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GHK-Hyaluronic acid conjugates affect the wound closure in the presence of copper ions

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Wound healing is a complex, efficient and highly regulated biological process that consists of four phases: hemostasis, inflammation, proliferation and migration of cells [1]. Copper-dependent stimulation of vessel formation during the wound healing has been mainly attributed to its regulation of vascular endothelial growth factor (VEGF) and angiogenin [2]. The human copper-binding peptide GHK (glycyl-l-histidyl-l-lysine) is a small, naturally occurring tri-peptide present in human plasma that can be released from tissues in the case of an injury and is able to control the fibrinogen biosynthesis in liver tissue [3,4]. Most authors attribute effects of GHK to its ability to bind copper (II) ions that can affect not only the copper metabolism but also regulate a number of human genes [5]. Hyaluronic acid (HA) is currently used in tissue regeneration either alone or conjugated with bioactive molecules [6,7]. 200 kDa HA affects tissue regeneration and pro-angiogenic and wound closure processes.

In the present work, we report on the protective and regenerative actions of the HA-GHK conjugate on mouse embryonic fibroblasts cell line (NIH/3T3) in the presence and in the absence of Cu(II) ion. Dose-response experiments show no significant effect on cell viability/proliferation with or without 1 μM copper. The effect of HA-GHK conjugates on wound healing was investigated; as expected, HA200 treatment slightly increases the wound closure, while the addition of HA-GHK with different % of GHK loading results in higher % of wound closure than with HA200. Addition of 1 μM copper or 50 μM copper chelator BCS, modify this effect. Altogether, our findings pinpoint that GHK-HA is a good candidate as new molecular entity in wound healing and skin repairing.

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