# Molecular Docking of Cathelicidin (LL-37) in Mesenchymal Stem Cells Metabolite to Growth Factor, Antibacterial and Inflammatory Cytokine Biomarkers

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**Abstract**

Salivary gland function impairment is one example of a Type 2 Diabetes Mellitus (T2DM) consequence caused by a loss of microcirculation. Mesenchymal stem cells' (MSCs) metabolite may modulate the immune response and fight pathogen infection through the synthesis of cathelicidin (LL-37) for tissue regeneration.

Objectives to investigate the active compound of the MSCs' metabolite, namely cathelicidin (LL-37), which binds to the effects of interleukin (IL)-10, IL-17, vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), tumor growth factor beta (TGFβ), insulin growth factor (IGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), tissue inhibitor matrix metalloproteinase-1 (TIMP-1), matrix metalloproteinase (MMP)-8 and -9, dectin, flaggelin, and peptidoglycan through a bioinformatics approach, in silico study.

RCSB PDB was used to prepare the peptide Cathelicidin (LL37) (RCSB ID: 2K6O) and the biomarker targets for IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, TIMP-1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, and MMP-8. PyMol v2.5 software for molecular docking optimization and standard publication-style visualization was used to remove water molecules and ligand impurities from target surfaces.

Cathelicidin (LL-37) has a great negative binding energy value with IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, TIMP1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, and MMP-8. Cathelicidins (LL-37) in MSC's metabolite has high negative binding energy value that may inhibits pro-inflammatory cytokines, microbial, tissue degradation enzyme related biomarkers and increase anti-inflammatory cytokines and growth factor as documented in silico.

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## Introduction

Diabetes mellitus (DM) is a systemic, metabolic, and endocrine illness characterized by high blood glucose levels that persist.[1] Type 1 diabetes mellitus (T1DM) is an autoimmune illness that causes the loss of insulin-producing pancreatic beta cells. T1DM has metabolic, genetic, and immunogenic variability, as well as age-related variances, necessitating a tailored strategy for each individual.[2] One of the most prevalent metabolic illnesses, Type 2 Diabetes Mellitus (T2DM), is caused by a combination of two basic factors: inadequate insulin production by pancreatic cells and the failure of insulin-

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sensitive tissues to respond correctly to insulin.[3] T2DM is regarded as a critical public health problem with a significant impact on human life and health care costs. Diabetes impairs people's functional capacities and quality of life, resulting in severe morbidity and early death. Concerns have recently been expressed that more than one-third of diabetes-related fatalities occur among adults under the age of 60. These developments have been blamed on increased consumption of poor foods and sedentary lifestyles, which result in a raised body mass index (BMI) and fasting plasma glucose.[4]

T2DM affects more than 90% of diabetic patients, causing microvascular and macrovascular problems that cause substantial psychological and physical anguish in both patients and caregivers, as well as a significant cost to health care systems. Despite increased understanding of type 2 diabetes risk factors and evidence for effective preventative programs, the disease's incidence and prevalence continue to climb globally.[5] Diabetes, if left untreated, causes a slew of health issues. Diabetes, as a hormonal and metabolic chronic illness, is a major contributor to a variety of other comorbid health problems, including cardiovascular disease, mental health issues, renal disease, eye-related disorders, neuropathy, rheumatoid arthritis, bone-related diseases, and so on.[6]

Salivary gland function impairment is one example of a T2DM consequence caused by a loss of microcirculation. Previous research found a malfunction in the submandibular salivary gland in a streptozotocin-induced hyperglycemic animal model.[7,8] T2DM impairs the function of the salivary glands. Poorly managed T2DM, on the other hand, has the greatest impact on stimulated whole saliva (SWS) flow rates. A previous study found a link between plasma and salivary CHGA levels and T2DM patients. Furthermore, the findings indicate that chromogranin A (CGHA) polymorphisms may be linked to salivary gland hypofunction and increased salivary CHGA production in T2DM patients.[9]

Salivary glands are the primary exocrine glands of the mouth and contribute physiologically to the maintenance of oral cavity homeostasis. The major glands are the parotid, submandibular, and sublingual glands, which are found in pairs, and the minor glands, which are considerably smaller and distributed throughout the buccal cavity. Salivary glands are characterized by their size, volume of secreted saliva, and location in the mouth cavity. Salivary glands, in particular, have been a focus of study and concentration in the diabetes study area. There is evidence that links the composition of salivary secretions to T2DM development.[10] Salivary gland impairments in T2DM has been shown to decrease the quality of life in patients. Because SWS flow rates tend to decrease in T2DM patients, several oral manifestations arise from that condition, such as oral candidiasis, dental caries, periodontitis, and oral halitosis.[11]

Nowadays, attention is directed to regenerative therapy using mesenchymal stem cells (MSCs) in an attempt to lessen the adverse effects of T2DM. MSCs are able to repair or replace damaged or degenerative tissues and improve functional recovery in experimental models and clinical trials.[12] human dental pulp stem cells (hDPSCs) transplanted in STZ-induced hyperglycemic rats were able to regenerate submandibular salivary gland defects by decreasing acinar cell vacuolization, increasing angiogenesis, increasing acinar cell number, interleukin-10, and tumor growth factor beta (TGF-β) serum levels. Human amnion-derived stem cells (hADSCs) have shown considerable advantages over other stem cells. the properties of hADSCs as a promising source of stem cells for cell therapy and regenerative medicine.[12] hADSCs or its exosome may possess advantageous molecules for regenerative therapy of tissue defects due to T2DM. MSCs originating from perinatal tissues such as the umbilical cord (UC) and amniotic membrane (AM) serve as ideal candidates for the treatment of T2DM due to their great advantages in terms of abundant source, proliferation capacity, immunomodulation, and plasticity for insulin-producing cell differentiation. Previous studies showed that hADSC-derived exosomes have shown encouraging results in enhancing diabetic wound healing.[14] During culture and passage, MSCs may release helpful exosomes, cytokines, and growth factors in the form of large or tiny molecules known as metabolites or conditioned media. MSC metabolites contained bioactive substances, including proteins, lipids, signaling molecules, and mRNAs.[15,16]

Among the many biological qualities of MSCs, their capacity to modulate the immune

response and fight pathogen infection through the synthesis of antimicrobial peptides (AMPs) has received a lot of attention in recent years. MSC-secreted AMPs are active against a variety of microbes, including bacteria, fungi, yeasts, and viruses. These cells primarily produce hepcidin, cathelicidin (LL-37), and defensin-2. These AMPs have been found to interact with MSCs to affect MSC proliferation, migration, and regeneration, demonstrating that such peptides have a broader biological function that may act as anti-inflammatory, pro-growth factors that may induce wound regeneration.[17] The co-culture of MSCs and their metabolites enhances cell migration and proliferation.[18] Metabolites of MSCs may act as anti-inflammatory and inhibit bone resorption markers such as Nuclear Factor Activated T-cells 1 (NFATc1), Tartate Resistant Acid Phospatase (TRAP), and Sclerostin in lipopolysaccharide-induced calvaria bone resorption in an animal model, as shown in a previous study.[19] Adipose mesenchymal stem cell metabolites (AdMSCM), a unique biological product, comprise a multitude of bioactive mediators capable of inducing a number of wound healing processes. AdMSCM oral gel has been shown to improve angiogenesis, vascular endothelial growth factor (VEGF), and fibroblast growth factor-2 (FGF-2) expression, as well as clinical results.[20] MSCs have direct antibacterial action, which is mediated in part by the production of cathelicidin (LL-37). The expression of LL-37 in MSCs increased following bacterial challenge, according to both m-RNA and protein expression data.[21]

There are several biomarkers that are important to monitoring the regeneration of the tissue defect due to T2DM, such as interleukin (IL)-10 as an anti-inflammatory marker[7], IL-17 as a pro-inflammatory cytokine[22], VEGF[20], FGF-2[20], TGF-β, insulin growth factor (IGF)[23], platelet-derived growth factor (PDGF)[24], epidermal growth factor (EGF)[25], hepatocyte growth factor (HGF)[26], tissue inhibitor matrix metalloproteinase-1 (TIMP-1), matrix metalloproteinase (MMP)-8 and -9.[26] In T2DM patients with obesity, macrophage activation and infiltration in adipose tissue contribute to persistent low-grade inflammation-induced insulin resistance. Although dectin-1 is primarily a pathogen identification receptor and a regulator of the innate immune response, its involvement in metabolic disorders is unknown. Dectin-1 may be considered an adipose tissue biomarker of metabolic inflammation in T2DM patients with obesity.[27] T2DM patients are prone to infection, which may lead to sepsis. Sepsis is a potentially fatal organ malfunction that needs specific attention for treatment, particularly given the participation of immunocompromised individuals. [28] The bacteria that make up the gut microbiota may influence a variety of host activities, including intestinal immune system maturation, obesity, cardiac metabolism, liver triglyceride storage, and brain development and behavior. The corresponding mechanisms involve increased energy harvesting via microbiota production of short-chain fatty acids for host use as well as the release of pro-inflammatory compounds like lipopolysaccharide (LPS), flagellin, and peptidoglycan, which may play an important role in T2DM and sepsis.[29]

The hypothesis of this study is Cathelicidin (LL-37) may have high negative binding energy value with IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, TIMP1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, & MMP-8 that act as anti-inflammatory, pro-growth factor, pro-regeneration and antibacterial, *in silico study*. Furthermore, the aim of this study was to investigate the active compound of the Metabolite mesenchymal stem cells, namely Cathelicidin (LL-37) which binds to the effects of IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, TIMP1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, & MMP-8 through a bioinformatics approach, in silico study.

## Materials and methods

The peptide cathelicidin (LL37) (RCSB ID: 2K6O) from the RCSB PDB (https://www.rcsb.org/) was employed as the ligand molecule in this work. RCSB PDB was also used to prepare targets for IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, TIMP1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, and MMP-8. PyMol v2.5 software for molecular docking optimization and standard publication-style visualization was used to remove water molecules and ligand impurities from target surfaces.[30,31]

In this investigation, the Ramachandran Plot was used to assess the validity of the peptide structure through the SAVESv6.0 server (https://saves.mbi.ucla.edu/). Valid models are

expected to be close to real-world circumstances and can be utilized for subsequent simulations. [32] The Expasy ProtParam site (https://web.expasy.org/protparam/) was used to assess the molecular stability of LL37 protein sequences in FASTA format. The purpose of this analysis is to determine stability using molecular parameters such as molecular weight, theoretical pI, amino acid composition, atomic composition, extinction coefficient, estimated half-life, instability index, aliphatic index, and grand average of hydropathicity.[33] When doing wet lab tests, the data generated by the prediction of peptide stability can be utilized as a reference.

The Cluspro v2.0 server (https://cluspro.bu.edu/login.php) was used to simulate the interaction of LL37 with IL-10, VEGF, FGF2, IFG, HGF, EGF, TGFβ, PDGF, TIMP1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, and MMP-8. The superimposed docking approach is used to provide binding energy data for assessing the amount of ligand activity on the target. The goal of this study's peptide-protein docking simulation is to inhibit and increase target response through ligand action. The ligand with the highest negative binding energy value is likely to cause a particular target action.[34]

The PyMol v2.5 program is used to display peptide-protein interactions in 3D structures, utilizing the color and structure selection approaches. The colors displayed are determined by the atomic composition of the ligands and the structure of a particular protein. In this study, structural types such as cartoons, sticks, and transparent surfaces with publishing requirements were employed. [35]

## Results

Cathelicidin LL37, RCSB ID: 2K6O acquired from a database with an organism source (*Homo sapiens*), molecular categorization is antimicrobial peptide, wild type (no mutation), wetlab visualization technique is NMR, molecular weight is about 4.5 kDa with atomic number 318, and residue total is 31 (Table 1). The database is searched for target information such as name, visualization technique, PDB ID, resolution, weight (kDa), sequence length (mer), and chain, after which the target and peptide are displayed with a clear 3D surface structure, cartoons, and sticks (Figure 1). The study's findings reveal that the favored region or core has a score of 93.8% (Figure 2), showing that the LL37 structure is real, as well as quantitative data for the evaluation (Table 2). The stability analysis results reveal that LL37 is stable (Table 3). Based on the findings of this study, LL37 is expected to be used as a reference while performing wet lab investigations.

| No | Name | Visualization Method | PDB ID | Resolution (Å) | Weight (kDa) | Sequence Length (mer) | Chain |
|---|---|---|---|---|---|---|---|
| 1. | IL-10 | X-RAY DIFFRACTION | 1INR | 2.00 | 18.67 | 160 | A |
| 2. | VEGF | X-RAY DIFFRACTION | 2VPF | 1.93 | 95.59 | 102 | A |
| 3. | FGF2 | NMR | 1BLA | - | 17.35 | 155 | A |
| 4. | IFG | NMR | 1B9G | - | 6.31 | 57 | A |
| 5. | HGF | X-RAY DIFFRACTION | 1BHT | 2.00 | 41.38 | 176 | A/B |
| 6. | EGF | NMR | 1P9J | - | 6.34 | 54 | A |
| 7. | TGFβ | NMR | 1KLA | - | 25.62 | 112 | A |
| 8. | PDGF | X-RAY DIFFRACTION | 3MJK | 2.40 | 116.4 | 169 | A/B |
| 9. | TIMP-1 | NMR | 1D2B | - | 14.27 | 126 | A |
| 10. | Dectin | X-RAY DIFFRACTION | 2CL8 | 2.80 | 32.92 | 139 | A/B |
| 11. | Flagelin | X-RAY DIFFRACTION | 2ZBI | 2.00 | 60.96 | 292 | A/B |
| 12. | Peptidoglycan | X-RAY DIFFRACTION | 2OQO | 2.10 | 23.77 | 200 | A |
| 13. | IL-17 | X-RAY DIFFRACTION | 5N92 | 2.30 | 31.41 | 132 | A |
| 14. | MMP-9 | X-RAY DIFFRACTION | 1L6J | 2.50 | 47.60 | 425 | A |
| 15. | MMP-8 | X-RAY DIFFRACTION | 1A85 | 2.00 | 18.22 | 158 | A |

**Table 1.** IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, TIMP-1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, MMP-8 as target samples information retrieved from RCSB PDB.

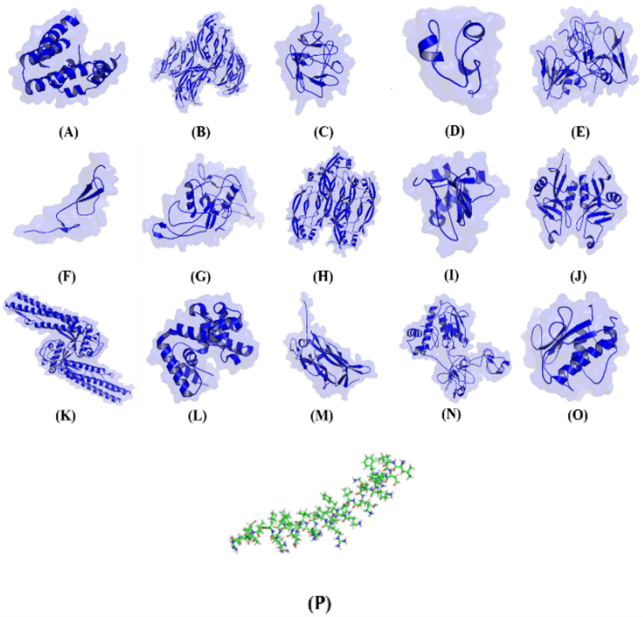


**Figure 1.** Targets and ligand structural visualization. (A) IL-10, (B) VEGF, (C) FGF2, (D) IFG, (E) HGF, (F) EGF, (G) TGFβ, (H) PDGF, (I) TIMP-1, (J) Dectin, (K) Flagellin (L) Peptidoglycan (M) IL-17 (N) MMP9 (O) MMP8 (P) LL37.

| Peptide | Ramachandran Plot | Residue Properties | G-factors | Planar Groups |
|---|---|---|---|---|
| Cathelicidin | 93.8% core<br>6.2% allow<br>0.0% gener<br>0.0% disall | Max.deviation: 4.6<br>Bad contacts: 0<br>Bond len/angle: 1.9<br>Class: 1,2,3 | Dihedrals: 0.19<br>Covalent: 0.63<br>Overall: 0.35 | 100.0% within limits<br>0.0% highlighted |

**Table 2.** Structural assessment quantitative data for validation.

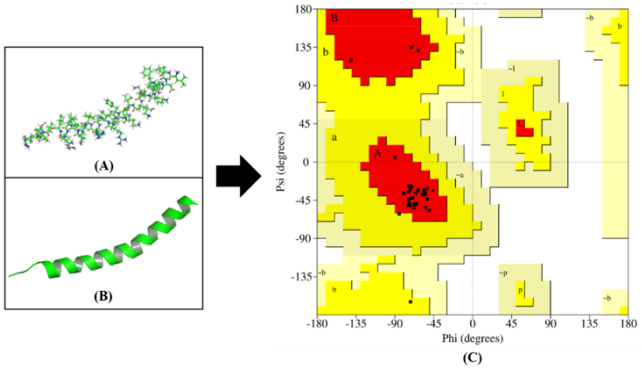


**Figure 2.** LL37 ligand Plot Ramachandran. (A) Ligand with stick structure (B) Ligand wih cartoons structure (C) Validation plot visualization.

| Peptide | FASTA Sequence | Molecular Count | Atomic Composition | Physicochemical Properties | Instability Index |
|---|---|---|---|---|---|
| Cathelicidin (LL-37) | >2K6O_1 LLGDFFR KSKEKIG KEFKRIV QRIKDFL RNLVPRT ES | Formula: $C_{205}H_{340}N_{60}O_{53}$<br>Amino Acid Number: 37<br>Postive Charged Residue: 5<br>Negative Charged Residue: 11<br>Total Number of Atoms: 658 | Carbon (C): 205<br>Hydrogen (H): 340<br>Nitrogen (N): 60<br>Oxygen (O): 53<br>Sulfur (S): 0 | Aliphatic index: 89.46<br>GRAVY: -0.724<br>Theoretical pI: 10.61<br>Molecular weight (kD): 4493.32 | Score: 23.34<br>Probable:Stable |

**Table 3.** The result of molecular stability analysis.

| No | Target | Binding Energy (kJ) | | |
|---|---|---|---|---|
| | | Cluster 1 | Cluster 2 | Cluster 3 |
| 1. | IL-10 | -1261.6 | -1176.3 | -1014.5 |
| 2. | VEGF | -1145.7 | -951.6 | -966.5 |
| 3. | FGF2 | -824.3 | -792.5 | -696.8 |
| 4. | IFG | -821.0 | -754.6 | -696.8 |
| 5. | HGF | -906.2 | -864.8 | -760.6 |
| 6. | EGF | -982.0 | -892.1 | -880.5 |
| 7. | TGFβ | -1000.0 | -942.9 | -791.8 |
| 8. | PDGF | -1014.8 | -1000.0 | -853.4 |
| 9. | TIMP1 | -942.5 | -883.7 | -888.4 |
| 10. | Dectin | -1042.2 | -985.6 | -927.4 |
| 11. | Flagelin | -856.8 | -836.1 | -781.6 |
| 12. | Peptidoglycan | -911.7 | -810.3 | -796.2 |
| 13. | IL-17 | -928.5 | -855.8 | -791.5 |
| 14. | MMP-9 | -1053.0 | -972.8 | -946.2 |
| 15. | MMP-8 | -872.8 | -836.8 | -802.7 |

**Table 4.** The docking result of Cathelicidin-biomarker targets.

The superimposed docking method was utilized in this investigation to determine the influence of the LL37 interaction on the activity of rising and decreasing targets based on binding energy. Because it has greater binding energy, LL37 is anticipated to boost the protein activity of IL-10, VEGF, FGF2, IFG, HGF, EGF, TGFβ, PDGF, and TIMP1 while decreasing dectin, flagellin, peptidoglycan, IL-17, MMP9, and MMP8. negative as compared to clusters 2 and 3 in mode cluster 1 (best binding) (Table 4). The docked ligand-target complexes are shown with clear surfaces, cartoons, and selected colors; the ligands have green and blue targets (Figure 3).

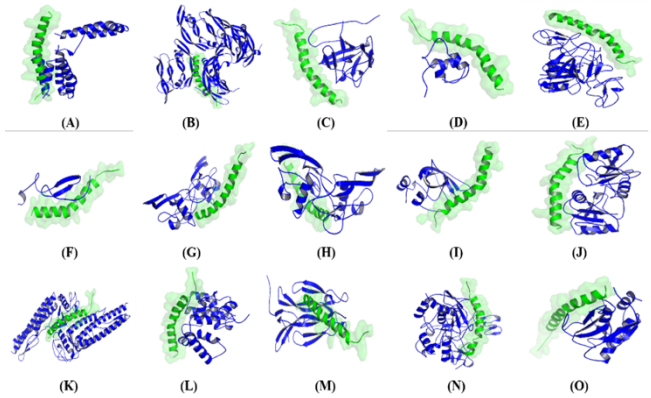


**Figure 3.** Targets-ligand structural visualization from the docking simulation. (A) IL-10_LL37, (B) VEGF_LL37, (C) FGF2_LL37, (D) IFG_LL37, (E) HGF_LL37, (F) EGF_LL37, (G) TGFβ_LL37, (H) PDGF_LL37, (I) TIMP1_LL37, (J) Dectin_LL37, (K) Flagellin_LL37 (L) Peptidoglycan_LL37 (M) IL-17_LL37 (N) MMP9_LL37 (O) MMP8_LL37

## Discussion

The structure validation includes the percentage value of the favorite region, residue characteristics, G-factors, and planar groups. The Ramachandran Plot was used to provide visual data from the identification findings of the structural validation in this investigation. A structure with a preferred value in the Ramachandran Plot greater than 90% indicates that the structure is suitable for further investigation. The fraction of preferred areas, residue characteristics, G-factors, and planar groups are the primary metrics utilized in structure validation identification. The Ramachandran plot is used to determine the validity level of the modeled structure while accounting for stereochemical factors. [36] The goal of peptide stability analysis is to determine stability using molecular parameters such as

molecular weight, theoretical pI, amino acid composition, atomic composition, extinction coefficient, estimated half-life, instability index, aliphatic index, and grand average of hydropathicity (GRAVY).[33] The goal of molecular docking is to detect patterns of molecular interactions and evaluate the amount of activity of the ligand bond on the target. The level of the binding energy score is referred to as the ability of ligand activity.[32,34] Binding energy is the energy created when the ligand binds to the target; this energy operates according to Gibbs' rule in thermodynamics. The bigger the negative binding energy value, the greater the potential for a ligand to influence target activity, such as increasing or reducing it.[31,35]

In this study, it was found that cathelicidin (LL-37) has a high negative binding energy value to several targeted biomarkers such as IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, TIMP-1, Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, and MMP-8, which indicates that LL-37 may have the potential to inhibit or enhance ligand activity. Based on the negative binding energy value of Cathelicidin (LL-37), it may enhance IL-10, VEGF, FGF2, IGF, HGF, EGF, TGFβ, PDGF, and TIMP-1 but decrease Dectin, Flagelin, Peptidoglycan, IL-17, MMP-9, and MMP-8 in silico.

MSCs have been widely employed in the treatment of several disorders in recent years. MSCs, according to recent research, play a crucial role in the treatment of illnesses, including infections, by generating antimicrobial peptides. Mesenchymal stem cells hasten wound healing via paracrine action. Mesenchymal stem cells carrying LL-37 promote human fibroblast migration, which is an important phase in the wound healing process. LL-37 hastens wound healing by interacting with bacteria and restoring tissue damage caused by infection. LL-37 is found in human neutrophils at high quantities (40 M or 630 g/$10^9$ cells) and is controlled in response to infection. The concentration of LL-37 differs between tissues and cells. The LL37 protein is required for the innate immune systems of live animals to combat dangerous pathogens. LL-37 has the potential to be employed as an antibacterial, anti-inflammatory, and other therapeutic agent.37 Previous studies showed the potential ability of MSCs' metabolite to enhance osteoblast number and decrease osteoclast number in an LPS-induced bone resorption animal model; this implies that MSCs' metabolite may act as an anti-inflammatory agent that can inhibit osteoclastogenesis.[38]

Like other antimicrobial peptides, LL-37 has direct antibacterial activity. LL-37 kills invasive pathogens by disrupting their cell membranes and can counteract endotoxin-mediated biological activity. LL-37 not only has antibacterial effects, but it may also have immunomodulatory functions. LL-37 has the capacity to regulate and control the activity of many cell types engaged in inflammatory processes, both directly and indirectly. LL-37 causes neutrophils, monocytes, macrophages, eosinophils, and mast cells to migrate and increases neutrophil longevity. LL-37 directly activates inflammatory cells, causing them to produce and release various pro-inflammatory and immunoregulatory mediators, cytokines, and chemokines. However, LL-37 may also mediate the production of anti-inflammatory cytokines and affect the activity of monocytes, dendritic cells, keratinocytes, or epithelial cells when combined with cytokines or defensins. TLR-mediated responses of monocytes, macrophages, dendritic cells, epithelial cells, and keratinocytes are indirectly balanced by LL-37. The microenvironment may influence LL-37's pro- and anti-inflammatory effects.[39] This may explain why LL-37 inhibits IL-17 but increases IL-10 during the inflammatory response to obtain homeostasis.

LL-37 is also capable of regulating angiogenesis and wound healing. Fibroblasts are responsible for the formation of the extracellular matrix, which is required for wound healing and tissue repair. Because of its angiogenesis impact and ability to attract MSCs, LL-37 has been used successfully in tissue regeneration. [40] In addition to controlling bone regeneration, LL37 has recently been shown to be a strong angiogenic inducer by increasing VEGF expression in human PDL cells via the extracellular signal-regulated kinases (ERK) and nuclear factor kappa beta (NF-kB) signaling pathways.[41,42] This is supported by a previous study that found LL-37 significantly increased growth factor production by gingival fibroblasts, emphasizing LL-37's importance in the regeneration response.[44]

LL-37 is a component of the innate immune system in humans, where it is involved in inflammation, tissue remodeling, and wound healing.[45,46] LL-37 is a multifunctional molecule

that has been proven to have a variety of immunomodulatory effects in addition to antibacterial action.[47,48] The link between LL-37, proliferation, and MMP activity is complicated. The effects of LL-37 on MMP activities, as well as the increased production of TIMP-1 by fibroblasts, might be viewed as a refined mechanism for limiting proteolytic activity in an effort to slow disease development. Previous research has shown that LL-37 can modulate cytokine, growth factor, and TIMP levels in vitro.44 In addition, LL-37 shows antibacterial action against periodontopathogen microorganisms' dectin, peptidoglycan, and flagellin.[49]

LL-37 has become a paradigm for the pleiotropic effects of peptides in host defense. It possesses an astoundingly extensive functional repertoire, including direct antibacterial activity against a variety of microbes. The LL-37 ability of 'alarmin' to locally modulate inflammation, both enhancing it to aid in combating infection and limiting it to prevent damage to infected tissues, the promotion of angiogenesis and wound healing, and possibly also the elimination of abnormal cells, LL-37 can carry out all of its listed operations because of its modest and simple amphipathic helical structure. Its interactions with bacterial membranes and capacity to function as a pore-forming toxin directed towards bacterial cells[50]

## Conclusions

Based on the molecular docking result in this study, the ligand-receptor binding of cathelicidins (LL-37) that are possessed in metabolite MSCs has a high negative binding energy value that may inhibit pro-inflammatory cytokines, microbial tissue degradation enzyme-related biomarkers, and increase anti-inflammatory cytokines and growth factors, as documented in silico.

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## Declaration of Interest

The authors declare there is no conflict of interest in this study

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