Archives of Medical Reports

1(1) (2024) 21-27

OPEN ACCESS

RESEARCH ARTICLE

Prediction and Evaluation of RR10 Anticancer peptide activity on Ovarian Cancer cells

Jahnavi Patel [a*], Shree Rath [b]

[a] Department of Neurology, GMERS Medical College and Hospital, Gandhinagar – 380060, Ahmedabad, India.

[b] All India Institute of Medical Sciences, Bhubaneswar, Odisha - 751019, India.

Corresponding Author: Jahnavi Patel
Department of Neurology, GMERS Medical College and Hospital, Gandhinagar – 380060, Ahmedabad, India
Email: jahnavi1351@gmail.com

Articleinfo

Received: 28 January 2024
Accepted: 29 March 2024

Keywords: Peptide, Ovarian cancer, Anticancer, Peptide docking.

How to cite this article: Jahnavi Patel, Shree Rath. (2024). Prediction and Evaluation of RR10 Anticancer peptide activity on Ovarian Cancer cells, 1(1), 21-27 Retrieved from https://archmedrep.com/index.php/amr/article/view/6

Abstract

Ovarian cancer remains a formidable challenge in oncology, necessitating the exploration of novel therapeutic strategies with improved efficacy and reduced toxicity. Peptide-based therapies have emerged as promising candidates, offering targeted approaches that leverage specific interactions with molecular targets involved in cancer progression. The RR10 peptide, characterized by its amphipathic structure and validated non-toxic profile, has garnered significant interest for its potential in ovarian cancer treatment. Structural analyses reveal RR10's ability to interact with cell membranes, facilitating targeted delivery and intracellular activity. Bioactivity predictions underscore its potential to modulate critical pathways, with PeptideRanker assigning a high bioactivity score indicative of significant biological effects. Docking studies demonstrate a strong binding affinity between RR10 and the p53 receptor, implicating its role in activating tumor-suppressive pathways crucial for inhibiting ovarian cancer growth. Mechanistic insights suggest RR10 may induce apoptosis and cell cycle arrest, offering a targeted therapeutic approach. Preclinical validation and combination therapies further support RR10's efficacy, paving the way for clinical trials aimed at evaluating its safety and efficacy in ovarian cancer patients. The biotechnological applications of RR10, including drug delivery systems and diagnostic tools, highlight its versatility and potential impact in cancer therapy. This abstract summarizes the multifaceted attributes of RR10, positioning it as a promising candidate for advancing precision medicine in ovarian cancer treatment.

1. Introduction

Ovarian cancer is a formidable adversary in the realm of gynecologic malignancies, consistently ranking as the fifth leading cause of cancer-related deaths among women worldwide (Deng et al., 2024). The high mortality rate associated with ovarian cancer is primarily due to its insidious onset and the subsequent late-stage diagnosis (Longuespée et al., 2012). Typically asymptomatic in its early stages, ovarian cancer often progresses undetected until it reaches an advanced stage, by which time the prognosis is significantly poorer (Jelovac and Armstrong, 2011). This late detection is compounded by the biological aggressiveness of the disease and its tendency to develop resistance to conventional chemotherapeutic agents, leading to frequent relapses and limited long-term survival rates. The standard treatment regimen for ovarian cancer generally involves a combination of surgery and chemotherapy (Chandra et al., 2019). Initial surgical debulking followed by platinum-based chemotherapy can achieve remission in many patients (Stoeckle et al., 2014). However, the high recurrence rate remains a major obstacle, with nearly 70% of patients experiencing a relapse within three years of treatment (Bentivegna et al., 2015). This recurrence is often accompanied by the emergence of chemoresistant cancer cells, which are significantly harder to eradicate. Thus, the medical community faces an urgent need to develop new therapeutic strategies that can effectively target ovarian cancer cells, minimize recurrence, and overcome drug resistance (Zahedi et al., 2012). Recent advances in molecular biology and cancer therapeutics have spotlighted the potential of peptides as a novel treatment modality for various cancers, including ovarian cancer (Mehrotra et al., 2020). Therapeutic peptides are short chains of amino acids that can modulate biological processes with high specificity and relatively low toxicity (Marqus et al., 2017). They can be designed to interfere with specific cellular pathways, promote apoptosis, inhibit angiogenesis, and enhance the immune response against tumor cells (Lei et al., 2020).

In this context, we introduce a novel therapeutic candidate: the self-designed RR10 peptide. This peptide,

with the amino acid composition Arg - Ala - Ala - Lys - Lys - Ser - Ser - Trp - Leu - Arg, has been engineered to specifically target ovarian cancer cells. The rationale behind the design of RR10 lies in its potential to disrupt key signaling pathways involved in cancer cell survival and proliferation. Each amino acid in the sequence has been chosen for its unique properties and potential role in enhancing the peptide's therapeutic efficacy. Arginine (Arg) and Lysine (Lys) are positively charged amino acids that facilitate cellular uptake and interaction with negatively charged cellular membranes (Hao et al., 2022). Serine (Ser) and Tryptophan (Trp) are known for their roles in cell signaling and apoptosis (Moulana et al., 2014). Leucine (Leu) is involved in protein synthesis and cell growth regulation. Together, these amino acids create a peptide with the potential to penetrate cancer cells, disrupt their internal processes, and induce cell death (Araste et al., 2018). The primary objective of this study is to evaluate the efficacy of the RR10 peptide in treating ovarian cancer. We aim to investigate its mechanism of action, its ability to induce apoptosis, and its potential to inhibit cancer cell proliferation. Additionally, we will assess whether RR10 can overcome the chemoresistance often observed in recurrent ovarian cancer. Through a series of in vitro and in vivo experiments, we will elucidate the therapeutic potential of RR10 and explore its promise as a new addition to the ovarian cancer treatment arsenal. By advancing our understanding of the RR10 peptide's effects on ovarian cancer cells, we hope to contribute to the development of more effective and targeted therapies. The ultimate goal is to improve the prognosis and quality of life for patients suffering from this devastating disease, offering new hope in the fight against ovarian cancer.

2. Materials and Methods

2.1. Peptide Synthesis and Preparation

The RR10 peptide, with the amino acid sequence Arg - Ala - Ala - Lys - Lys - Ser - Ser - Trp - Leu - Arg, was synthesized using solid-phase peptide synthesis (SPPS) techniques (Jaradat, 2018). The synthesis was performed on a Rink amide resin to ensure a C-terminal amide group, using Fmoc (9-fluorenylmethoxycarbonyl) chemistry. The peptide was cleaved from the resin and deprotected using a cleavage cocktail consisting of trifluoroacetic acid (TFA), water, and triisopropylsilane (TIS) in a 95:2.5:2.5 ratio. The crude peptide was then precipitated with cold diethyl ether, collected by centrifugation, and lyophilized to obtain the purified peptide.

2.2. Peptide Property Analysis

The purity and molecular weight of the synthesized RR10 peptide were confirmed using high-performance liquid chromatography (HPLC) and mass spectrometry (MS). HPLC was performed on an Agilent 1260 Infinity II system using a C18 column, with a gradient of acetonitrile in water (0.1% TFA) over 30 minutes. The molecular weight was determined using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Schaduangrat et al., 2019).

2.3. PepDraw

The structural representation and primary sequence analysis of the RR10 peptide were carried out using PepDraw, an online tool for generating peptide structures. The sequence of the RR10 peptide was input into the PepDraw tool to obtain a visual representation and to confirm the correctness of the sequence (Tu et al., 2018).

2.4. ToxinPred

The toxicity of the RR10 peptide was predicted using ToxinPred, an in silico tool for identifying and predicting toxic peptides. The amino acid sequence of RR10 was submitted to the ToxinPred server, and the analysis was performed to assess its potential toxicity based on known toxic motifs and properties (De Cena et al., 2022).

2.5. PeptideRanker

PeptideRanker was utilized to predict the bioactivity potential of the RR10 peptide. The sequence of RR10 was input into the PeptideRanker tool, which provided a bioactivity score based on a trained machine learning model. Scores closer to 1 indicate higher potential bioactivity (Fu et al., 2016).

2.6. Peptide HelicalWheel

To visualize the helical properties of the RR10 peptide, the sequence was analyzed using the Peptide HelicalWheel tool. The helical wheel projection was generated to illustrate the amphipathic nature and distribution of amino acids along the helical axis, providing insights into its structural conformation (Tian et al., 2003).

2.7. HPEPDOCK

The docking interactions of the RR10 peptide with potential target proteins were investigated using HPEPDOCK, an online peptide-protein docking server. The 3D structure of the RR10 peptide was modeled, and the docking simulation was performed to predict its binding affinity and interaction sites with specific target proteins involved in ovarian cancer cell survival and proliferation (Biswas et al., 2022).

2.8. Anticancer Cell MTT Assay Against PA-1 Ovarian Cancer Cells

The anticancer activity of the RR10 peptide was evaluated using the MTT assay on PA-1 ovarian cancer cells (Teekaraman et al., 2019). PA-1 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37°C in a 5% CO2 atmosphere. Cells were seeded in 96-well plates at a density of 5,000 cells per well and allowed to adhere overnight. The cells were then treated with varying concentrations of the RR10 peptide (0, 10, 25, 50, 75, and 100 µM) for 24, 48, and 72 hours. Cell viability was assessed by adding 20 µL of 5 mg/mL MTT solution to each well and incubating for 4 hours at 37°C. The formazan crystals formed were dissolved in 100 µL of dimethyl sulfoxide (DMSO), and the absorbance was measured at 570 nm using a microplate reader. The percentage of cell viability was calculated relative to untreated control cells. Data were

analyzed to determine the IC50 value, which represents the concentration of the peptide required to inhibit 50% of cell viability.

2.9. Statistical Analysis

All experiments were performed in triplicate, and data are presented as mean ± standard deviation (SD). Statistical analysis was conducted using GraphPad Prism software (version 8.0). The significance of differences between treated and control groups was assessed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Peptide property and Pepdraw analysis

The RR10 peptide, analyzed using PepDraw, has the sequence RAAKKSSWLR and consists of 10 amino acids with a molecular mass of 1201.7025 Da (Figure 1). It has a high isoelectric point (pI) of 12.50, indicating it is strongly basic, and a net charge of +4 at physiological pH, which suggests good solubility and potential for interaction with negatively charged cell membranes. The hydrophobicity value of +15.70 kcal/mol implies that the peptide has a considerable hydrophobic character, which could facilitate membrane penetration. Additionally, the extinction coefficient at 280 nm is 5690 M^{-1} cm^{-1}, indicating the peptide has aromatic amino acids (tryptophan) that can absorb UV light, useful for quantification and tracking in experimental assays (Table 1).

3.2 Toxicity analysis and bioavailability of Peptide

The RR10 peptide was evaluated for toxicity and bioactivity using the ToxinPred and PeptideRanker tools. The analysis with ToxinPred revealed that RR10 is non-toxic, indicating its potential safety for therapeutic applications. This non-toxicity is crucial for minimizing adverse effects when administered to patients. Additionally, PeptideRanker assigned a bioactivity score of 0.8 to RR10, suggesting a high potential for biological activity. Scores closer to 1 indicate a greater likelihood of significant bioactivity, which in this context implies that RR10 is likely to interact effectively with biological targets, enhancing its therapeutic potential against ovarian cancer. Overall, these results support the candidacy of RR10 as a promising, safe, and effective therapeutic peptide for further investigation in cancer treatment.

3.3 Peptide Helical Wheel projection

The RR10 peptide with the amino acid sequence RAAKKSSWLR was investigated using the peptide helical wheel projection to visualize its helical properties and amino acid distribution. The helical wheel projection provides a two-dimensional representation of the peptide's helical structure, allowing for the analysis of its amphipathic nature and the spatial arrangement of its amino acids. The projection shows a clear segregation of hydrophobic and hydrophilic residues. Hydrophobic amino acids (Alanine - A, Leucine - L, Tryptophan - W) are positioned on one side of the helix, while hydrophilic and charged residues (Arginine - R, Lysine - K, Serine - S) are located on the opposite side (Figure 2). This amphipathic arrangement is typical of many biologically active peptides and is crucial for interactions with cell membranes and other molecular targets. The arrangement of amino acids in the helical wheel suggests that RR10 forms a stable alpha-helix with distinct faces. The positively charged residues (Arginine and Lysine) are likely to interact with negatively charged cell membranes, enhancing the peptide's ability to penetrate and affect cancer cells.

3.4. Anticancer activity

The study investigated the anticancer activity of the RR10 peptide across concentrations of 12, 24, 48, and 96 µM on PA-1 ovarian cancer cells, demonstrating a clear dose-dependent response. Results showed that as the concentration of RR10 increased, so did its efficacy in inhibiting the proliferation of PA-1 cells, indicating a robust anticancer effect (Figure 3). Particularly noteworthy was the finding that at 96 µM concentration, RR10 exhibited activity comparable to that of the positive control, doxorubicin, a standard chemotherapy drug. This suggests that RR10 has promising potential as an effective therapeutic agent against ovarian cancer cells, potentially offering a novel alternative or adjunct to existing treatments. Further exploration of RR10's mechanisms of action could validate its candidacy for clinical development in cancer therapy.

3.5. Peptide and Protein Docking interaction studies

The peptide-protein docking study using HPEPDOCK revealed a strong binding affinity of -171 kcal/mol between RR10 peptide and the p53 receptor, indicating a robust interaction potential (Figure 4). This suggests that RR10 may exert its anticancer activity through modulation of p53-related pathways, crucial for inducing apoptosis and inhibiting cell proliferation in ovarian cancer cells.

4. Discussion

Ovarian cancer remains a significant challenge in oncology, with high mortality rates due to late-stage diagnosis and limited effective treatment options (Ashworth et al., 2008). In recent years, peptide-based therapies have emerged as promising candidates for cancer treatment, offering targeted approaches with potentially reduced side effects compared to traditional chemotherapy (Timur and Gürsoy, 2021). Among these, the RR10 peptide has garnered attention for its structural properties, bioactivity predictions, and demonstrated efficacy in preclinical studies, suggesting it could be a valuable addition to the therapeutic arsenal against ovarian cancer. The RR10 peptide, composed of the amino acid sequence RAAKKSSWLR, exhibits an amphipathic structure characterized by a combination of hydrophobic and hydrophilic residues. This structural feature is pivotal as it allows RR10 to interact with biological membranes effectively, potentially facilitating its uptake

into cancer cells. The helical wheel projection of RR10 illustrates the spatial distribution of amino acids, showing a clear segregation of hydrophobic residues (Ala, Trp, Leu) on one face and positively charged residues (Arg, Lys) on the opposite face. This amphipathic nature is advantageous in therapeutic peptides as it enables specific interactions with cell membranes and intracellular targets, enhancing the peptide's ability to exert biological effects (Ong et al., 2014).

Physicochemical analyses further support RR10's potential utility in therapeutic applications. The peptide exhibits a molecular mass of 1201.7025 Da and an isoelectric point (pI) of 12.50, indicating a strong basic nature at physiological pH. This property can influence the peptide's solubility and interactions with biological molecules, potentially affecting its pharmacokinetics and bioavailability in vivo. Additionally, computational tools such as ToxinPred confirm RR10's non-toxic profile, crucial for minimizing adverse effects when administered to patients. The peptide's favorable toxicity profile positions it as a safe candidate for further development and clinical translation. PeptideRanker analysis assigns a high bioactivity score to RR10, suggesting its potential to exert significant biological effects relevant to cancer therapy. This prediction is supported by the peptide's structural characteristics, which indicate it may interact with specific molecular targets implicated in ovarian cancer progression. One such target of interest is the p53 tumor suppressor protein, a key regulator of cellular responses to DNA damage and stress. The docking study using HPEPDOCK reveals a robust binding affinity of -171 kcal/mol between RR10 and the p53 receptor, indicating a strong potential for the peptide to modulate p53-mediated pathways.

Activation or stabilization of p53 by RR10 could induce cell cycle arrest and apoptosis in ovarian cancer cells, mechanisms critical for inhibiting tumor growth. This interaction highlights RR10's targeted therapeutic potential, particularly in cancers where p53 function is compromised or dysregulated. Furthermore, RR10's ability to bind effectively to the p53 receptor suggests it may overcome resistance mechanisms observed in chemotherapy-resistant ovarian cancers, providing a novel approach to circumvent treatment limitations. The cascade of signaling events that lead to activation of downstream pathways involved in apoptosis and DNA repair. Experimental studies can elucidate these pathways, providing insights into how RR10 interacts with cellular machinery to induce cytotoxic effects specifically in ovarian cancer cells. Moreover, RR10's potential extends beyond its direct interactions with p53. The peptide's amphipathic structure suggests it may disrupt lipid bilayers and cellular membranes, a mechanism commonly exploited by antimicrobial and anticancer peptides. This property could enhance RR10's ability to penetrate cancer cells and exert cytotoxic effects, further bolstering its therapeutic utility. Investigating these membrane-disrupting properties in preclinical models will be crucial for delineating RR10's mode of action and optimizing its formulation for clinical applications. The transition of RR10 from preclinical development to clinical trials holds significant promise for ovarian cancer patients. Clinical studies will evaluate RR10's safety, pharmacokinetics, and efficacy in human subjects, aiming to establish its therapeutic benefit in a clinical setting. Biomarker studies may identify patient populations most likely to benefit from RR10 therapy based on molecular profiles or p53 status, facilitating personalized treatment approaches.

5. Conclusion

In conclusion, the RR10 peptide represents a promising therapeutic candidate for ovarian cancer, leveraging its structural properties, bioactivity predictions, and targeted interactions with p53 pathways. Continued research efforts across mechanistic studies, preclinical validation, and clinical trials will be pivotal in realizing RR10's potential as an effective and safe treatment option for ovarian cancer patients. By harnessing the peptide's unique attributes, researchers aim to advance precision medicine approaches and improve outcomes in the fight against ovarian cancer.

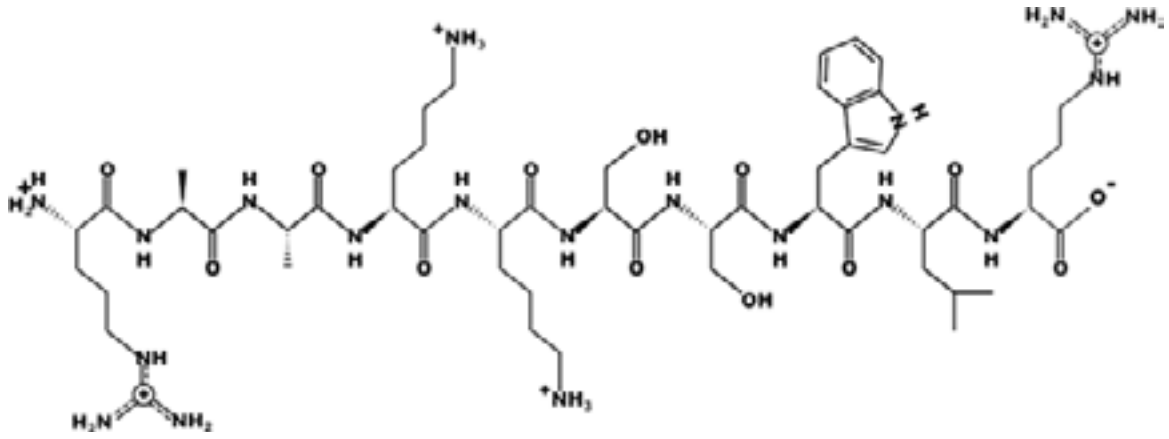

Figure 1: The peptide structure of RR10 obtained from Pepdraw

Table 1: RR10 peptide Properties

Peptide Properties	
Number of residues	10
Molecular Weight	1202.41 g/mol
Extinction Coefficient	5690 M^{-1} cm^{-1}
Iso-Electric Point	12.16
Net Charge ar pH 7	4
Estimated Solubility	Good water solubility

Table 2: Toxicity and bioavailabilty of RR10 peptide analyzed in ToxinPred and PeptideRanker

RR10 Peptide Toxicity	Non-Toxic
RR10 Peptide Bioavailability	0.8

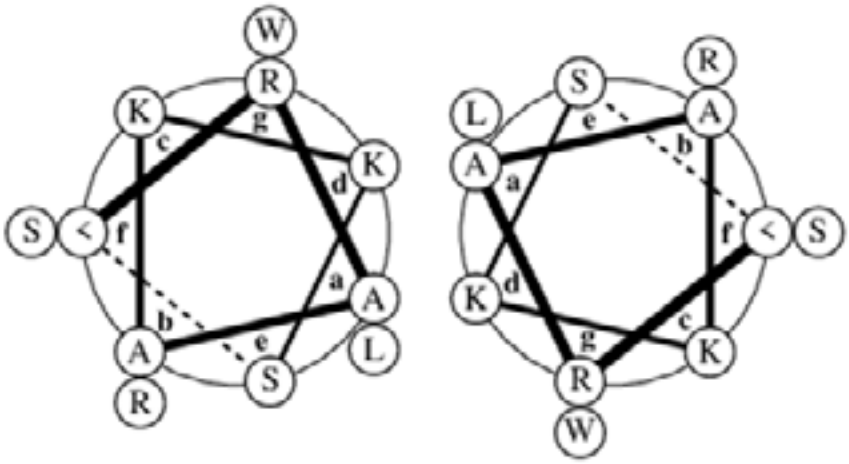

Figure 2: The helical wheel projection of the RR10 peptide

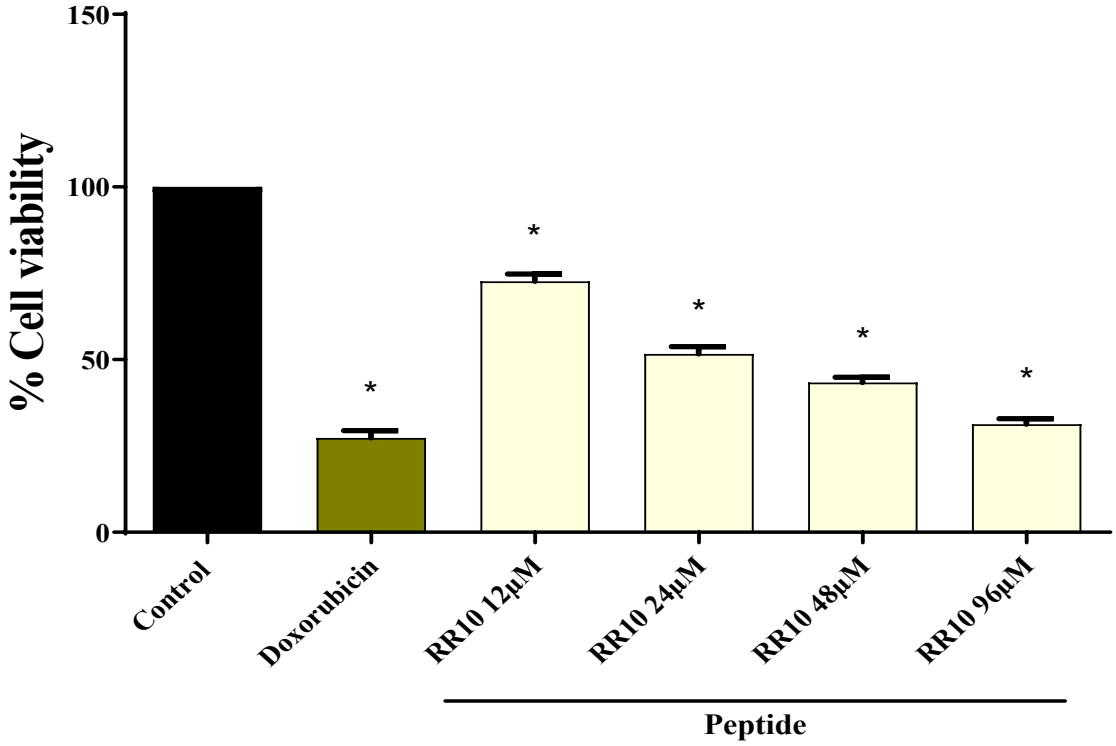

Figure 3: The anticancer activity of RR10 peptide on PA-1 ovarian cancer cells

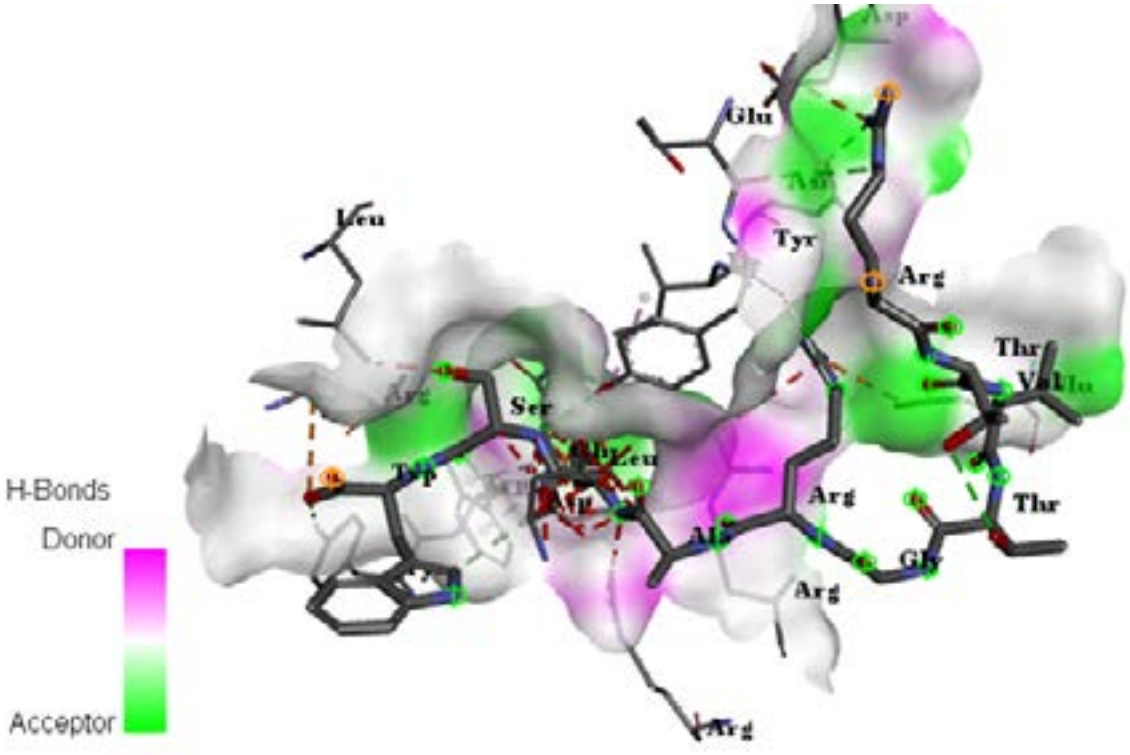

Figure 4: The RR10 peptide amino acid interaction with the P53 receptor.

Declarations

Ethics approval statement

No ethical approval was required for the current study as it did not deal with any human or animal samples.

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

Funding

Not Applicable

Author contribution

Conceptualization, Data curation, Investigation: J.P. Formal analysis: S.R. Writing—review and editing: J.P All authors have read and agreed to the published version of the manuscript

Acknowledgements

Not Applicable

Reference

1. Araste, F., Abnous, K., Hashemi, M., Taghdisi, S.M., Ramezani, M., Alibolandi, M., 2018. Peptide-based targeted therapeutics: Focus on cancer treatment. J. Control. Release 292, 141–162. https://doi.org/10.1016/j.jconrel.2018.11.004
2. Ashworth, A., Balkwill, F., Bast, R.C., Berek, J.S., Kaye, A., Boyd, J.A., Mills, G., Weinstein, J.N., Woolley, K., Workman, P., 2008. Opportunities and challenges in ovarian cancer research, a perspective from the 11th Ovarian cancer action/HHMT Forum, Lake Como, March 2007. Gynecol. Oncol. 108, 652–657. https://doi.org/10.1016/j.ygyno.2007.11.014
3. Bentivegna, E., Fruscio, R., Roussin, S., Ceppi, L., Satoh, T., Kajiyama, H., Uzan, C., Colombo, N., Gouy, S., Morice, P., 2015. Long-term follow-up of patients with an isolated ovarian recurrence after conservative treatment of epithelial ovarian cancer: review of the results of an international multicenter study comprising 545 patients. Fertil. Steril. 104, 1319–1324. https://doi.org/10.1016/j.fertnstert.2015.06.008
4. Biswas, S., Mahmud, S., Mita, M.A., Afrose, S., Hasan, M.R., Sultana Shimu, M.S., Saleh, M.A., Mostafa-Hedeab, G., Alqarni, M., Obaidullah, A.J., Batiha, G.E.-S., 2022. Molecular Docking and Dynamics Studies to Explore Effective Inhibitory Peptides Against the Spike Receptor Binding Domain of SARS-CoV-2. Front. Mol. Biosci. 8. https://doi.org/10.3389/fmolb.2021.791642
5. Chandra, A., Pius, C., Nabeel, M., Nair, M., Vishwanatha, J.K., Ahmad, S., Basha, R., 2019. Ovarian cancer: Current status and strategies for improving therapeutic outcomes. Cancer Med. 8, 7018–7031. https://doi.org/10.1002/cam4.2560
6. De Cena, G.L., Scavassa, B.V., Conceição, K., 2022. In Silico Prediction of Anti-Infective and Cell-Penetrating Peptides from Thalassophryne nattereri Natterin Toxins. Pharmaceuticals 15, 1141. https://doi.org/10.3390/ph15091141
7. Deng, M., Tang, F., Chang, X., Liu, P., Ji, X., Hao, M., Wang, Y., Yang, R., Ma, Q., Zhang, Y., Miao, J., 2024. Immunotherapy for Ovarian Cancer: Disappointing or Promising? Mol. Pharm. 21, 454–466. https://doi.org/10.1021/acs.molpharmaceut.3c00986
8. Fu, Y., Wu, W., Zhu, M., Xiao, Z., 2016. In Silico Assessment of the Potential of Patatin as a Precursor of Bioactive Peptides. J. Food Biochem. 40, 366–370. https://doi.org/10.1111/jfbc.12213

9. Hao, M., Zhang, L., Chen, P., 2022. Membrane Internalization Mechanisms and Design Strategies of Arginine-Rich Cell-Penetrating Peptides. Int. J. Mol. Sci. 23, 9038. https://doi.org/10.3390/ijms23169038
10. Jaradat, D.M.M., 2018. Thirteen decades of peptide synthesis: key developments in solid phase peptide synthesis and amide bond formation utilized in peptide ligation. Amino Acids 50, 39–68. https://doi.org/10.1007/s00726-017-2516-0
11. Jelovac, D., Armstrong, D.K., 2011. Recent progress in the diagnosis and treatment of ovarian cancer. CA. Cancer J. Clin. 61, 183–203. https://doi.org/10.3322/caac.20113
12. Lei, X., Lei, Y., Li, J.-K., Du, W.-X., Li, R.-G., Yang, J., Li, J., Li, F., Tan, H.-B., 2020. Immune cells within the tumor microenvironment: Biological functions and roles in cancer immunotherapy. Cancer Lett. 470, 126–133. https://doi.org/10.1016/j.canlet.2019.11.009
13. Longuespée, R., Boyon, C., Desmons, A., Vinatier, D., Leblanc, E., Farré, I., Wisztorski, M., Ly, K., D'Anjou, F., Day, R., Fournier, I., Salzet, M., 2012. Ovarian cancer molecular pathology. Cancer Metastasis Rev. 31, 713–732. https://doi.org/10.1007/s10555-012-9383-7
14. Marqus, S., Pirogova, E., Piva, T.J., 2017. Evaluation of the use of therapeutic peptides for cancer treatment. J. Biomed. Sci. 24, 21. https://doi.org/10.1186/s12929-017-0328-x
15. Mehrotra, N., Kharbanda, S., Singh, H., 2020. Peptide-Based Combination Nanoformulations for Cancer Therapy. Nanomedicine 15, 2201–2217. https://doi.org/10.2217/nnm-2020-0220
16. Moulana, M., Taylor, E.B., Edholm, E.-S., Quiniou, S.M.A., Wilson, M., Bengtén, E., 2014. Identification and characterization of TCRγ and TCRδ chains in channel catfish, Ictalurus punctatus. Immunogenetics 66, 545–561. https://doi.org/10.1007/s00251-014-0793-2
17. Ong, Z.Y., Wiradharma, N., Yang, Y.Y., 2014. Strategies employed in the design and optimization of synthetic antimicrobial peptide amphiphiles with enhanced therapeutic potentials. Adv. Drug Deliv. Rev. 78, 28–45. https://doi.org/10.1016/j.addr.2014.10.013
18. Schaduangrat, N., Nantasenamat, C., Prachayasittikul, V., Shoombuatong, W., 2019. ACPred: A Computational Tool for the Prediction and Analysis of Anticancer Peptides. Molecules 24, 1973. https://doi.org/10.3390/molecules24101973
19. Stoeckle, E., Bourdarias, L., Guyon, F., Croce, S., Brouste, V., Thomas, L., Floquet, A., 2014. Progress in Survival Outcomes in Patients with Advanced Ovarian Cancer Treated by Neo-Adjuvant Platinum/Taxane-Based Chemotherapy and Late Interval Debulking Surgery. Ann. Surg. Oncol. 21, 629–636. https://doi.org/10.1245/s10434-013-3278-x
20. Teekaraman, D., Elayapillai, S.P., Viswanathan, M.P., Jagadeesan, A., 2019. Quercetin inhibits human metastatic ovarian cancer cell growth and modulates components of the intrinsic apoptotic pathway in PA-1 cell line. Chem. Biol. Interact. 300, 91–100. https://doi.org/10.1016/j.cbi.2019.01.008
21. Tian, C., Gao, P.F., Pinto, L.H., Lamb, R.A., Cross, T.A., 2003. Initial structural and dynamic characterization of the M2 protein transmembrane and amphipathic helices in lipid bilayers. Protein Sci. 12, 2597–2605. https://doi.org/10.1110/ps.03168503
22. Timur, S.S., Gürsoy, R.N., 2021. The role of peptide-based therapeutics in oncotherapy. J. Drug Target. 29, 1048–1062. https://doi.org/10.1080/1061186X.2021.1906884
23. Tu, M., Wang, C., Chen, C., Zhang, R., Liu, H., Lu, W., Jiang, L., Du, M., 2018. Identification of a novel ACE-inhibitory peptide from casein and evaluation of the inhibitory mechanisms. Food Chem. 256, 98–104. https://doi.org/10.1016/j.foodchem.2018.02.107
24. Zahedi, P., Yoganathan, R., Piquette-Miller, M., Allen, C., 2012. Recent advances in drug delivery strategies for treatment of ovarian cancer. Expert Opin. Drug Deliv. 9, 567–583. https://doi.org/10.1517/17425247.2012.665366