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Novel anticancer mechanisms of JinYingZi-derived oleanolic acid against renal cell carcinoma: an *in silico* analysis

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Abstract

Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for 90% of all estimated cases. Advanced RCC often carries poor prognosis due to its high metastases rate, the lack of early-warning signs, as well as its complex clinical manifestations and its resistance to chemotherapy. Ethnopharmacologically, *Fructus Rosae laevigata* (JinYingZi) has been employed by Chinese medicine to treat various urinary tract and gastrointestinal disorders. This study aimed at performing a series of mechanistic analyses in order to unlock the anticancer potential of JinYingZi-derived bioactive components against RCC. Several network pharmacology tools were employed so as to analyse the drug-disease interactions. Our data revealed that more than 2,214 genes were dysregulated in RCC, whereas the JinYingZi-derived bioactive compounds modulated 347 genes. The intersecting between RCC and the bioactive compounds revealed 132 cross targets. Our results were further validated by conducting molecular docking, which revealed a stable association between oleanolic acid with each of the following targets: androgen receptor (*AR*), dipeptidyl peptidase (*DPP*), estradiol (*ESR1*), nitric oxide synthase 2 (*NOS2*), and cyclooxygenase-2 (*PTGS2*). Our approach is being used successfully in order to evaluate a panel of novel medicinal plant-derived bioactive compounds, and may lead to the identification of safe and effective chemical scaffolds that could act as templates for drug discovery or yield potential drug candidates.

KEYWORDS
renal cell carcinoma, JinYingZi, oleanolic acid, network pharmacology, molecular docking

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1. INTRODUCTION

Kidney cancers are highly prevalent malignant tumours worldwide, with an estimated 431,288 cases in 2020. In the United States, it is the sixth most common cancer among men and the ninth most prevalent malignant tumour among women, with an estimated 81,800 cases in 2023. Renal cell

carcinoma (RCC) is the most common type of kidney cancers, accounting for 90% of all estimated cases [1]. Advanced RCC often carries poor prognosis due to its high metastases rate, the lack of early-warning signs, as well as its complex clinical manifestations and its resistance to chemotherapy [2]. *Rosa laevigata* Michx. is one of the recognised ethnic medicinal plants that have been used in Chinese traditional medicine in order to treat different debilitating illnesses. Two main herbal remedies are derived from *R. laevigata*, namely *Fructus R. laevigata* and *Radix R. laevigata*. Ethnopharmacologically, *Fructus R. laevigata* (JinYingZi) has been employed by Chinese medicine to treat various urinary tract and gastrointestinal disorders [3]. This study aimed at performing a series of mechanistic analyses in order to unlock the anticancer potential of *Fructus R. laevigata*-derived bioactive components against RCC.

2. METHODS

This study was carried out in order to evaluate the anticancer activity of JinYingZi against RCC, by speculating the potential disease targets of the plant's bioactive components. Several network pharmacology tools were utilised throughout this study, including the Encyclopaedia of Traditional Chinese Medicine (ETCM), the Bioinformatics Analysis Tool for Molecular Mechanisms in Chinese Medicine (BATMAN-TCM), the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), DisGeNET, GenCards, SymMap, STRING, the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis, the DAVID platform, Cytoscape 3.6.0, and molecular docking.

3. RESULTS

Our analyses revealed that more than 2,214 genes were dysregulated in RCC, while the JinYingZi-derived bioactive components were found to be able to modulate 347 targets. The intersection between RCC and the bioactive compounds revealed 132 cross targets. The data were further analysed for the protein-protein interaction (PPI) network and GO and KEGG pathways. Among 14 bioactive components, the novel oleanolic acid seems to be one of the promising candidates to combat RCC *via* targeting several signalling pathways, including the advanced glycation end products / receptor for advanced glycation end products (AGE/RAGE) signalling, cellular senescence, the response to hormones, and apoptosis (Figure 1). The results were further validated by conducting molecular docking, which indicated stable associations between oleanolic acid with each of the following targets: androgen receptor (*AR*; 8.1 Kcal/mol), dipeptidyl peptidase (*DPP*; -7.5 Kcal/mol), estradiol (*ESR1*; -8.8 Kcal/mol), nitric oxide synthase 2 (*NOS2*; -6.6 Kcal/mol), and cyclooxygenase-2 (*PTGS2*; -8.8 Kcal/mol).

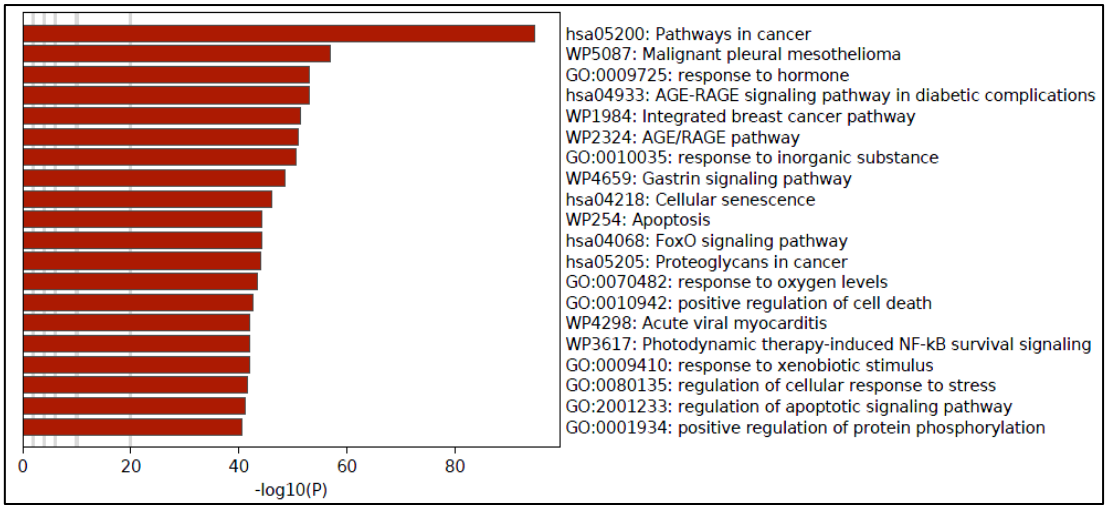

Figure 1. The heatmap of major Gene Ontology (GO) terms and disease prediction by Metascape shows common renal cell carcinoma - oleanolic acid target pathways.

4. DISCUSSION

Our analyses showed that the highest possible targets of oleanolic acid are hormones (*AR* and *ESR1*), inflammation (*NOS2* and *PTGS2*), and cancer metabolism (*DPP*). *AR* has been shown to play an integral role in developing tumour-initiating vasculogenesis and metastasis in RCC, *via* promoting and modulating the *Twist1*-associated long noncoding RNA regulated by *AR* (lncRNA-TANAR/TWIST1) signalling pathway [4]. Interestingly, the high cytoplasmic immunohistochemical expression of estrogen receptors is associated with poor prognosis as well as short overall survival and disease-free survival of RCC patients [5]. Likewise, high NOS expression is linked to bad prognosis and large tumour size in RCC patients [6]. The suppression of COX-2 is associated with the inhibition of RCC tumour progression and angiogenesis while improving patients' prognosis and survival rates [7]. Moreover, DPP (particularly DPP-4) has been identified as a cancer stemness related-protein and, therefore, targeting such a protein can enhance the sensitivity and overcome the RCC resistance to tyrosine kinase inhibitors; the main therapeutic line for treating advanced RCC [8].

Oleanolic acid has been shown to have substantial chemopreventive and antitumor activities against hepatic cancer cells, exerted *via* the inhibition of nuclear factor kappa-B (NF-κB) and the suppression of COX-2 [9]. Similarly, oleanolic acid is known to exert anti-tumour effects against breast and lung cancers by targeting the purine salvage pathway (PSP), thereby inducing metabolic perturbation *via* the activation of the superoxide dismutase 1 (SOD1) / reactive oxygen species (ROS) / AMP-activated protein kinase (AMPK) / mammalian target of rapamycin complex 1 (mTORC1) / macroautophagy / lysosomal pathway [10]. Taken together, oleanolic acid has shown a clear anticancer potential against different cancers by targeting the inflammation, the antioxidant system, the cellular senescence, and metabolic pathways. To our best knowledge, this is the first study to report the anticancer potential of oleanolic acid against RCC. The study also represents a theoretical basis for the undertaking of future experiments in order to test the cancer-supressing activities of oleanolic acid against RCC, and provides a strong foundation for further molecular analyses aiming to study its mechanism of action. Our approach is being used successfully in order to evaluate a panel of novel medicinal plant-derived bioactive compounds, and may lead to the identification of safe and effective chemical scaffolds that could act as templates for drug discovery or yield potential drug candidates.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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