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ANTICANCER EFFECTS OF HUMAN BREAST MILK-DERIVED PEPTIDES ON MCF-7 CELLS: OMICS – GUIDED EVALUATION

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ABSTRACT. This study evaluated the anticancer potential of peptides from enzymatically hydrolyzed human breast milk on MCF-7 breast cancer cells, focusing on protein expression alterations associated with cell death. Human breast milk was enzymatically hydrolyzed under controlled conditions to simulate gastrointestinal processing, generating bioactive peptides. The hydrolysate was applied to MCF-7 cells for 24 hours, and proteomic changes were characterized using LC-MS/MS-based analysis. Application of the hydrolysate to MCF-7 cells led to notable proteomic alterations, particularly in proteins regulating apoptosis, cell survival, and cancer-related signalling pathways. In silico docking analyses identified three abundant peptides (AGFAGDDAPR, LAADDFR, and DAEAWFNEK) predicted to interact with key regulatory proteins, including myeloid cell leukemia-1, Ras suppressor protein-1, and galectin-3. These peptides showed favorable docking scores, which may indicate their potential involvement in apoptosis- and metastasis-related pathways. Omics-guided evaluation highlights these peptides as promising lead candidates for peptide-based anticancer strategies. This integrative approach demonstrates the utility of combining enzymatic hydrolysis, proteomic profiling, and computational analyses to identify human-derived bioactive molecules with therapeutic potential.

Keywords: *Bioactive peptides, bioinformatic analysis, breast milk, breast cancer*

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INTRODUCTION

Breast cancer raises from the uncontrolled proliferation of epithelial cells within ducts or lobules of the breast [1]. The development and homeostasis of mammary ductal epithelial cells are regulated by growth factors, differentiation signals, and the balance between pro- and anti-apoptotic pathways [2]. Consequently, modern therapy targets multiple molecular pathways, and research into novel compounds that influence apoptosis remains active [3]. Studies have shown that different types of milk have antiproliferative and apoptotic effects on cancer cells. The majority of these studies focused on the antiproliferative and apoptotic mechanisms of cow's milk, camel's milk, and goat's milk-based proteins [4-6]. Different recombinant casein forms (κ and α – casein) have also been found to stimulate the apoptotic signalling pathway by reducing cell growth in the breast cancer cell lines [7, 8]. Svanborg et al have found the anticancer properties of α-lactalbumin-oleic acid, a natural compound derived from breast milk (BM). This complex, known as human alpha-lactalbumin made lethal to tumor cells (HAMLET), was identified during their research on antiadhesive components in human milk [9]. In recent years, the studies related to bioactive peptides in cancer treatment have increased [10].

Bioactive peptides are encrypted within parent proteins and become functional only after *in vitro* or *in vivo* digestion [11]. Their immuno-modulatory, antihypertensive, antithrombotic, antioxidant or anticancer activities depend on their amino-acid sequence and three-dimensional conformation [12]. In this study, BM-based bioactive peptides were used to investigate their effects on breast cancer cell line.

Human BM is a complex fluid known for its nutritive, immunomodulatory, and developmental roles [13]. Although some studies have suggested potential anticancer properties, BM is primarily designed to support infant growth and immune development rather than to exhibit strong anticancer effects. However, specific bioactive components, such as peptides, may carry therapeutic potential, and their individual functions warrant further investigation [14]. Studies have indicated that BM-based bioactive peptides have immunoregulatory [15], antimicrobial [16], antihypertensive [17], antithrombotic [18], anticancer [19], and antioxidant [20] properties.

In parallel with *in vitro* studies, *in silico* approaches have become essential tools for predicting peptide bioactivity and potential molecular targets [21]. Previous research has employed computational methods to investigate transcriptional regulation and apoptotic mechanisms in breast cancer cells [22-24].

This study aims to evaluate the antiproliferative potential of bioactive peptides derived from enzymatically digested human BM on MCF-7 breast cancer cells, with a particular focus on their molecular mechanisms of action.

RESULTS AND DISCUSSION

LC-MS/MS analysis of the *in vitro* digested BM identified 94 peptides. Subsequent toxicity screening using the ToxinPred program revealed that none of these peptides possessed toxic potential. Furthermore, 14 of the identified peptides were predicted to exhibit significant biological activity (Table 1).

Table 1. Sequences of potential bioactive BM peptides

Peptide	Master Protein Accession Number	Potential Bioactive Peptide Sequences*	Amino Acid Length	Peptide Ranker Scores
1	P35908	HGGGGGGFGGGGFGSR	16	0.86
2	P35527	SGGGGGGGLGSGGSIR	16	0.83
3	P13929-1	FGANAILGVSLAVCK	15	0.77
4	P07602-1	SLPCDICK	8	0.76
5	P35908	GGSISGGGYGSGGGK	15	0.64
6	P01857	GPSVFPLAPSSK	12	0.64
7	P04745	HMWPGDIK	8	0.60
8	P07602-1	LGPGMADICK	10	0.58
9	P35527	QGVDADINGLR	11	0.58
10	P60709	AGFAGDDAPR	10	0.56
11	P02533	LAADDFR	8	0.54
12	P13645	DAEAWFNEK	9	0.53
13	P01614	FSGSGSGTDFTLK	13	0.53
14	Q32P51	SHFEQWGTLTDCVVMR	16	0.51

*Potential bioactive peptides were evaluated by the Peptide Ranker ($p>0.5$)

Bioactivity predictions performed through the BIOPEP-UWM database have revealed various potential functionalities for the identified peptides. These include inhibitory activities against angiotensin-converting enzyme (ACE), dipeptidyl peptidase III (DPP-III), dipeptidyl peptidase IV (DPP-IV), and α-glucosidase. Furthermore, the peptides are predicted to possess antioxidant, antithrombotic, and hypotensive effects, as well as the ability to stimulate glucose uptake and influence various enzyme activities such as phosphoglycerate kinase.

Several identified peptides originated from master proteins not classically classified as milk proteins, including cytoskeletal (e.g., keratins, actin), immune-related (e.g., immunoglobulins, β2-microglobulin), and regulatory proteins (e.g., annexin A1). This observation is consistent with previous proteomic studies demonstrating that human breast milk is a complex biological fluid containing not only secreted milk proteins but also cellular and immune components derived from mammary epithelial cells, immune cells, and extracellular vesicles. Enzymatic digestion of these proteins can generate bioactive peptide fragments, some of which have been reported to exhibit regulatory or signalling-related biological activities.

MTT assay results revealed that BM hydrolysate exhibited significant cytotoxic activity on MCF-7 breast cancer cells (Figure 1A). Interestingly, the most potent inhibition was observed at lower concentrations, particularly 5 µg/mL; at this concentration, cell viability was significantly reduced by approximately 18% compared to the control group ($p<0.001$). As the concentration increased above 25 µg/mL, the inhibitory effect remained statistically significant but showed a slight plateau ($p<0.05$); this suggests a non-linear dose-response relationship typical of complex biological hydrolysates. On the other hand, Real-Time Cell Assay (RTCA) growth curves (Figure 1B) also confirmed the MTT findings, demonstrating that the antiproliferative effect began shortly after treatment. Lower concentrations (0.31-5 µg/mL) of BM hydrolysate showed a significant divergence from the control curve, with the 5 µg/mL concentration consistently maintaining a lower Cell Index value throughout the 96-hour period. At higher concentrations (5-100 µg/mL) of BM hydrolysate, the growth curves initially showed fluctuations, followed by a gradual decrease in Cell Index towards the end of the 96-hour incubation period; this indicates that BM hydrolysate maintains inhibitory suppression for an extended period without significant cell recovery.

The 18% decrease in viability observed in MCF-7 cells following treatment with BM hydrolysate, along with a plateau-type dose-response pattern at higher concentrations, reflects the characteristic biochemical behavior of complex food-derived peptide mixtures. Such plateau-type responses are frequently reported in studies investigating bioactive protein hydrolysates [25, 26]. This non-linear profile can primarily be explained by concentration-dependent intermolecular hydrophobic interactions that promote peptide aggregation at high doses (50–100 µg/mL). Peptide aggregation can reduce the effective concentration of biologically active monomers and limit further biological activity by sterically inhibiting their interaction with cellular target [27]. Consistent with the nature of food-derived bioactive peptides, such hydrolysates typically function not as aggressive cytotoxic agents, but as modulator molecules capable of exhibiting maximum biological activity at lower concentration ranges, sometimes displaying hormetic-like dynamics [25, 26].

Importantly, no IC_{50} value could be determined in the tested concentration range, indicating that BM hydrolysate does not cause strong acute cytotoxicity under the current conditions. However, the observed moderate but statistically significant and reproducible effect supports the conclusion that BM-derived peptides exhibit a sustained growth inhibitory effect. Taken collectively, these findings suggest that BM hydrolysate has potential not as a conventional chemotherapeutic agent, but rather as a long-term protective or adjuvant bioactive component, requiring further fractionation and mechanistic characterization.

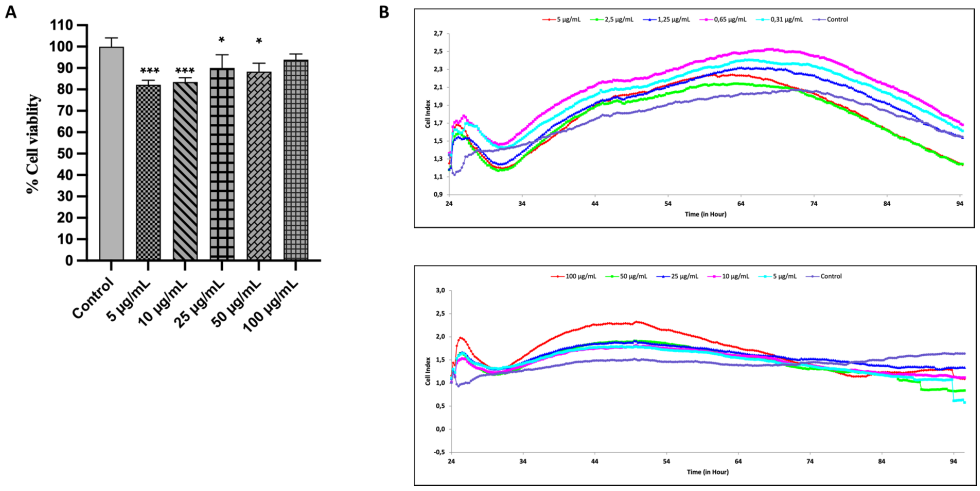

Figure 1. The dose-dependent antiproliferative effects of BM hydrolysate on MCF-7 cells. A) MTT results, B) Impedance-based cell index results. ***p<0.001 and *p<0.05 compared to control group.

Proteomic analysis BM-treated MCF-7 cells revealed differential expression of 160 proteins, with 80 upregulated (2- to 32-fold) and 80 downregulated (2- to 43-fold) compared to untreated MCF-7 cells. These proteins were found to be associated with cytosolic signal transduction, apoptosis regulation, and stress responses.

Table 2 presents the HPepDock interaction scores (kcal/mol) for bioactive BM peptides and differentially expressed proteins in MCF-7 cells. Lower values indicate stronger binding affinity.

Table 2. HPepDock docking scores of BM hydrolysate peptides and up-regulated or down-regulated proteins of BM-treated MCF-7 cells

Peptide	HPepDock Docking Scores (kcal/mol)	Galectin-3	Ras suppressor protein-1	Myeloid cell leukemia-1	Apoptosis-inducing factor-1
1	HGGGGGGFGGGGFGSR	-177.7	-190.8	-222.6	-192.8
2	SGGGGGGGLGSGGSIR	-148.5	-164.8	-176.1	-167.4
3	FGANAILGVSLAVCK	-189.0	-176.5	-209.5	-179.4
4	SLPCDICK	-143.1	-124.7	-165.5	-139.7
5	GGSISGGGYGSGGGK	-159.5	-193.0	-201.1	-183.2
6	GPSVFPLAPSSK	-169.2	-172.1	-212.7	-189.1
7	HMWPGDIK	-170.1	-178.9	-209.9	-204.1
8	LGPGMADICK	-156.1	-154.6	-173.9	-159.1
9	QGVDADINGLR	-165.0	-157.7	-162.1	-156.3
10	AGFAGDDAPR	-163.8	-166.2	-171.4	-180.2
11	LAADDFR	-160.8	-161.1	-169.1	-172.2
12	DAEAWFNEK	-180.8	-172.7	-172.0	-166.9
13	FSGSGSGTDFTLK	-174.8	-169.1	-188.01	-186.6
14	SHFEQWGTLTDCVVMR	-194.0	-213.6	-222.2	-216.0

Peptide 14 exhibited the most favorable docking scores with both the downregulated protein Galectin-3 (1A3K; −194.0 kcal/mol) and the upregulated protein Ras suppressor protein-1 (7D2S_A; −231.6 kcal/mol). Peptide 1 showed the most favorable docking scores with the downregulated protein Myeloid cell leukemia-1 (Mcl-1) (8G3S; −222.6 kcal/mol), while peptide 14 also demonstrated comparatively favorable interaction scores with the upregulated protein Apoptosis-inducing factor-1 (AIF-1) (4LII; −216.0 kcal/mol) (Table 2).

Table 3 shows the AutoDock Vina docking scores of bioactive peptides with the same set of up- and downregulated MCF-7-associated proteins*. In silico* docking analysis was performed to explore potential interactions between the identified peptides and selected target proteins associated with cancer-related pathways. Several peptides demonstrated docking scores indicating potential interactions with Ras suppressor protein-1 (7D2S-A) and Apoptosis-inducing factor-1 (4LII). These results suggest that certain peptides may interact with these proteins, although further experimental validation is required.

Table 3. Molecular docking scores of BM peptides and BM-treated MCF-7 cells

Peptide	Molecular docking scores (kcal/mol)	Galectin-3	Ras suppressor protein-1	Myeloid cell leukemia-1	Apoptosis-inducing factor-1
1	HGGGGGGFGGGGFGSR	-6	-6.1	-6.5	-8
2	SGGGGGGGLGSGGSIR	-6.1	-5.3	-7	-5.9
3	FGANAILGVSLAVCK	-5.7	-5.9	-7.3	-6.5
4	SLPCDICK	-5.2	-6	-7.1	-6.1
5	GGSISGGGYGSGGGK	-4.9	-6.5	-7.9	-6.6
6	GPSVFPLAPSSK	-6	-6.6	-7.8	-6.4
7	HMWPGDIK	-5.8	-6.1	-8	-6.5
8	LGPGMADICK	-5	-5.9	-7.9	-5.8
9	QGVDADINGLR	-5.3	-4.9	-7.4	-6.5
10	AGFAGDDAPR	-5.4	-6.8	-8.1	-5.7
11	LAADDFR	-5.8	-5.7	-8.5	-7.8
12	DAEAWFNEK	-6.3	-6.6	-8	-9.1
13	FSGSGSGTDFTLK	-6	-6.5	-7.4	-6.8
14	SHFEQWGTLTDCVVMR	-6	-6.3	-6.6	-6.3

Binding site analysis indicated specific amino acid residues involved in peptide–protein interactions. For Galectin-3 (1A3K), DAEAWFNEK (peptide 12) yielded the most favorable docking score (−6.3 kcal/mol) and was predicted to interact with ARG144, ASP148, ARG162, GLY165, LYS176, TRP181, GLY235, SER237, and GLY238 (Figure 2).

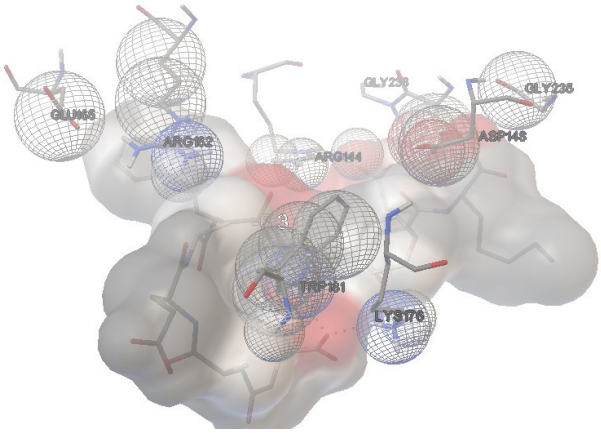

Figure 2: Autodock visualization of Galectin-3 and DAEAWFNEK peptide (Peptide 12)

Galectin-3, typically associated with cancer progression and apoptosis resistance, was found to be downregulated in BM-treated MCF-7 cells. In silico docking analyses indicated that several peptides particularly DAEAWFNEK, could potentially interact with galectin-3. These observations may be related to alterations in apoptosis-associated pathways; however, further experimental validation is required [28].

Ras suppressor protein-1, a protein involved in cell-matrix adhesion and tumor suppression, was upregulated in BM-treated MCF-7 cells. The AGFAGDDAPR peptide showed one of the most favorable docking scores with Ras suppressor protein-1 which may influence adhesion-related signalling and metastasis [29].

Peptide 10 (AGFAGDDAPR) showed a favorable docking score with Ras suppressor protein-1 (−6.8 kcal/mol), and predicted to interact with residues such as HIS49, ASN69, PHE71, and HIS186 (Figure 3).

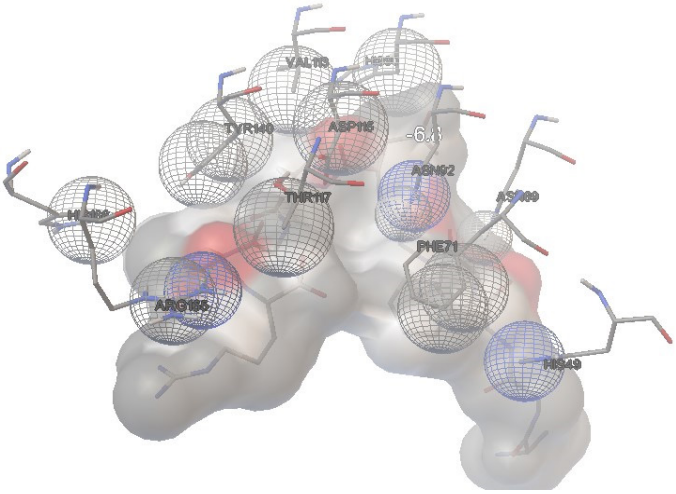

Figure 3: Autodock visualization of Ras suppressor protein-1 and AGFAGDDAPR (Peptide 10).

Mcl-1, an anti-apoptotic protein from the Bcl-2 family, was downregulated in BM-treated MCF-7 cells. Its inhibition has been associated with suppressed tumor growth and enhanced apoptosis in breast cancer [30, 31].

LAADDFR (Peptide 11) (−8.5 kcal/mol) showed one of the most favorable binding affinities toward Mcl-1 and was predicted to interact with residues ARG130, GLN139, and ARG300 (Figure 4).

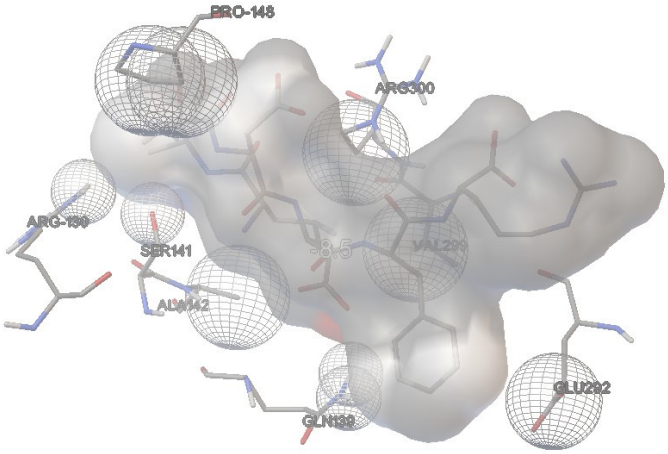

Figure 4: Autodock visualization of Mcl-1 and LAADDFR (Peptide 11)

AIF-1 expression was found to be upregulated in BM-treated MCF-7 cells following peptide treatment. DAEAWFNEK (Peptide 12) demonstrated the most favorable docking score with AIF-1 (−9.1 kcal/mol), and was predicted to interact with residues including ARG172, PHE284, and LEU497 (Figure 5).

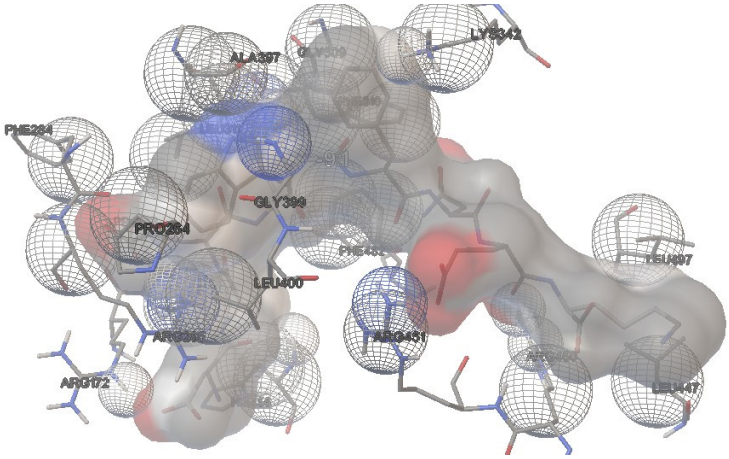

Figure 5: Autodock visualization of AIF-1 and DAEAWFNEK (Peptide 12)

In silico docking analysis revealed favorable docking score between AIF-1 and the peptide 12 (DAEAWFNEK), suggesting potential interactions **with the lowest docking score.** Since AIF-1 is known to induce caspase-

independent cell death [32], this *in silico* observation may be relevant to the apoptosis-related changes observed in BM-treated MCF-7 cells; however, no direct functional inference can be drawn without further experimental validation.

CONCLUSION

Docking analyses indicated that the peptides AGFAGDDAPR (peptide 10), LAADDFR (peptide 11), and DAEAWFNEK (peptide 12) exhibited favorable docking scores with several regulatory proteins and may influence the apoptotic regulation and cancer cell survival in MCF-7 cells. This study highlights the potential of combining enzymatic hydrolysis, proteomic profiling, and computational analyses to identify bioactive peptides that may be relevant to anticancer related pathways, providing a basis for the development of novel peptide-based therapeutic strategies.

EXPERIMENTAL SECTION

Breast Milk Collection

Human BM collection was approved by the Marmara University School of Medicine Ethics Committee (Approval no: 09.2019.893, Date: 04.10.2019). Eight volunteer mothers signed informed consent before donation. Samples were expressed via pump, pooled, and stored at −80 °C until use.

Gastrointestinal Digestion of BM

The simulated *in vitro* gastrointestinal digestion was performed by the method of Brodkorb et al. [33]. Simulated digestion fluids were prepared for the stomach and intestinal stages by the method of Minekus et al. [34]. Before digestion, milk was skimmed by centrifugation at 5000xg for 15 min at 4º C.

In oral stage, BM was mixed with equal volume of simulated salivary fluid (pH 7.0) and incubated at 37 ºC for 2 min.

In gastric stage, oral mixture was mixed with simulated gastric fluid. pH was adjusted to 3.0 and then 150 mg/mL pepsin was added to the mixture and incubated at 37°C for 2 hours.

In intestinal stage, gastric chyme was treated with simulated intestinal fluid. The pH was adjusted to 7.0. Pancreatin (2mg/mL) and bile salts (2mg/mL) were added to the mixture. And incubated at 37 ºC for 2 h. Digestion was stopped by adjusting pH to 9.0.

For epithelial barrier simulation, samples were dialyzed using a 100–500 Da molecular weight cut-off (MWCO) membrane against water for 2 h, then overnight at 4 °C to remove low–molecular-weight digestion products. After dialysis, the retentate fraction containing peptides above the MWCO was collected, filtered (Whatman No.1), and freeze-dried.

LC-MS/MS Analysis of BM Peptides

The resulting hydrolysate was then processed using the FASP kit (ab270519, Germany) for sample clean up and preparation prior to LC-MS/MS analysis. Peptides were analyzed using LC-MS/MS (Thermo Scientific Q Exactive HF, UltiMate 3000 RSLC). Data analysis was carried out using Proteome Discoverer 2.4 software with the Sequest HT search algorithm [35].

In Silico Prediction of Peptide Bioactivity and Toxicity

Peptide bioactivity was predicted using PeptideRanker [36]. The PeptideRanker program ranks peptides according to their potential for bioactivity on a scale of 0 to 1. Toxicity was assessed with ToxinPred [37]. Peptides with bioactivity scores >0.5 were further analyzed using BioPep for functional classification [38]. These peptides were examined for interactions with proteins differentially expressed in MCF-7 cells.

Assessment of Antiproliferative Effects of BM hydrolysate

MCF-7 cells (ATCC HTB22) were used in this study to investigate the antiproliferative effects of BM hydrolysate. The cells were cultured in a DMEM medium supplemented with 10% FBS and 1% penicillin-streptomycin at 37 °C and 5% CO_2 atmosphere. The antiproliferative effects of BM hydrolysate were evaluated using two complementary methods: The colorimetric MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay for metabolic activity assessment and the xCELLigence Real-Time Cell Assay (RTCA) (ACEA Bioscience) system for label-free, continuous monitoring of cell viability.

For the MTT assay, the cells (1×10^4 cells/well) were seeded in 96-well plates and cultured for 24 h prior to treatment. The next day, the cells were treated with different concentrations (5-100 µg/mL) of BM hydrolysate for 24 h. After incubation, 10 µL MTT solution was added, and the cells were incubated in a CO_2 incubator for 4 h. The optical density (OD) was read at 570 nm using 630 nm as reference wavelength on a multiwell plate reader (Biotech Instruments, Winooksi, VT, USA). All experiments were repeated twice, and each treatment was run in triplicate. The percentage of cell viability was calculated using the equation:

[mean (OD) of treated cells/mean OD of control cells] × 100

To evaluate the real-time antiproliferative profile of BM hydrolysate, MCF-7 cells were monitored using the xCELLigence RTCA platform. Baseline resistance was recorded by adding 100 µL of medium to 16 wells of an e-plate. Following a 24-hour pre-incubation period for cellular equilibration, cells were exposed to various concentrations of BM hydrolysate. Each treatment was performed in triple replicates, and cellular behavior was continuously monitored for 96 hours. Proliferation profiles were determined via the Cell Index (CI), reflecting changes in electrical impedance proportional to cell viability, adhesion, and density.

Proteomic Profiling of MCF-7 Cell Proteins

Cell lysates were prepared using RIPA buffer [39] and proteins were digested via FASP for LC-MS/MS analysis. The same instrumentation and software were used as for BM peptides. Proteomic alterations were analyzed to identify up-/down-regulated proteins.

In Silico *Analysis of Protein-Peptide Interactions*

In silico analysis of the biochemical pathways and the locations of the up-regulated and down-regulated proteins of MCF-7 cell lines were determined by using the Reactome software program [40].

Galectin-3 (P17931), Ras suppressor protein-1 (Q15404), Mcl-1 (Q07820), and AIF-1 (O95831) were selected based on their relevance to apoptosis, metastasis, and cell differentiation. Their 3D structures (PDB IDs: 1A3K, 7D2S_A, 8G3S, 4LII) were prepared in Maestro 13.7 (Schrödinger Release 2023-4: Maestro, Schrödinger, LLC, New York, NY, 2023).

Docking studies were performed using HPepDock (http://huanglab.phys.hust.edu.cn/hpepedock/), a program that evaluates protein-peptide interactions and validated with AutoDock Vina 1.1.2 [41]. The docking result was visualized by AutoDock Tools (version 1.5.6). The binding modes with the lowest binding free energy and the most cluster members were chosen for the optimum docking conformation.

Statistical Analysis

Data generated in this study were presented as mean ± standard deviation (SD). Data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Differences were considered statistically significant at $*p<0.05$ and $***p<0.001$. For cell culture experiments, at least six replicate experiments were carried out. Statistical analyses were conducted using GraphPad Prism 5.0 software (GraphPad Software, San Diego, CA, USA).

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