Anti-Tumorgenic Impact of Nano-Formulated Peptide HIF-Alpha Therapy by DMBA Induced Mammary Carcinoma in Rodent Type

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ABSTRACT

Over the past decade, personalized medicine has acquired considerable attention, emerging as a promising avenue for enhancing cancer treatment and therapy. Within this rapidly increasing field, the latest research introduces an innovative approach focused on a nano-formulated peptide, HIF-alpha, distinguished by its unique dual pharmacological potential. Various tumor-induced rat model has been undertaken to assess the peptide's efficacy in combatting DMBA-induced breast cancer. The findings clearly demonstrate the synthesized peptide's profound impact on various feature of tumor biology, including the proliferation of malignant cells, the synthesis of fatty acids crucial for cellular metabolism, and the regulation of lactate levels implicated in tumor progression. Histopathological analyses provide compelling evidence of the peptide's ability to established multifaceted pharmacological effects within the tumor microenvironment. Moreover, it has been demonstrated that regulatory influence on key membrane receptors, namely HER2 and EGFR, further underscores its therapeutic promise. In summary, the peptide HIF-alpha emerges as a potential landmark, offering a more efficacious therapeutic adjunct to existing medications, irrespective of the malignancy's stage. This innovative discovery holds transformative potential in reshaping conventional cancer treatment paradigms, heralding a new era of precision medicine in oncology.

Keywords: Personalized medicine, HIF-alpha, breast cancer, Peptide and Therapeutic adjuvant.

1. INTRODUCTION

Breast cancer is the most ubiquitous, persistent, leading cause of invasive fatalities and illnesses among women worldwide in developed and developing nations. These cells become altered and uncontrolled once breast cancer progresses, resulting in the formation of a tumor. The greatest mortality is driven mostly by a lack of treatment choices for late disease stages. Regardless of stage of the illness, a range of therapeutic techniques have been granted for use in traditional therapies reduce the therapeutic efficacy [1, 2, 3, 4, 5, 6].

Peptides found diverse applications in cancer treatment, including their direct use as drugs such as angiogenesis inhibitors, as well as serving as tumor-targeting agents to deliver cytotoxin drugs and radionuclides for targeted chemotherapy and radiation therapy. With their ability to bind to various receptors and participate in biochemical pathways, peptides also play a crucial role as diagnostic tools and biomarkers in understanding cancer progression [7, 8, 9].

Peptide hormone treatment and tumor-targeting drugs with radionuclides for imaging and therapy are the main sources of the peptide medications that are currently available on the market [10]. Bortezomib and mifamurtide

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are two shorter peptide medications that deviate from the requirements [11, 12].

A significant mechanism in which cancer cells adapt to low oxygen levels in their environment is by activating hypoxia inducible factors (HIFs). These factors with two subunits: either HIF-1α or HIF-2α, which responds to oxygen levels, and HIF-1β, which remains consistently expressed. Activation of HIFs leads to the expression of genes crucial for invasion, metastasis, and resistance to treatment, contributing to increased metastasis and decreased survival rates in breast cancer patients [13]. HIF-1α specifically plays essential roles in various aspects of breast cancer progression, including metastatic site formation, angiogenesis, stem cell maintenance, metabolic changes, epithelial-mesenchymal transition (EMT), invasion, metastasis, and resistance to radiation and chemotherapy [14]. Recent studies indicate that the HIF-1 pathway regulates breast cancer metastasis through multiple mechanisms [15]. The HIF knocked mice mainly showed abnormal vascular development. In further research reported that HRE-/-Estumor produced the same level of VEGF as the VEGF-/-ES tumors indicating the role of HIF/HRE in transcription regulation of VEGF production in tumor cell [16]. Therefore, understanding these molecular and cellular processes is crucial for accurate prognosis and the development of new treatment strategies.

Chemotherapy is one among the many major therapy in order to treat cancer, for it delivers the cytotoxic agent to the cancer cell. But here again is the limitations whereas in there is the inability to deliver the appropriate amount of the drug to be directly affect the cancer without disturbing the normal cell. Other effects also noted are that the drug resistance, the altered bio distribution, and clearance of the drug also seem to be set as a common problem. Yet the process of the targeted chemotherapy and the techniques of drug delivery have now become as a powerful method to come across these problems [8, 17]. Hence forth this will allow doing a selective and an effective localization of the drug in the predefined areas thus increase the therapeutic index and reducing toxicity.

Cancer nanotechnology has been recently employed in drug design and research to encounter the aforementioned drawbacks of cancer therapies, resulting in more therapeutically efficient and safer drugs [18]. Nanotechnology is revolutionizing the pharmaceutical and medical industries, particularly in cancer research. By merging chemistry, engineering, biology, and medicine, nanotechnology enables targeted and efficient drug delivery through nanoparticles that interact with cells [19, 20]. The primary goal of nanoparticle drug delivery systems is to enhance drug effectiveness while reducing harmful side effects, thereby optimizing treatment outcomes [21].

Chitosan-based nanoparticles (ChNPs) provided appealing prospects to be explored as biodegradable and biocompatible drug delivery [22]. Chitosan-based nanoparticles (ChNPs) exhibit strong biodegradability and biocompatibility, making them promising for targeted drug delivery systems. ChNPs can deliver a variety of anticancer medicines to specific locations via passive and active targeting routes. The alteration of ChNPs attracted the researcher's interest in medication delivery to cancer cells. [23]. Accordingly, the present study was designed to evaluate the effect of nano formulated peptide HIF-alpha inhibition of HIF-alpha by introducing PCN-M04 against 7,12-dimethylbenz(a) anthracene (DMBA) induced mammary carcinoma to Sprague Dawley (SD) rats.

2. MATERIALS AND METHODS

2.1 Drugs and chemicals

Chitosan, and sodium tri poly-phosphate were procured from Sigma Aldrich (USA). All other chemicals used in this study were of analytical grade.

2.2 HIF9 Peptide Chitosan nanoparticles (PCN) Preparation

PCN was prepared by ionic cross-linking chitosan using sodium tripolyphosphate (TPP) anions. 20 mg/mL chitosan was suspended in 2%v/v aqueous acetic acid

solution at pH 5.5 with steady stirring at 10 °C (1 h).The aqueous solution comprising of chitosan: TPP ratio of 1/0.1(v/v) was incorporated in droplets to the solution and maintained in the magnetic stirrer for 3 h. 100ng/mL HIF9 (Hypoxia-Inducible Factors 9) peptide dissolved in HPLC water grade) was added and continuously swirled for 6 hours at 4 °C. The resulting solution was centrifuged at 13000rpm for 20 min at 4°C (REMI Cooling Centrifuge, Chennai -India). The resulting supernatant was collected, then peptide chitosan nanoparticles (PCN) were dried in the deep freezer (-55 °C) for further analysis [24].

2.3 Experimental animals and ethical

Female Sprague-Dawley (SD) rats (21 days old) were purchased from India's NIN (National Institute of Nutrition). The animals were reared in polypropylene cages with a 12-hour light/12-hour dark cycle, 50% humidity, and a temperature of 25 °C. Food and water were readily available. The study accompanied the ethical criteria established by Periyar University's Institutional Animal Ethical Committee, with clearance number IAEC/BT01/2016/1085/PO/OC/07/CPCSEA.

2.4 Carcinoma induction of mammary carcinoma with DMBA

Mammary cancer was developed in 36 rats by dissolving 120 mg of DMBA (Sigma Aldrich, USA) in 24 mL of olive oil and thoroughly mixing it (a yellow-colored solution is produced). The DMBA solution was administered orally to the animals through an oral feeding syringe at a dosage of 25 milligram per kilogram [25]. Following the removal of the excess DMBA, the region was cleansed and chemically inactivated using a diluted solution of sodium carbonate.

2.5 Experimental design and protocol

- Healthy SD rats were divided in six groups and each group consists of six animals:
- Group 1: Rats received Olive oil alone as control (P.O).
- Group 2: Rats in group II received that DMBA alone 25 mg/kg as negative control (P.O).
- Group 3: Rats in group III were treated with DMBA and Tamoxifen (medication used to treat breast cancer) 10 mg/kg/day (P.O) after one month of PIP (Post Induction Period) as the positive control.
- Group 4: Rat in group IV treated that with DMBA and after one month of PIP onwards 10 mg/kg/week of chitosan nanoparticles was added (I.V route).
- Group 5: Rats were treated with DMBA and after one month of PIP the animals treated with Peptide HIF9 60 µg/kg/week (I.V route).
- Group 6: Rats were treated with DMBA and after one month of PIP the animals treated with PCN-M04 5mg/kg/week (I.V route) containing of peptide HIF9 (426.18 mg of PCN-M04 contains 14 ng of Peptide HIF9).

At the end of experiment (120 days), rats were sacrificed with an excess of diethyl ether anesthesia, the breast tissues were processed for further studies.

2.6 Body weight and breast tumor weight changes

Weekly recordings of food consumption and body weight were maintained. After 20 days of DMBA injection, all rats were examined for breast tumors using palpation. The number, size, and location of tumors were noted throughout the procedure. After a histological diagnosis, the tumors' onset period was identified. Each rat was examined daily for signs of illness, and those found to be in a moribund condition were swiftly placed to death. Additionally, rats with tumors that exceeded 10% of their body weight, were larger than 15 to 20 mm in diameter, hindered normal mobility, or ulcerating during the investigation were immediately subjected to death. The tumor volume was assessed at the final stage of the experiment [26].

2.7 Hematoxylin and Eosin stain (HE stain)

Mammary tissues were surgically removed and promptly embedded in paraffin wax after being treated with 10% (v/v) formalin fixative. Five-micron thick slices were cut with a microtome (Leica, RM2135, Germany), laid out on glass slides, and cleaned with xylene. The slices

were rehydrated using a succession of ethanol solutions, rinsed with water, stained with hematoxylin, and washed with running water (20 minutes). The slides were counterstained with eosin and dehydrated using a succession of ethanol solutions. Finally, slides were mounted in DPX, photographed, and checked under a microscope (Olympus, MLXi, Japan).

2.8 Immunohistochemistry

To quantitatively measure the in vivo expression of extracellular proteins as well as the receptor occupancy of any ligand-of-interest (i.e., therapeutics or imaging agents) was an important tool for personalized medicine, including tumor detection the portions were deparaffinized and rehydrated in xylene. Immunohistochemistry for epidermal growth factor receptors (ErbB-1) was performed using the ScyTek (PolyTekTM) kit protocol. Concurrently, IHC for the tyrosine-protein receptor erbB2 (HER2) was carried out using the NovolinkTMpolymer detection system (Leica) kit in accordance with the manufacturer's protocol.

2.9 Statistical analysis

All data were presented as mean ± Standard Error (SE) of number of experiments. The statistical significance was evaluated by one-way analysis of variance (ANOVA) using Graphpad PRISM (Version-5.01, USA) and the individual comparison were obtained by "Dunnett" or "Bonferroni" (Chapter II) comparisons. A value of $P<0.05$ was considered to indicate a significant difference between groups.

3. RESULTS

3.1 The reduction of tumor incidence

Figure 1 illustrates the initial and final body weight variations. Initially, there were no significant differences in the body weights of the control and experimental animals. However, when compared to control groups, there was a significant decrease in body weight in the experimental groups. Significant weight differences were noted across the different groups. Figures (2 and 3) indicate the mean tumor incidence and average number of tumors for each treatment group. At the end of experiments, the tumor incidence and average number of tumors among the groups observed as a consequence of Tamoxifen treated animals (Group-3) were insignificant. However, the DMBA and PCN-M04 treated rats (Group 6) exhibited a larger reduction in tumor incidence (25-30%) and tumor number (1-1.5). Groups 2 and 3 showed no change.

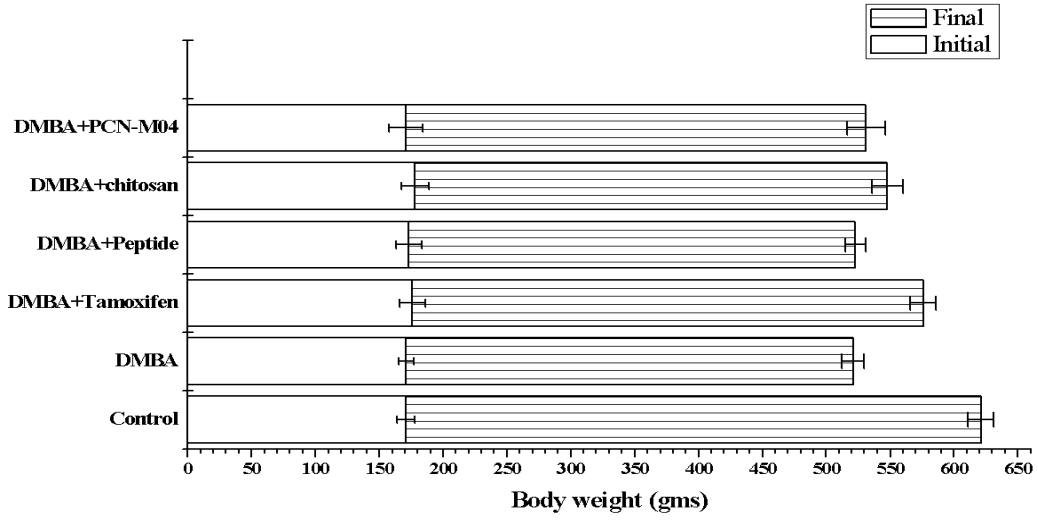


Fig.1. Variations in body weight of control and experimental animals.

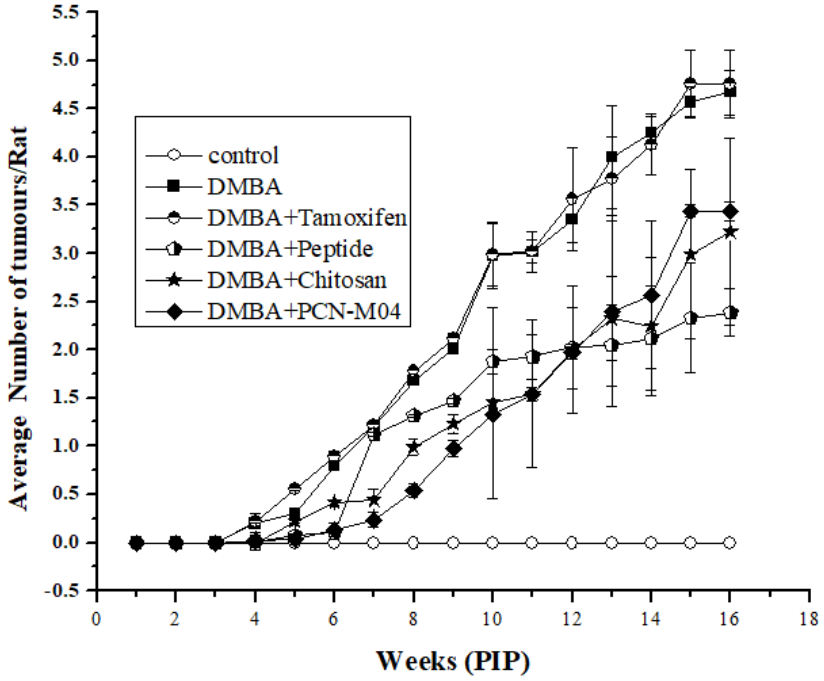


Fig.2. The incidence of rat mammary tumour growth in groups of experiments under control.

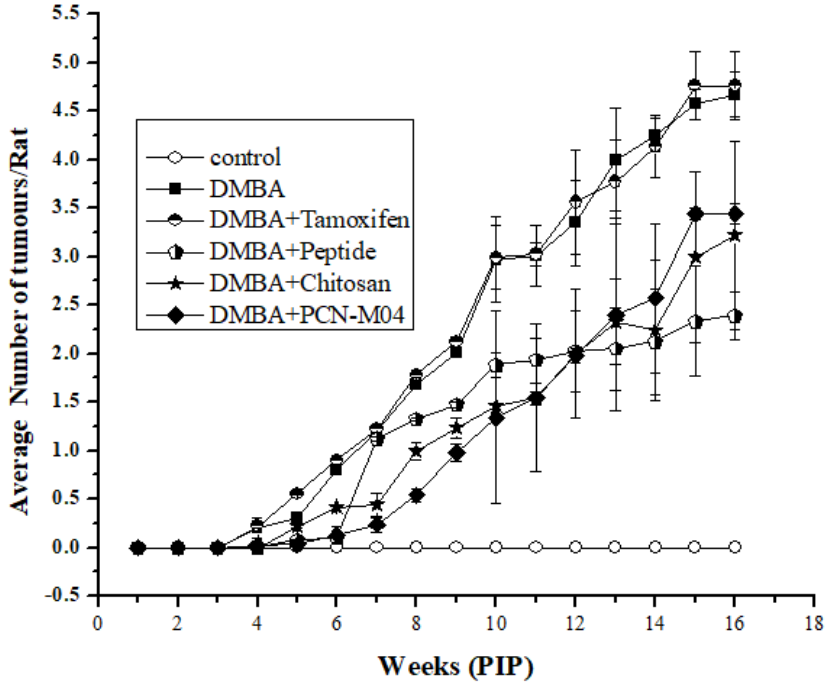


Fig.3. The normal amount of tumours observed in the experimental and control groups.

3.2. Histological Examination

Figure 4 depicts microscopic findings that occurred after treatment with PCN-M04 cells, demonstrating signs of apoptosis such as remarkable decrease in matrix, cristae, and lipid bodies. The sole DMBA treated group demonstrated endoplasmic reticulum abnormalities, aberrant nucleus organization, and mitochondrial enlargement.

3.3 Immunohistochemistry

The HER2 protein test is designated on IHC slides based on FDA scoring requirements. (Figure 5). Group 1 membrane staining reveals fewer than 10% of tumor cells (Negative). Group 4 showed faint/barely perceptible membrane staining (Negative), Group 5 and 6 showed week to moderate staining and Group 2 and 3 showed a strong and complete membrane staining with more than 10% tumor cells (Strongly Positive).

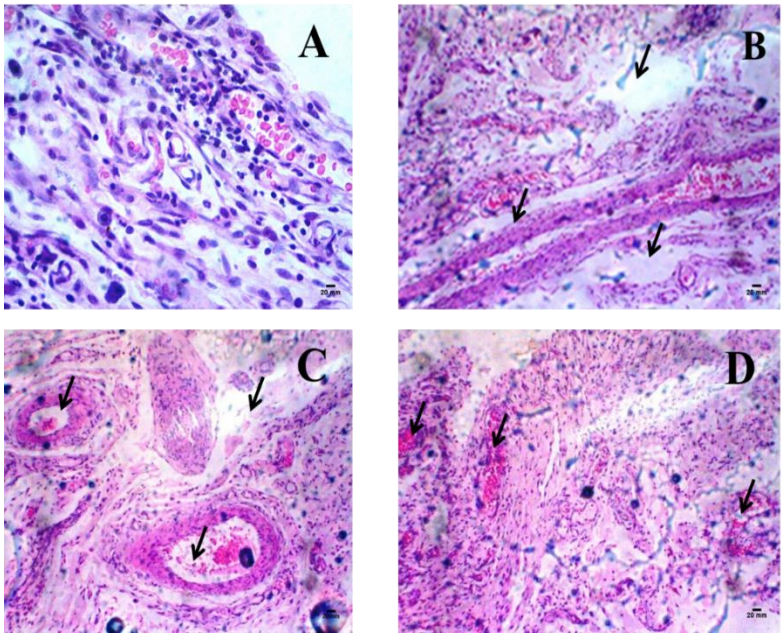


Fig.4. Breast tissue histopathology (A) Showing normal architecture (Group-1), (B) (Group-3: DMBA + Tamoxifen) Tumor section showing reactive lymphatic follicular hyperplasia with numerous mitotic feature (Group-3),(C) Section showing neoplastic cells invasive feature- (Group-2) and (D) Papillary tumor invasive feature with apoptosis (Group-5).Treatment- Group 1:Olive oil, Group 2 : DMBA, Group 3: DMBA + Tamoxifen, Group 4: DMBA + Peptide (HIF9), Group 5: DMBA + Chitosan, Group 6: DMBA + PCN –M04.

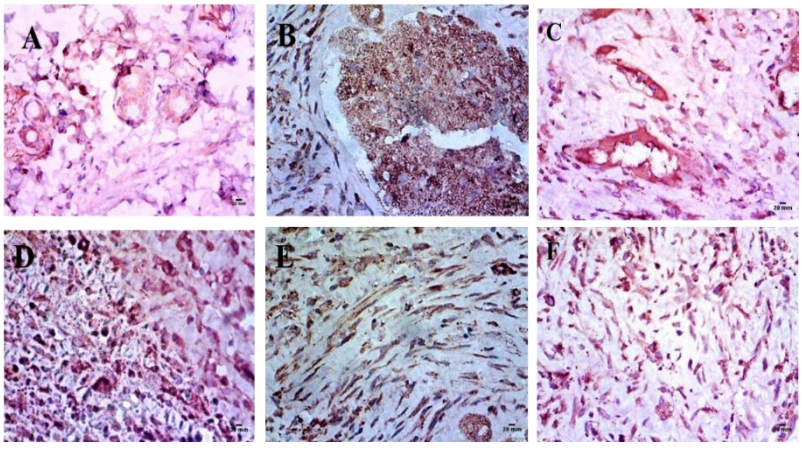
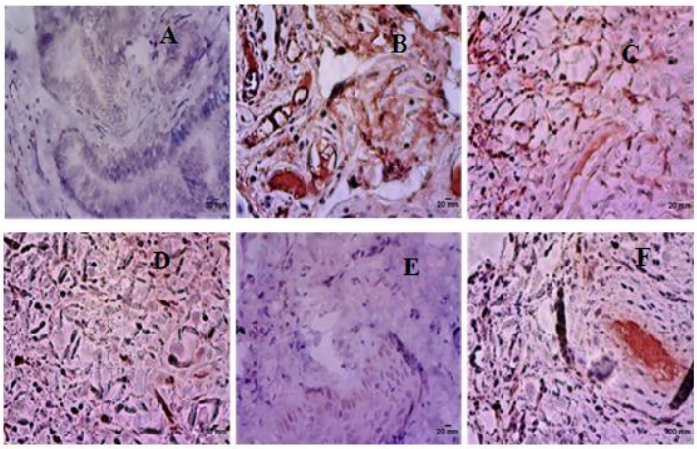


Fig.5. DAB Chromogen expression of HER2 protein in rat mammary tissues. Tissues with HER2 IHC Scores of 3+ (B & C), 2+ (E &F), 1+(D) and 0 (A) were subjected to HER2 Immunohistochemistry (IHC). Treatment- (A) Group 1: Olive oil, (B) Group 2: DMBA, (C) Group 3: DMBA + Tamoxifen, (D) Group 4: DMBA + Peptide (HIF9), (E) Group 5: DMBA + Chitosan, (F) Group 6: DMBA + PCN – M04.



. Fig.6. DAB Chromogen expression of EGFR Protein in rat mammary tissues. Score 0 by ICH (A, E),Score 3 by IHC B,D & E, Score 2 by IHC (C) .Treatment- (A) Group 1: Olive oil, (B) Group 2: DMBA, (C) Group 3: DMBA + Tamoxifen, (D) Group 4: DMBA + Peptide (HIF9), (E) Group 5: DMBA + Chitosan, (F) Group 6: DMBA + PCN – M04.

4. DISCUSSION

Nowadays, the initial stage of cancer therapy would be targeted medication delivery and finding an effective targeting agent and look for would be critical. Some of the substances which may show beneficial effect on exact targeting site that would pave the way to take forward the substance for next level of cancer therapy. DMBA is known as a site-specific cancer-causing agent and it is a lipophilic agent diversely used to study the mammary carcinogenesis. Considering this fact, the present study was planned to analyze the effect of PCN-M04 on DMBA induced mammary carcinogenesis. Further, histogenesis a therapeutic strategy is adopted in this study.

Number of studies revealed that breast cancer is infiltrated by mast cells in particular breast cancer itself exhibiting a high heterogeneity. Cancer cell might adopt in the hypoxic microenvironment, and it can be activated by HIF-α factor which act as a key factor for metastatic niche formation, angiogenesis, stem cell maintenance, metabolic reprogramming, epithelial-mesenchymal transition, invasion, metastasis and radiation therapy resistance and chemotherapy [27]. Recently, HIF-1α in human breast cancer cells inhibits primary tumor growth and lung metastasis and blocks metastatic niche formation in the lungs of mice bearing primary breast tumors [28]. The present study revealed that PCN therapy for DMBA treated rats showed reduced tumor cell proliferation was significantly decreased when compared to negative control. This phenomenon perhaps owes to the hypoxic nature happened in the tumor site on PCN-M04 received groups in our study whereas the nutritional starvation (lipids) and oxidative stress happened in the tumor site on PCN received groups.

An increased presence of mast cells has been observed in the formation of new blood vessels associated with vascular tumors, as well as various solid and blood-related cancers. However, it is particularly evident in experimental cancer development that mast cells play a significant role in tumor blood vessel formation. Mast cells located in inflamed areas more frequently contain lipid droplets, which may provide a source of amino acids for mast cell function. Thus, the role of lipids indirectly emphasizes the importance of mast cell count [29] as our findings also indicate that blocking lipid synthesis leads to some control over mast cell numbers.

Angiogenesis associated with vascular neoplasms is the major cause of solid and hematopoietic tumor as well as to increase the mast cells. Most importantly, mast cell contribution is most evident in tumor angiogenesis [21] So, the role of HIF-1 circuitously possesses the importance for mast cell count as in our results also suggest that barrier of hypoxic condition leads to nominal controlling of mast cell count.

Overexpression of HIF-1α inhibits cell death in breast

tumors and encourages the advancement of the cell cycle. Suppressing HIF-1α leads to cell cycle interruption and reduced growth. HIF-1α signaling boosts the migration of breast tumors, primarily inducing EMT to facilitate metastasis [30]. Our findings revealed that the tumor experienced higher oxidative stress because of increased energy requirements.

The findings not only strengthen the hypothesis that the activity of HIF-1α and FSN associated with breast cancer is an important molecular target for the development of cancer drugs, but they also show a close relationship between Her2 and EGFR protein, the regulation of these proteins overexpression and activation is recognized to be a significant contributing factor to their formation. The signaling molecules involved in the physiological processes that ensued from the suppression of fatty acid synthesis activity by HIF-1α and FSN were identified. Interestingly, we found in our study that group 5 and 6 showed lower levels of Her2 and EGFR proteins. This could be due to ligand-dependent hypo activation of GF receptors (GFRs) as well as loss of function of signaling cascade components like phosphatase and tensin homologue (PTEN) function [31].

5. CONCLUSION

The findings of this research offer demonstrable support for HIF-alpha peptide treatment against breast cancer, which works by preventing de novo lipogenisis. Her2 and EGFR protein control provides proof of this peptide's dual activity. This peptide can be used alone or in conjunction with current treatments to provide an efficient anti-cancer treatment.

Ethical Approval

The study accompanied the ethical criteria established by Periyar University's Institutional Animal Ethical Committee, with clearance number IAEC/BT01/2016/1085/PO/OC/07/CPCSEA.

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Declaration of conflict

The authors declare that they have no conflicts of interest.

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التأثير المضاد للورم لعلاج الببتيد HIF-alpha المصاغ بالنانو بواسطة سرطان الثدي الناجم عن DMBA في نوع القوارض

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[2] قسم التكنولوجيا الحيوية، كلية العلوم البيولوجية، جامعة بيريار، سالم، تاميل نادو، الهند

ملخص

على مدى العقد الماضي، اكتسب الطب الشخصي اهتمامًا كبيرًا، حيث ظهر كطريق واعد لتعزيز علاج السرطان. وفي هذا المجال المتزايد بسرعة، يقدم أحدث الأبحاث نهجًا مبتكرًا يركز على ببتيد مُصاغ على شكل نانو، HIF-alpha، يتميز بإمكاناته الدوائية المزدوجة الفريدة. تم إجراء نماذج مختلفة للفئران المستحثة بالورم لتقييم فعالية الببتيد في مكافحة سرطان الثدي الناجم عن DMBA. توضح النتائج بوضوح التأثير العميق للببتيد المُصنَّع على سمات مختلفة من بيولوجيا الورم، بما في ذلك تكاثر الخلايا الخبيثة، وتخليق الأحماض الدهنية الضرورية لعملية التمثيل الغذائي الخلوي، وتنظيم مستويات اللاكتات المتورطة في تطور الورم. توفر التحليلات النسيجية المرضية أدلة دامغة على قدرة الببتيد على إحداث تأثيرات دوائية متعددة الأوجه داخل بيئة الورم. علاوة على ذلك، فقد ثبت أن التأثير التنظيمي على مستقبلات الغشاء الرئيسية، وهي HER2 وEGFR، يؤكد بشكل أكبر على وعده العلاجي. باختصار، يبرز الببتيد HIF-alpha كمعلم بارز محتمل، حيث يقدم مكملًا علاجيًا أكثر فعالية للأدوية الحالية، بغض النظر عن مرحلة الخباثة. يحمل هذا الاكتشاف المبتكر إمكانات تحويلية في إعادة تشكيل نماذج علاج السرطان التقليدية، ويبشر بعصر جديد من الطب الدقيق في علم الأورام.

الكلمات الدالة: الطب الشخصي، HIF-alpha، سرطان الثدي، الببتيد والمكمل العلاجي المساعد.

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