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IN VITRO WOUND HEALING ACTIVITY OF ALPHA-LIPOIC ACID

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Chronic wounds represent a worldwide healthcare and socio-economic problem which significantly affects the patients' quality of life. Healing of chronic wounds is a very complex process and requires constant wound management and treatment with agents that should stimulate wound healing. Alpha-lipoic acid (ALA) is a naturally occurring organosulfur compound with two thiol groups in its structure. It is a very potent antioxidant with other beneficial activities such as anti-inflammatory, anti-ageing and neuroprotective. This study aimed to investigate *in vitro* wound healing activity of ALA and its effect on the proliferation of L929 fibroblasts. Wound healing activity was examined using an *in vitro* 'scratch' assay, while the impact on cell proliferation was assessed using the MTT test. A concentration-dependent effect of ALA on fibroblasts' proliferation was observed. ALA stimulated the wound closure and migration of fibroblasts in used *in vitro* wound healing model, which suggests that ALA can be used as a potent agent in various pharmaceutical formulations for wound management and wound healing.

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Key words: *wound healing, chronic wounds, alpha-lipoic acid, cell proliferation, fibroblasts*

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Introduction

Wound healing (WH) represents a highly dynamic biological process in the human body (1). Interruptions, aberrancies, or prolongation in the programmed phases of WH, such as hemostasis, inflammation, proliferation, and tissue remodeling, can lead to delayed WH or a non-healing chronic wound (2). The complex and long-term process of chronic wound healing starts with wound formation, can take months or years (3) and can result in a significant negative impact on healthcare systems with serious impacts on the life quality of patients (4). Recent estimations show that non-healing chronic wounds represent a huge socio-economic problem, and represent a silent epidemic that affects 1–2% of the world population (5).

Despite numerous research studies in the field of WH and chronic wounds, critical gaps in the impaired healing process remain (6). Therefore, there is an immediate need for further analysis of factors associated with delayed healing, as well as identification of new candidates that can stimulate the proliferation of fibroblasts, which are the cells that play a crucial role in all phases of WH (7). Chronic inflammation and oxidative stress are distinguished as important factors of healing dysfunctions (8). Therefore, regulation of redox balance through the modulation of reactive oxygen species (ROS) and antioxidant levels may improve the WH process. The interest in using antioxidants for wound treatment is growing, and numerous studies have been performed with the aim of developing and examining different compounds with antioxidant properties which can enhance the healing process (3). Among a large number of natural antioxidant compounds, alpha-lipoic acid (ALA) stands out due to its noteworthy effects, and is considered today as "the universal antioxidant" (9). The molecular nature of ALA puts this unique dithiol compound in

special focus, because ALA acts as an antioxidant and can exert immunomodulatory properties (10, 11). Therefore, our aim was to examine the effect of ALA on the proliferation of fibroblasts and WH activity *in vitro*.

Materials and Methods

Cell line and culturing

In vitro WH activity testing of alpha lipoic acid ((±)-α-Lipoic acid, purity ≥ 98.0%, Cat. No. 62320, Sigma Aldrich, Germany) was performed on L929 fibroblast cell line (mouse skin fibroblasts). L929 fibroblasts were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS), 2 mM stable glutamine, and antibiotic-antimycotic solution (which makes complete DMEM), at 37 °C in an incubator with humidified atmosphere and 5% CO_2. Cell culture media and reagents used in the study were purchased from Capricorn Scientific GmbH, Germany.

Cell Proliferation Assay

L929 cells were seeded in standard 96-well plates (purchased from Greiner Bio-One, Germany) at a density of 5,000 cells per well of the 96-well plate. Twenty-four hours after cultivation of cells, ALA was added in various concentrations (ranging from 0 to 1,000 μM). Concentrations of ALA for testing were prepared by diluting the stock solution of ALA with complete DMEM. A stock solution of ALA was prepared according to the manufacturer's instructions by dissolving ALA in methanol (purity p.a.) in a concentration of 100 mg/mL. The cells incubated only with complete DMEM, without ALA, were used as a control (untreated cells). Each tested concentration of ALA was examined in four to six replicates, and complete DMEM was used as a control as well. The cells were incubated with different concentrations of ALA or control medium for the next 72 hours. After the incubation period ended, the MTT test was performed. The experiment was performed twice under the same conditions. The MTT test is widely used for assessment of cell proliferation and is based on the reduction of tetrazolium salt MTT (purchased from Carl Roth, Germany) by mitochondrial dehydrogenases of living cells, resulting in formazan crystals that correspond to the number of viable cells. Prior to the addition of 100 μL of MTT solution at a concentration of 1 mg/mL, media with ALA were discarded, and cells were washed with phosphate buffer saline (DPBS, Capricorn, Germany). MTT substance was purchased from Carl Roth, Germany. The cells were incubated with MTT solution for the next three hours, followed by dissolution of the formed formazan crystals with 2-propanol (purchased from Thermo Fisher Scientific, USA). The absorbance of dissolved formazan was measured on a Multiskan Ascent Photometric plate reader (Thermo Labsystems, Finland) at a wavelength of 540 nm with a reference wavelength of 650 nm for correction. The mean absorbance values were calculated for each tested sample, as well as for the control. The cell proliferation rate was calculated as: (absorbance value of cells treated with fibers/absorbance value of untreated cells) × 100.

In Vitro Wound Healing Assay

A "scratch" assay was performed to examine the *in vitro* WH effect of ALA, according to our previously published protocol (12−14). Briefly, L929 fibroblasts were seeded in 48-well plates and incubated under the standard cell culture conditions previously described in the section "Cell line and culturing". After reaching the complete confluence, a wound ('scratch') was created by a pipette tip in a cell monolayer, in the middle of each well. The cells were then washed with DPBS, and 100 μM of ALA, as well as complete DMEM (control), were added. ALA and complete DMEM were tested in three replicates, and the experiment was performed twice under the same conditions. Created "wounds" were incubated with ALA and complete DMEM for the next three days. A microscopic analysis of wounds' closure was then performed using an inverted light microscope, Observer Z1 (Carl Zeiss, Germany), and morphometric measurements were made in ZEN 2 (blue edition) software (Carl Zeiss, Germany) after imaging the "wounds". To assess the wound closure, we measured the width of the remaining wounded area after three days of incubation with the ALA as well as with complete medium (control), and compared it to the width of the area of initial wounds, before incubation with ALA. The WH activity was expressed as a percentage of wound closure. Additionally, the cell migration zone was measured starting from the initial edge of the wound.

Statistical Analysis

The results of the MTT test and morphometric measurements were analyzed using one-way analysis of variance (ANOVA). Results are expressed as a percentage of cell proliferation regarding the control culture, which represented cells incubated in complete DMEM (untreated cells) under the same conditions and for which we considered the cell proliferation rate to be 100%. Wound closure is expressed as a percentage with relative standard deviation. As statistically significant, we considered those values for which $p < 0.05$.

Results

The effect of ALA on the proliferation of fibroblasts

The effect of various concentrations of ALA is shown in Figure 1. Concentration-dependent effect of ALA on L929 fibroblasts proliferation was observed and was mostly pronounced in concentrations from 50 to 1,000 μM. A slight anti-proliferative effect at concentrations 250 μM and above was observed, with the most pronounced effect of the highest examined concentration, while lower concentrations did not exhibit an anti-proliferative effect instead, they even exerted a mild stimulatory effect.

In vitro wound healing activity of ALA

The wound healing effect of ALA, determined by *in vitro* 'scratch' assay, is shown in Figure 2. The effect of ALA was compared with the control, which represented complete DMEM without ALA. Three parameters were measured after three days of incubation: cell migration zone (the extent of cell growth and migration starting from the initial edge of the wound), wound area after the treatment (width of remained wound area) and the percentage of wound closure (calculated by the formula: 100% - (width of remained wound area – width of the initial wound area) x 100%). For WH activity testing, we chose a concentration which did not alter fibroblasts' proliferation.

The stimulating WH effect of ALA was noticed, determined by an *in vitro* 'scratch' assay. Statistically significant greater migration zone, smaller width of the remained wound area and higher percentage of wound closure in the presence of ALA were observed when we compare ALA treatment with the control.

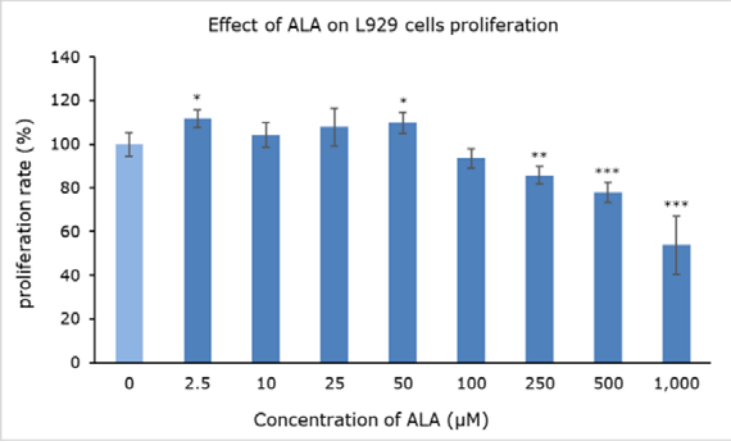

Figure 1. The effect of various ALA concentrations on L929 cells' proliferation, measured by MTT test. Results presented as mean % of cell proliferation compared to the control cell culture with relative standard deviation; (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$.

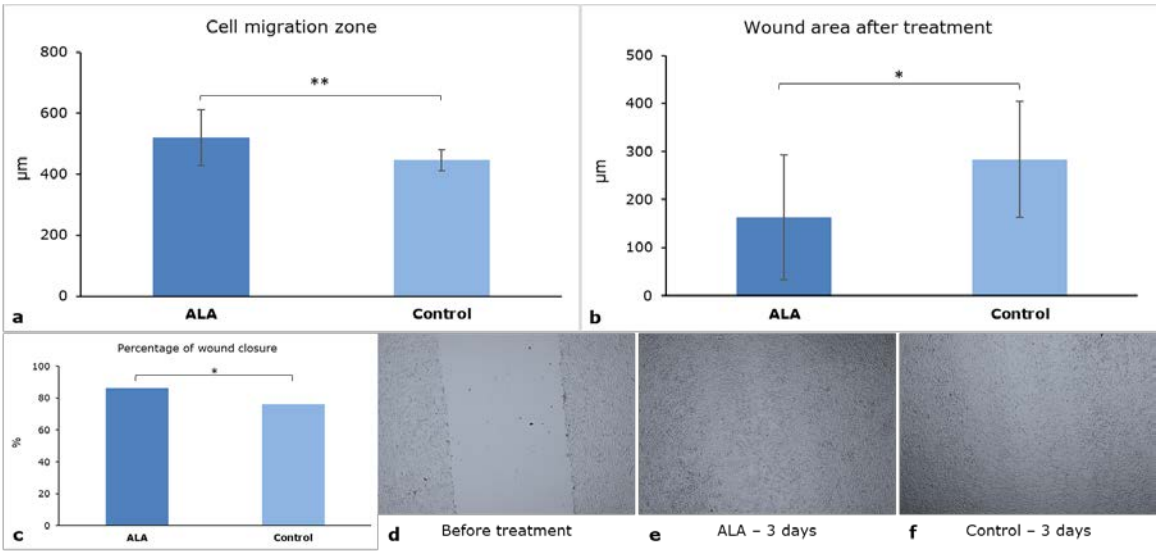

Figure 2. The wound healing effect of ALA, determined by the 'scratch' assay. Results presented as mean width (μm) ± SD of cell migration zone (a) and remained wound area after treatment (b) and % of wound closure after treatment (c); microscopical image of the wound before treatment (d), after three days of incubation with ALA (e) and control medium (f); (*) $p < 0.05$, (**) $p < 0.01$.

Discussion

A meticulous and very complex process of WH is achieved through several phases and requires the interaction and communication of different cell types present in the wound (15). Fibroblasts are distinguished as key effector cells in all phases of the WH process, with the note that accumulation and activation of the fibroblasts is closely related to and is responsible for the formation and deposition of granulation tissue, and finally leads to the wound contraction (16). Therefore, quick WH might be due to stimulation of proliferation and migration of fibroblasts, but it is also necessary to take into account a level of reactive oxygen species (ROS) playing a crucial role in the WH process (17). Growing evidence supports the fact that oxidative stress plays a significant role in WH phases and processes such as regulation of inflammation, angiogenesis, cell proliferation, formation of granulation tissue and the formation of extracellular matrix (ECM) (18). Because of the complexity of the WH process and the participation of oxidative stress in that process, various antioxidant compounds have become the focus of research (17).

Alpha-lipoic acid is a naturally derived organosulfur compound with two thiol groups in its structure, which may participate in redox reactions (19). It exists in oxidized and reduced forms and is characterized by unique antioxidant potential, since both endogenously and exogenously synthesized form is actively involved in ROS neutralization, restores the intrinsic antioxidant systems and supports their production (10, 19). ALA occurs usually in mitochondria, acting as a coenzyme for some enzyme complexes, and plays a major role in protein, carbohydrate and fatty acid metabolism, and manages gene activation (11). Its amphiphilic characteristic sets ALA apart from other antioxidants, and can elicit antioxidant and anti-inflammatory actions in both the cytosol and plasma membrane (20). Currently, it is attracting attention because of its distinctive antioxidant properties and influence on various cellular functions, leading to the beneficial effects on human health (21).

In this study, we analyzed the WH activity of ALA using a well-established *in vitro* cell 'scratch' assay. Before performing the WH assay, we investigated the effect of ALA on the proliferation of fibroblasts. We observed a concentration-dependent effect of ALA on the proliferation of L929 fibroblasts, with a slight anti-proliferative effect in concentrations above 250 μM. Lower concentrations of ALA did not exhibit an anti-proliferative effect and they even had a mild stimulatory effect on fibroblasts' proliferation, which makes ALA a good candidate for topical applications (Figure 1). The cell scratch assay using skin cells, such as fibroblasts, is a widely used method as an *in vitro* WH model that provides information about the activity of different compounds and natural products (22). In the present study, we used this assay with a focus on three parameters: cell migration zone, resting wound area and percentage of wound closure after three days of incubation with ALA. Representative images in Figure 2, statistically significant larger migration zone, smaller width of the remained wound area and higher percentage of wound closure comparing to the control, clearly show that ALA significantly stimulated WH in an *in vitro* cell model and may be used as a powerful WH agent in numerous topical pharmaceutical formulations intended for wound treatment and healing. The obtained results might be due to the strong and already confirmed antioxidative activity of ALA (22, 23), however, we assume that ALA exerts other activities that are involved in the stimulation of fibroblasts' proliferation and migration.

ALA has been in the research focus for several decades, and literature data reveals the effectiveness of ALA in the prevention of many oxidative stress-mediated pathologic conditions such as obesity, cardiovascular disease, diabetes and related complications, osteoporosis, cognitive dysfunction, malignant diseases, glaucoma, and many others (24). However, its potential application in WH has not yet been thoroughly investigated. There is a limited number of studies with different experimental designs making it difficult to compare the results (*in vitro*, animal models or human clinical studies) (23, 25, 26). Türkez et al. showed that ALA conjugated boron nanoparticles (concentrations of 50 ug/mL and lower) enhanced WH and antimicrobial processes in human dermal fibroblasts cell culture (25). The group of authors from China showed that ALA enhanced injury repair in a dose-dependent manner in human colon epithelial cells NCM460 (27). Reported results of one study conducted by Külkamp-Guerreiro et al. confirmed that topical application of non-encapsulated ALA induces increased skin WH, which is shown using an in vivo model of experimentally induced skin wounds (23). Human clinical study conducted in Italy showed that supplementation with ALA, in combination with hyperbaric oxygen therapy, promotes progression of the healing process by down-regulating the growth factors and inflammatory cytokines production (26). The results of our study presented here, together with the literature data, indicate that ALA shows good potential to be used as a WH agent in wound treatment, and provide a basis for further investigation to clarify the therapeutic potential of ALA in WH. Further *in vivo* research on experimental animals is necessary to explain the precise role of ALA in the complex and chronic WH process.

Conclusion

We can conclude that alpha-lipoic acid, besides many beneficial effects, shows a great wound healing activity determined *in vitro* using the "scratch" assay on fibroblasts. This indicates that ALA can be used as a potent agent in various

pharmaceutical formulations for wound management and wound healing.

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IN VITRO EFEKAT ALFA LIPOINSKE KISELINE NA ZARASTANJE RANA

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Hronične rane predstavljaju svetski zdravstveni i socioekonomski problem koji umnogome utiče na kvalitet života bolesnika. Zarastanje hroničnih rana veoma je složen proces i zahteva stalnu obradu i tretiranje rana sredstvima koja treba da stimulišu njihovo zarastanje. Alfa lipoinska kiselina je prirodno organsko sumporno jedinjenje koje u svojoj strukturi ima dve tiolne grupe. Veoma je moćan antioksidans, a zabeležena su i druga značajna svojstva koja ova kiselina ima: antiinflamatorna, antiejdžing i neuroprotektivna. Cilj ove studije bio je da se ispita efekat alfa lipoinske kiseline na zarastanje rana *in vitro*, kao i efekat ove kiseline na proliferaciju L929 fibroblasta. Efekat na zarastanje rana ispitivao se korišćenjem *in vitro* testa koji podrazumeva pravljenje „ogrebotine" u monosloju ćelija u kulturi, dok je za ispitivanje efekta na proliferaciju ćelija upotrebljen MTT test. Zabeleženo je da je efekat alfa lipoinske kiseline na proliferaciju fibroblasta zavisio od koncentracije. Činjenica da je alfa lipoinska kiselina stimulisala zarastanje, tj. zatvaranje načinjene rane (ogrebotine) i migraciju fibroblasta u korišćenom *in vitro* modelu zarastanja rana ukazuje na to da se alfa lipoinska kiselina može koristiti kao snažan agens u različitim farmaceutskim formulacijama za lečenje i zarastanje rana.

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***Ključne reči**: zarastanje rana, hronične rane, alfa lipoinska kiselina, proliferacija ćelija, fibroblasti*