



# The Multifaceted Properties of Copper and Zinc in Skin Healing

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Received: August 29, 2025 / Accepted: October 13, 2025  
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## ABSTRACT

Copper (Cu) and zinc (Zn) are trace elements required for a multitude of physiological processes, including wound healing, and there has been a long history of including both metal ions in topical skin repair formulations. Wound healing involves complex and dynamic cellular mechanisms in the main phases of platelet

hemostasis, inflammation, granulation tissue formation, re-epithelialization, and extracellular matrix remodeling. This process is influenced by the balance in the skin's commensal microbiota, and the risk of microbes becoming pathogenic through migration and colonization of the deeper tissues. We examine the antimicrobial effects of Cu/Zn versus their roles in the innate immune response that prevents the invasion and proliferation of microorganisms and in the cellular mechanisms that promote wound healing. Cu/Zn modulates macrophage polarization, promoting the transition from the pro-inflammatory M1 phenotype to the pro-healing M2 phenotype, which is critical for tissue repair. Both elements also act as cofactors that modulate the activities of important growth factors, mediators, and enzymes, including antioxidant enzymes, such as superoxide dismutase, which have a role in the innate immune response to pathogens and protect cells from oxidative damage, reducing inflammation and promoting healing. These divalent ions stimulate angiogenesis, and the Cu/Zn combination can also modulate integrin expression in keratinocytes, which are needed for re-epithelialization, supporting cellular mobility and differentiation, and enhancing the healing process. The synergistic roles of Cu/Zn in preventing infection while stimulating the skin's natural immune defenses encourage efficient tissue repair after injury. Topical

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Cu/Zn-containing formulations therefore hold promise for improving wound management.

**Keywords:** Wound healing; Microbiota; Topical; Copper; Zinc

### Key Summary Points

Despite long-standing empirical use, the clinical integration of copper and zinc in wound care remains controversial.

Copper (Cu) and zinc (Zn) act synergistically in wound healing, enhancing antimicrobial defense, immune modulation, and tissue regeneration through their combined biochemical roles.

Clinical and preclinical evidence supports the safety, tolerability, and efficacy of Cu/Zn-containing topical therapies in accelerating wound closure and improving healing outcomes.

Topical Cu/Zn formulations provide targeted antibacterial activity that reduces pathogenic burden while preserving commensal skin flora, supporting balanced wound microbiota and optimal healing.

## INTRODUCTION

The process of wound healing is dynamic, involving various cellular mechanisms associated with the main phases of platelet hemostasis, inflammation, granulation tissue formation, re-epithelialization, and extracellular matrix remodeling [1, 2]. While wound healing is a natural physiological reaction to tissue injury, as it proceeds through the different stages, it involves a complex interplay among various cell types, molecular mediators, and the vascular system [1]. Essential elements, which cannot be synthesized by living organisms and must therefore be supplied by an external source (food, dietary supplements, topical formulations, etc.), have important roles in these mechanisms [3]. This

includes divalent metal ions that are needed for the catalytic and structural functioning of proteins, enzymes, and transcription factors [3, 4]. The second and third most abundant trace metal elements in the human body after iron are zinc (Zn) and copper (Cu) [2, 3].

Ointments containing Cu and Zn have been used for centuries as topical antiseptic preparations, such as the Dalibour formula, also known as Dalibour or Alibour water [5]. As first described by French surgeon Jacques Dalibour in the eighteenth century, the original formula contained copper sulfate and zinc sulfate, and was used to treat skin irritations and minor wounds, including soldiers' wounds during armed conflicts [6]. The Smith Papyrus, Egyptian medical text written between 2600 and 2200 BC, provides the oldest recorded medical use of Cu compounds in wound treatment [7, 8].

In the modern era, the most common approaches taken towards wound healing are mechanical and involve protecting the damaged areas with dressings [9, 10]. Topical preparations containing tissue-repairing and antibacterial ingredients that speed up the wound healing process are also used in the early phase to cleanse the wound, attract growth factors to the injured site, and prevent secondary infections [11, 12]. Moreover, recent research has highlighted the wound microbiome and related host-microbiota interactions that could influence the healing process, particularly the importance of maintaining a balance in the skin microbiota [13]. The negative effect of broad-spectrum antibiotic therapy on this balance is well recognized [14], as well as the fact that antibiotic therapy is often used inappropriately and unsuccessfully in chronic wound infections, and overuse is associated with antimicrobial resistance [15]. Modern wound care practices must therefore integrate specific considerations to attain the desired antimicrobial outcomes.

The development of topical skin repair products with enhanced properties to prevent infection is therefore of increasing interest, as well as those that also promote rapid and scarless healing, thereby improving the quality and aesthetics of wound healing [16, 17]. This needs better understanding of the wound microbiome and the relationship between it and cellular

responses involved in wound healing. Topical Cu/Zn-containing preparations have antiseptic properties that could have a negative effect on the wound healing process. However, alteration of the skin's microbiota balance by Cu/Zn has never been demonstrated, and Cu and Zn have additional roles in the processes that prevent tissue invasion by pathogens, the innate immune response to skin damage, and the cellular mechanisms that promote healing. Here, we provide a concise and pragmatic overview of the antimicrobial effects of Cu and Zn, the roles of these divalent ions in the immune response and wound healing process, and evidence supporting their use in wound healing formulations.

### Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## THE SKIN MICROBIOTA AND WOUND HEALING

The skin is the first protective barrier of the human body against its environment, and the skin's microbiota, which contains bacteria, fungi, and viruses, helps to maintain this function and hence regulate health and disease via a symbiotic relationship between the skin and its resident microorganisms [17]. A breach of the skin barrier enables opportunistic infection, where commensal microbes migrate from the surface to the interior of the skin, grow, and colonize the deeper tissues. The risk of wound infection increases as microbial load increases and according to microbial species, microbial interactions, and synergy [15]. Additionally, bio-film formation, characterized by the aggregation and attachment of bacterial cells to a surface, protected by a self-produced extracellular polymeric substance, can impair the healing process, a scenario commonly seen in chronic wounds [15, 18].

The subsequent impact of wound infection is dependent on various factors, including the

host's immune system, and the virulence and location of the microorganisms [15]. Pathogenic microorganisms with high potentials for proliferation and causing inflammation can have a negative impact on the wound healing process because chronic inflammation can prevent wound closure and therefore delay healing [17, 19]. A common example is opportunistic *Staphylococcus aureus* infection, which is responsible for most bacterial skin and soft tissue infections [20] and renowned for its negative effect in many types of wounds [21].

When treating skin lesions, it is therefore essential to prevent the invasion of surrounding tissues by microbiota and maintain a balance among commensal species [13, 17]. Steady state interactions between bacteria and the immune system induces specific T cell responses that are important for tissue repair [22, 23] and commensal microbiota in the skin trigger type I interferon-dependent innate repair responses in injured skin [24]. The recruitment of antigen-presenting cells to the skin has been shown to be microbiota-dependent [25], and skin regeneration in wound repair is enhanced by microbes via interleukin-1 $\beta$  signaling [26]. It has also been demonstrated that commensals can promote epidermal production of antimicrobial peptides [27, 28] and produce antimicrobials [29, 30]. Consequently, broad-spectrum antibiotic treatments could eliminate potentially beneficial commensal bacteria, disrupting the symbiotic, homeostatic relationship that exists with the skin epithelium. Optimal wound healing should instead be encouraged by preventing the invasion and proliferation of microorganisms from the wound site. Moreover, in acute burns or after skin grafts, it is essential to control local infection to prevent skin graft rejection [31, 32]; again, the bacterial and septic environment is a crucial element for achieving good healing.

## ROLE OF CU AND ZN IN WOUND HEALING

The key roles of Cu and Zn in the functioning of proteins, enzymes, and transcription factors [3, 4] translate into multifaceted roles in the wound

healing process. These roles can be categorized broadly into those that relate to the prevention of tissue invasion by microbiota at the wound site and to the cellular process of wound healing.

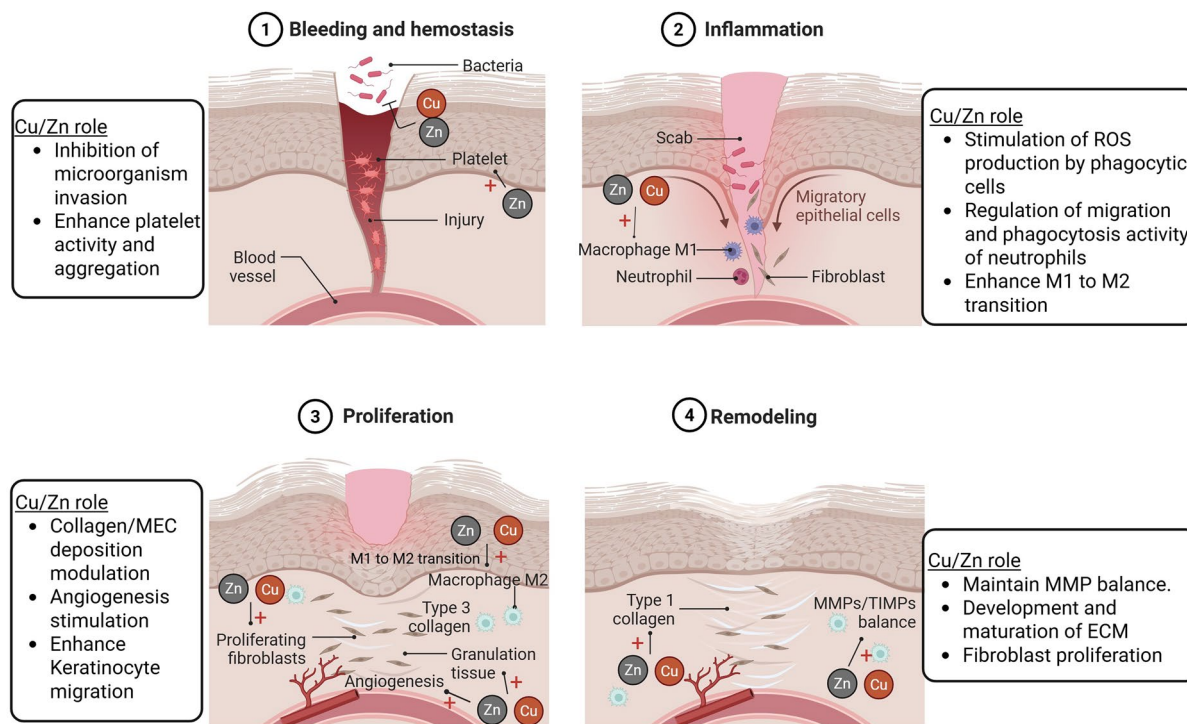
Both trace elements have two important properties that are relevant to the prevention of tissue invasion by pathogens: (1) mechanisms of toxicity towards microorganisms; (2) mechanisms related to stimulation of the innate immune system.

As positively charged ions, it is thought that one of the main mechanisms of toxicity involves the electrostatic binding of Cu and Zn to negatively charged bacterial membranes, thereby altering the charge balance of the cell surface, leading to cell structure deformation and killing of the microorganism [33–38]. Moreover, there is evidence, mostly from in vitro studies of pathogens such as *S. aureus* and *Escherichia coli*, that Cu/Zn generates reactive oxygen species (ROS) [35, 36, 38], which play a major role in cell signaling pathways when present at a low level but have harmful oxidative effects on essential cellular macromolecules when present at high concentrations [39]. ROS thereby induce DNA degradation and membrane lipid peroxidation, which has a bactericidal effect [34, 37]. Zn may also exert an antimicrobial effect by antagonizing the uptake of other key trace metal nutrients and by binding to sites that do not normally contain a metal ion, thereby inhibiting key enzymes [33]. There have been no reports of an alteration in the balance of the skin's commensal microbiota in vivo by Cu/Zn treatment.

Cu and Zn ions also stimulate ROS generation by phagocytic cells (macrophages and neutrophils) as a defense against pathogenic microorganisms by the host innate immune system [39]. Cu and Zn are essential cofactors for the enzyme Cu/Zn superoxide dismutase (SOD), which is involved in ROS regulation [2, 35, 40]. Cofactors are components that are essential for the biologic activity of enzymes, thereby maintaining cellular redox balance and driving synthetic and catabolic reactions by the cell [41]. Additionally, ROS production by phagocytes relies on nicotinamide adenine dinucleotide phosphatase (NADPH) oxidase, a process that requires Zn [42, 43], and Cu increases the genetic expression of this enzyme [44].

Cu and Zn are involved in each of the major cellular activities associated with skin healing (Fig. 1) [2, 34, 45]. After injury, hemostasis is established via coagulation and clot formation, during which time Zn enhances platelet activity and aggregation and serves as a hemostatic cofactor [46], providing the basis for the inflammatory phase and tissue formation. At the beginning of the inflammatory phase, Zn regulates the migration and phagocytosis activities of neutrophils [45], as shown in conditions of Zn deficiency by the promotion of monocyte differentiation into pro-inflammatory (M1) and inhibition of immune-regulatory (M2) macrophages [47]. Deficiency of Zn has also been shown to reduce the B lymphocyte population, thereby reducing antibody production, negatively affecting phagocytosis, and preventing wound bed clearance [48]. During the proliferation phase of wound healing, Zn acts as an important cofactor during the development of granulation tissue by modulating collagen/extracellular matrix deposition [49], stimulating angiogenesis [45], and enhancing keratinocyte migration by increasing the expression of integrins, the main mediators of cell migration, and promoting epidermal re-epithelialization [50]. During the proliferation and remodeling stages, Zn is required for maintaining balance in matrix metalloproteinases (MMPs), which are Zn-dependent enzymes that digest dermal basal membranes and the extracellular matrix [2]. Zn has a particularly important role in the proteolytic activity of MMP-1, which is obligatory for keratinocyte migration [51]. Re-epithelialization is crucial to prevent infection through the re-establishment of the barrier function of the epidermis and the secretion of antimicrobial and immune-related peptides [52].

At the beginning of the wound healing process, Cu is also involved in the recruitment of macrophages to the wound and their polarization to M1 or M2 macrophages [34]. During the proliferation phase, Cu promotes angiogenic factor expression and wound angiogenesis [53], and accelerates wound contraction and re-epithelialization [34]. Important Cu-dependent factors and enzymes are involved in this process, including vascular endothelial growth factor (VEGF), which is secreted by platelets, macrophages, fibroblasts, and endothelial cells



**Fig. 1** The impact of copper and zinc in the different stages of wound healing Created in BioRender. Genies, C. (2025) <https://BioRender.com/56qn0jg>. *Cu* copper, *ECM* extracellular matrix, *M1* pro-inflammatory macrophages,

*M2* immune-regulatory macrophages, *MMP* matrix metalloproteinases, *ROS* reactive oxygen species, *TIMP* tissue inhibitor of metalloproteinase, *Zn* zinc, + activation

[2, 34]. This triggers the chemotaxis of neutrophils and fibroblasts, initiates fibroblast proliferation, induces matrix protein and MMP synthesis, and stimulates angiogenesis. Additionally, the expression of integrins  $\alpha 2$ ,  $\beta 1$ , and  $\alpha 6$ , known to mediate cell migration, re-epithelialization, and granulation tissue formation, is Cu-dependent [50]. During the remodeling phase, Cu stimulates the expression of MMPs within dermal fibroblasts [54] and may have an impact on the balance between MMPs and tissue inhibitor of metalloproteinase (TIMP) [55]. Cu also acts as a cofactor for lysyl oxidase, which facilitates the formation, development, and maturation of extracellular matrix during wound healing [34] by catalyzing the formation of covalent cross-links between collagens [2, 56]. The key role of Cu in extracellular matrix remodeling is also suggested by the clinical spectrum of Wilson disease (progressive liver damage, inflammation, fibrosis,

and cirrhosis), which is caused by poor cellular excretion of Cu [57].

Cu and Zn ions therefore work together in the wound healing process (Fig. 1). Both regulate the immune response by modulating macrophage polarization, promoting the transition of macrophages from the pro-inflammatory M1 phenotype to the pro-healing M2 phenotype, which is critical for tissue repair [58]. Cu stimulates angiogenesis, enhancing the expression of angiogenic growth factors [59, 60], and both Cu and Zn act as cofactors for antioxidant enzymes, such as SOD, which not only have a role in the innate immune response to pathogens but also protect cells from oxidative damage, reducing inflammation and promoting healing [61, 62]. Additionally, Zn has been shown to induce metallothionein, which is antioxidative, in human epidermal wounds [63]. Both Cu and Zn also modulate integrin expression in keratinocytes and maintain the MMP balance needed for

re-epithelialization, supporting cellular mobility and differentiation, and enhancing the healing process [64].

Increased understanding of the mechanisms of action of Cu and Zn in wound healing is accompanied by clinical and preclinical evidence from the application of topical formulations containing Cu or Zn, which are well established in wound healing [2, 8, 65–67]. Zn ions released from Zn-containing wound dressings have been shown to upregulate the genes relevant to tissue remodeling, collagen deposition, and fibroblast growth activities, hence enhancing wound repair [2, 68], and wound dressings containing Cu-based nanomaterials and nanoparticles have also been confirmed to accelerate wound healing [2, 8]. One study of 20 patients, 10 with diabetes, who responded poorly to silver wound dressings, found that treatment with Cu dressings enhanced wound healing, with a mean wound area reduction approximately 2.4 times higher than with silver dressing treatment [69]. Further evidence of the potential benefits of Cu and Zn inclusion in topical wound preparations is available from preclinical studies. A mouse model study found that topical treatment with copper sulfate not only improved the speed of wound contraction and closure but also improved the quality of the regenerated tissue [70]. Other studies have shown that materials doped with both Cu and Zn can enhance wound healing by modulating immune responses and promoting tissue repair. For instance, in a mouse model of wounds infected with methicillin-resistant *S. aureus*, a Cu/Zn-doped hydrogel was demonstrated to have enhanced antibacterial activity and accelerated healing in comparison to control groups given hydrogel without Cu/Zn [58]. Another in vivo study showed the wound healing rate was significantly faster in a group treated with a Cu/Zn loaded nanofiber dressing than in groups given the same dressing without Cu/Zn [71]. In both studies, Cu/Zn promoted macrophage polarization towards the regenerative M2 phenotype [58, 71]. Other preclinical or in vitro studies of different wound healing compositions containing Cu and Zn showed evidence of the synergistic inhibition of bacterial growth and biofilm formation [72–74]. Moreover, in a study of patients operated on

for pilonidal sinus disease, topical Zn treatment tended to increase Cu in the wounds and adjacent skin, suggesting a positive synergistic effect between Cu and Zn [75].

There is also real-world evidence of the benefits of topical skin healing formulations containing Cu and Zn for treating minor skin impairments and wounds. For example, formulations containing a postbiotic *Aquaphilus dolomiae* extract, and copper and zinc salts have proved to be effective and are indicated for use in patients with various conditions, including radiation dermatitis [76] and hand eczema [77]. In a study of 1317 infants, children, and adults with various types of superficial skin impairment, daily use of a formulation containing *A. dolomiae* extract, copper sulfate, and zinc sulfate for around 3 weeks was highly effective and well tolerated, with positive feedback from most participants [78, 79]. Another study, involving 40 adults who used this skin healing preparation in tattoo aftercare, showed it was well tolerated and, in self assessments, was regarded as efficient or very efficient in the healing process [80]. The good tolerability and safety of topical products containing Cu or Zn could be expected since they are designed to act on the skin surface, with minimal systemic absorption [81, 82], and are not intended for long-term use or for use on large wounds or severe burns. However, while the risk of interfering with mineral metabolism (e.g., Cu) is low, caution may be advised in patients with metabolic disorders, such as Wilson disease [57].

As well as cumulative evidence of the benefits of Cu/Zn-containing formulations in different settings, understanding is also required of patient-specific lifestyle, dietary, and genetic factors that may influence wound healing [83] and theoretically mitigate the beneficial effects of Cu/Zn. For example, patients who smoke display delayed and/or compromised wound healing, which is thought to be related to the negative vascular effects of nicotine and carbon monoxide displacement, and the toxic effect of chemicals, such as hydrogen cyanide, in cigarette smoke [84]. Also, poor diet or malnutrition will impair wound healing if there are insufficient amino acids to aid tissue regeneration, or a deficiency of minerals and vitamins to support

increased cellular activity and the regenerative pathways during the healing response [85, 86]. Vitamin C, for example, serves to not only stimulate collagen gene expression but is required for prolyl hydroxylase and lysyl hydroxylase activity, enzymes that are needed for mature collagen formation [86, 87]. Genetic and epigenetic factors can also influence the wound healing process, with certain patient genotypes dictating cutaneous microbiome composition and diversity [88], and changes in DNA methylation from ageing and lifestyle, histone modification, and chromatin remodeling alter the transcription of genes related to all three phases of the wound healing process [89].

## CONCLUSION

There is a wealth of literature examining the roles and effects of Cu and Zn in wound healing. In this article, we focus on the properties of Cu/Zn that are relevant to preventing the invasion and proliferation of microorganisms into the deeper skin tissues, which is essential for an optimal wound healing process after injury. Cu and Zn are essential trace elements in many physiological processes and have long been recognized for their abilities to promote wound healing and help control infection. While Cu and Zn have antiseptic properties that could, in theory, slow down healing, there is no evidence that Cu/Zn alters the skin's microbiota balance, and Cu- and Zn-dependent mechanisms are involved in the innate immune response to skin injury, which may stimulate the skin's natural immune defenses. Moreover, Cu and Zn have been shown to work together in various stages of the wound healing process, with synergistic effects that enhance antimicrobial activity, immune regulation, and tissue repair. Clinical research indicates that existing Cu/Zn-containing formulations are generally well tolerated and safe for topical use. However, despite their widespread application in wound healing, there remains a lack of consensus in the literature regarding the optimal concentration ratios of copper and zinc. While both elements are essential, their efficacy can vary significantly

depending on the specific wound environment and individual patient characteristics. Therefore, we advocate for further research to explore and refine topical Cu/Zn-containing formulations, as their continued development holds promise for improving wound management while ensuring safety.

**Medical Writing, Editorial and Other Assistance.** Enovalife Medical Communication Service Center provided editorial assistance and publications coordination, on behalf of Pierre Fabre Dermo-Cosmétique, and Joanne Knowles (Joanne Knowles Medical Writing Ltd.) provided medical writing support, on behalf of Pierre Fabre Dermo-Cosmétique.

**Author Contributions.** All authors (Nicolas Kluger, Edward Lain, Nicolas Frasson, Gautier Doat, Aline Stennevin and Pascale Bianchi) participated in the development of this manuscript. All authors gave final approval before submission.

**Funding.** The development of this paper and its Rapid Service Fee was funded by Pierre Fabre Dermo-Cosmétique & Personal Care.

**Data Availability.** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## Declarations

**Conflict of Interest.** Nicolas Kluger has served as an investigator in clinical studies, a lecturer, and an expert for Pierre Fabre and Bioderma NAOS; and has provided expert services for La Roche Posay and Bayer, all in relation to wound healing through tattoos. Outside the field of wound healing, the author has provided expertise to UCB Finland and Novartis Finland, and served as a lecturer for Eucerin (Beiersdorf) and Astellas Finland. Edward Lain has received consulting fees and honoraria for lectures, presentations, and expert testimonies, as well as financial support for attending meetings and/or travel from Pierre Fabre unrelated to this manuscript. Nicolas Frasson has received

funding from Pierre Fabre Dermo-Cosmétique (for conducting clinical trials) unrelated to this manuscript. Gautier Doat, Aline Stennevin, and Pascale Bianchi are employees of Pierre Fabre Dermo-Cosmétique & Personal Care.

**Ethical Approval.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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