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ORIGINAL ARTICLE

Clinical and Translational Research

Network pharmacology combined with molecular docking revealed the potential targets of Coridius chinensis in prostate cancer treatment

Mei Zhang, Jing Ma, Feng-Yin Zeng, Xiao-Hui Hou

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Abstract

BACKGROUND

Prostate cancer (PCa) has high morbidity and mortality rates in elderly men. With a history of thousands of years, traditional Chinese medicine derived from insects could be an important source for developing cancer-targeted drugs to prevent tumorigenesis, enhance therapeutic effects, and reduce the risk of recurrence and metastasis. Multiple studies have shown that Coridius chinensis (Cc) has anticancer effects.

AIM

To elucidate the mechanism of action of Cc against PCa *via* network pharmacology and molecular docking.

METHODS

Potential targets for Cc and PCa were predicted using ChemDraw 19.0 software, the PharmMapper database and the GeneCards database. Then, the STRING database was used to construct the protein–protein interaction network. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment and molecular docking analyses were subsequently conducted to identify the key targets, active ingredients and pathways involved.

RESULTS

GO and KEGG analyses indicated that the PI3K-Akt signalling pathway was the critical pathway (P value < 1.0×10^{-8}). Multiple targeting ingredients that can affect multiple pathways in PCa have been identified in Cc. Seven active compounds (asponguanosines A, asponguanine B, asponguanine C, aspongpyrazine A, N-acetyldopamine, aspongadenine B and aspongpyrazine B) were selected for molecular docking with 9 potential targets, and the results revealed that aspongpyrazine A and asponguanosine A are the main components by which

Cc affects PCa (affinity<-5 kcal/mol, hydrogen bonding), but more studies are needed.

CONCLUSION
We used network pharmacology to predict the bioactive components and important targets of Cc for the treatment of PCa, supporting the development of Cc as a natural anticancer agent.

Key Words: Coridius chinensis; Molecular docking; Network pharmacology; Prostate cancer; Traditional Chinese medicine

Core Tip: In our study, network pharmacology was used to predict the mechanism of action of Coridius chinensis (Cc) in the treatment of prostate cancer to identify bioactive molecules, important targets, and major pathways involved. Molecular docking analysis of active molecules and important targets revealed highly active molecules, providing some ideas for the later development of Cc as an anticancer drug.

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INTRODUCTION

Prostate cancer (PCa) is a common cancer in males, especially elderly males. Second only to lung cancer, prostate cancer has a 15% incidence rate and is expected to cause more than 800000 deaths per year in 2024[1,2]. Albertsen *et al*[3] recently reported a mortality rate of 3.3% in the first 15 years of follow-up after conservative treatment of PCa patients with few comorbidities. Currently, some of the leading drugs and methods for treating PCa include docetaxel, cabazitaxel, abiraterone acetate, radium-223 therapy, sipuleucel-T, and surgery[4]. Due to the remarkable androgen-dependent nature of PCa, androgen blockade therapy is an effective treatment for advanced PCa and is a major cause of death in patients who eventually develop hormone-resistant PCa[5]. Therefore, the development of an effective treatment for PCa is crucial. Clinical trials have shown that traditional Chinese medicine has several unique advantages in the treatment of PCa, and many compounds isolated from traditional Chinese medicines also exhibit distinct anti-PCa activity[6]. The advantages of traditional Chinese medicine include low toxicity, few side effects, prevention of tumour occurrence, enhancement of therapeutic effects, and reduction in the recurrence rate[7]. Many components of Chinese medicine, such as andrographolide, evodiamine, guttiferone F, honokiol and isorhapontigenin, have obvious anticancer activity[6]. Studies have shown that the use of traditional Chinese medicine can significantly improve the survival rate of PCa patients[8-10]. Coridius chinensis (Cc) is a type of Chinese medicine that is effective against liver cancer, stomach cancer, and breast cancer[11-13]. Cc blocks the liver cancer cell cycle and promotes apoptosis, and tumour growth is inhibited in animals[11]. Chen *et al*[12] demonstrated that the active peptide from Cc inhibited cell proliferation in stomach cancer cells, but the underlying mechanism has not been demonstrated. In addition, the most active component has been shown to have an anticancer effect, but the underlying mechanisms are not yet clear[14]. In this study, network pharmacology and molecular docking technology were used to explore the potential of Cc to treat PCa. The molecular docking results verified that the core active compounds were associated with Cc and key targets associated with PCa, providing a scientifically sound basis for further elucidation of the mechanisms of action of these drug components and disease-related targets. Figure 1 shows the flow chart of the anti-PCa analysis of the components of Cc *via* network pharmacology and molecular docking technology.

MATERIALS AND METHODS

Component collection

The principal ingredients of Cc were obtained from CNKI, the Web of Science and PubMed. These components were probed in the PubChem database. Some core bioactive components have been identified[15,16]. This study, as a bioinformatics study, is exempt from Institutional Review Board approval.

Target prediction

ChemDraw 19.0 software was used to draw the structure of the active ingredients and predict the targets with the PharmMapper database, with the following filter criteria: Accuracy ≥ 0.7 and probability > 0.9[17]. The targets associated with PCa were collected from the GeneCards and OMIM databases using “Prostate cancer” and “prostatic carcinoma” as keywords, and duplicates were removed. After the prediction targets from different databases were merged, the repeat

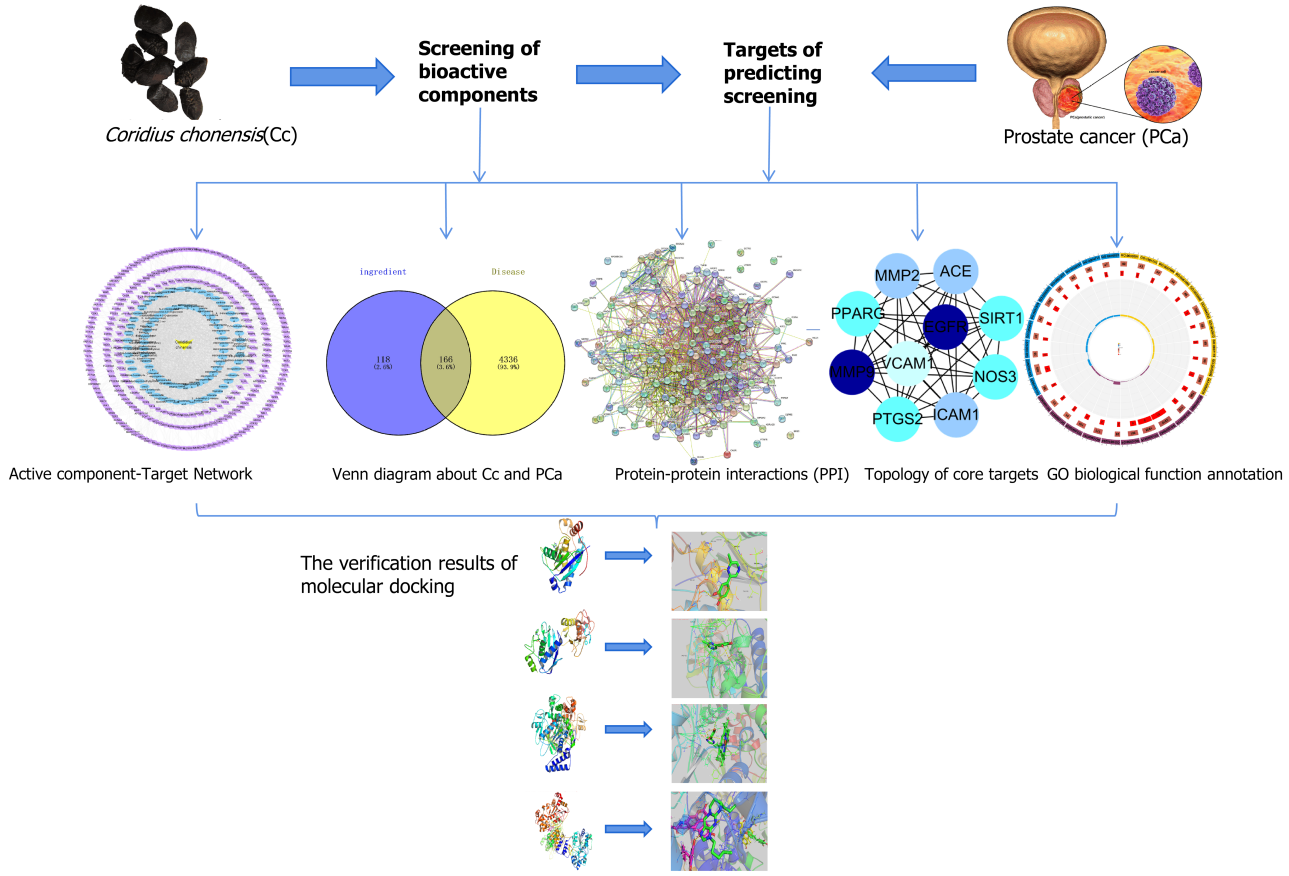

Figure 1 A schematic diagram of the study on Coridius chinensis as an anti-prostate cancer treatment. Network pharmacology was used to filter the compounds of Coridius chinensis for the treatment of prostate cancer; after 63 molecular docking studies, four bioactive compounds were found to bind tightly with candidate molecules.

entries were removed. Venn diagrams were generated *via* Venn website to reveal the common genes among Cc targets and PCa-related genes.

Network construction

A "component–target" network was constructed with Cytoscape 3.7.5 software. These targets and information on protein interactions were collected. Then, the protein–protein interaction (PPI) network and "top 10 targets" network were constructed with Cytoscape software[18].

Gene Ontology enrichment analysis

Gene Ontology (GO) enrichment analysis was performed using the DAVID database. GO enrichment was used to determine the biological function of Cc in PCa[19]. GO enrichment was conducted for biological process (BP), cell component (CC), and molecular function (MF)[20,21]. The top 90 entries were selected for visualization.

KEGG enrichment analysis

The DAVID database was used to analyse the functional and pathway enrichment of potential genetic targets for Cc and PCa. The DAVID database was utilized to identify significantly enriched pathways. Then, a Sankey diagram of the pathway enrichment analysis results was generated to visualize the enriched pathways obtained by using the DAVID database[19,22].

Molecular docking

Network pharmacology analysis revealed and predicted the bioactive compounds of Cc and the core targets and pathways involved in the anti-PCa effects of Cc. To validate the outcomes of the predicted targets, molecular docking of 7 key bioactive compounds and 9 key targets was conducted. The active compounds of Cc were selected as the ligands, and their three-dimensional structures were searched and downloaded from the Protein Data Bank database[23,24]. The molecular docking results were visualized using PyMoL 2.5.4. and establish the molecular docking interaction pattern diagram. The 3D structures of the active compounds were imported into PyMoL software by removing water molecules and small acceptors and imported into Autodock 1.5.6 tools by adding hydrogen atoms, calculating the total charge, and setting the atomic type, which were then saved in the PDBQT format. The Vina score (affinity in kcal/mol) indicates the binding capacity of the receptor to the ligand[25]. The higher the affinity, the lower the binding energy below -5 kcal/

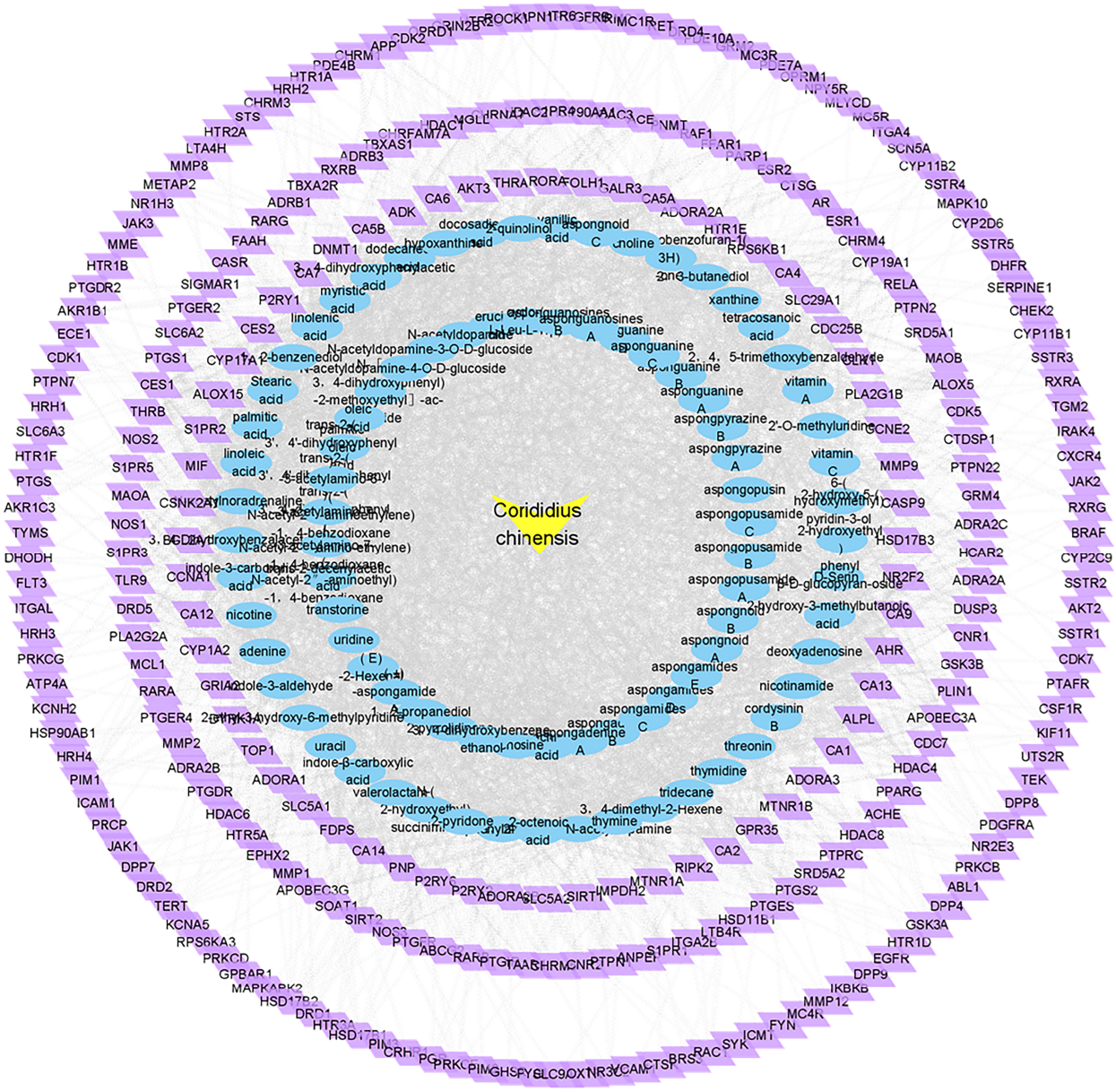

Figure 2 The component–target network of Coridius chinensis. The network consists of 89 components and 284 corresponding targets. The yellow triangle represents Coridius chinensis (Cc), the blue circles represent the components of Cc, and the purple quadrangles represent potential targets.

mol, and the more stable the interaction between the target protein and the bioactive compound[26].

RESULTS

Component–target network construction

The Cc active component–target network with 89 components and 284 corresponding targets of Cc was obtained *via* Cytoscape software; this indicates a multicomponent and multitarget pathway as shown in Figure 2.

There were 357 nodes and 6392 edges. The connection between the blue circle and the green quadrangle represents the interaction between the components of Cc and its corresponding targets. The more lines a node has, the more important the component or target it represents in the component–target network.

Analysis of the PPI network

A Venn diagram of the targets of Cc and PCa was generated with the Venn platform, as shown in Figure 3A. The results showed that the intersection of 243 potential targets in Cc and 581 genes related to PCa yielded 41 common target genes.

The results of 166 targets identified in this analysis were imported into Cytoscape to construct the PPI network. In the PPI network (Figure 3B), a total of 166 nodes and 1248 edges were discovered that represent protein interactions. A thicker edge indicates a closer relationship among targets. A PPI network with 476 edges was obtained through analysis

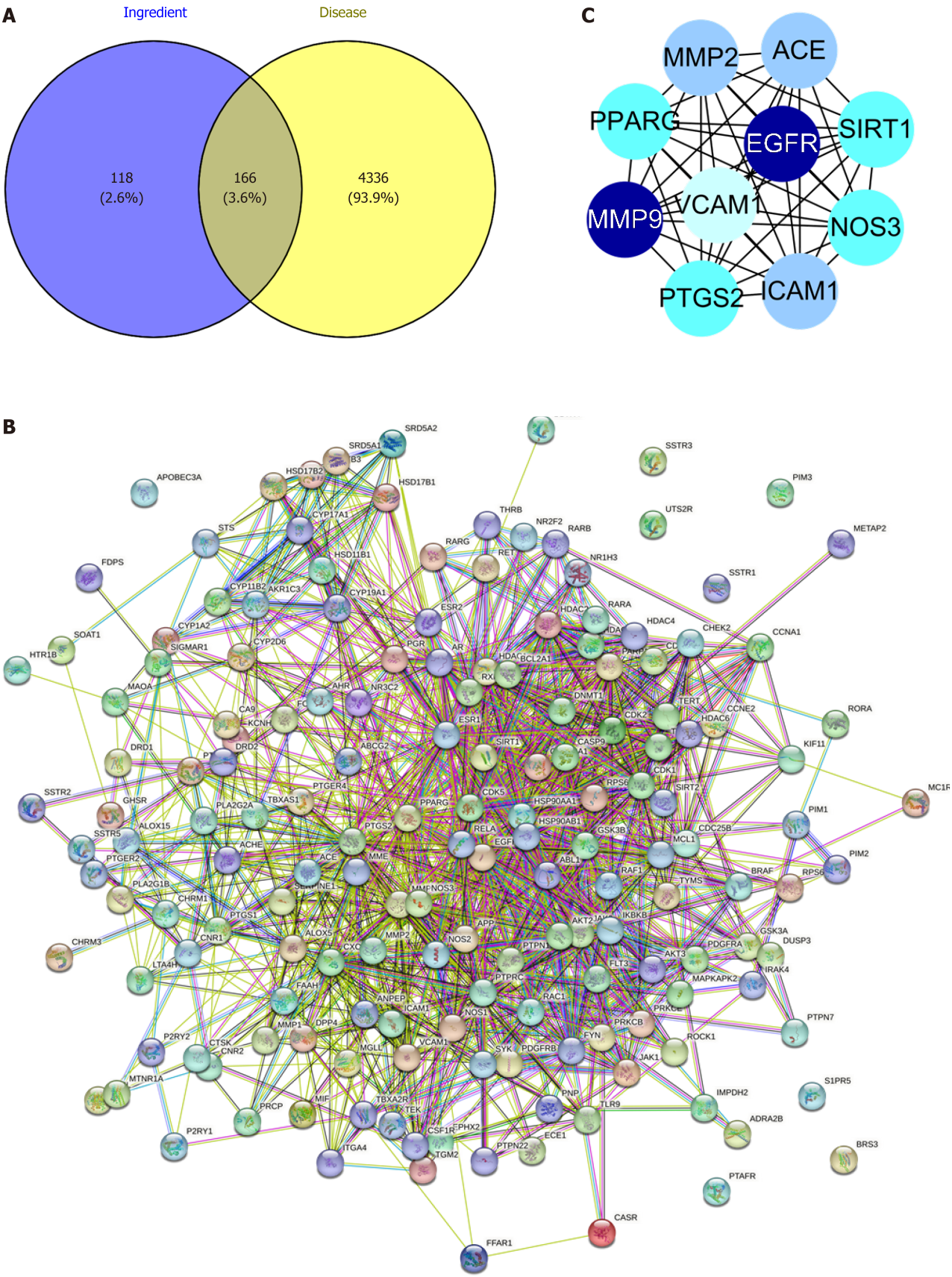

Figure 3 Potential targets and network analyses. A: Venn diagram of the targets of Coridius chinensis and the targets of prostate cancer; B: Structural diagram of the protein-protein interaction network; C: Diagram of the topology of the core targets. The darker the colour of a node is, the more important the gene it represents.

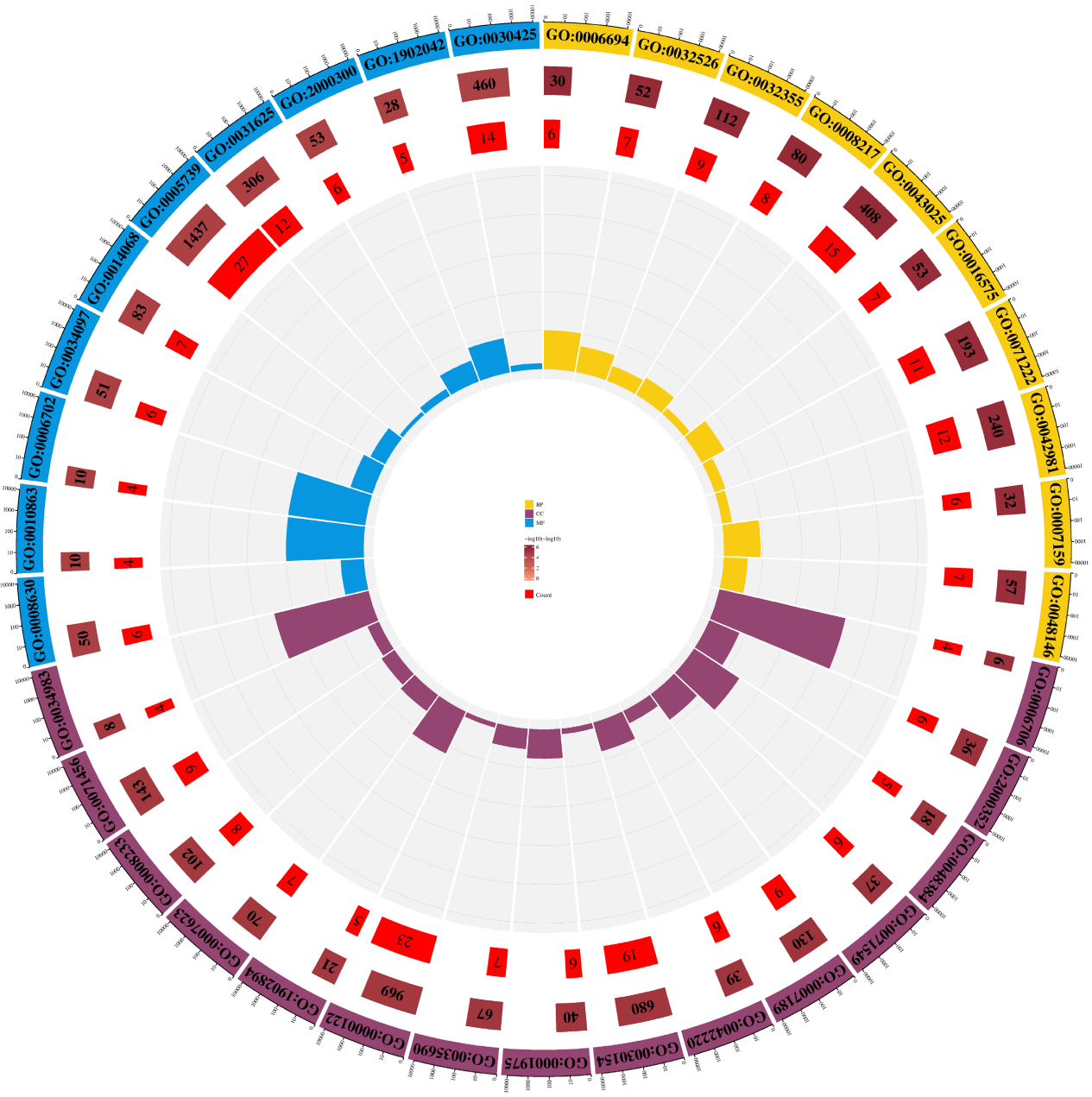

Figure 4 Gene Ontology pathway enrichment analyses of Coridius chinensis in anti-prostate cancer yellow, purple, and blue represent biological process, cell component, and molecular function, respectively.

with a *P* value < 10^{-16}. PPI network analysis revealed 10 genes with scores higher than the mean, which were selected as key targets. The top 10 nodes were *EGFR*, *MMP9*, *PTGS2*, *SIRT1*, *NOS3*, *ICAM1*, *VCAM1*, *PPARG*, *MMP2* and *ACE*, and these nodes had 49 edges (Figure 3C). The proteins corresponding to these pivotal nodes interacted with a greater number of target proteins than did the proteins in the other nodes of the PPI network. Therefore, the 10 key nodes play an important role in the PPI network.

GO enrichment analyses

GO enrichment was performed on the 166 common targets to more deeply analyse the anti-PCa effect of Cc. According to the GO enrichment analysis, a total of 373 GO terms, containing 134 BP terms, 26 CC terms and 77 MF terms, were enriched. Then, to determine the statistical significance of the results, the first 10 BPs, CCs, and MFs were selected for visual analysis, as shown in Figure 4. Many BP terms, including positive regulation of guanylate cyclase activity, regulation of protein localization, cellular response to interleukin-3, protein phosphorylation, the retinoic acid receptor signalling pathway, and the response to starvation, were highly enriched. These BPs were connected with the following MFs: Somatostatin receptor activity, protein kinase activity, transcription factor binding, ATPase binding and transmembrane receptor protein tyrosine kinase activity. Furthermore, the main enriched CCs were the defence response to gram-negative bacteria, transcription factor complexes and the centrosome.

Table 1 The binding energy of Coridius chinensis core active compounds and core common targets

Compounds\affinity (kcal/mol)	ACE (6WF3-COA)	EGFR (7JXQ-ANP)	ICAM1 (1P53-NAG)	MMP2 (4WK7-3PQ)	MMP9 (2OVZ-5MR)	NOS3 (1M9K-7NI)	PPARG (3ET0-ET0)	PTGS2 (5IKR-ID8)	SIRT1 (5BTR-STL)
Asponguanosines A	-8	-8.4	-5.8	-8.7	-7.8	-6.6	-5.6	-5.4	-8
Aspongadenine B	6.6	-6.2	-4.7	-6.4	-5.6	-7.1	-6.2	-7	-6.6
Asponguanine B	-6.5	-6.2	-5.1	-6.9	-6.7	-7.7	-6.3	-5.8	-6.8
Aspongpyrazine A	-7.5	-7	-5.7	-8.1	-8.4	-8	-7.2	-7.4	-7.5
Aspongpyrazine B	-5.2	-5	-3.8	-6.1	-6.1	-5.9	-5	-4.9	-5
Asponguanine C	-6.6	-6.4	-5.1	-7.1	-7.1	-7.5	-6.8	-7.2	-6.6
N-acetyldopamine	-6.6	-6.4	-5.1	-7.4	-7.5	-7.9	-6.4	-5.7	-7.1

KEGG enrichment analysis

The top 27 pathways with the lowest *P* values were obtained, and a visual Sankey diagram was produced (Figure 5). The mechanism of action of Cc in PCa involves each of the enriched pathways from 27 pathways obtained *via* the DAVID database. Through analysis, the five targets that were most enriched among the signalling pathways were selected because they play important roles in multiple pathways. The top five pathways in terms of the number of target genes were screened from 27 pathway species. The five pathways in cancer, namely, the PI3K-Akt signalling pathway, the neuroactive ligand-receptor interaction pathway, the chemical carcinogenesis-receptor activation pathway and the MAPK signalling pathway, play major regulatory roles in the effects of Cc on PCa. In addition, the PI3K-Akt signalling pathway had the lowest *P* value (*P* value < 1.0×10^{-8}), suggesting that this pathway may have a strong effect.

Molecular docking

The top 9 targets were analysed and verified for molecular docking with the active compounds of Cc, which included ACE EGFR, MMP9, PTGS2, NOS3, ICAM1, PPARG, MMP2 and SIRT1, according to the topology of the core targets. The top 4 targets, including MMP2, MMP9, NOS3 and SIRT1, had the greatest binding affinity for the 2 main active components of CC (asponguanosines A and aspongpyrazine A) (Table 1). The binding sites of the two active compounds to the top 10 targets are shown in Figure 6. The docking feedback indicated that the affinities of aspongpyrazine A, asponguanosines A, asponguanine B, asponguanine C and N-acetyldopamine for the 9 top targets were lower than -5 kcal/mol, which indicated that the binding forces between these active compounds and all the core targets were strong. The number of hydrogen bonds between aspongpyrazine A and MMP2, aspongpyrazine A and MMP9, and aspongpyrazine A and NOS3 as well as between asponguanosines A and SIRT1 was high, which indicated that these components and targets could stably interact. The results showed that aspongpyrazine A and asponguanosines A play an especially important role in PCa treatment. The molecular docking model diagrams of aspongpyrazine A and MMP2, aspongpyrazine A and MMP9, aspongpyrazine A and NOS3 and between asponguanosines A and SIRT1 were selected for visualization, as shown in Figure 6.

DISCUSSION

Cc has been widely applied in the treatment of cancer in the clinic. As several studies have shown, Cc induces antitumorigenic effects and could be used as a novel therapeutic option for metastatic breast cancer and gastric cancer[13,14]. However, whether Cc can be used to treat PCa and the underlying mechanisms are still unclear.

Based on earlier studies, the bioactive ingredients in Cc, including asponguanosines A, asponguanine B, asponguanine C, aspongpyrazine A, N-acetyldopamine, aspongadenine B, and aspongpyrazine B, have not been fully characterized or assessed in animal experiments. Among them, asponguanine B has better biological activity, but only in terms of stimulating the proliferation of neural stem cells[16,17].

By analysis of the PPI network, our study revealed that the core targets were EGFR, MMP9, PTGS2, SIRT1, NOS3, ICAM1, PPARG, MMP2 and ACE. EGFR is expressed in 100% of hormone-refractory PCa metastases, which indicates that this receptor is the main transduction pathway for tumour growth[27]. The progression of PCa can be inhibited by regulating the expression of cathepsin B and MMP9 in three PCa cell lines[28]. SIRT1 is highly expressed in PCa in multiple human PCa cell lines and in a prostate-specific PTEN knockout mouse model[29]. The Glu298Asp polymorphism in the NOS3 gene has been implicated as a risk factor for PCa[30]. The main pathways identified by KEGG analysis were pathways in cancer, the PI3K-Akt signalling pathway, neuroactive ligand-receptor interaction, chemical carcinogenesis-receptor activation and the MAPK signalling pathway. There were 17 enriched pathways involving EGFR, such as the PI3K-Akt signalling pathway and EGFR tyrosine kinase inhibitor resistance. There were 8 pathways related to MMP9, such as pathways in cancer and PCa, and 10 pathways related to MMP9, such as the VEGF signalling pathway and arachidonic acid metabolism.

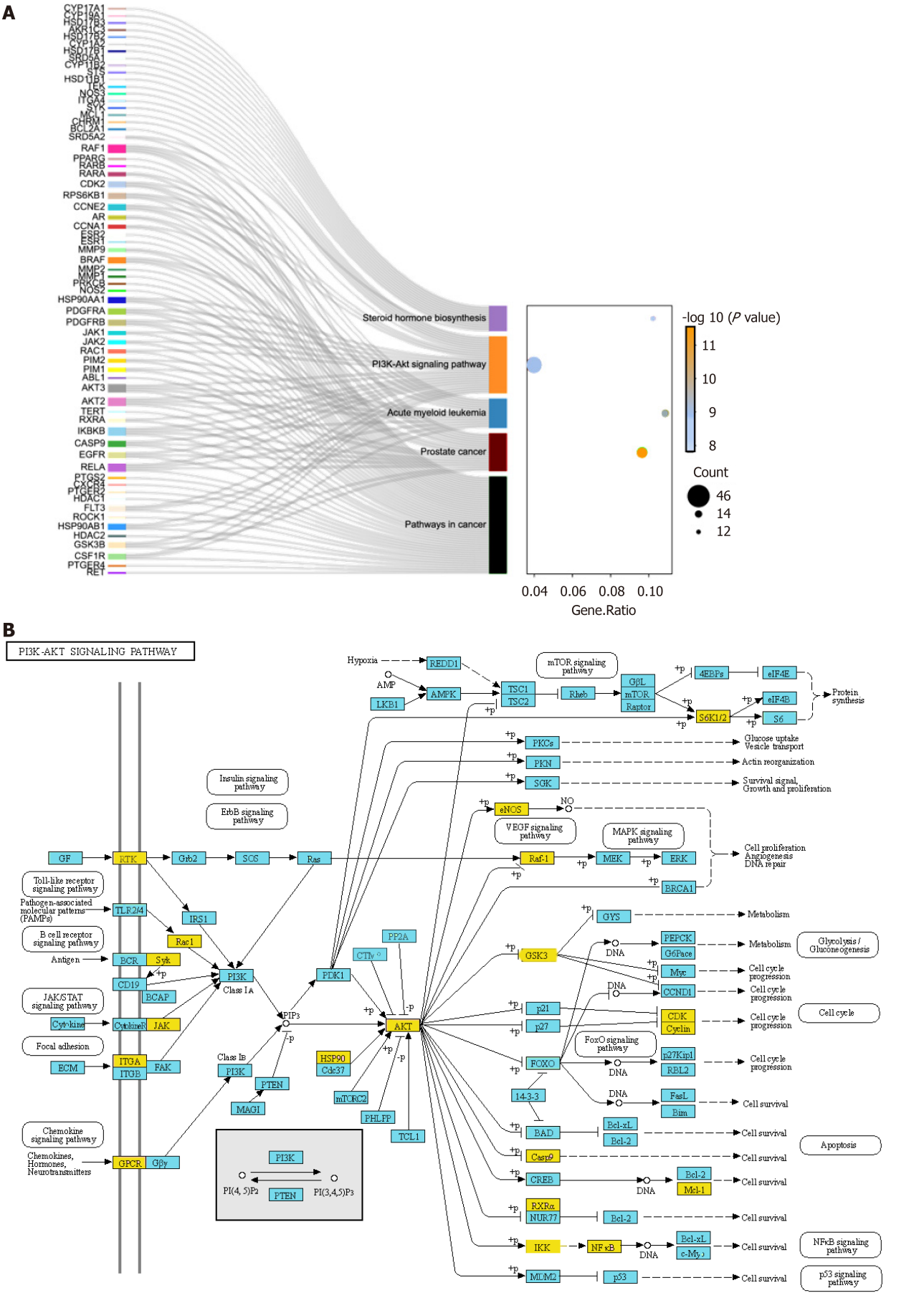

Figure 5 Sankey diagram of the top 5 pathways (selected according to the *P* value) and the main involved pathways. A: The different coloured rectangles on the left of the figure represent potential target genes; B: Reprinted images of the PI3K-Akt signalling pathway. Gene ratio: Count/set size.

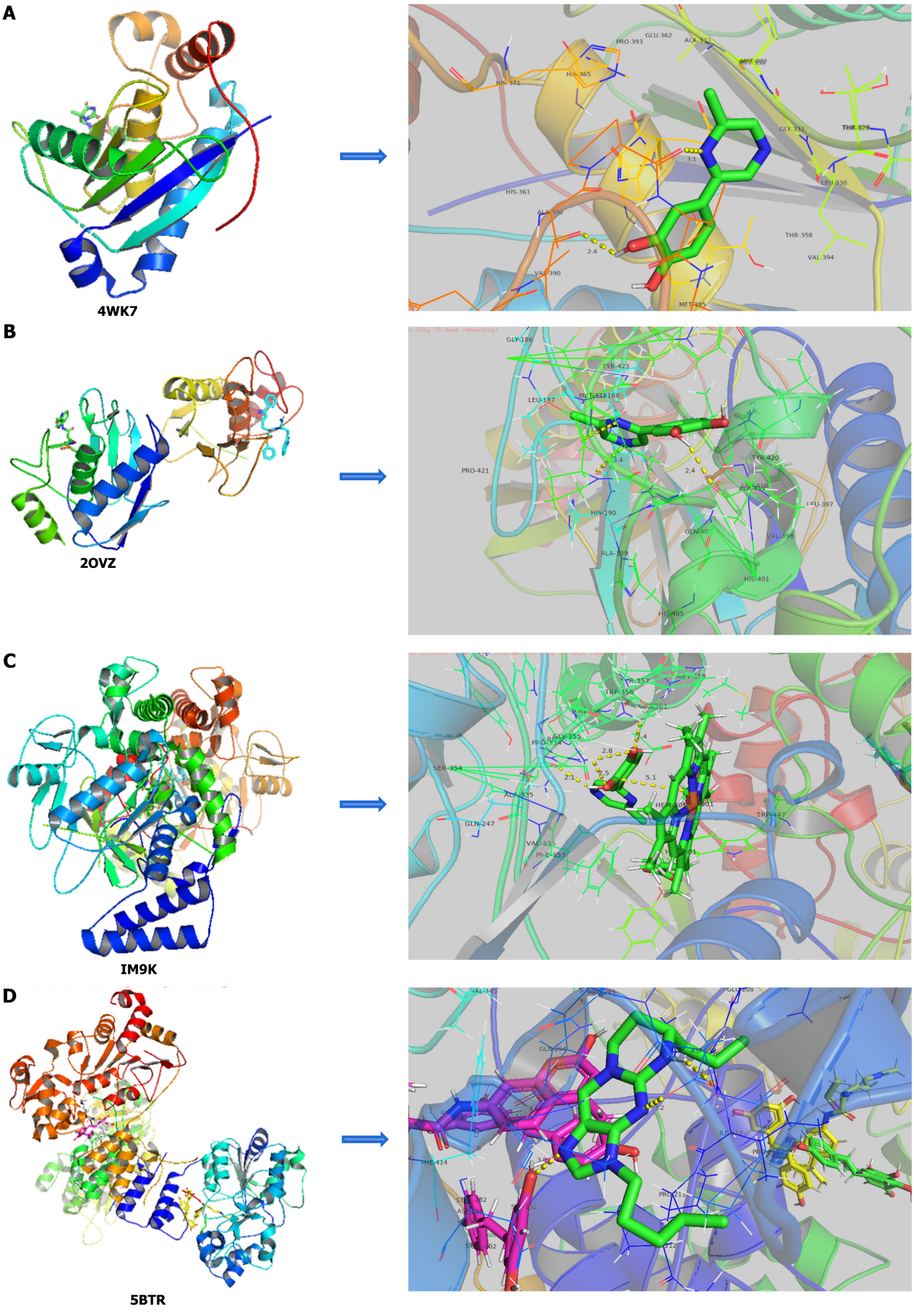

Figure 6 Molecular docking diagrams of prostate cancer-related targets with important compounds of Coridius chinensis. The optimal

binding conformations for A: aspongpyrazine A-MMP2; B: aspongpyrazine A-MMP9; C: aspongpyrazine A-NOS3; D: asponguanosines A-SIRT1.

Molecular docking analysis showed that the 7 key bioactive components had a certain binding activity with 9 representative targets based on the above study results (Table 1). A total of 71% of the interactions among these components and targets had a binding energy lower than -6 kcal/mol, which indicated that the potential efficacy of Cc against PCa is great. The docking results showed that the two compounds asponguanosines A and aspongpyrazine A could bind the targets well, and the docking results also showed that asponguanosines A bound to MMP2 with the highest binding energy (-8.7 kcal/mol), indicating that this interaction was the most stable. In addition, aspongpyrazine A bonding to MMP9, aspongpyrazine A bonding to NOS3 and asponguanosines A bonding to SIRT1 also showed great potential effects against PCa, with binding energies lower than -8 kcal/mol and two or more hydrogen bonds.

The present study still has several limitations. We employed only a bioinformatics approach to investigate the effects of Cc on PCa. Although we identified multiple important bioactive components of CC for the treatment of PCa in the present study, these compounds are not fully representative of Cc. Therefore, there is a need to consider molecular biological approaches to further validate our findings. Furthermore, because the effects and mechanisms of other potentially active compounds on PCa have not yet been explained and validated, further research is needed.

CONCLUSION

The results of this study indicated that Cc has multiple active ingredients that exert anti-PCa effects. Aspongpyrazine A and asponguanosines A of Cc had high binding affinities for representative targets, indicating that they may be the most promising PCa-targeting drugs in terms of their drug binding capacity; however, more studies are needed. The proteins EGFR, MMP9, ICAM1, PPARG, MMP2 and ACE are potential therapeutic targets of Cc for the treatment of PCa. The experimental data of this study provide a theoretical basis for the development of anti-PCa drugs. However, the anti-PCa effects of the two components of Cc still need to be verified in additional *in vitro* and *in vivo* experiments. Our study may provide some direction for the treatment of PCa.

FOOTNOTES

Author contributions: Zhang M designed the research; Zhang M and Ma J conducted the research; Zeng FY provided analysis software; Zhang M wrote the manuscript; and Hou XH reviewed and revised the manuscript; All the authors have read and approved the final manuscript.

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