Review Article

Glycyl-L-histidyl-L-lysine-Cu2+ in Clinical Science: Purpose and Prospects

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Glycyl-L-histidyl-L-lysine-Cu2+ (GHK-Cu), a naturally occurring tripeptide complexed with copper, has emerged as a significant bioactive molecule with diverse physiological roles. This review highlights the molecular mechanisms and clinical applications of GHK-Cu, focusing on its role in wound healing, neurological disorders, cancer, and inflammatory diseases, including leprosy and tuberculosis. We discuss the peptide's antioxidant, anti-inflammatory, tissue-regenerative, and anti-cancer properties, along with its potential translational applications in clinical medicine.

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Introduction

Copper is an essential trace element required for multiple enzymatic reactions, playing a key role in mitochondrial energy production, antioxidant defense, and connective tissue maintenance[1]. Copper-dependent enzymes, including cytochrome oxidase and lysyl oxidase, are critical for cellular respiration and collagen cross-linking[2].

Glycyl-L-histidyl-L-lysine-Cu^{2+} (GHK-Cu), a tripeptide with a strong affinity for copper ions, facilitating various physiological processes. First identified in human plasma, it has also been detected in urine and saliva, indicating its systemic presence and biological significance[3]. GHK-Cu levels decline with age, correlating with reduced regenerative capacity and increased tissue degradation[4]. Due to its ability to modulate gene expression, stimulate collagen synthesis, and enhance wound healing, it has been proposed as a therapeutic agent for skin aging, chronic wounds, neurodegenerative disorders, and inflammatory diseases[4,5]. Furthermore, GHK's ability to bind and transport Cu^{2+} efficiently enhances its therapeutic potential in cellular repair and tissue regeneration[6]. This review explores the biological functions and clinical applications of GHK-Cu, emphasizing mechanistic insights and experimental evidence.

Methodology

A comprehensive literature review was conducted using electronic databases such as PubMed, Scopus, and Web of Science. Articles published in peer-reviewed journals between 2000 and 2025 were included, with a focus on studies evaluating the molecular mechanisms, preclinical and clinical applications, and safety profiles of GHK-Cu. Key search terms included "GHK-Cu," "copper peptide,""wound healing," "anti-inflammatory properties," "gene expression modulation," "skin regeneration," and "clinical applications".

Inclusion criteria encompassed studies reporting on experimental models, including *in-vitro* assays, *in-vivo* animal studies, and human clinical trials. Exclusion criteria involved studies with insufficient data, poor methodological design, or those lacking statistical validation. The selected studies were categorized based on molecular mechanisms, therapeutic applications, and safety assessments. Data synthesis focused on GHK-Cu's

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effects on cellular signaling pathways, gene expression profiles, and clinical outcomes.

GHK-Cu in health and disease

GHK-Cu and wound healing: A multifaceted approach to tissue repair

GHK-Cu has emerged as a potent biomolecule in the field of wound healing and regenerative medicine. Its involvement in tissue repair is multifaceted, encompassing collagen synthesis, angiogenesis, fibroblast proliferation, keratinocyte migration, and extracellular matrix (ECM) remodeling. These processes are essential for effective wound healing, making GHK-Cu a promising candidate for therapeutic applications (Table 1).

Role of GHK-Cu in Collagen Synthesis and ECM Remodelling

One of the pivotal roles of GHK-Cu in wound healing is its ability to stimulate collagen synthesis. Collagen, primarily types I and III, is crucial for maintaining skin integrity and providing structural support to newly formed tissue. Research has shown that fibroblasts treated with GHK-Cu exhibit enhanced production of these collagen types, along with an increase in glycosaminoglycans, which aid in maintaining hydration and structural integrity of the ECM[7]. GHK-Cu also plays a significant role in ECM remodeling, a crucial step in wound repair. This process is mediated through the activation of matrix metalloproteinases (MMPs), which facilitate the removal of damaged ECM proteins and promote new matrix deposition. By modulating MMP activity, GHK-Cu ensures a balanced degradation and synthesis of ECM components, preventing excessive scar formation and fibrosis[8].

GHK-Cu and Angiogenesis: Enhancing Blood Vessel Formation

Effective wound healing necessitates the formation of new blood vessels, a process known as angiogenesis. GHK-Cu has been shown to upregulate the expression of vascular endothelial growth factor (VEGF), a key mediator of neovascularization[9]. By enhancing VEGF levels, GHK-Cu promotes endothelial cell proliferation and migration, leading to improved blood supply and oxygenation at the wound site. This is particularly beneficial in chronic wounds and diabetic ulcers, where impaired angiogenesis contributes to delayed healing[10].

Anti-Inflammatory and Antioxidant Properties of GHK-Cu

Another critical aspect of GHK-Cu's function in wound healing is its ability to modulate inflammation. Chronic inflammation is a major barrier to effective tissue repair, often resulting in delayed wound closure and fibrosis. GHK-Cu exerts anti-inflammatory effects by downregulating pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[11] By suppressing excessive inflammation, GHK-Cu facilitates a smoother transition from the inflammatory phase to the proliferative phase of wound healing.

Moreover, GHK-Cu demonstrates potent antioxidant activity by scavenging free radicals and reducing oxidative stress. Oxidative damage can impede cellular function and ECM integrity, ultimately delaying wound healing. The ability of GHK-Cu to prevent lipid peroxidation and protect cellular components from oxidative injury underscores its role in maintaining an optimal healing environment[4].

GHK-Cu in Cellular Migration and Tissue Regeneration

GHK-Cu also contributes significantly to cellular migration, particularly in fibroblasts and keratinocytes, which are essential for wound re-epithelialization and wound closure. Additionally, the peptide has been found to promote stem cell recruitment to the wound site, further enhancing its regenerative potential[12,13].

Clinical Applications of GHK-Cu in Wound Healing

Given its diverse biological activities, GHK-Cu has been investigated for its potential in treating various types of wounds, including diabetic ulcers, pressure sores, and burns. Several clinical and preclinical studies have demonstrated the efficacy of GHK-Cu-containing formulations in accelerating wound closure and improving overall healing outcomes. Its incorporation into hydrogel dressings, creams, and topical formulations has shown promise in optimizing tissue repair and minimizing scar formation[14]. Future researches are required to focus on optimizing its delivery mechanisms and exploring its synergistic effects with other bioactive molecules to further enhance wound healing outcomes.

GHK-Cu in neurological disorders: mechanisms and therapeutic potential

GHK-Cu, a naturally occurring copper-binding peptide, has garnered attention for its neuroprotective properties, including its ability to promote neuronal survival, reduce oxidative stress, and enhance neurogenesis. Emerging evidence suggests that GHK-Cu plays a crucial role in brain repair mechanisms by modulating gene expression involved in synaptic plasticity, neuronal differentiation, and neurotrophic signaling[4]. This makes it a promising candidate for the treatment of neurodegenerative

Table 1: The effect and relation of GHK-Cu peptide on different genes/pathways in the body

Gene/Pathway	*Role in Disease or Health*	*Effect of GHK-Cu*	*Reference*
VEGF	Promotes angiogenesis and vascular repair	Upregulates VEGF expression, improving oxygen delivery to damaged tissues	Pickart & Margolina, 2018
Nrf2 Pathway	Antioxidant defense and ROS neutralization	Activates Nrf2, increasing SOD and catalase activity to reduce oxidative stress	Ahmed *et al*., 2024
NF-κB Pathway	Regulates pro-inflammatory cytokine production	Suppresses NF-κB activation, reducing TNF-α, IL-6, and IL-1β levels	Pickart & Margolina, 2018
TGF-β	Anti-inflammatory cytokine	Promotes tissue repair and fibrosis resolution	Ahmed *et al*., 2024
IL-10	Anti-inflammatory cytokine	Increases IL-10 production, aiding in inflammation resolution	Ahmed *et al*., 2024
MMP1 / MMP9	Extracellular matrix remodeling	Upregulates MMP1 for collagen turnover; downregulates MMP9 to prevent damage	Pickart &Margolina, 2018

VEGF → Vascular Endothelial Growth Factor, Nrf2 Pathway → Nuclear Factor Erythroid 2-Related Factor 2 Pathway, NF-κB Pathway → Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells Pathway, TGF-β → Transforming Growth Factor Beta, IL-10 → Interleukin-10, MMP1 → Matrix Metalloproteinase 1, MMP9 → Matrix Metalloproteinase 9

disorders such as Alzheimer's and Parkinson's disease. One of the key mechanisms through which GHK-Cu exerts its neuroprotective effects is the regulation of neurotrophic factors. Studies have demonstrated that GHK-Cu increases the expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), both of which are essential for neuronal survival, synaptic function, and cognitive processes[15]. The upregulation of these neurotrophic factors is particularly relevant in conditions associated with neuronal atrophy and cognitive decline, such as Alzheimer's disease.[16]

Another significant function of GHK-Cu is its anti-inflammatory action. Neuroinflammation, characterized by the overexpression of pro-inflammatory cytokines like interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), is a major contributor to neurodegenerative diseases. Research has indicated that GHK-Cu suppresses the activation of microglia and astrocytes, thereby reducing the levels of these pro-inflammatory mediators[17]. This mechanism is particularly beneficial in mitigating the chronic inflammatory responses observed in Alzheimer's and Parkinson's disease, which exacerbate neuronal damage and cognitive dysfunction. Beyond neuroinflammation, GHK-Cu has demonstrated the capacity to promote neuronal regeneration and enhance synaptic function. Experimental models of neurodegeneration have shown that GHK-Cu administration leads to improved behavioral outcomes related to memory and cognition, suggesting a direct role in synaptic remodeling and plasticity[18]. Furthermore, its antioxidative properties help combat oxidative stress, a well-documented factor in neuronal aging and neurodegenerative diseases[19].

In the context of aging-related cognitive decline, GHK-Cu has been shown to restore gene expression profiles associated with neuronal repair and survival. Aging is accompanied by alterations in gene expression that contribute to reduced neurogenesis and synaptic dysfunction. By reversing these changes, GHK-Cu presents a potential therapeutic avenue for age-related neurodegeneration, traumatic brain injuries, and stroke recovery. Studies exploring its epigenetic regulatory mechanisms suggest that GHK-Cu can modulate chromatin remodeling, thereby enhancing the expression of genes critical for neuronal health and longevity[20,21]. Ongoing research into the molecular mechanisms of GHK-Cu and its clinical applications is essential for the development of novel neuroprotective strategies. Future studies should focus on optimizing its bioavailability, delivery methods, and therapeutic efficacy in human clinical trials to fully harness its potential in neurological disorders.

Anti-cancer properties of GHK-Cu

GHK-Cu, a naturally occurring copper peptide, has demonstrated significant anti-cancer properties through multiple mechanisms, including the induction of apoptosis, inhibition of cancer cell proliferation, suppression of angiogenesis, and modulation of tumor-suppressor gene expression. GHK-Cu can regulate gene expression in a manner that promotes tumor suppression while concurrently inhibiting pathways associated with

tumor progression[4,22]. These findings suggest its potential as a therapeutic agent in oncology, warranting further investigation into its molecular mechanisms and clinical applications.

A pivotal mechanism underlying the anti-cancer activity of GHK-Cu is its ability to induce apoptosis in malignant cells. This effect is achieved through the activation of both intrinsic and extrinsic apoptotic pathways, which lead to an increase in caspase activity, crucial for the execution of programmed cell death[23]. Additionally, GHK-Cu modulates the expression of key pro-apoptotic and anti-apoptotic proteins, including Bax and Bcl-2, thereby tipping the balance in favor of apoptosis[24]. The ability to selectively induce apoptosis in cancer cells while sparing normal cells highlights its potential as a targeted cancer therapy. Beyond apoptosis induction, GHK-Cu has been found to exert inhibitory effects on cancer cell proliferation across various malignancies, including breast, prostate, and colorectal cancer[25,26]. This anti-proliferative action is attributed to its capacity to disrupt the cell cycle, preventing uncontrolled cellular division, which is a hallmark of cancer progression. Moreover, GHK-Cu has been shown to downregulate oncogene expression, thereby suppressing tumorigenic pathways that drive aggressive cancer phenotypes[2].

Another critical anti-cancer mechanism of GHK-Cu is its ability to suppress angiogenesis, a process essential for tumor growth and metastasis. By downregulating vascular endothelial growth factor (VEGF) and other pro-angiogenic factors, GHK-Cu effectively impairs the formation of new blood vessels necessary for sustaining tumor development[27]. This anti-angiogenic activity restricts the tumor's ability to acquire nutrients and oxygen, thereby limiting its growth and metastatic potential. Furthermore, GHK-Cu has been shown to enhance the expression of tumor suppressor genes, including p53 and PTEN, both of which play fundamental roles in regulating cell proliferation and maintaining genomic stability.[22] By restoring the function of these tumor suppressors, GHK-Cu contributes to the inhibition of aberrant cell growth and promotes cellular mechanisms that safeguard against malignancy.

Emerging research also suggests that GHK-Cu may influence epigenetic modifications associated with cancer progression. It has been implicated in the modulation of chromatin structure, potentially restoring the expression of genes linked to normal cellular function[22]. This epigenetic regulatory capability introduces a novel dimension to its anti-cancer properties, indicating potential utility in personalized cancer treatment strategies. While preclinical studies have provided compelling evidence of GHK-Cu's anti-cancer potential, further clinical investigations are required to fully elucidate its therapeutic efficacy and safety in human malignancies. The exploration of its molecular interactions, optimal delivery methods, and combination therapies with existing cancer treatments could pave the way for the development of GHK-Cu-based interventions in oncology.

GHK-Cu in lung disease

GHK-Cu has garnered interest in the context of lung diseases, particularly those characterized by chronic inflammation, oxidative stress, and fibrosis. Lung conditions such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and acute lung injury (ALI) involve complex pathological mechanisms that GHK-Cu may help modulate[7]. One of the key attributes of GHK-Cu in lung diseases is its anti-inflammatory effect. Chronic lung diseases are often driven by persistent inflammation, leading to tissue damage and progressive decline in lung function. GHK-Cu has been found to reduce levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), while simultaneously increasing anti-inflammatory mediators such as interleukin-10 (IL-10)[7]. By modulating the NF-κB signaling pathway, which plays a central role in inflammation, GHK-Cu helps to mitigate lung tissue damage and reduce inflammatory burden[28].

In addition to its anti-inflammatory properties, GHK-Cu exhibits strong antioxidant and anti-aging effects, which are particularly relevant in lung diseases associated with oxidative stress. Excessive reactive oxygen species (ROS) generation contributes to DNA damage, apoptosis, and fibrosis in lung tissues. GHK-Cu enhances the activity of key antioxidant enzymes such as superoxide dismutase (SOD) and catalase, reducing oxidative stress and preventing lipid peroxidation[4]. Through this mechanism, GHK-Cu may help slow the progression of lung aging and functional decline seen in chronic respiratory conditions. Lung diseases such as pulmonary fibrosis involve excessive extracellular matrix (ECM) deposition and impaired tissue repair, leading to irreversible scarring and loss of lung function. GHK-Cu has demonstrated the ability to promote fibroblast proliferation, regulate collagen synthesis, and enhance elastin production, all of which contribute to improved lung tissue remodeling. Its effect on matrix

metalloproteinases (MMPs), particularly their activation and regulation, supports ECM degradation and prevents excessive fibrosis[28,29]. Furthermore, by inhibiting transforming growth factor-beta 1 (TGF-β1), a key driver of fibrotic processes, GHK-Cu suppresses fibroblast-to-myofibroblast differentiation and limits the accumulation of pathological fibrotic tissue[30].

The potential therapeutic role of GHK-Cu is not limited to chronic conditions but extends to acute lung injuries such as acute respiratory distress syndrome (ARDS), which often results from severe infections, including viral pneumonia and sepsis. The pathophysiology of ARDS involves excessive inflammation, endothelial permeability, and disruption of the alveolar-capillary barrier, leading to respiratory failure. GHK-Cu has been shown to mitigate endothelial dysfunction, reduce neutrophil infiltration into lung tissues, and support epithelial repair mechanisms[31]. By restoring barrier integrity and modulating immune responses, it may help improve outcomes in patients suffering from acute lung injury.

At a molecular level, GHK-Cu exerts its effects by regulating gene expression associated with tissue remodeling, inflammation resolution, and antioxidant defense. It modulates multiple cellular signaling pathways, including NF-κB inhibition for inflammation control, TGF-β1 suppression to prevent fibrosis, and nuclear factor erythroid 2-related factor 2 (Nrf2) activation to enhance antioxidant responses. Additionally, GHK-Cu provides bioavailable copper, which is crucial for enzymatic activities involved in lung repair, including lysyl oxidase (LOX), an enzyme responsible for collagen cross-linking and structural integrity.[4]

Thus, GHK-Cu exhibits promising therapeutic potential in lung diseases through its ability to reduce inflammation, counteract oxidative stress, and modulate fibrotic pathways. Its regenerative and protective effects on lung tissue make it a potential candidate for treating conditions such as COPD, IPF, and ARDS. Further research, particularly clinical trials, is necessary to determine its efficacy and safety in pulmonary medicine, as well as to establish optimal dosing strategies for therapeutic use.

GHK-Cu in chronic inflammatory diseases: Leprosy and Tuberculosis

GHK-Cu, a naturally occurring copper-binding peptide, has been extensively studied for its anti-inflammatory, wound-healing, and immunomodulatory properties[7] (Figure 1). These attributes suggest a potential role in managing chronic infectious diseases such as leprosy and tuberculosis, where excessive immune activation contributes to disease progression and tissue destruction[32]. Both leprosy and tuberculosis, caused by *Mycobacterium leprae* and *M. tuberculosis*, respectively, involve complex host immune responses characterized by prolonged inflammation, granuloma formation, and subsequent fibrosis or necrosis. This persistent inflammatory state not only delays recovery but also exacerbates tissue damage, leading to severe morbidity.

In leprosy, immune response variability determines disease severity, ranging from tuberculoid leprosy, associated with a strong cellular immune response, to lepromatous leprosy, where immune suppression leads to uncontrolled bacterial proliferation[33]. Similarly, tuberculosis manifests either as latent infection or active disease, with the latter resulting in chronic inflammation, caseous necrosis, and fibrosis. In both conditions, excessive production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) drives the tissue destruction. While TNF-α plays a key role in maintaining granuloma integrity in tuberculosis, its dysregulation contributes to widespread necrotic damage[34]. Similarly, IL-1β and IL-6 amplify inflammation, exacerbating systemic effects such as fever, weight loss, and immune exhaustion.

GHK-Cu exerts its beneficial effects through multiple mechanisms, primarily by suppressing inflammatory cytokines and promoting tissue regeneration[4]. Studies have demonstrated its ability to downregulate TNF-α, IL-1β, and IL-6[35], thereby mitigating the hyper-inflammatory response associated with mycobacterial

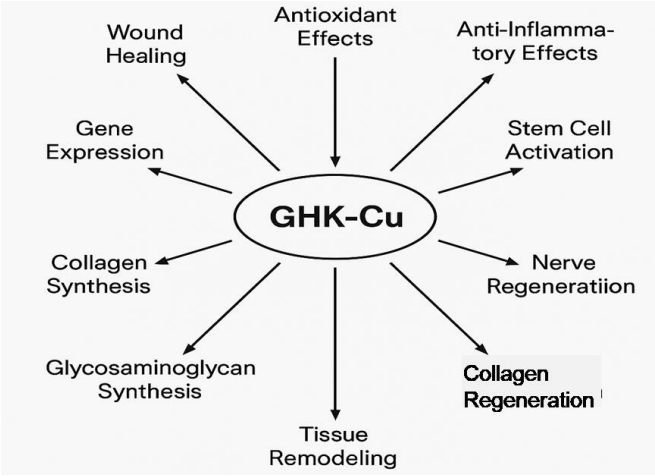

Figure 1: The interaction and effect of GHK-Cu peptide in the body

infections. This effect is largely mediated through inhibition of the NF-κB signaling pathway, a key regulator of inflammation[36]. By modulating this pathway, GHK-Cu prevents the excessive immune activation that contributes to chronic tissue damage in leprosy and tuberculosis.

Beyond its anti-inflammatory properties, GHK-Cu also plays a crucial role in wound healing and tissue repair. Chronic mycobacterial infections often result in fibrosis, ulceration, and permanent structural damage to affected tissues. GHK-Cu has been shown to enhance collagen synthesis, stimulate angiogenesis, and promote extracellular matrix remodeling, thereby facilitating the repair of damaged tissues. Additionally, its strong antioxidant properties provide protection against oxidative stress-induced cellular injury, which is commonly observed in chronic infectious diseases.[37] Macrophages, central to immune responses in leprosy and tuberculosis, exist in two functional states: the pro-inflammatory M1 phenotype, which contributes to pathogen clearance but also tissue damage, and the anti-inflammatory M2 phenotype, which supports tissue repair. GHK-Cu has been reported to modulate macrophage activity by shifting their polarization toward the M2 phenotype, thereby reducing inflammation while enhancing the resolution phase of the immune response[4]. This macrophage modulation could be particularly advantageous in tuberculosis, where sustained M1 activation leads to extensive caseous necrosis and cavitations of lung tissue. Macrophages, central to immune responses in leprosy and tuberculosis, exist in two functional states: the pro-inflammatory M1 phenotype, which contributes to pathogen clearance but also tissue damage, and the anti-inflammatory M2 phenotype, which supports tissue repair. GHK-Cu has been reported to modulate macrophage activity by shifting their polarization toward the M2 phenotype, thereby reducing inflammation while enhancing the resolution phase of the immune response.[38] This macrophage modulation could be particularly advantageous in tuberculosis, where sustained M1 activation leads to extensive caseous necrosis and cavitations of lung tissue.[39]

Another potential benefit of GHK-Cu in managing mycobacterial infections is its ability to enhance the efficacy of antimicrobial therapy. Chronic inflammation and fibrosis often impair drug penetration into infected tissues, reducing treatment effectiveness. By promoting vascularization and reducing fibrotic scarring, GHK-Cu may facilitate better drug delivery, thereby improving therapeutic outcomes when used in combination with conventional antibiotics.[40]

Despite its promising properties, the clinical application of GHK-Cu in infectious diseases likes leprosy and tuberculosis remains largely unexplored. Future research should focus on preclinical studies assessing its efficacy in animal models of mycobacterial infections, as well as clinical trials evaluating its safety and therapeutic potential in human patients[41]. Investigations into combination therapies with standard anti-leprosy and anti-tuberculosis drugs could further elucidate its role as an adjunctive treatment.

GHK-Cu represents a promising candidate for modulating excessive inflammation in chronic infectious diseases such as leprosy and tuberculosis. By targeting key inflammatory pathways while simultaneously promoting tissue repair, it may help mitigate disease progression, reduce tissue destruction, and improve treatment outcomes. Further research into its mechanisms and clinical applications could pave the way for novel therapeutic strategies in the management of mycobacterial diseases.

In conclusion, GHK-Cu's unique ability to combine anti-inflammatory, neuroprotective, and angiogenic effects provides a holistic approach to mitigating necrosis in both leprosy and tuberculosis. In leprosy, it reduces nerve inflammation while facilitating tissue repair, while in tuberculosis, it prevents hypoxia-induced damage while controlling granuloma-associated inflammation.[42]

Challenges in the Therapeutic Application of GHK-Cu

Stability and Delivery Mechanism

One of the primary challenges associated with GHK-Cu is its limited stability in biological systems. Due to enzymatic degradation and rapid clearance from the body, the bioavailability of GHK-Cu is significantly reduced, limiting its therapeutic potential. To overcome this issue, advanced drug delivery strategies such as nanoparticle encapsulation, liposomal formulations, and peptide conjugation have been explored. These methods aim to enhance stability, prolong circulation time, and ensure targeted delivery, thereby improving the compound's overall efficacy in clinical applications.

Large-Scale Synthesis

The large-scale and cost-effective synthesis of GHK-Cu remains a significant hurdle. Traditional peptide synthesis methods are often expensive and yield limited quantities of the bioactive complex. Optimizing peptide synthesis techniques, such as solid-phase synthesis

with improved coupling reagents or recombinant production strategies, could help increase yield while reducing production costs. Advances in biotechnological approaches, including microbial expression systems and enzymatic catalysis, may also offer alternative routes for large-scale GHK-Cu production, making it more accessible for pharmaceutical and cosmeceutical applications.

Regulatory Approvals

For GHK-Cu to be widely accepted as a therapeutic agent, comprehensive clinical trials are required to establish its safety, efficacy, and potential side effects. While preclinical and early-stage studies have shown promising biological activity, regulatory bodies such as the FDA and EMA require extensive data from well-designed clinical trials before approving its use in medical applications. Addressing regulatory concerns, including potential toxicity, immunogenicity, and long-term effects, is crucial for obtaining necessary approvals and ensuring patient safety.

Future Perspectives on GHK-Cu

Molecular Mechanisms and Omics-Based Investigations

Future research on GHK-Cu should prioritize the detailed characterization of its molecular mechanisms, particularly its interactions with key transcription factors and epigenetic regulators. Among these, nuclear factor-kappa B (NF-κB) plays a crucial role in inflammation and immune modulation, making it a critical target for understanding GHK-Cu's therapeutic effects.[43] Investigating how GHK-Cu modulates NF-κB signaling and influences gene expression patterns could provide significant insights into its anti-inflammatory properties. The application of advanced omics technologies, including proteomics, transcriptomics, and metabolomics, can offer a comprehensive understanding of the downstream pathways regulated by GHK-Cu.[44] These approaches will help identify novel therapeutic targets and biomarkers associated with its regenerative and immunomodulatory effects. Additionally, studying the interactions of GHK-Cu with key cellular components, such as cytokines, growth factors, and matrix metalloproteinases, may further elucidate its role in tissue repair and fibrosis prevention.

Nanoparticle-Based Drug Delivery Systems

Given the limitations of GHK-Cu's stability and bioavailability, novel drug delivery strategies have emerged to enhance its therapeutic potential. Several nanoparticle-based formulations are being investigated to improve its pharmacokinetic properties such as Polymeric and solid lipid nanoparticles (SLNs), Inhalable formulations for tuberculosis, potentially improving outcomes in pulmonary tuberculosis[45], Topical applications for leprosy-related skin lesions, by enhancing collagen synthesis and reducing oxidative stress[7], Hydrogels and scaffold-based platforms by incorporating GHK-Cu into bioengineered scaffolds, its regenerative effects in chronic wounds, burns, and fibrotic lesions can be significantly enhanced.[46]

Also, despite the promising preclinical data, clinical trials are necessary to validate the safety, efficacy, and optimal dosage of GHK-Cu in human populations.

Key areas for further investigation include

Clinical trials for leprosy and tuberculosis

The anti-inflammatory, tissue-regenerative, and antioxidant properties of GHK-Cu need to be rigorously tested in well-designed clinical studies to assess its therapeutic potential in infectious diseases with significant inflammatory components.

Combination therapy with existing treatments

GHK-Cu may act synergistically with conventional antibiotics or immune modulators, potentially enhancing the efficacy of standard treatments for tuberculosis and leprosy (Ahmed *et al*., 2024). Exploring such combinatory approaches could lead to improved patient outcomes and reduced drug resistance.

Potential applications in chronic inflammatory and fibrotic diseases

Beyond infectious diseases, GHK-Cu's immunomodulatory properties may have therapeutic implications for other chronic inflammatory and fibrotic conditions, including Crohn's disease, sarcoidosis, and pulmonary fibrosis (Min *et al*., 2024). Expanding research into these conditions could unlock new clinical applications for this bioactive peptide.

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