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The influence of topical antioxidant use on hair regrowth and skin condition after chemical depilation

A influência do uso de antioxidante tópico no crescimento do cabelo e no estado da pele após depilação química

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ABSTRACT

Introduction: Hair restoration treatments for alopecia using existing medications are not always effective, highlighting the need for new therapeutic options.

Objective: This study aimed to evaluate the effects of a topical gel containing ethyl-methyl-hydroxypyridine succinate (EMHPS) on hair regrowth and biochemical and histological skin parameters in animals following chemical depilation.

Methods: Experiments were conducted on 50 adult male Wistar rats. Alopecia was induced using a commercial depilatory product containing potassium thioglycolate. A 5% EMHPS gel (125 mg/kg) was applied daily to the depilated skin. Trichoscopy, biochemical analysis, and histological examination of skin samples were performed on days 3, 9, and 21 of treatment.

Results: The EMHPS gel demonstrated a tendency to accelerate hair regrowth, reduce lipid peroxidation, normalize antioxidant enzyme activity, and restore hydroxyproline and glycosaminoglycan levels in the treated skin compared to the untreated pathology control.

Conclusions: The EMHPS gel primarily influences skin biochemical parameters and may be beneficial for treating forms of alopecia associated with oxidative stress.

Keywords: Hair; Hair Removal; Skin.

RESUMO

Introdução: *A restauração capilar durante a alopecia com o auxílio dos medicamentos existentes nem sempre é eficaz, por isso é importante a busca de novos medicamentos para o seu tratamento.*

Objetivo: *Nosso trabalho tem como objetivo estudar o efeito da aplicação tópica de novo gel com succinato de etilmetilhidroxipiridina na restauração capilar e nos parâmetros bioquímicos e histológicos da pele em animais após depilação química.*

Métodos: *Foram utilizados 50 ratos Wistar machos adultos em experimentos. A alopecia foi modelada com um produto depilatório comercial à base de tioglicolato de potássio. Todos os dias, foi aplicado gel succinato de etilmetilhidroxipiridina a 5% (125 mg/kg) na pele. Após 3, 9 e 21 dias do início do tratamento, realizaram-se tricoscopia, análise bioquímica e investigação histológica das amostras de pele.*

Resultados: *Foi demonstrado que o novo gel succinato de etilmetilhidroxipiridina causou tendência à aceleração do crescimento do cabelo, diminuição da peroxidação lipídica, normalização da atividade das enzimas antioxidantes e do conteúdo de hidroxiprolina e glicosaminoglicanos na pele da área de teste em comparação com o controle.*

Conclusões: *Portanto, o gel succinato de etilmetilhidroxipiridina atua predominantemente nos parâmetros bioquímicos da pele e será útil no tratamento das formas de alopecia que se desenvolvem num contexto de intenso estresse oxidativo.*

Palavras-chave: *Cabelo; Remoção de Cabelo; Pele.*

Original Article

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INTRODUCTION

Healthy hair is often associated with beauty, and hair loss can significantly impact quality of life.[1] Alopecia is one of the most common dermatological concerns, with various types requiring pathogenetic treatments aimed at stimulating the anagen phase, delaying catagen, and restoring proper hair thickness.[2,3] While oral treatments are available, they carry a high risk of side effects,[4] making topical therapy the preferred approach.[5]

Topical formulations of finasteride and minoxidil are the most widely recognized treatments for alopecia. However, other options include prostaglandins, ketoconazole, vitamins, minerals, herbal preparations, platelet-rich plasma, growth factors, microneedling, laser therapy, and cell-based therapies.[6] In cases of scarring alopecia, hair transplantation remains the most effective treatment.[7] Despite these options, topical hair restoration treatments are not always effective, highlighting the need for new therapeutic agents or the repositioning of existing drugs.[6]

From this point of view, antioxidants—particularly ethyl-methyl-hydroxypyridine succinate (EMHPS), also known as Mexidol—are of interest.[8] This synthetic heterocyclic antioxidant is considered low-toxic, has a significant safety margin, and is prescribed in some post-Soviet countries for psychoneurological and cardiovascular conditions.[9] Computational modeling using the Drug2Ways approach has predicted potential dermatological benefits of EMHPS, suggesting its possible therapeutic application in alopecia.[10]

Oxidative stress is known to contribute to the development of skin disorders,[11] potentially serving as a link between dermatological conditions and hair loss.[12] Despite its potent antioxidant properties, topical application of EMHPS in dermatology and cosmetology remains unexplored, and no topical formulations of the drug currently exist. This motivated us to develop an EMHPS gel. The gel formulation was chosen for its ability to deliver bioactive substances promoting tissue regeneration while remaining stable on the treated area and resisting evaporation longer than liquid formulations.[13] We decided to investigate the effects of EMHPS gel on hair restoration and skin condition in laboratory rats following chemical depilation, a widely used animal model for studying hair loss in the preclinical testing of drugs and cosmetic products.[14] The aim of our study is to evaluate the impact of topical application of the newly developed EMHPS gel on hair regrowth and skin biochemical and histological parameters in animals after chemical depilation.

MATERIALS AND METHODS

Materials

Gel-forming and auxiliary substances, as well as all reagents for biochemical analysis and dyes for histological examination, were obtained from Merck KGaA (Germany). EMHPS was obtained from SPF Microchem LLC (Ukraine). The gel formulation contained 5.0 g of EMHPS, 0.5 g of sodium metabisulfite, 1.0 g of polyvinyl alcohol, 2.0 g of carbomer 940, 2.8 g of TRIS, and distilled water up to 100.0 g. It was prepared using standard laboratory techniques. First, EMHPS and sodium metabisulfite were dissolved in 2/5 of the required total amount of water. Separately, polyvinyl alcohol was dissolved in another 2/5 of the total water by heating in a water bath. The two solutions were then combined. Finally, carbomer 940 and TRIS, which had been pre-dissolved in the remaining 1/5 of the total water, were gradually added with continuous stirring until a gel was formed.

Model pathology and experimental therapy

A total of 50 adult male Wistar rats (122–126 days old, weighing 185–215 g) were housed in groups of five per cage under standard laboratory conditions (standard diet and water ad libitum). They were maintained on a standard laboratory diet with ad libitum access to water in a temperature-controlled room with a 12-hour light-dark cycle. The study protocol was approved by the Committee on Bioethics and Ethical Issues at Poltava State Medical University (No. 220, October 25, 2023).

All rats were pre-selected to be in the telogen phase of the hair growth cycle based on their age.[15] They were then randomly assigned to four groups: intact control, pathology control, reference, and experimental groups.

Alopecia was induced by chemically depilating the animals' backs. An 8 cm × 4 cm skin area was treated with a commercial depilatory product containing potassium thioglycolate.[16] The product was applied in a thin layer for 10 minutes. Once the hair was dissolved, it was removed, and the skin was thoroughly washed with water and dried with a napkin. Treatment began immediately after the depilated skin area was dried.

The EMHPS gel was applied to the test area at a dose of 125 mg/kg (approximately 0.5 mL per rat). Treatment was administered once daily at the same time each day. After gel application, each animal was isolated for 30 minutes before being returned to its cage. Treatment continued until 24 hours before euthanasia.

As a reference treatment, a 2% minoxidil solution (Industrial Pharmaceutics Cantabria, S.A., Spain) was applied to the depilated skin at a dose of 30 mg/kg (approximately 0.3 mL per rat) once daily.[15]

Throughout the experiment, animals' behavior was monitored, and their body weight was recorded periodically. On days 3, 9, and 21 post-depilation, animals were euthanized by terminal hemorrhage induced by general anesthesia with sodium thiopental (50 mg/kg, JSC Kyivmedpreparat, Ukraine).[17]

Macroscopic analysis

Trichoscopy and photography were performed with a Firefly DE330T digital trichoscope (USA). Hair growth was scored using a four-tier scoring system: type 1 = uneven, weak hair growth with clearly visible skin; type 2 = low hair density with partially visible skin; type 3 = moderate hair density with no visible skin; type 4 = high hair density with full, thick fur.[18]

Histological analysis

On day 21, skin samples were collected from the test area of euthanized rats and processed for histological analysis. Samples were stained with hematoxylin and eosin (H&E) according to a standard protocol.[19] Microscopic examination was performed using an Olympus BX41 microscope (Olympus, Japan).

Biochemical assays

A 10% tissue homogenate was prepared from the affected skin area using 0.2 M Tris-HCl buffer solution (pH = 7.4). Malondialdehyde (MDA) content was determined based on its reaction with 1-methyl-2-phenyl-indole.[20] Superoxide dismutase (SOD) activity was measured by monitoring the kinetics of adrenaline autoxidation.[21] Catalase activity was assessed using the molybdate colorimetric method.[22] The concentration of free hydroxyproline was determined by a colorimetric assay, which relies on the reaction of pyrrole-2-carboxylic acid, formed during hydroxyproline oxidation, with p-dimethylaminobenzaldehyde in a modified procedure.[23] Glycosaminoglycan (GAG) content in skin was analyzed by measuring the concentration of hexuronic acids, which form a colored product in reaction with carbazole, following a modified version of the Dische method.[24]

All methods were previously validated for 10% tissue homogenate analysis. Optical density measurements were performed using a Ulab 101 spectrophotometer (Ulab, China).

Statistical analysis

The results of biochemical assays were expressed as mean ± standard error of the mean (M±SE). Data were statistically analyzed using one-way analysis of variance (ANOVA) followed by a post-hoc Tukey test. Data normality was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was applied to evaluate the semi-quantitative assessment of hair regeneration. A p-value < 0.05 was considered statistically significant.

RESULTS

Trichoscopy and visual assessment of hair regeneration

Throughout the observation period, no behavioral abnormalities were detected in the control or experimental groups. Changes in body weight were statistically insignificant compared to baseline values.

According to visual examination, intact rats exhibited a thick fur coat typical of this species (Figure 1D), corresponding to type 4 (5/5) (Figure 2). Immediately after chemical depilation, all groups displayed a hairless test area with clean skin (Figure 1A). By day 3, hair regrowth had begun, with similar progression across all groups (Figure 1B). At this stage, hair regeneration was classified as type 1 (5/5) and remained significantly different from the intact group ($p < 0.005$) (Figure 2A).

By day 9, differences between the groups became apparent. In the control pathology group, the test area showed noticeable hair regeneration, classified as type 2 (5/5) (Figure 1C),

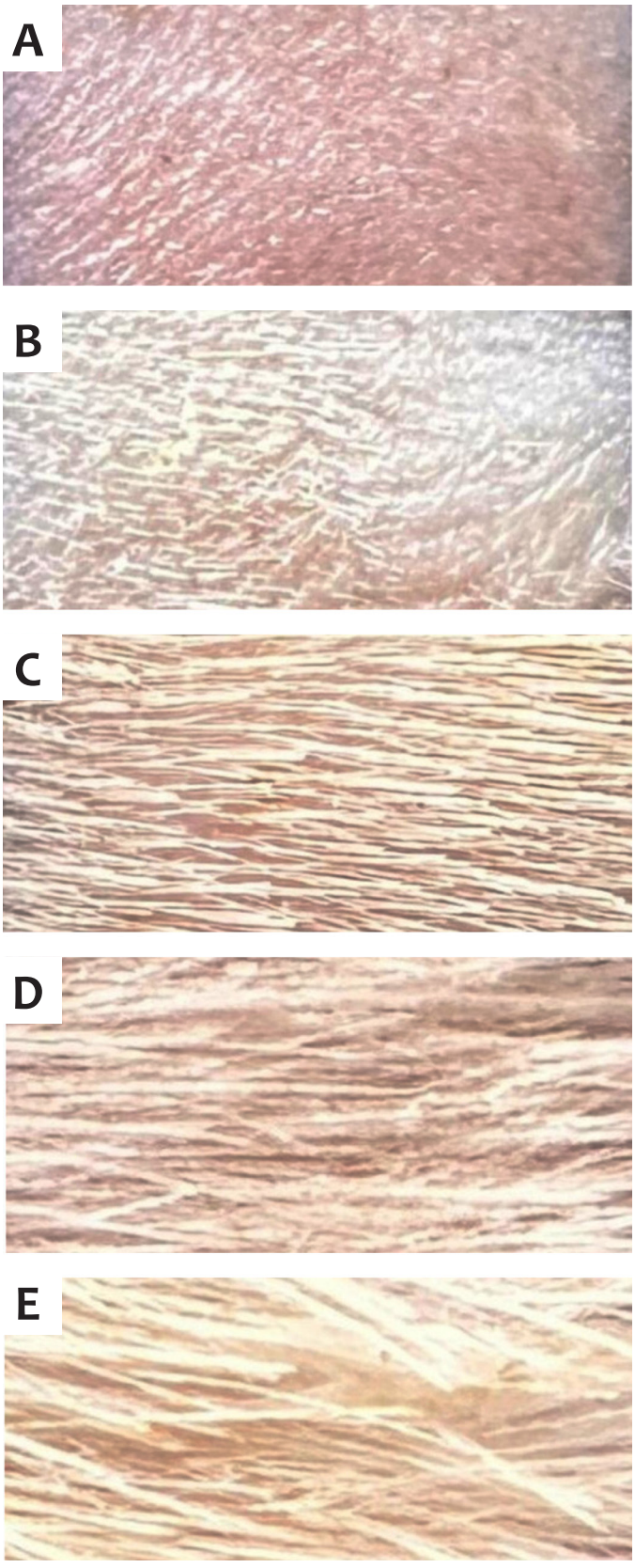

Figure 1: Visual assessment of hair regeneration

which remained significantly different from the intact control ($p < 0.005$) (Figure 2B). In the reference group (minoxidil-treated), there was a trend toward greater hair growth, with type 3 (3/5) ($p < 0.1$) compared to the control pathology group (Figure 1D, Figure 2B). At the same point, hair regeneration in the EMHPS-treated group was similar to that in the reference group (Figure 1D, Figure 2B), though some hairs in the EMHPS group appeared longer.

By day 21, in the control pathology group, hair coverage had almost returned to normal, with a mix of type 3 (3/5) and type 4 (2/5) pelage (Figure 1D, E). In the EMHPS-treated group, hair regeneration was predominantly type 4 (4/5), though the difference compared to the control pathology group was not statistically significant (Figure 2C). A similar pattern was observed in the reference group, though visually, the fur in this group appeared more uniform than in the EMHPS-treated rats (Figure 2C).

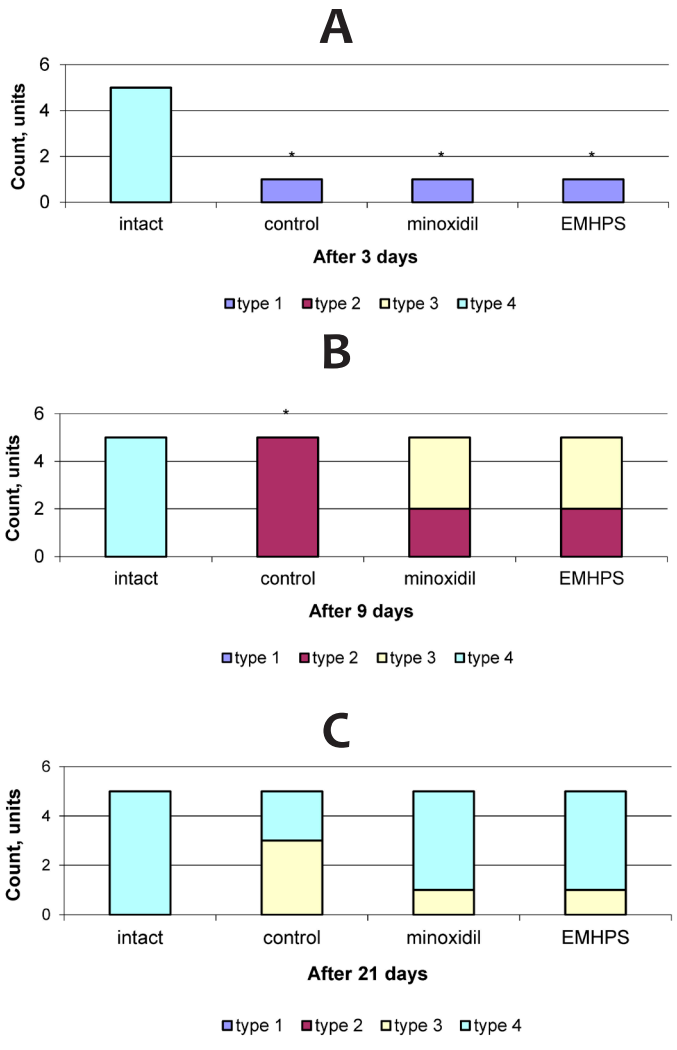

FIGURE 2: Trichoscopy and visual assessment of hair regeneration

Overall, macroscopic evaluation suggests both the EMHPS gel and the reference treatment (minoxidil) tended to accelerate hair regrowth following chemical depilation.

Histological changes in skin

After 21 days, rats in the control pathology group exhibited basal cell reactivity, indistinct layer boundaries, granular layer hypertrophy, and the presence of single intraepithelial cysts (Figure 3A). Dermal papillae were well or moderately developed, while hair follicles varied in location and diameter.

In the EMHPS-treated group, the epidermis contained numerous epitheliocytes with hydropic dystrophy and intraepithelial leukocytes (Figure 3B). Stratum corneum showed localized hypertrophy, and basal cell reactivity was still present. A few lymphoplasmacytic infiltrates were observed in the dermis, and microvessels displayed signs of reduced blood supply. Papillae formation was moderate, and hair follicles were unevenly distributed, with some sebaceous glands hypertrophied.

In the minoxidil-treated group, a significant number of epitheliocytes with optically empty vacuoles, intraepithelial leukocytes, and areas of basal cell reactivity were noted in the epidermis (Figure 3C). Dermis contained an increased number of cellular elements and focal clusters. Papillae were well or moderately developed, with a substantial number of hair follicles. Their diameters varied slightly, and some sebaceous glands showed signs of hypertrophy.

For comparison, the histological pattern of intact skin is shown in Figure 3D. Epidermis consisted of 2–6 cell layers with distinct boundaries, with single intraepithelial lymphocytes present. Some epitheliocytes showed signs of hydropic dystrophy. Dermis was composed of connective tissue with well-defined collagen fibers and scattered cellular elements. Papillae were moderately developed, and hair follicles were diffusely distributed or grouped in clusters of 3–5, mostly small to medium in diameter. Sebaceous glands were located near hair follicles, sometimes maintaining a visible connection with them.

Overall, hair regeneration after chemical depilation, both in the absence of pharmacological treatment and following topical application of EMHPS or the reference drug (minoxidil), was associated with histological changes in skin. Notably, pharmacotherapy intensified the skin response compared to the control pathology group.

Biochemical changes in skin

Throughout the observation period, control pathology was associated with increased lipid peroxidation, as evidenced by a significant elevation in MDA concentration ($p < 0.001$) in the affected skin area compared to intact animals (Figure 4). Minoxidil treatment reduced MDA levels by 1.3-fold ($p < 0.001$) after 3 days, 1.4-fold ($p < 0.001$) after 9 days, and 1.2-fold ($p < 0.001$) after 21 days, compared to untreated depilated skin at the same time points. The EMHPS gel produced a similar effect, reducing MDA concentration by 1.4-fold ($p < 0.001$) after 3 days, 1.3-

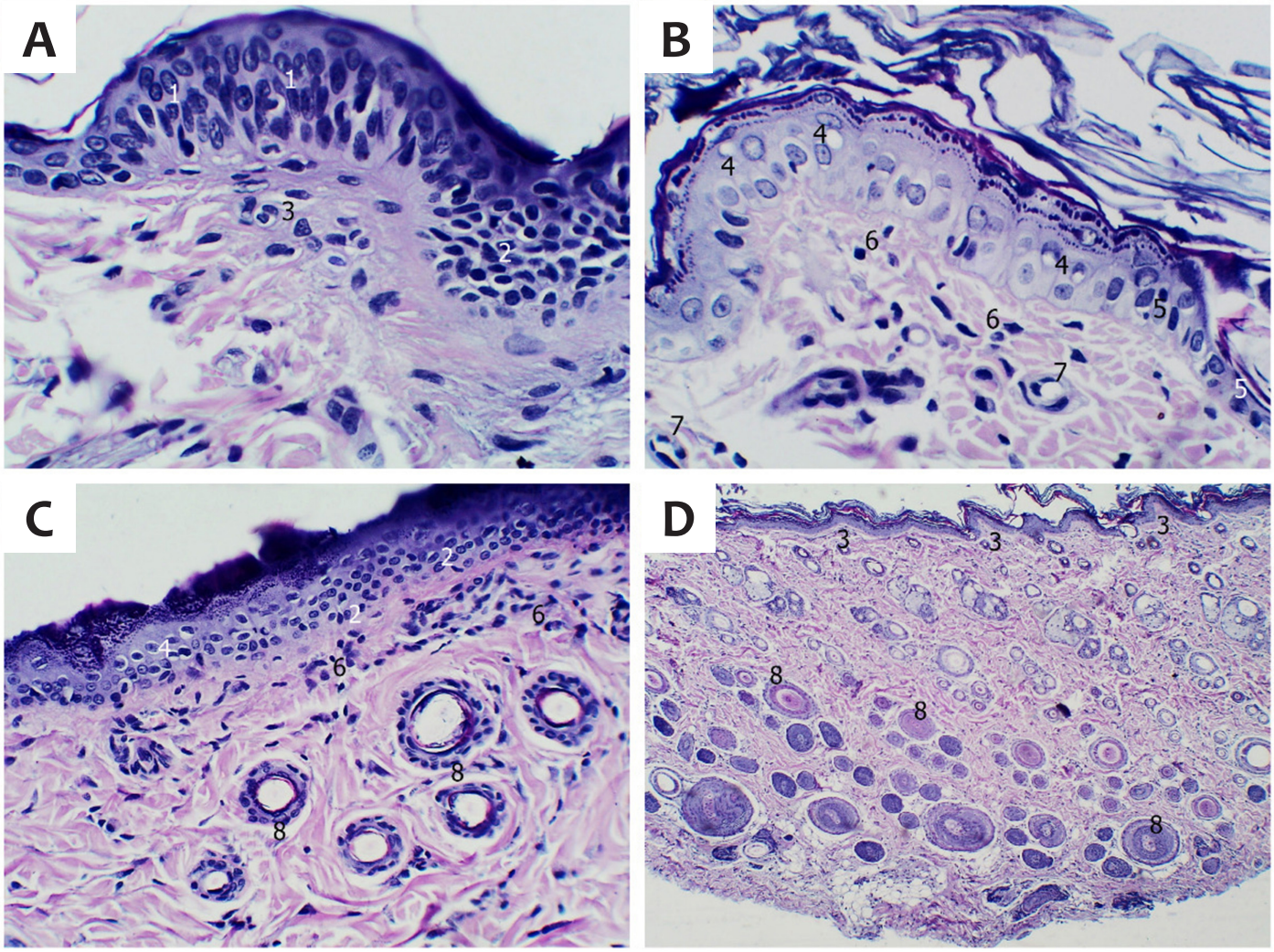

Figure 3: Histological pattern of the skin in animals 21 days after the start of experiment. **A -** Animals with control pathology (hematoxylin and eosin [H&E], x400). **B -** Animals with topical application of EMHPS gel (H&E, x400). **C -** Reference group received topical minoxidil (H&E, x250). **D -** Intact animals (H&E, x30). 1 – areas of stratification in the epidermis; 2 – basal cell hyperplasia; 3 – dermal papilla; 4 – epitheliocytes with hydropic dystrophy; 5 – intraepithelial leukocytes; 6 – lymphoplasmacytic infiltrates in the dermis; 7 – blood vessels; 8 – hair

fold ($p < 0.001$) after 9 days, and 1.2-fold ($p < 0.001$) after 21 days relative to the control pathology group. However, at later observation periods, the EMHPS gel had a slightly weaker effect than minoxidil ($p < 0.001$).

In the control pathology group, SOD activity in the skin decreased 3 days after depilation ($p < 0.05$) compared to intact rats (Figure 5A). This reduction became even more pronounced after 9 and 21 days ($p < 0.001$) as the model pathology progressed (Figure 5B, C). Minoxidil treatment increased SOD activity by 1.5- to 1.4-fold ($p < 0.001$) compared to untreated depilated skin. The EMHPS gel also enhanced SOD activity, with increases of 1.3-fold ($p < 0.001$) at 3 days, 1.8-fold ($p < 0.001$) at 9 days, and 1.3-fold ($p < 0.001$) at 21 days relative to the control pathology group. Notably, after 3 and 21 days, the antioxidant effect of EMHPS was weaker than that of minoxidil ($p < 0.002$ and $p < 0.001$, respectively), but after 9 days, it was stronger ($p < 0.001$).

In the control pathology group, catalase activity initially increased after 3 days ($p < 0.001$), decreased after 9 days ($p < 0.002$), and remained unchanged after 21 days compared to the intact control (Figure 6). Minoxidil further increased catalase activity by 1.2-fold ($p < 0.001$) in 3 days, normalized it after 9 days ($p < 0.005$), and had no significant effect at 21 days compared to the control pathology group. The EMHPS gel initially reduced catalase activity after 3 days ($p < 0.05$), increased it by 1.3-fold

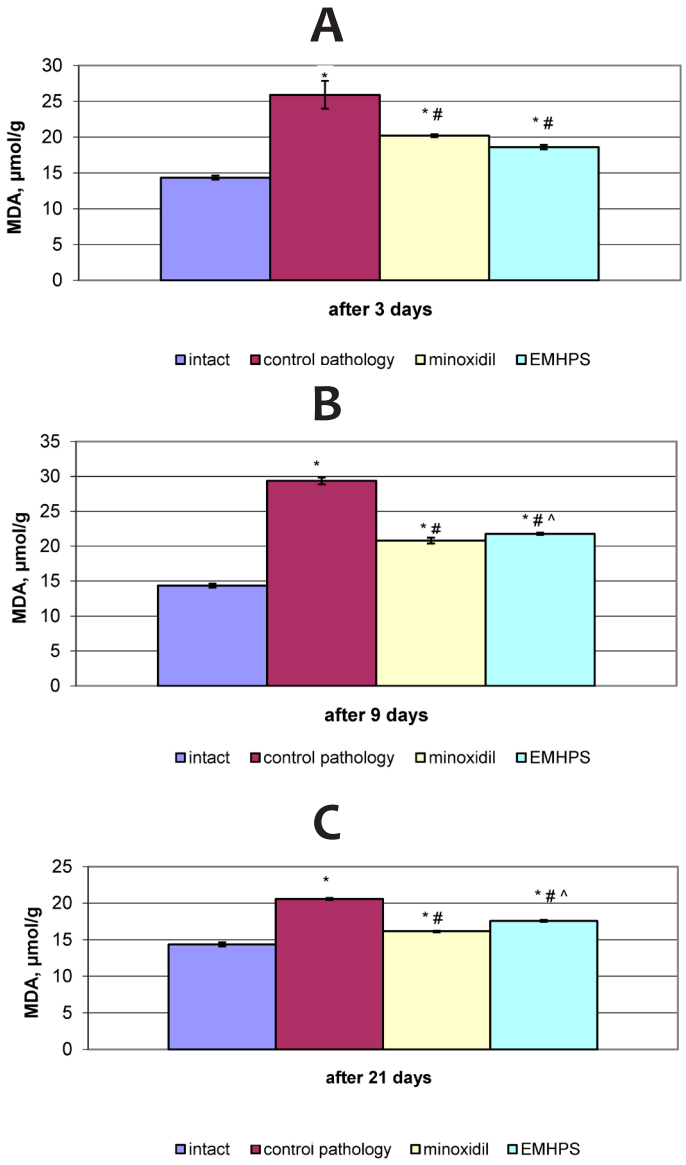

FIGURE 4: MDA concentration in skin

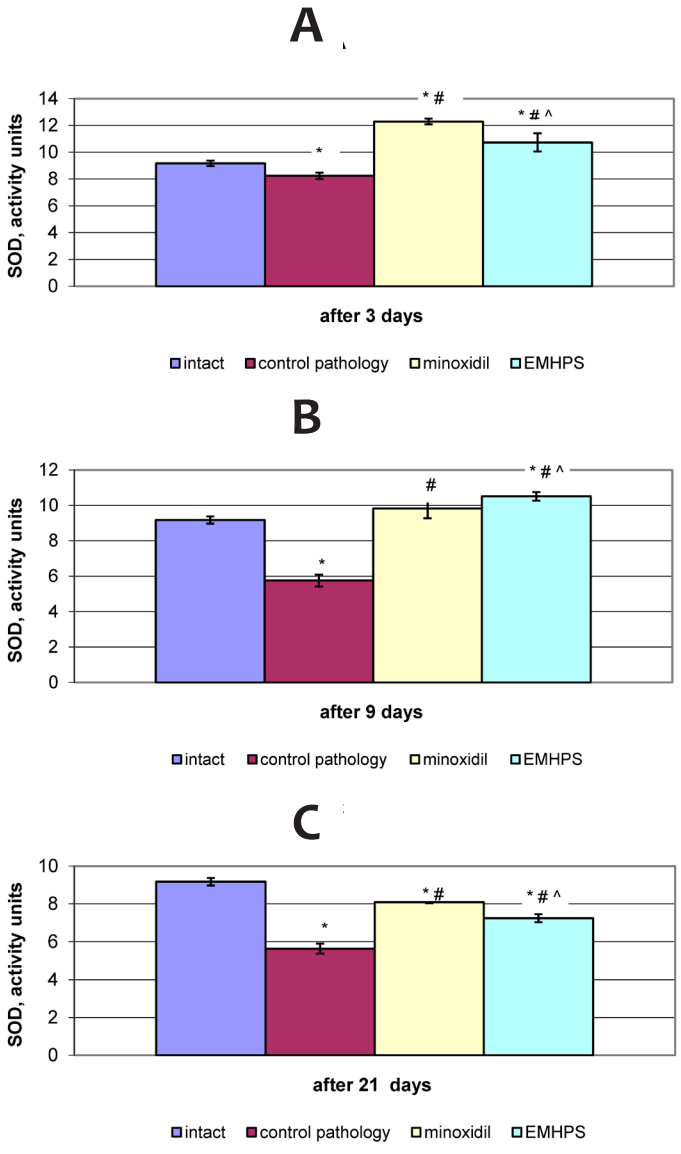

FIGURE 5: SOD activity in skin

($p < 0.001$) after 9 days, and had no significant effect at 21 days. The effect of EMHPS differed from minoxidil only in the early observation period ($p < 0.001$).

The results of biomarker analysis for connective tissue condition in the affected skin area are shown in Figure 7 and Figure 8. In the control pathology group, free hydroxyproline levels remained elevated throughout the study period. After 3 days, hydroxyproline increased 1.9-fold ($p < 0.001$), after 9 days, 2.0-fold ($p < 0.001$), and after 21 days, 1.5-fold ($p < 0.001$) compared to the intact control (Figure 7). Minoxidil significantly reduced these values, decreasing hydroxyproline concentration by 1.5-fold ($p < 0.001$) after 3 days, 1.4-fold ($p < 0.001$) after 9 days, and 1.2-fold ($p < 0.001$) after 21 days relative to the control pathology group. The EMHPS gel also lowered hydroxyproline levels, reducing them by 1.5-fold ($p < 0.001$) in 3 days, 1.3-fold ($p < 0.001$) in 9 days, and 1.1-fold ($p < 0.001$) in 21 days compared to the control pathology group. In the early observation period, the effects of EMHPS and minoxidil did not differ, but with continued treatment, EMHPS had a weaker effect on hydroxyproline levels than minoxidil ($p < 0.001$).

Three days after depilation without pharmacotherapy, GAG concentration in the affected skin increased 1.3-fold ($p < 0.001$) compared to intact rats (Figure 8A). It remained elevated by 1.2-fold after 9 and 21 days ($p < 0.001$) (Figure 8B, C). Minoxidil significantly normalized GAG levels after 3 days ($p < 0.001$) and gradually reduced them over

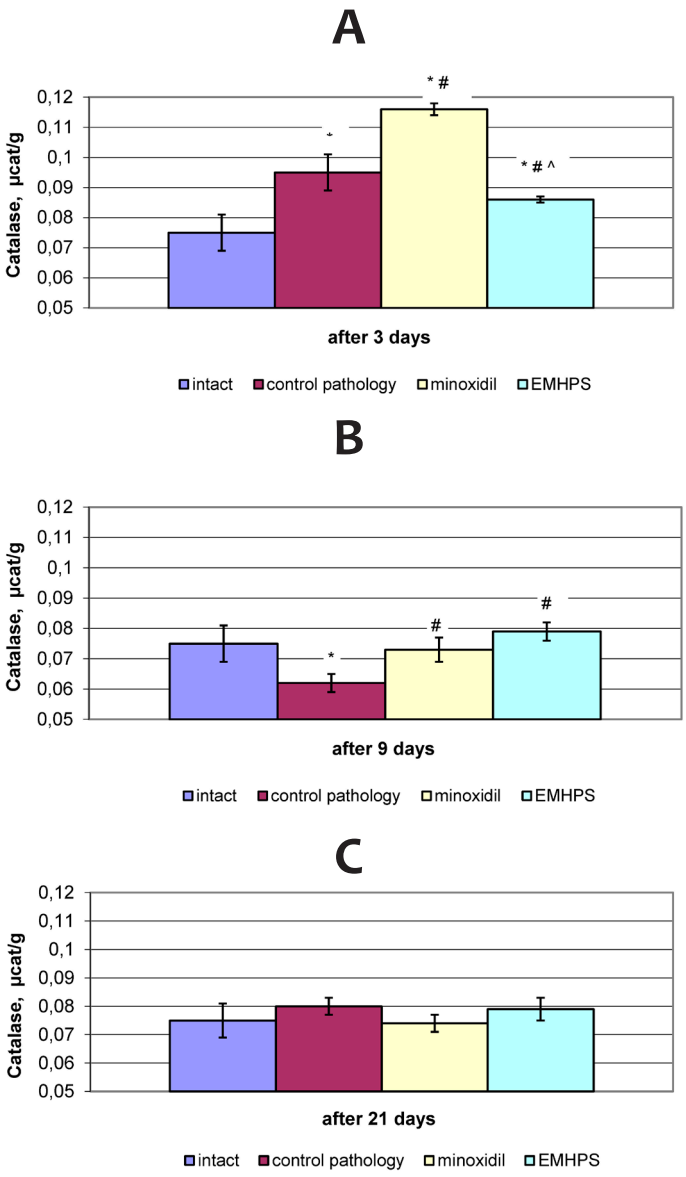

FIGURE 6: Catalase activity in skin

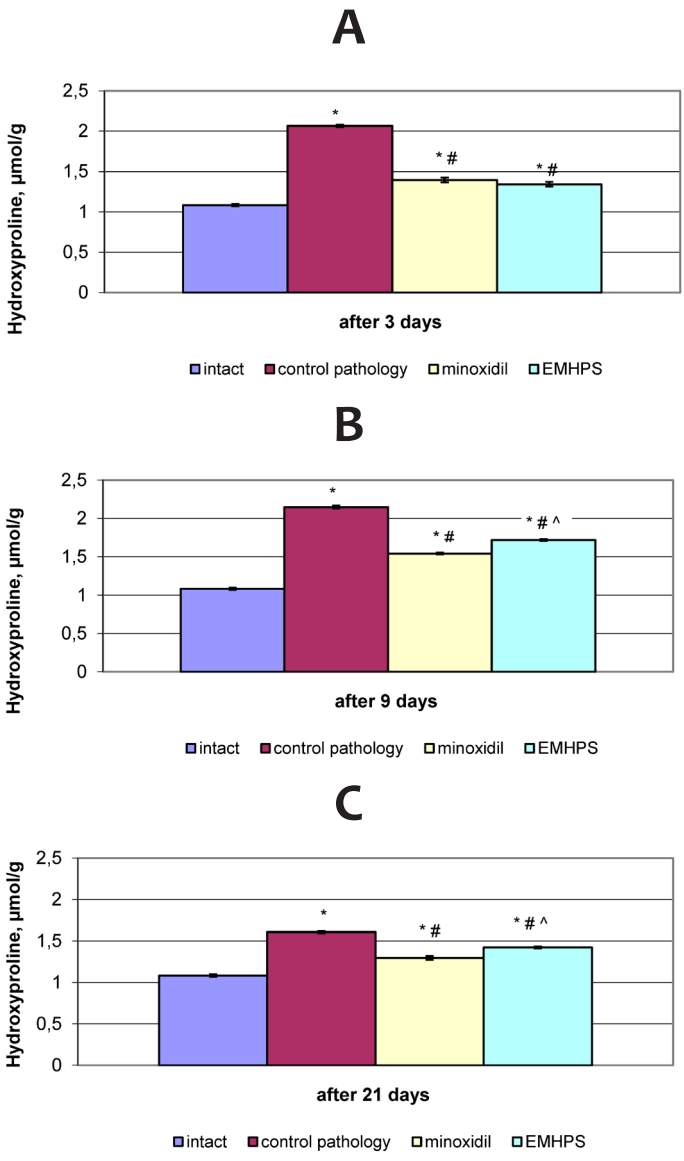

FIGURE 7: Hydroxyproline content in skin

time ($p < 0.001$) compared to the control pathology group (Figure 8). The EMHPS gel produced a similar effect: after 3 days, it normalized GAG levels to those of the intact control, and after 9 and 21 days, GAG levels decreased similarly to the minoxidil-treated group.

The EMHPS gel effectively inhibited MDA accumulation, modulated SOD and catalase activity, and reduced free hydroxyproline and total GAG concentrations in a manner comparable to minoxidil, though slightly less effective at certain time points.

DISCUSSION

Visual assessment of hair regeneration after chemical depilation revealed an acceleration of this process in both the EMHPS-treated group and the minoxidil-treated reference group. However, this improvement was observed as a trend rather than a statistically significant effect, likely due to individual variations in hair regrowth among animals, increasing result variability.[14] When examining the test area, differences in hair coat uniformity were also noted. The reference group exhibited a more homogeneous hair coat, whereas in the EMHPS-treated group, particularly after 9 days, individual long hairs were observed. This suggests that EMHPS may have a weaker effect on synchronizing follicle development cycles compared to minoxidil, which is known to influence this process.[25]

Histopathological analysis showed that chemical depilation without treatment led to basal cell reactivity and an increase

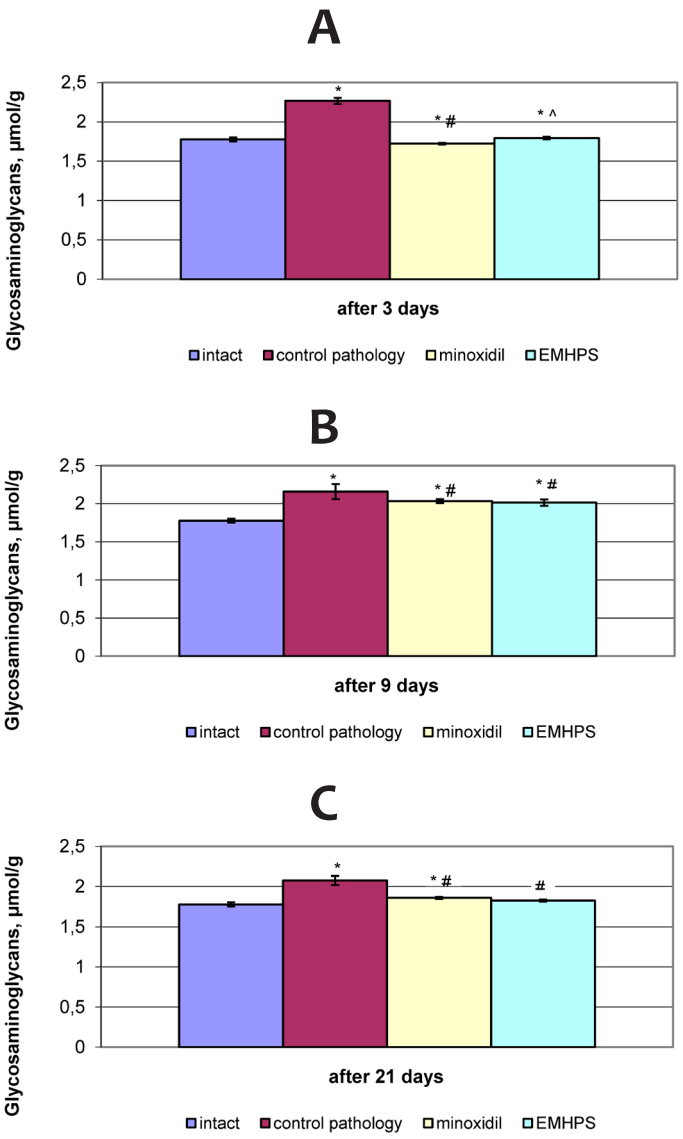

FIGURE 8: Glycosaminoglycan concentration in skin

in intraepithelial leukocytes, which persisted until the end of the experiment. These findings align with previous studies reporting histopathological changes in laboratory mice following exposure to conventional depilatory creams.[26] The observed reactive inflammation may be attributed to the alkaline properties of the depilatory agent, which can trigger a stronger reaction in rodent skin due to its thinner structure compared to human skin.[14,18]

Interestingly, the EMHPS gel enhanced reactive skin changes compared to the control pathology group. At first glance, this might seem contradictory, given that EMHPS inhibits free radical-driven prostaglandin synthesis mediated by cyclooxygenase and lipoxygenase.[8] However, in the context of hair regeneration, the interplay between inflammation, damage repair, and regeneration through inflammatory cytokines and Wnt signaling factors may be more relevant.[27, 28] This assumption is further supported by the histopathological observations in the minoxidil-treated group, which also exhibited enhanced reactive skin changes compared to control pathology. The only notable difference between the EMHPS gel and minoxidil was that minoxidil produced greater uniformity in hair follicle size and distribution, which could be considered an advantage of minoxidil.

In addition to histopathological changes, untreated depilation induced oxidative stress, as indicated by increased MDA levels, decreased SOD activity, and fluctuations in catalase activity. This suggests that oxidative stress development was linked to cytokine profile modifications caused by depilation,[29] and in the early post-depilation phase, potentially to a general adaptation syndrome. Given interspecies differences in skin structure and hair function, chemical depilation over a large body area in animals likely represents a more severe intervention than localized hair removal in humans.[14,18]

In depilated animals without pharmacological treatment, MDA levels remained elevated, and SOD activity remained suppressed until the end of the experiment. The early-stage suppression of SOD could result from enzyme inhibition by excess reaction products, whereas in the later stages, it may reflect a decrease in superoxide anion radical production. Since catalase works in tandem with SOD, its fluctuations likely correspond to hydrogen peroxide variations in the superoxide dismutase reaction. Both EMHPS and minoxidil reduced MDA levels, increased SOD activity, and modulated catalase activity, demonstrating antioxidant effects. This outcome was expected for EMHPS, given its established antioxidant properties.[8] Considering the known role of oxidative stress in hair growth impairment,[30] the inhibition of lipid peroxidation suggests a potentially beneficial pharmacodynamic effect of EMHPS on hair regeneration.

The antioxidant activity of minoxidil extended to both inducible antioxidant enzymes (SOD and catalase) and MDA accumulation. Although this property is rarely discussed in literature, it is plausible the effect of minoxidil on oxidative stress biomarkers is related to its ability to chelate intracellular iron.[31] Minoxidil exerts multiple pharmacodynamic effects, contributing to hair regrowth through vasodilation, anti-inflammatory action, Wnt/β-catenin pathway activation, and antiandrogenic activity, all of which influence anagen and telogen phase duration.[32]

When analyzing free hydroxyproline levels, untreated depilation led to a sustained increase throughout the observation period. In this study, a modified hydroxyproline assay (excluding the hydrolysis step) was used, allowing for the interpretation of increased hydroxyproline levels as an indicator of collagen degradation under oxidative stress.[33] The EMHPS gel reduced hydroxyproline content, exerting a normalizing effect similar to minoxidil, though less pronounced at 9 and 21 days. For both treatments, this suggests a potential role in regulating the extra-

cellular matrix (ECM) and hair follicle regeneration, possibly by reducing oxidative stress intensity and modulating ROS-related signaling pathways.

The ECM is a complex network composed of collagen, proteoglycans, and GAGs.[34] In addition to hydroxyproline, GAG content was analyzed, revealing that untreated depilation led to increased GAG levels, which declined following pharmacological treatment. This suggests that GAG accumulation in depilated skin may be linked to proteoglycan degradation caused by excessive ROS generation. The subsequent GAG reduction under treatment may be at least partially attributable to the antioxidant activity of both pharmacological agents, with potential implications for hair follicle function.[35]

The initial findings on EMHPS gel use are promising. It stimulates hair regrowth, exhibits antioxidant activity, and positively influences ECM components in a preclinical hair loss model. Further research is necessary to assess its efficacy in more specific experimental models of different alopecia types.

CONCLUSION

The 5% EMHPS gel, a synthetic antioxidant, promoted hair regrowth, exhibited antioxidant activity, and reduced damage to dermal ECM components caused by chemical depilation in an animal model. ●

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