figure 4 B - F). These findings suggest that PTGS1, PTGS2, AR, and PREP may contribute to the effects of ACP against GC.

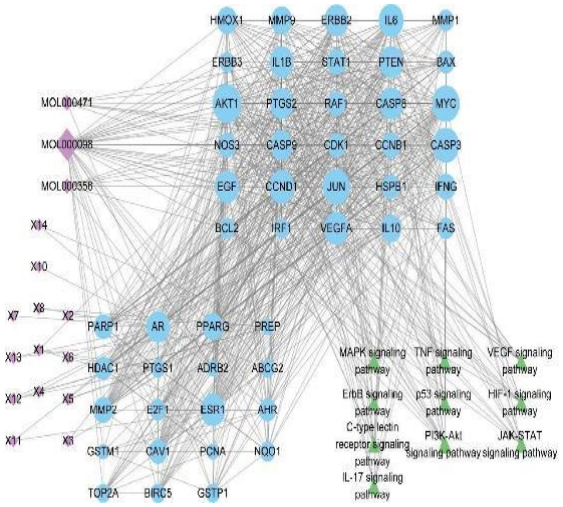

Figure 3: The compound-target-pathway network of ACP against GC

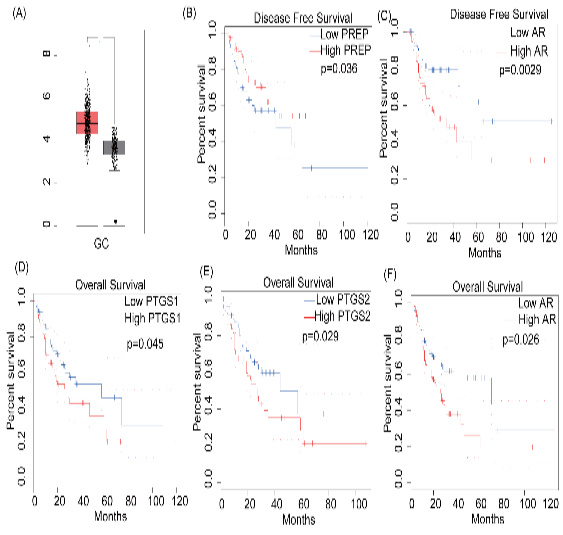

Figure 4: Expressions and survival analysis of genes in GC. (A) The expressions of PREP in GC, respectively. (F-J) The disease-free survival of GC patients stratified PREP and AR, respectively. (K-O) The overall survival of GC patients stratified PTGS1, PTGS2, and AR, respectively

Molecular docking analysis

Targets of x1-x5 were predicted via computer programs, and the prognostic significance of these targets for GC was demonstrated through the above analysis. Therefore, the binding affinities between x1-x5 compounds and their targets were assessed through molecular docking (Table 2). x4 and x5 exhibited lower binding energies when compared to leelamine, an inhibitor of AR. However, in the 3D complex, the positions of x4 and x5 were not adjacent to the binding sites of standard inhibitors (Figure 5). Compounds except x4 showed better binding affinities than PREP inhibitor (SUAM-1221), where x3 and x4 presented closer positions in the 3D structure (Figure 6). The binding postures of the corresponding bioactive compounds of PTGS1 and PTGS2 were very similar to those of the standard inhibitors (Figure 7 and Figure 8). In addition, hydrogen bonds and hydrophobic contacts were found in all ligand-receptor complexes. These data indicated that x1-x5 interacted with corresponding proteins to form compact complexes.

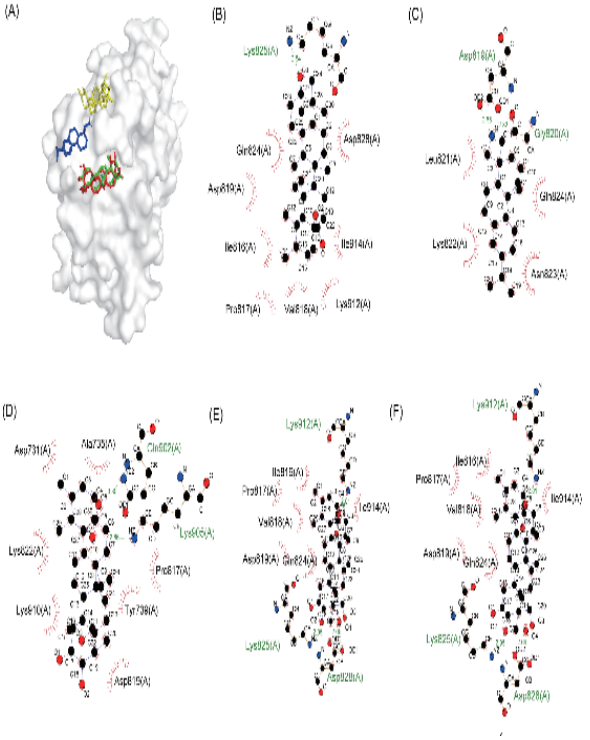

Figure 5: The 3D and 2D diagrams of binding conformation of AR with bioactive compounds. (A) The 3D diagram of binding conformation of AR with compound x5 (green), leelamine (blue), x2 (yellow) and x4 (red). (B-F) The 2D diagram of binding conformation of AR with x5, leelamine, x2 and x4, respectively

Table 2: Binding energies between the compounds and targets

Compound	Target	Binding energy (kcal/mol)
x2: 2α, 3α,23-trihydroxyurs-12-en-28-oic acid	AR	-5.74
x4: 2α,3β,23,24- tetrahydroxyurs-12-en-28-oic	AR	-6.25
x5: 3-oxo-urs-12-en-28-oic acid	AR	-6.8
Leelamine	AR	-6
x2: 2α, 3α,23-trihydroxyurs-12-en-28-oic acid	PREP	-5.46
x3: 2α, 3α,24-trihydroxyurs-12-en-28-oic acid	PREP	-5.52
x4: 2α,3β,23,24- tetrahydroxyurs-12-en-28-oic	PREP	-4.8
x5:3-oxo-urs-12-en-28-oic acid	PREP	-6.65
SUAM-1221	PREP	-5.26
x1: ursolic acid	PTGS1	-8.86
x5: 3-oxo-urs-12-en-28-oic acid	PTGS1	-8.39
Sulindac sulfoxide	PTGS1	-8.74
x1: ursolic acid	PTGS2	-10.06
Mefenamic acid	PTGS2	-6.32

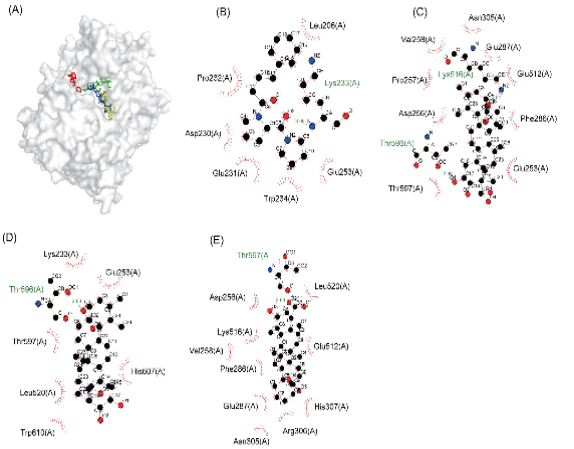

Figure 6: The 3D and 2D diagrams of binding conformation of PREP with bioactive compounds. (A) The 3D diagram of binding conformation of PREP with compound SUAM-1221 (red), x4 (blue), x2 (green) and x3 (yellow). (B-E) The 2D diagram of binding conformation of PREP with SUAM-1221, x4, x2 and x3, respectively

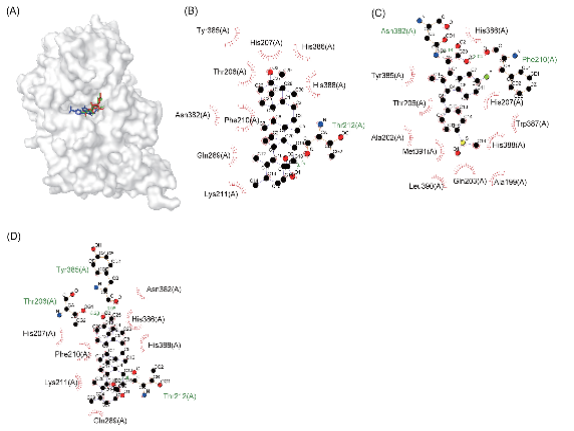

Figure 7: The 3D and 2D diagrams of binding conformation of PTGS1 with bioactive compounds. (A) The 3D diagram of binding conformation of PTGS1 with compound x5 (red), sulindac sulfoxide (blue), and x1 (green). (B-D) The 2D diagram of binding conformation of PTGS1 with x5, sulindac sulfoxide, and x1, respectively

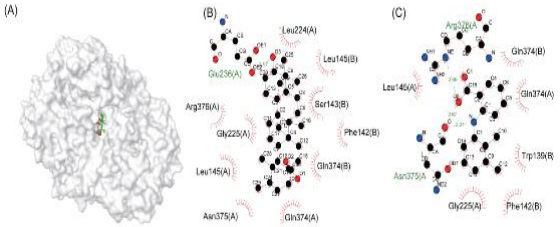

Figure 8: The 3D and 2D diagrams of binding conformation of PTGS2 with bioactive compounds. (A) The 3D diagram of binding conformation of PTGS2 with compound x1 (green), and mefenamic acid (red). (B and C) The 2D diagram of binding conformation of PTGS2 with compound x1, and mefenamic acid, respectively

DISCUSSION

Accumulating evidence supports the anti-cancer activity of the ACP. It was reported that ACP inhibited the progression of GC by regulating the cancer cell apoptosis and ferroptosis, as well as by suppressing mesenchymal phenotype[4,14]. However, little is known about the underlying molecular mechanisms of the action of ACP on GC. In this study, a combination of network pharmacology and molecular docking was used to investigate the mechanism of anti-GC effects of ACP. A total of 49 genes were identified as candidate targets mediating the anti-GC activity of ACP. Through PPI network analysis, it was revealed that AKT1 occupied the most important position in the whole network, suggesting that it had a significant anti-GC effect. A variety of crucial pathways and biological processes were mediated by AKT1, and it was associated with the tumorigenesis and progression of GC. The oncogenic AKT1 gene is frequently mutated, thus contributing to a variety of abnormalities in GC cells. Importantly, AKT1 has been considered a vital protein as a drug target for the treatment of GC, and plays an important role in the chemoresistance of GC cells.

Previous studies have made great efforts to discover the anticancer components and targets of ACP. In addition to GC, ACP was also effective against hypopharyngeal carcinoma, hepatocarcinoma, breast carcinoma, and lung cancer. Mechanistically, the anti-tumor effect of ACP was mediated by various pathways and targets including the AKT/GSK-3βsignal pathway, the DLX2/TARBP2/JNK/AKT pathway, E2F1-mediated MNX1-AS1, PCSK9, EP3, and p-p38. In this study, the candidate targets of the action of ACP against GC were revealed to be significantly associated with multiple pathways related to signal transduction, including TNF signaling pathway, p53 signaling pathway, IL17 signaling pathway and C-type lectin receptor signaling pathway. Meanwhile, the PPI network of the candidate targets also highlighted the pivotal role of AKT1 and other targets such as CASP3 and ESR1 in the action of ACP against GC.

Six compounds of ACP, including sitosterol, beta-sitosterol, (+)-catechin, ent-epicatechin, aloe-emodin, and quercetin met the screening criteria for active compounds. Meanwhile, network analysis suggested that three compounds (quercetin, beta-sitosterol, and aloe-emodin) may play pivotal role in the action of ACP against GC. Beta-sitosterol is a traditional plant-derived compound with anti-cancer effects in various cancers. It can regulate cell cycle, apoptosis, proliferation, and metastasis by targeting various proteins such as MAPK, CDK4, and PCNA [15]. Aloe-emodin is an anthraquinone derivative with various pharmacological properties such as anti-cancer, anti-virus, and anti-inflammatory activities. A recent study showed that aloe-emodin induced the release of apoptosis-inducing factor and cytochrome c from mitochondria, and activated caspase-3 [16]. In this study, CASP3 was observed to be targeted by aloe-emodin and presented with a high degree value in the compound-target-pathway network, suggested that the interaction between aloe-emodin and CASP3 is pivotal for the anti-GC effects of ACP. Quercetin exerts its anti-cancer effects by regulating cell viability, apoptosis, and autophagy through the modulation of the PI3K/Akt/mTOR, SIRT1/AMPK signaling pathway, and MAPK/ERK1/2 pathways[17]. Recently it was reported that catechin resensitized SNU620/5FU GC cells to 5-fluorouracil by targeting lactate dehydrogenase A[18].

In addition, a series of triterpenoids of ACP was identified as potential anti-cancer active compounds, and the corresponding targets were further predicted. Survival analysis demonstrated that most of these targets had significant influences on the prognosis of patients with GC. In addition, have provided data revealing the relationship between these genes and gastric cancer. For example, the prolyl endopeptidase (PREP) is a serine peptidase involved in the differentiation, development, and proliferation of several tissues. Higher activity of PREP in cancers has been proven to be associated with a better prognosis. Bioinformatic analysis revealed the overexpression of PREP in GC and a poorer disease-free survival of GC patients with a lower PREP expression. In the present study, several bioactive compounds showed lower binding energy to PREP that SUAM-1221, indicated that ACP. Androgen receptor (AR) was an independent risk factor for GC progression and metastasis, and the mRNA level of AR in GC was associated with its overall survival as well as disease-free survival. Ursolic acid has been shown to present anti-tumor activity by targeting PTGS2, PTGS1, and HDAC1. This study found that as compared to reference ligands, bioactive compounds of ACP generally had better binding affinities with these proteins. These findings suggested that these compounds of ACP might play an intracellular role by binding to these targets. This study not only provides a comprehensive understanding of ACP's molecular mechanism of action on GC, but also provides a reliable reference and direction for future experimental and clinical research.

Limitations of study

There are several limitations in this study. Firstly, due to methodological flaws, the incomplete nature of the target prevented easy grasp of the comprehensive anti-GC mechanism of ACP, but this will be continuously improved in future studies with the advancement of technology. Secondly, there was no experimental validation *in vivo* or *in vitro*, especially for those prognosis-related targets in GC.

CONCLUSION

Twenty active compounds and 209 corresponding targets have been identified in ACP, and 49 genes as candidate targets of the action of ACP against GC. These genes are primarily enriched in stress response, apoptosis, proliferation, signal transduction, and cancer-related pathways. The compound-target-pathway network was constructed to illustrate the hub mechanism of ACP against GC, and survival analysis and molecular docking further confirmed the significant roles of triterpenoids in the action of ACP on GC via the targeting of several prognosis-related proteins. This study has laid

the foundation for investigating the anti-GC effects of ACP in the future.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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