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Design and Synthesis of certain Novel Peptides for Dual Selective Activity of Specific Cells

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ABSTRACT

Cancer and the multi-resistant diseases that plague people today must be controlled to lower mortality rates. With the low susceptibility to resistance, the design and synthesis of peptide assembling was a superior alternative upgrading source for future chemotherapeutic medications. This paradigm first appeared in the pharmaceutical industry. It has been demonstrated that specific peptides exhibit dual functions as antibacterial and anticancer peptides (ACPs). Using a minimalized approach, a 10-residue peptide P1 and Rhodamine tagged peptide P2 were designed and synthesized using solid phase peptide synthesis method (SPPS) for selective activity against microbial and cancer cell lines. Peptide P1 contains RGD sequence has a net charge of +2 and peptide P2 has net charge of -4. The peptide P1 and P2 are characterized by using spectroscopic techniques. Circular dichroism studies showed changes in the secondary structure of peptide 1 and peptide 2 with buffer. Cytotoxicity assay exhibited the viability of normal and cancer cells up to 5 μg concentrations of peptide 1.Thus, Peptide 1 acts on therapeutic properties like antibacterial and anticancer. Both peptide activities are checked against gram-positive and gram-negative bacteria at lower concentration. We can ensure the toxicity level of designed both peptides. Peptide P1 and peptide P2 sequence are non-toxic and recognition of selective activity against cancer cells.

Keywords : Designed Peptide, Antimicrobial Activity, Hydrophobic, Solid-Phase Peptide Synthesis, Cytotoxicity

I. INTRODUCTION

Currently, the world is faced with complicated diseases encountered by various viruses, fungi, bacteria and cancer cells. Therapeutic peptides influenced some factors needed for drug resistance, lack of tumor selectivity and solubility. Recently many cancer therapy has been developed, but anticancer peptide

(ACP) as lesser side effect compare to that of other therapy methods. Antimicrobial peptides2.3, 43, 44, (AMPs) are the host defense peptides, (Tossi et al., 2005). with most of them being the cationic (positively charged) and amphiphilic (hydrophilic and hydrophobic) α-helical peptide molecules—above instructions beneficial synthesis of peptide work. Modify peptide sequences in RGD-like amino acid residue with more biological properties and capabilities. Cationic peptides have most probably played antimicrobial activity. We have discussed AMP, especially positive charge amino acid arginine; more in the sequence.RGD peptide sequence has tumor-homing efficiency in the literature survey. Likewise, peptides1 containing Arg-Gly-Asp (RGD) 13motifs have been identified and used to target tumor cells. Another anionic peptide modified sequence iEFA as followed by Fmoc-chemistry protocols4, the designed anionic peptide can be expected to bind bacteria that are resistant to cationic peptides15 and drugs. A minimalist design approach has been adopted to find a short active segment of antimicrobial peptides in the present study. Using MSI-367 as the template peptide, a decapeptide segment was identified. Since the cationic nature of MSI-367 (Ayyalusamy Ramamurthyet al 2010) has been attributed to its activity against bacteria, the lysine amino acids in the sequence were changed to (Perumal& Pandey et al., 2013) glutamic acid. Thus, the designed anionic peptide can be expected to bind bacteria that are resistant to cationic peptides and drugs. Mostly electrostatic interaction between peptide and surface of cell membranes. Modify both synthesis decapeptides as activities checked normal and cancer cells. A current study showed that both iRGD and iEFA peptides depend upon the amino acid sequence's ability to penetrate tumor tissue. We to make design and synthesis curable diseases of the antimicrobial peptide and anticancer drug deliver peptide. The designed peptide was a possible secondary structure like α-helix, β-sheet, β-turn and random coil. Secondary structure11 helpful to antimicrobial activities of the peptide. Those peptide activities against Gram-positive and Gram-negative bacteria and cancer cells. N-terminal modification and Rhodamine attached peptide are potential of the drug deliver agent's chemical, biological properties and selective cancer cells. Efficiency of design peptide needed physicochemical properties, amino acid composition and the addition of chemical groups on the(Chiangjong et al. 2020) ACP sequence influences their conformation, net charge and exposure of the secondary structure, leading to an effect on targeting particularity and ACP-cell interaction, as well as peptide insertion capability, stability and efficacy.

From the above literature review, we design and synthesis of RGD sequence containing peptide P1 which is over expressed in cancer cell31 shows better anticancer activity compares to that of peptide P2 and Circular dichroism shows both peptide P1 and P2 having secondary structure from unorderedstructure. It helps to determine the selective activity of specific cells, because cationic peptide P1 is slightly preference to bind with anionic membrane of both cancer cell and bacterial cell.

II. METHODS AND MATERIAL

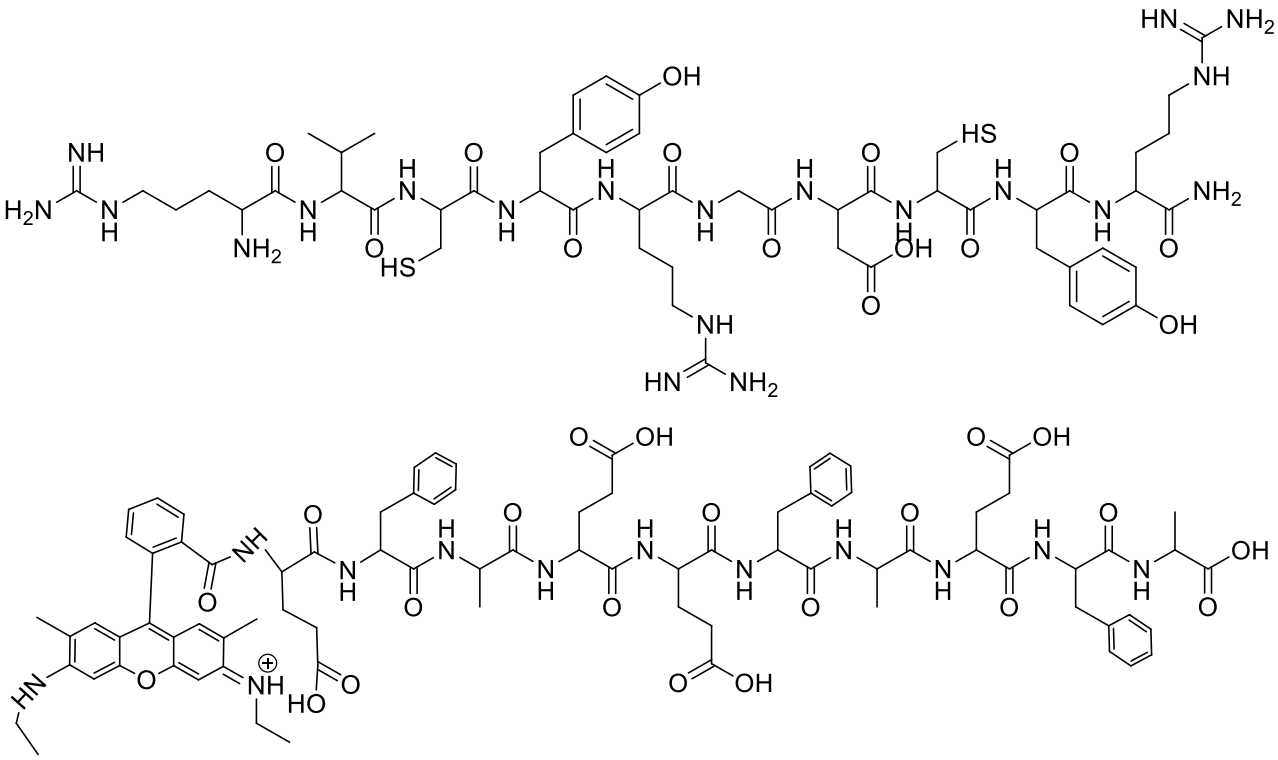
2.1 Chemicals and Reagents

Rink amide-methylbenzhydrylaminehydrochloride (MBHA) resin, 9-fluorenylmethoxy carbonyl (Fmoc) protected amino acids (Arginine, Valine, Cysteine, Tyrosine, Glycine, Aspatic acid, Alanine, Glutamic acid, Phenyl alanine), DIPEA- N, N-Diisopropyl ethyl amine, HOBt-1- Hydroxybenzotriazole, HBTU-2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate, TFA- Trifluoroacetic acid ordered from Sigma Aldrich Chemical Inc, Fluka and TCI chemicals. Thioanisole, m-cresol, indole and mercaptoethanol Rhodamine 6G,were ordered from Alfa Aesar and Sigma Aldrich Chemical Inc. Solvents using acetonitrile, Milli Q water or HPLC Grade water,

ethanol, dichloromethane, dimethylformamide, chloroform, acetic acid, diethyl ether, and methanol were purchased from Rankem chemicals ltd and Spectrochem. Pvt. Ltd. All chemicals and solvents were used peptide synthesis without purification and followed by Fmoc-chemistry protocols. The water-soluble tetrazolium-1 (WST1) reagent was purchased from Roche life Science, USA. Cell culture media, antibiotic-antimycotic solution and foetal bovine serum of United States origin were purchased from Sigma-Aldrich, USA.

2.2 Peptide synthesis

Fmoc-chemistry protocol with solid support material of Rink amide MBHA resin5,6 was used for the peptide synthesis21,38. Resin was deprotection with 20% piperidine, then washed and decanted Fmoc group removed from the resin. For synthesizing two peptides, one is peptide P1 (NH2-RVCYRGDCYR-CONH2), and another one is peptide P2 (Rh-EFAEEFAEFA-CONH2). Each amino acid was coupled as HBTU active esters in the presence of one equivalent amount of HOBT.DIPEA acts as a catalyst to convert the carboxylic acid into an activated ester form. In the coupling process, reagents were treated with resin and shaking for 2 hrs. TFA and scavengers such as Thioanisole, m-cresol, indole, and mercapto ethanol mixture (9.0:0.5:0.5, v/v) at room temperature 2 hrs, lead to the final step of peptide cleavage from resin. The purpose of the cleavage process as permanently removes the Fmoc protective group from the resin. The cleavage mixture was collected by filtration and concentrated using a roto evaporator, and treated with cold diethyl ether to precipitate the crude peptide. The crude peptide was isolated by centrifugation, dried using dry air, and stored at 4°C. Using rotavapor, the TFA in the peptide was removed. Diethyl ether was added to precipitate the peptide, and the peptide was again washed with acetic acid to remove impurities and by-products.(Scheme 1) Molecular weight was determined by the peptide using the ESI-Mass spectrum (+mode and - mode).



Scheme 1.Synthesis of N-terminal decapeptide and Rhodamine tagged decapeptide.

2.3 Reversed-phase high performance liquid chromatography (RP-HPLC)

RP-HPLC techniques for structural characterization, isolation and purification of peptides. Before starting, the analysis column was thoroughly washed with polar solvents. (Waters 1525 Binary HPLC) equipped with a C-18 reversed-phase column (4.6 × 150 mm) at room temperature. Separation of the peptide-based on hydrophobicity. The concentration of the peptide solution was fixed at 3mg/ml, and 25µl of the peptide solution was injected into the column at 25 µl loop volume capacity for four times to collect the pure peptide for further characterization. The gradient mode of separation of eluted peptide and flow rate is 1.0 ml/min. Gradient program showed here: 5–10 min, isocratic elution [90% eluent A (0.1%TFA in water) and 10% eluent B (0.1% TFA in acetonitrile)]; 10–45 min, linear gradient elution up to 80 to 100% B; 47–52 min, linear gradient elution back to 100% B; and 57–65 min, isocratic elution using 10% B. The flow rate was 1ml/min, and the UV detector wavelength was fixed at 214 nm.

2.4 ESI-MASS Spectrum:

The mass spectrum was recorded using LC/MS/MS-PE sciex API-3000 with an ESI source. Molecular weight determined of the peptide sequence using ionization technique involves the addition of a proton or multiple protons.ESI with quadrupole or ion trap analyzers also allows for MS analysis at relatively high LC flow rates (1.0 ml/min) and high mass accuracy (±0.01%), adding a new dimension to the capabilities of LC characterization. In polar organic solvents, the sample concentration is 3mg/ml. The combination of LC and ESI-MS is excellent for routine and reproducible molecular weight determinations on a wide variety of compounds, whether they are positively (i.e., peptides) or negatively (i.e., oligonucleotides) charged

2.5 FT-IR spectroscopy:

FT-IR absorption spectral peak characterization was used to determine the peptide structures. Especially the amide group of peptides has identified and recorded the IR spectrum by Perkin Elmer spectrum Two UATR FT-IR spectrometer. The Spectra region is shown in the frequency range of 400 – 4000 cm-1, under a resolution of 2 cm-1 with a rate of 2 mm sec-1 in 20 scans. Spectrum peak was analyzed on the peptide's secondary structure, and evidence of the amide I spectra was performed.[11,12]

2.6 CD spectroscopy:

CD spectrum was characterized and studied by the secondary structure of the peptide. A Jasco J-715 spectropolarimeter was used to record the circular dichroism spectra. Samples are **P1** and **P2** were recorded to various solvents like water alone, phosphate buffer alone at pH 7.4, Ethanol alone, Ethanol with phosphate buffer and Ethanol with Water using 0.2 mg/ml solution were taken in a quartz cuvette (path length =0.1 cm), and the spectra were recorded at 25°C with a scan rate of 50 nm/min over the range from 197 to 250 nm.

2.7 NMR Spectroscopy :

The molecular structure of the peptide compound has been examined using Nuclear magnetic resonance, and this technique has been used to structurally elucidate and characterize amino acid residues in the peptide sequence. A BRUKER-DMX 400 Spectrometer would be used to record the NMR spectrum at a proton resonance frequency of 400 MHz In the peptide compound; the chemical shift value of the various resonance protons is assured. Especially backbone of the NH amide bond in the peptide sequence[13,30] has been identified. NMR had been used to record deuterated solvents like DMSO (d6).

2.8 Antimicrobial studies

2.8.1 Antibacterial studies:

Peptides 1 and 2 possess antibacterial activity against gram-positive and gram-negative bacteria. Check the activity of the peptides P1 and P2 using the well diffusion method (Manikandan et al., 2017) at different concentrations of the peptides. With the use of cotton swabs, a fresh overnight (24 hours) bacterial culture (1x105cells/ml) was disseminated evenly on the top of the nutritional agar[41]. Then, using a sterile cork borer, 6 mm holes were punctured. Peptides in various volumes (25-75 µl) were aseptically loaded into the holes. For all of the tests, Ampicillin (10 mg/ml) was employed as a positive control sample; following that, the test plates were incubated for one day (24 hours) at 372°C, and the zone of inhibition was measured.

2.9 Anticancer studies

2.9.1Cell culture

The MDA-MB-231 cell line was acquired from American type culture collection (ATCC), USA. The cells were maintained in Dulbecco's modified eagle medium (DMEM) supplemented with 10% heat-inactivated foetal bovine serum (FBS) and the antibiotic-antimycotic solution containing streptomycin, amphotericin B and penicillin. Sub-culturing was done by detaching the adhered cells using 0.25% trypsin– ethylene diamine tetra acetic acid (EDTA). Cell culture flasks were maintained under a humidified atmosphere with 5% CO_2 at 37°C.

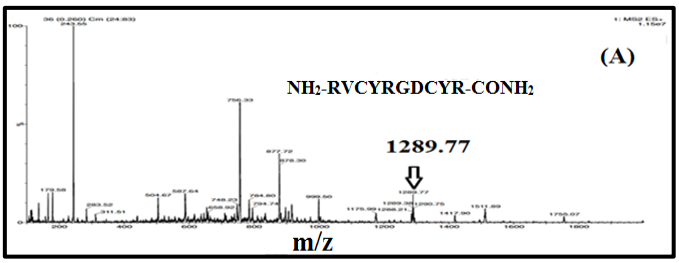
2.9.2 Cell proliferation assay

To examine the effect of peptide samples (P-I and P-II) on the proliferation of MDA-MB-231 cells, the water-soluble tetrazolium-1 proliferative assay (WST-1)[45,46] was performed. Briefly, the MDA-MB-231 cells were seeded at a density of 2×10^4 cells/wells with 100 µl volume in 96-well plate. After 24 h, the cells treated with specified concentrations (1 µg and 5 µg) of each sample for 24 h. Cells without sample served as control. After treatment, 5 µl of WST-1 reagent was added to each well and incubated at 37°C for 1 h. The absorbance was measured at 450 nm using a multi-mode plate reader (BioTek, USA). The cells were also visualized under a phase-contrast microscope at 10X magnification (Leica, Germany) and the images were captured and analyzed.

III. RESULTS AND DISCUSSION

Fmoc-chemistry protocol is based on synthesized peptide compounds using the solid-phase synthesis method. The peptide has ten amino acids and peptide P1 is designed and synthesized from Tachyplesin peptide and P2 is obtained from MSI-367 antimicrobial peptide, and modified with Rhodamine at N-terminal region. During peptide synthesis, each amino acid was coupled with Rink amide MBHA resin to form protected amino acids, The entire synthesis process took place in a simple peptide vessel without transfer to any vessels, heating and hazardous chemicals. During isolation and purification of the cleaved crude peptide, various instruments suitable for the characterization study are used to evaluate the peptide's molecular weight and structural details.

3.1 ESI-Mass Spectroscopy



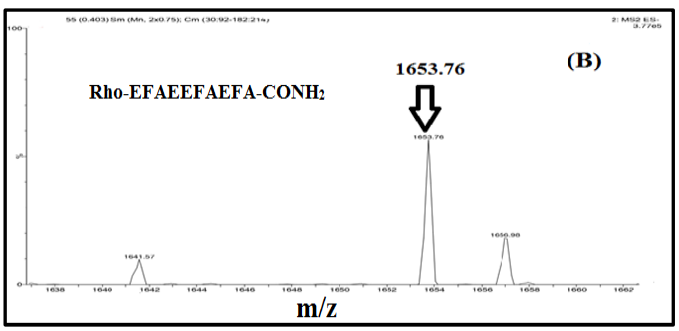


Figure 1.1(A). ESI-Mass analysis molecular weight of N-terminal decapeptide **1289.77** and (**B**) Rhodamine tagged decapeptide molecular mass **1653.76.**

(**Figure 1.1 A)**The molecular weight of peptides are confirmed by ESI-MASS spectroscopy. The calculated mass of P1 (1289.57) is matched with the observed molecular weight (1289.77) and also the calculated mass of P2 (1650.32) is matched with the observed molecular weight (1653.76).**(Figure 1.1 B).**

3.2 Reversed phase - High performance liquid chromatography (RP-HPLC)

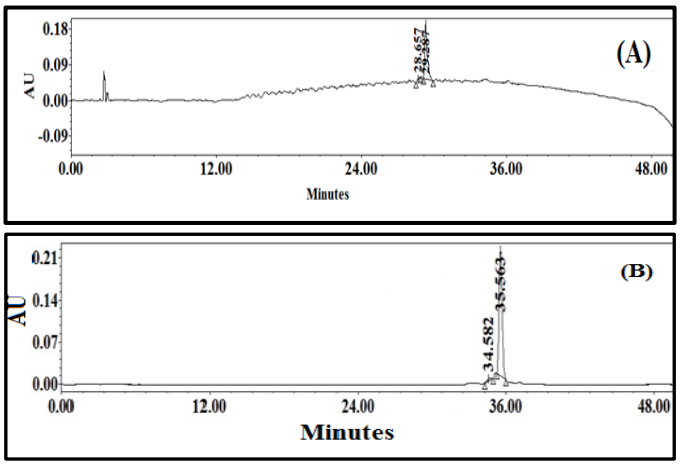


Figure 1.2(A) RP-HPLC Purification of peptide (P1) 98.36 % and RT of peptide (P2) 29.287 Minutes and**(B)** RP-HPLC Purification of Rhodamine attached peptide (P2) 98.22 % and RT of peptide (P2) 35.563 Minutes.

The purity of the peptides are analyzed by RP-HPLC, the peptide P1 shows 98.36 % purity & retention time is 29.28 minute and Peptide **P2** shows 98.22% purity & retention time is 35.56 minutes. **Figure 1.2** A and B.

3.3 FT-IR Studies

From the FT- IR analysis, the amide I band (between 1600 and 1700 cm^{-1}), predominantly associated with the C=O stretching vibration and directly related to the backbone conformation, was the most intense absorbance band.At 1,663 cm-1, Amide I shows a stretching vibration of C=0 associated with backbone conformation. N-H bending and C-N stretching vibration are evident in the Amide II band's IR range between 1470 and 1570 cm-1, which appears peat at 1510 cm-1.FT-IR Peak obtained spectra in this amide III band at 1238 cm-1 in the IR range of Amide III bands from 1231 to 1238 cm-1. The IR spectrum predicts two different structure forms, with amide I peak assigned helix turn and amide II and III denoting an unordered structure of **P1**.same literature survey following in **P2**, amide I peak at 1630 cm-1 and amide II peak in IR at 1531 cm-1 and amide III peak at 1210 cm-1 in the IR spectrum. As discussed, secondary structure predicts **P2** for β-turn and unordered structure from the FT-IR Fig 1.3.

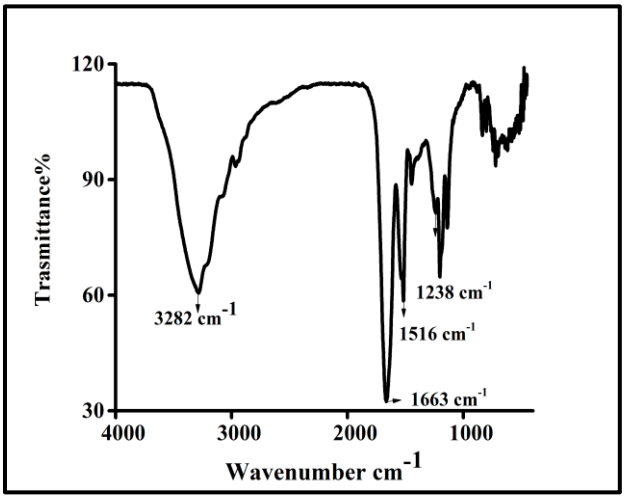


Figure 1.3 (A) FTIR spectrum of P1

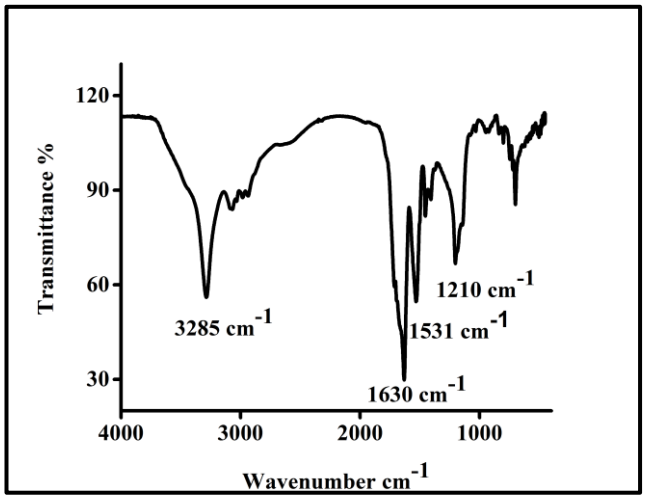


Figure 1.3 (B) FTIR spectrum of P2

3.4 ^{1}-H NMR Spectroscopy study

Both peptide **P1** and **P2 (Figure 1.4)** comprise aromatic proton peaks that have been identified utilizing ^{1}H NMR, which has been used to record the chemical shift value of the backbone NH bond peak.

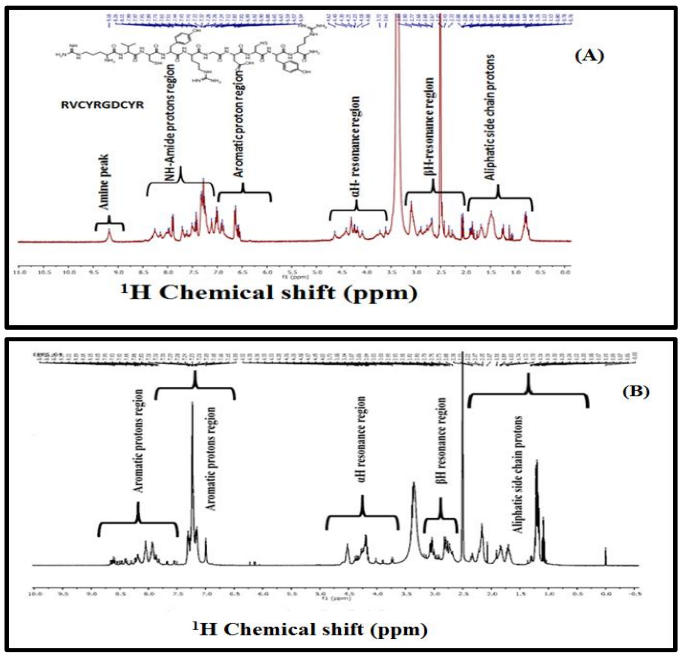


Figure. 1.4A (P1) and **B** (P2) represented ^{1}H-NMR (Bruker Advance 400 MHz, Dmso-d_6) range shows aromatic proton resonances and amide proton resonances.

3.5 CD Spectrum analysis

The CD spectrum peptides are tested by using different solvents and it reveals that, peptide **P1** exhibited negative minimum value at ~222 nm. As a result, random coil conformation at pH 7.4 absence of any positive CD signal shows the lack of a β-sheet or β-turn conformation. The CD spectra for peptide **P2** shows a positive band at ~219 nm and a negative minimum at ~200 nm were visible in the CD spectra.

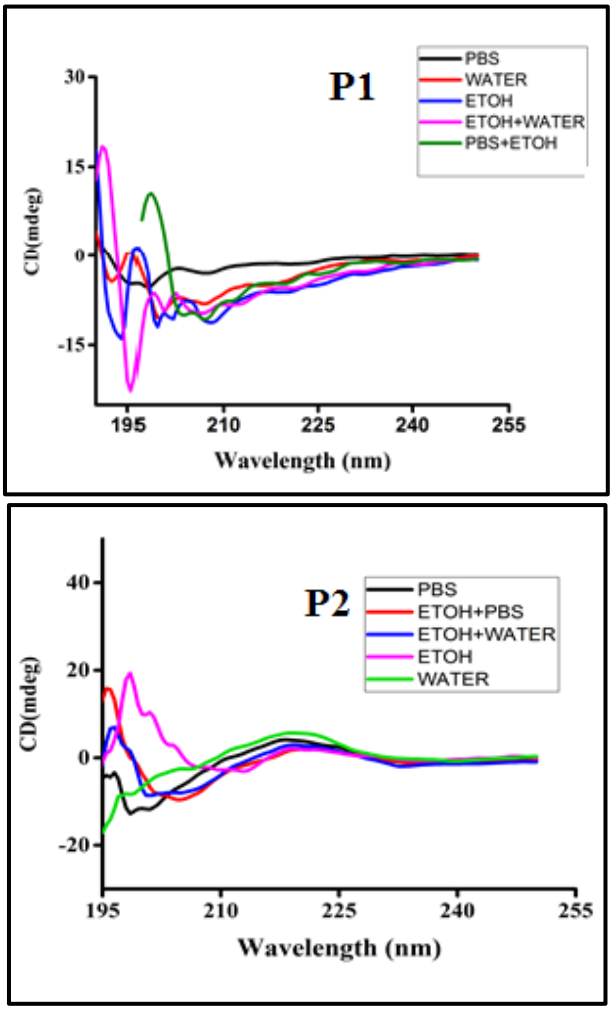


Figure. 1.5 – CD spectra (195-250nm) of P1 and P2 peptides as well as N-Terminal decapeptide and Rhodamine attached decapeptide.

Given that the peptide's sequence comprises aromatic amino acids, both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions are anticipated, The negative minima

at ~200 nm indicate a considerable quantity of random coil, even though the positive band at~219 nm is attributed to β-turn conformation (unordered structure) It is commonly known that in aq. buffer, the terminal regions frequently take on an extended or random coil shape. The peptide **P1** thus appears to contain nascent -helix turns.

3.6 Antibacterial activity

Gram-positive and gram-negative bacteria were used to treat the antibacterial tested, employing the well diffusion method for **P1** and **P2**.Both gram-positive and gram-negative bacteria were more susceptible to peptide **P1**. However, neither bacteria responded to peptide **P2**.As illustrated in **figure 1.7**, further experiment results revealed that both peptides suppressed antibacterial activity at different concentrations, with peptide **P1** being more efficient than **P2** against both gram-positive and gram-negative bacteria.

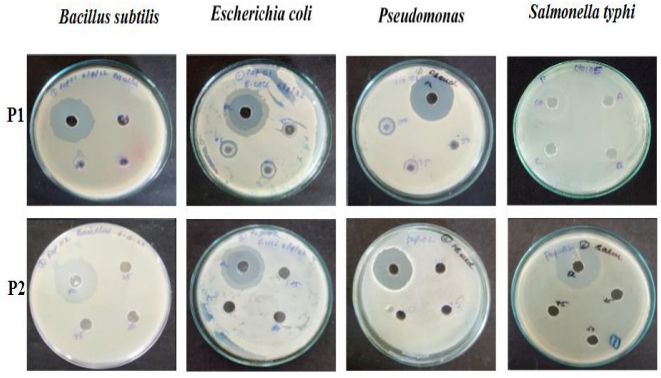


Figure 1.6. Peptide 1 and Peptide 2 treated with gram positive and negative bacteria.

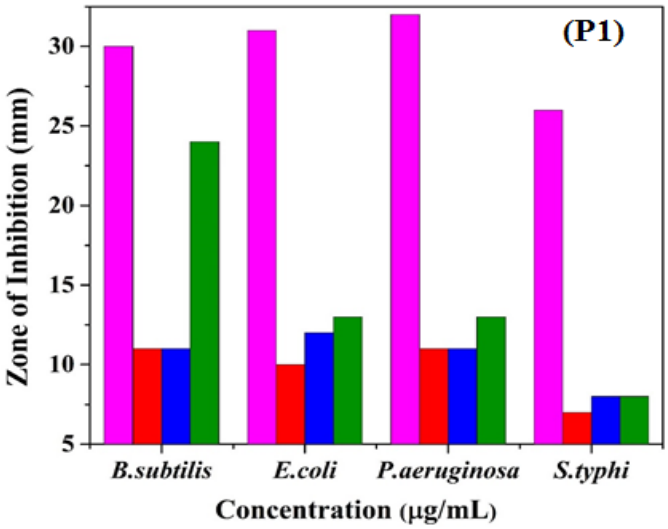


Figure 1.7. Concentration of P1

3.7 Anticancer Activity

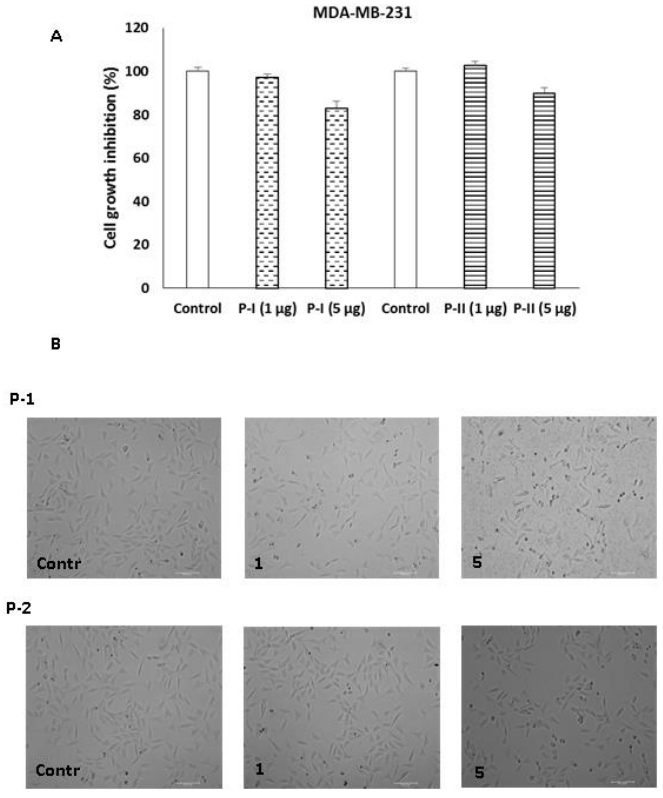


Figure 1.8 Effect of peptides on the growth of human breast cancer (MDA-MB-231) cells

The growth inhibitory efficacy of peptide samples (P1 and P2) in human breast cancer (MDA-MB-231) cells is shown in **figure 1.8**. The results showed that both the samples at 5 µg concentration significantly inhibited the growth of MDA-MB-231 cells **(Fig. 1.8 A)**. However, P1 exhibited slightly better growth inhibitory effect (17 %) compared to P2 (11 %). The microscopic observation confirms the data obtained in the cell proliferation assay, where reduced cell number with increased dead cells was observed in 5 µg peptide treated cells**. (Figure 1.8 B)**. The data indicate that the peptide concentration of 5 µg and above could be used for cancer therapy applications.

RGD is based on a decapeptide sequence that chooses cancer cells, and gram-positive and negative bacteria must meet particular criteria to access the microorganism and cancer cell membrane.RGD sequence (RVCYRGDCYR), modified for the anticancer property, was derived from tachyplesin.MSI-367 antimicrobial peptide sequence was used to create an EFA decapeptide sequence. Following the formation of the dermcidinantimicrobial peptide sequence base drug, MSI-367 sequence as KFAKKFAKFAKKFAKFAKKFA was examined after being modified EFAEEFAEFA to act as an anticancer peptide. In clinical Gram-negative bacteria, antibiotic resistance is frequent, severely restricting the therapeutic options available. Due to the increased probability of antibacterial characteristics, the RGDsequence (NH_2-RVCYRGDCYR-$CONH_2$) of decapeptide in positive charge of arginine residue is the predominant makeup of this peptide chain. Moreover, it was determined that an EFA-modified peptide had a higher binding affinity to E. coli than to S. aurous.

IV. CONCLUSION

Cationic and anionic decapeptides were synthesized and modified like RGD and EFA, but net charges various as +2 and -4.peptides confirm the structure elucidation, molecular weight, secondary structure and other characterization also.Secondary structure of peptide primary role in the targeted microbial membrane. ACP therapy influences cancer-related molecular targets, bind anticancer therapeutics and stimulates cancer-related and healthy cell environments in biological systems. Notably, natural and synthetic peptides have been produced as cutting-edge cancer treatment methods. Peptide**1**have antibacterial activities compared to no activities for Peptide**2**. Peptide**1**and Peptide**2** have various volumes consumed in activities study but significant changes in the antibacterial activities due to electrostatic interaction between peptide and bacteria cell membrane in the data evidence. Especially breast cancer cells against our peptides 5 µg and above concentration reduced and increased death cells for the proved in the Cell proliferation assay. Both peptides could be consider used for cancer therapy applications.

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