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Study on the Use of CADD Virtual Screening to Identify Natural Products Targeting UCP2 for the Treatment of Gastric Cancer

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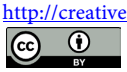


Abstract

Objective: This study aims to investigate the potential of natural compounds targeting UCP2 as a foundation for molecular targeted therapy in gastric cancer. **Methods:** We conducted a database analysis to assess UCP2 expression in tumors, examined the correlation between UCP2 expression levels and survival rates in gastric cancer patients, and explored the association between UCP2 expression and the tumor immune microenvironment in gastric cancer. Virtual screening and molecular docking techniques were employed to identify optimal natural products targeting UCP2. **Results:** UCP2 is overexpressed in gastric cancer, and this overexpression is associated with poor prognosis. Additionally, UCP2 expression influences the tumor immune microenvironment. Virtual screening identified that Anhydronotoptol, Naringenin chalcone, Paliperidone, Retinoic acid, β-Anhydroicaritin, and β-Naphthoflavone exhibit strong interactions with UCP2. **Conclusion:** Anhydronotoptol, Naringenin chalcone, Paliperidone, Retinoic acid, β-Anhydroicaritin, and β-Naphthoflavone may offer therapeutic benefits in gastric cancer by targeting UCP2.

Keywords

Gastric Cancer, UCP2, Virtual Screening, Natural Products

1. Introduction

Gastric cancer (GC) is a malignant neoplasm and ranks as one of the most prevalent cancers globally, positioned fourth in both incidence and mortality rates. Over 95% of gastric cancer cases are adenocarcinomas [1]. In its early stages, when metastasis has not yet occurred, gastric cancer can be completely eradicated

through surgical intervention. Unfortunately, the majority of patients are diagnosed at an advanced stage or with metastasis [2]. The primary effective treatments for gastric adenocarcinoma include systemic chemotherapy, radiotherapy, surgical procedures, immunotherapy, and targeted therapy [3]. Molecular targeted therapy, in particular, functions by specifically targeting molecular markers of tumor cells (such as gene mutations and protein overexpression), thereby inhibiting tumor growth and metastasis with precision and low toxicity. Advances in research on precise targeted therapy offer the potential to decrease the mortality rate associated with gastric cancer. Consequently, the search for effective drugs with minimal side effects remains an urgent challenge in the treatment of gastric cancer.

Uncoupling protein 2 (UCP2), identified in 1997, is a member of the uncoupling protein subfamily and functions as an integral membrane protein within the mitochondrial inner membrane, expressed across various tissues [4]. UCP2 is implicated in numerous physiological and pathological processes, including the regulation of macromolecular biosynthesis, antioxidant defense, anti-apoptotic mechanisms, cell growth promotion, and chemotherapy resistance. These functions influence the development and progression of autoimmune diseases, cardiovascular disorders, and cancer [5]. UCP2's ability to respond to and regulate metabolic changes positions it as a potential target for treating metabolic diseases associated with this gene. Elevated UCP2 expression has been documented in several cancers, such as breast, liver, colorectal, pancreatic, non-small cell lung, and gallbladder cancers [6]-[11]. It is recognized as a significant target in tumor metabolic reprogramming, offering potential as a cancer-specific drug target [12]. Investigations into UCP2 in these tumors enhance our understanding of its role in disease progression and therapeutic targeting, suggesting UCP2 as a promising target for cancer prevention and treatment. However, the role of UCP2 in gastric cancer remains unexplored, with its prognostic impact and relationship with immune infiltration yet to be elucidated.

This study employs bioinformatics approaches to examine the expression of UCP2 in gastric cancer, focusing on its expression within tumors, its prognostic significance, and its association with immune infiltration. Our findings reveal that UCP2 is overexpressed in gastric cancer, with its expression levels positively correlating with poor prognosis. Additionally, UCP2 expression is linked to immune infiltration within the tumor microenvironment. Consequently, UCP2 emerges as a potential target for novel gastric cancer treatment strategies. We further identified the top six natural products targeting UCP2 through computer-aided drug design, providing a theoretical basis for developing effective and low-toxicity gastric cancer therapies.

2. Materials and Methods

2.1. Expression of UCP2 in Tumors

The expression levels of the UCP2 gene in various cancer tissues were obtained by

entering the gene name UCP2 in the "Gene_DE" section of the TIMER2.0 database (http://timer.cistrome.org/). For the expression level of UCP2 in gastric cancer, the GEPIA database's Expression DIY Box Plots option was used, where the gene UCP2 and the abbreviation for gastric cancer, STAD, were input, with other conditions set to default.

2.2. Relationship between UCP2 and Survival in Gastric Cancer

The Kaplan-Meier Plotter database, which contains survival prognosis data for 875 gastric cancer patients, was utilized. By selecting the Start KM Plotter gastric cancer module in the Kaplan-Meier Plotter database (https://www.kmplot.com/analysis/), the gene name UCP2 was entered in the Affy id/Gene symbol field. The Log-rank test method and median value were selected, with other conditions set to default. Subsequently, OS was selected to calculate overall survival, FP for first progression survival, and PPS for post-progression survival.

2.3. Relationship between UCP2 and Tumor-Associated Immune Microenvironment

Within the TIMER2.0 database (http://timer.cistrome.org/), navigate to the "Gene" module and enter the gene symbol UCP2. Under the Immune Infiltrates section, sequentially select NK cell, T cell CD8+, T cell CD4+, B cell, DC, and Macrophage. Proceed by selecting STAD from the Cancer options to examine the immune cell infiltration profile. In the TISIDB database, input UCP2 in the Gene Symbol field and choose the "Lymphocyte" module to explore the association between UCP2 expression and immune cell involvement in gastric cancer. In the TIMER2.0 database's "Gene-Corr" module, enter UCP2 as the Interested Gene and include immune checkpoint-related genes and common mismatch repair genes in the Gene Expression field. After submission, select STAD from the Cancer options to retrieve the relevant findings.

2.4. Virtual Screening for Natural Products Targeting UCP2

Initially, acquire a library of natural products (L6010), comprising 3840 natural product monomers, from TargetMol (https://www.targetmol.cn/). Subsequently, utilize the AlphaFold database (https://alphafold.ebi.ac.uk/) to download the PDB structure of UCP2. Employ the PyRx software to designate the compounds in the natural product library as receptors and the UCP2 protein as the ligand. Conduct extensive molecular docking using the vina module within the software. Finally, export and rank the docking results for comprehensive analysis.

2.5. Analysis of Molecular Docking and Binding Interactions

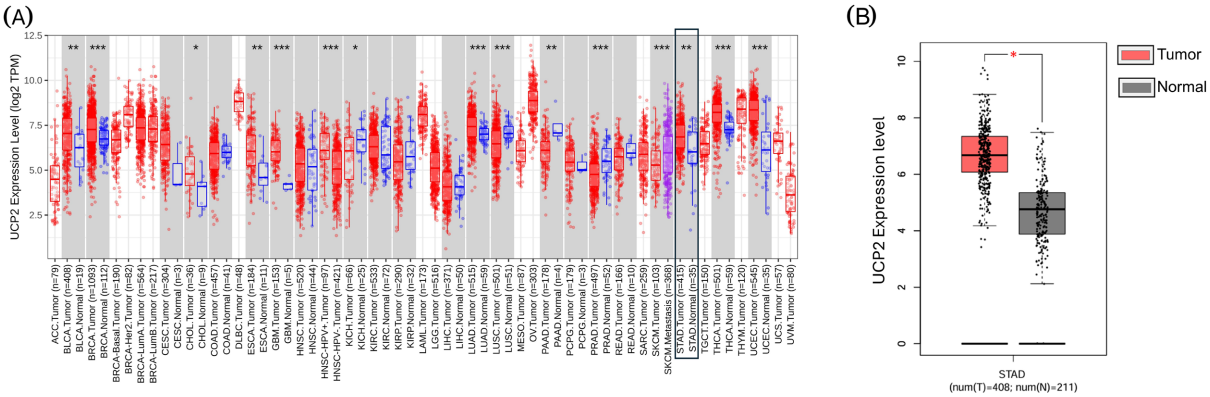
Mol2 files of natural products were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). These natural products were designated as receptors, while the protein UCP2 was set as the ligand. Molecular docking simu-

lations were conducted using the AutoDockTools-1.5.7 software, with the final docking outcomes saved in the pdbqt file format. The results were then visualized in three dimensions using the PyMOL software.

3. Results

3.1. Abnormally High Expression of UCP2 in Various Tumors

We assessed the differential expression of UCP2 between tumor tissues and adjacent normal tissues using the integrated data from the TCGA public database available in the TIMER database. Our analysis revealed that UCP2 is significantly overexpressed in a variety of human tumors compared to normal tissues. These tumors include bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), prostate adenocarcinoma (PRAD), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC) (**Figure 1(A)**). Additionally, we utilized the GEPIA database to analyze data from TCGA and GTEx, confirming that UCP2 expression is significantly elevated in gastric cancer tissues, consistent with the findings from the TIMER analysis (**Figure 1(B)**). These findings indicate that UCP2 could serve as a potential biomarker for differentiating gastric cancer tissues from normal tissues.



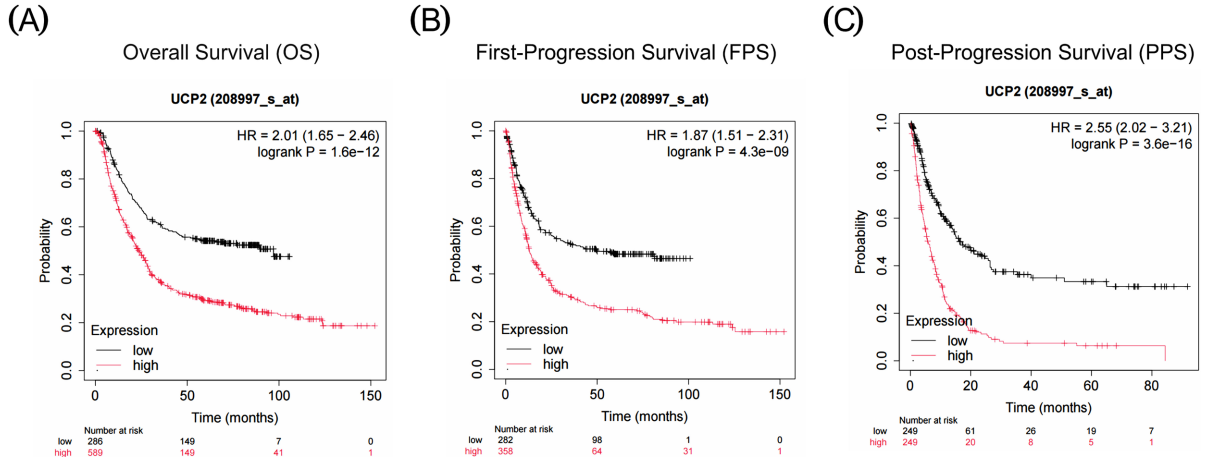
(A) Analysis of UCP2 expression across different tumor tissues using the TIMER tool on TCGA database data. (B) Examination of UCP2 expression in gastric cancer (STAD) using combined data from TCGA and GTEx via the GEPIA database. (*P < 0.05, **P < 0.01, ***P < 0.001).

Figure 1. Elevated expression of UCP2 in various tumors.

3.2. Association of UCP2 with Survival Outcomes in Gastric Cancer Patients

UCP2 exhibits low expression in normal gastric tissues but is upregulated in gastric cancer tissues. This raises the question of whether UCP2 expression levels influence the prognosis of gastric cancer patients. We subsequently evaluated the relationship between UCP2 expression and the survival outcomes of gastric cancer patients using the Kaplan-Meier Plotter database [13]. The findings revealed

that patients with high UCP2 expression had significantly lower overall survival, first progression survival, and post-progression survival compared to those with low UCP2 expression, indicating that high UCP2 expression is linked to poor prognosis in gastric cancer patients (**Figures 2(A)-(C)**). These results suggest that aberrantly high UCP2 expression serves as a biomarker for poor prognosis in gastric cancer.



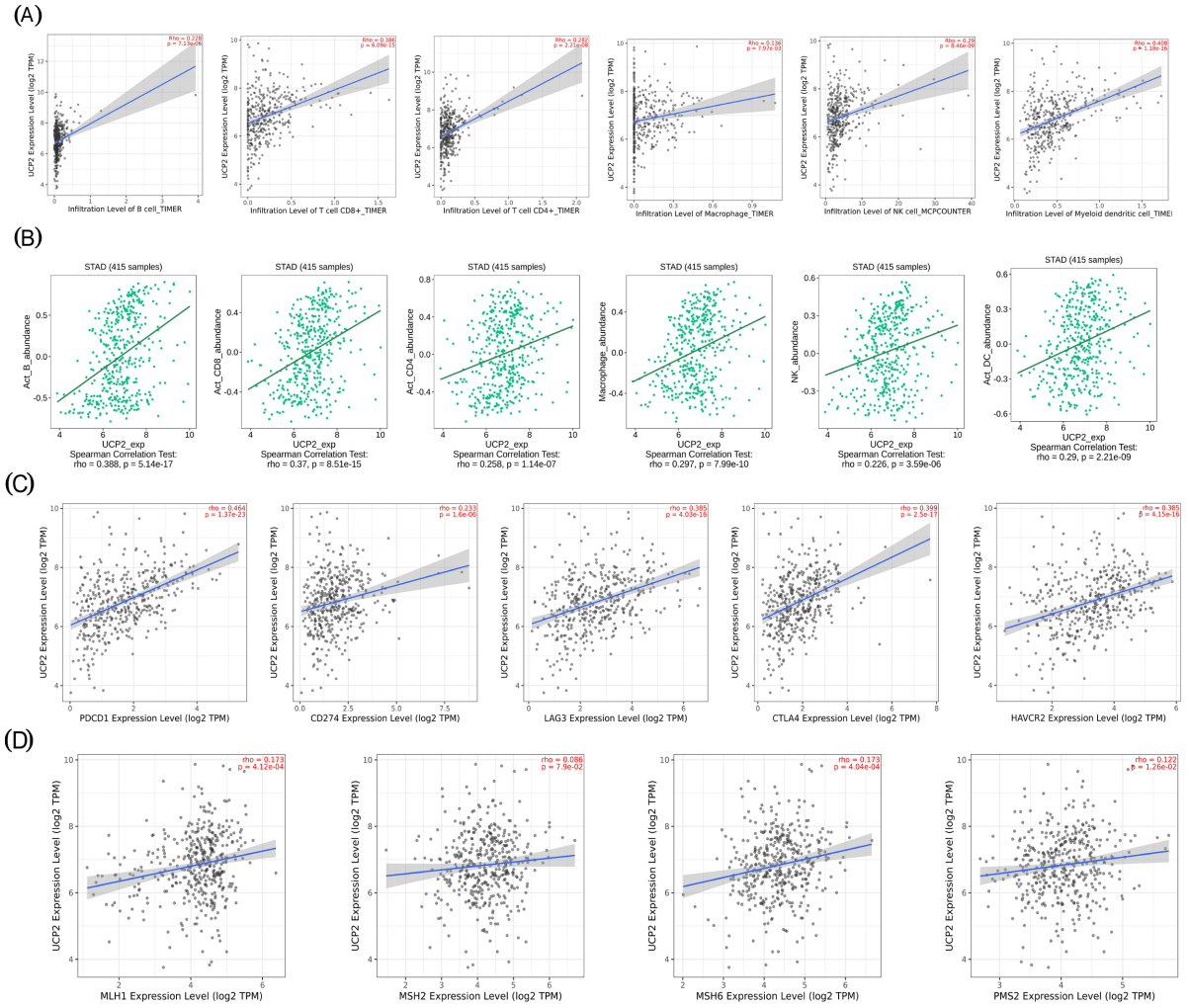
(A) TIMER analysis of UCP2 expression across various tumor tissues in the TCGA database. (B) Analysis of UCP2 expression in gastric cancer using data from TCGA and GTEx databases through the GEPIA platform.

Figure 2. Correlation between UCP2 and survival in gastric cancer patients.

3.3. Association of UCP2 with the Immune Microenvironment in Gastric Cancer Patients

In this section, we further investigated the association between UCP2 expression levels and the tumor immune microenvironment. Biomarkers for predicting the efficacy of immune checkpoint inhibitors (ICIs) are a focal point in current tumor immunotherapy research. Among these, tumor-infiltrating lymphocytes (TILs), immune checkpoint-related genes, and mismatch repair deficiency (dMMR) are either well-studied or hold significant research potential. The TIMER database employs a deconvolution method to discern the infiltration status of various immune cells from the gene expression data of tumor tissues [14]. Initial analyses using the TIMER database indicated that UCP2 expression in gastric cancer is positively associated with the infiltration of CD8+ T cells, CD4+ T cells, macrophages, NK cells, and dendritic cells (**Figure 3(A)**). TISIDB, a comprehensive tumor immune analysis database, integrates resources from multiple databases [15]. We utilized TISIDB to further examine the correlation between the abundance of tumor-infiltrating lymphocytes (TILs) and UCP2 gene expression profiles. It was observed that UCP2 in gastric cancer is positively correlated with the infiltration of Act_B cells, Act_CD8 cells, Act_CD4 cells, macrophages, NK cells, and dendritic cells (**Figure 3(B)**). These findings suggest that UCP2 expression plays a significant regulatory role in the infiltration of immune cells in gastric cancer, potentially exerting specific functions. Subsequently, we con-

firmed the correlation between UCP2 and several immune checkpoint genes, including PD1, PD-L1, CTLA-4, LAG-3, and TIM-3, using the TIMER 2.0 database. Co-expression analysis revealed that UCP2 is positively correlated with these immune checkpoint genes (**Figure 3(C)**). Further analysis of the correlation between UCP2 and MMR-related genes showed that UCP2 is positively correlated with MLH1, MSH6, and PMS2 (**Figure 3(D)**), indicating that UCP2 plays a crucial role in maintaining the functionality of the MMR system. These findings imply a potential association between UCP2 and immune infiltration in gastric cancer, highlighting its potential role within the tumor immune microenvironment.



(A) Analysis using TIMER to assess the relationship between UCP2 expression and the infiltration of immune cells, including B cells, CD4+ T cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells, within tumors. (B) Examination via the TISIDB database to determine the correlation between the abundance of tumor-infiltrating lymphocytes—specifically B cells, CD4+ T cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells—and the expression of UCP2. (C) TIMER analysis exploring the correlation between UCP2 expression and immune checkpoint molecules PD1, PD-L1, CTLA-4, LAG-3, and TIM-3. (D) TIMER analysis investigating the correlation between UCP2 expression and DNA mismatch repair proteins MLH1, MSH2, MSH6, and PMS2.

Figure 3. The association of UCP2 with the immune microenvironment in gastric cancer patients.

3.4. Virtual Screening of Natural Products Targeting UCP2

Computer-aided drug design (CADD) is an essential tool in the early stages of drug discovery, significantly accelerating the drug development process, reducing costs, and enhancing success rates through computational simulations and predictions. Its application in drug discovery is expected to expand further. Molecular docking, a structure-based CADD method, is extensively used in virtual screening to streamline and expedite the drug discovery process [16]. In this study, we employed virtual screening to identify candidate molecules from a large compound library that may bind to the UCP2 target. PyRx, an open-source CADD software, is widely utilized in virtual screening, molecular docking, and drug discovery research [17]. Using the vina module within PyRx, we conducted large-scale molecular docking to pre-screen compounds and identify natural products most likely to bind with UCP2. The Vina-Affinity score, a crucial metric in molecular docking, predicts the binding strength between ligands and receptors, typically expressed as binding free energy (kcal/mol), with negative values indicating binding affinity (the more negative the value, the stronger the binding). The docking results were ranked by binding free energy, and the top 6 natural products were selected, with their docking energy rankings presented in **Table 1**. The binding energies of these 6 natural products are all below −5.0 kcal/mol, suggesting good affinity.

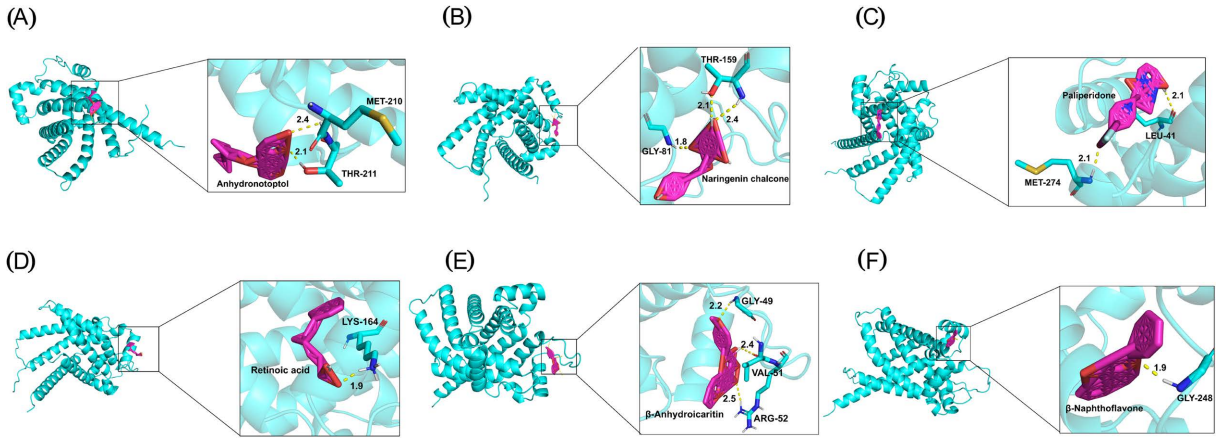
Table 1. Natural products identified through virtual screening targeting UCP2.

ID	Compound	Vina-Affinity Score (kcal/mol)
1	Anhydronotoptol	−12.3
2	Naringenin chalcone	−9.9
3	Paliperidone	−9.9
4	Retinoic acid	−9.4
5	*β*-Anhydroicaritin	−9.2
6	*β*-Naphthoflavone	−9

3.5. Molecular Docking Analysis of Natural Products with UCP2

Autodock is a widely utilized molecular docking software, employing a semi-flexible docking approach to predict the binding interactions between small molecules (such as substrates or potential drugs) and receptors (proteins) with known three-dimensional structures [18]. Using AutoDockTools, we conducted molecular docking simulations of five natural products identified through virtual screening with the UCP2 protein to elucidate their interaction mechanisms. In molecular docking studies, hydrogen bonds are crucial driving forces for ligand-receptor interactions, influencing both binding affinity and specificity. These bonds enhance the stability of ligand-receptor complexes, and the presence of multiple hydrogen bonds can significantly improve binding affinity through synergistic effects. Our docking analysis revealed that Anhydronotoptol forms one or more hydrogen bonds with the MET210 and THR211 residues of the UCP2 protein (**Fig-**

ure 4(A)); Naringenin chalcone forms one or more hydrogen bonds with the GLY81 and THR159 residues (Figure 4(B)); Paliperidone interacts through one or more hydrogen bonds with the LEU41 and MET274 residues (Figure 4(C)); Retinoic acid establishes a single hydrogen bond with the LYS164 residue (Figure 4(D)); β-Anhydroicaritin forms a hydrogen bond with the GLY49, VAL51, and ARG52 residues (Figure 4(E)); and β-Naphthoflavone forms a hydrogen bond with the GLY248 residue of the UCP2 protein (Figure 4(F)).



(A) Three-dimensional representation of Anhydronotopto at the binding site of UCP2. (B) Three-dimensional representation of Naringenin chalcone at the binding site of UCP2. (C) Three-dimensional representation of Paliperidone at the binding site of UCP2. (D) Three-dimensional representation of Retinoic acid at the binding site of UCP2. (E) Three-dimensional representation of β-Anhydroicaritin at the binding site of UCP2. (F) Three-dimensional representation of β-Naphthoflavone at the binding site of UCP2. (The UCP2 framework is illustrated as a blue tubular model, with natural products depicted in purple. Yellow dashed lines indicate hydrogen bonds, and the adjacent numbers denote the distances of these hydrogen bonds).

Figure 4. Interaction of natural products with UCP2 through molecular docking.

4. Discussion

In this study, we conducted a bioinformatics analysis of UCP2 using multiple public databases. Our findings indicate that UCP2 is overexpressed in most cancer tissues compared to normal tissues. Specifically, in gastric cancer, UCP2 expression is significantly elevated in cancerous tissues relative to normal tissues. Kaplan-Meier survival analysis demonstrates that patients with high UCP2 expression have a significantly shorter survival time than those with low expression, suggesting that elevated UCP2 levels may be linked to poor patient prognosis. Therefore, UCP2 could serve as a potential prognostic biomarker and therapeutic target in gastric cancer. Additionally, we observed a positive correlation between UCP2 expression and immune cells, including CD8+ T cells, CD4+ T cells, macrophages, NK cells, and dendritic cells. Further co-expression analysis revealed a positive association between UCP2 and immune checkpoint genes such as PD1, PD-L1, CTLA-4, LAG-3, and TIM-3, which may significantly impact tumor immune evasion and response to immunotherapy. The mismatch repair (MMR) system, composed of genes like MLH1, MSH2, MSH6, and PMS2, is responsible for

correcting errors during DNA replication [19]. Investigating the interaction between UCP2 and the MMR system could enhance our understanding of the molecular mechanisms underlying tumorigenesis. Our analysis revealed a positive correlation between UCP2 expression and MMR-related genes MLH1, MSH2, MSH6, and PMS2, suggesting that UCP2 is crucial for maintaining MMR system functionality. These results imply a potential link between UCP2 and immune infiltration in gastric cancer. However, further research is necessary to validate this association. Consequently, we propose that UCP2 may play a role in tumor initiation or progression and could influence the effectiveness of immunotherapy.

Natural products are highly valued in drug development due to their structural diversity, potent anti-tumor activity, ability to target multiple pathways, low toxicity, reduced risk of resistance development, and immune system enhancement. These compounds are also abundant in nature, making them excellent lead compounds that can be chemically modified into novel therapeutic agents, often serving as a source of inspiration for new drug development. Many anti-tumor drugs derived from natural products have offered hope to numerous clinical patients. In this context, we focus on screening natural compounds targeting UCP2 to establish a theoretical and experimental foundation for synthesizing more effective compounds. Utilizing virtual screening techniques, we identified six natural products with strong binding affinity to UCP2: Anhydronotoptol, Naringenin chalcone, Paliperidone, Retinoic acid, β-Anhydroicaritin, and β-Naphthoflavone. We conducted an analysis of existing research on these compounds. Anhydronotoptol, primarily found in the traditional Chinese medicine Qianghuo, is a potent inhibitor of nitric oxide (NO) production, significantly reducing NO levels in LPS-induced RAW 264.7 cells [20]. Safety is a critical consideration in drug screening, and according to the ETCM database, Anhydronotoptol exhibits no hepatotoxicity. Although research on Anhydronotoptol is limited and its anti-tumor properties have not been reported, it holds considerable potential and innovation for future cancer research. Naringenin chalcone, a chalcone compound extracted from the stems of *Machaerium isadelphum*, exhibits antibacterial and anti-inflammatory properties [21]. However, its pharmacological properties are underresearched, and no studies have explored its potential in cancer, marking it as a compound of significant research interest. Paliperidone, an FDA-approved antipsychotic for schizophrenia [22], also possesses antioxidant, anti-inflammatory, and anti-tumor properties. It is well-tolerated, with minimal side effects, and is effectively absorbed orally [23]. Current studies on Paliperidone's role in cancer treatment include reports on glioblastoma [24]. The concept of "repurposing old drugs" explores new therapeutic uses by identifying direct drug targets, thereby accelerating new therapy development, reducing R&D costs, and providing precise treatment options. Thus, Paliperidone offers new avenues for gastric cancer treatment as a repurposed drug. Retinoic acid, a natural derivative of vitamin A, is crucial in cell proliferation, apoptosis, differentiation, and embryonic development, and is implicated in various diseases, including inflammatory disorders and

cancer [25]. In gastric cancer, Retinoic acid has been shown to arrest the cell cycle, promote apoptosis, and reduce stem cell-like properties in gastric cancer cells [26], though its precise mechanisms require further investigation. *β*-Anhydroicaritin, derived from Epimedium, exhibits significant biological and pharmacological activities, including anti-osteoporosis, anti-inflammatory, and anti-tumor effects. It demonstrates strong cytotoxicity against human ovarian, cervical, and breast ductal carcinoma cells [27]. As a potential selective anti-cancer agent, *β*-Anhydroicaritin's role in gastric cancer treatment remains unexplored, warranting further research. Recent studies emphasize the role of flavonoids in inducing tumor cell apoptosis, highlighting their importance in cancer therapy. *β*-Naphthoflavone, a synthetic flavonoid derivative, has garnered attention for its anti-cancer activity, particularly in lung [28] and breast cancers [29]. However, its application in gastric cancer remains unstudied, presenting an opportunity for further investigation into its therapeutic potential and underlying mechanisms.

In conclusion, this research has demonstrated that UCP2 is overexpressed in gastric cancer and is positively associated with poor prognosis. UCP2 can be considered a potential biomarker for adverse prognosis, aiding in the identification of gastric cancer patients with unfavorable clinical outcomes, and may have a specific role in immune infiltration. Consequently, UCP2 is regarded as a significant risk factor in gastric cancer. A screening from a natural product library has identified six compounds with strong interactions with UCP2: Anhydronotoptol, Naringenin chalcone, Paliperidone, Retinoic acid, *β*-Anhydroicaritin, and *β*-Naphthoflavone. The above results suggest that UCP2 plays a certain role in the occurrence and development of gastric cancer, but relevant experiments need to be carried out for verification. Moreover, the six natural compounds targeting UCP2 for the treatment of gastric cancer also need further experimental verification. However, the above research results provide a theoretical basis for the follow-up experimental verification.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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