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"Plant exosomes for hair loss prevention though dermal papilla cell stimulation and protection"

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1. Introduction

Exosomes are nanoscale extracellular vesicles, typically ranging from 30 to 200 nanometers in diameter, secreted by various cell types. They play a pivotal role in intercellular communication by transporting a diverse array of bioactive molecules, including proteins, lipids, and nucleic acids, to recipient cells [1]. This mechanism facilitates numerous physiological processes, such as immune responses, tissue regeneration, and cellular homeostasis. In recent years, exosomes have garnered significant attention in the biomedical and cosmetic industries due to their potential as natural delivery vehicles for therapeutic agents and cosmetic ingredients [2].

Exosomes can be classified based on their cellular origin, encompassing those derived from mammalian cells, plants, and microorganisms. In the cosmetics field, exosomes are increasingly utilized for their ability to enhance skin rejuvenation, promote collagen synthesis, and improve overall skin health. Their capacity to encapsulate and deliver active compounds efficiently makes them valuable in formulations aimed at anti-aging, hydration, and skin repair [3].

Plant-derived exosomes (PDEVs) have emerged as a promising alternative to their mammalian counterparts, offering several advantages. PDEVs are naturally occurring vesicles secreted by plant cells, encapsulating a rich cargo of proteins, lipids, nucleic acids, and secondary metabolites. Their biocompatibility, stability, and low immunogenicity make them suitable for topical applications. Moreover, PDEVs are considered sustainable and ethical, aligning with the growing consumer demand for plant-based and environmentally friendly cosmetic products [4].

Recent studies have explored the potential of PDEVs in targeting key skin processes, including aging and pigmentation [5]. Thus, research has shown that PDEVs can act cross-species to modulate key cellular pathways and exert a significant biological response in human cells. In particular, aloe vera exosomes (AVEs) have been described to possess regenerative, anti-inflammatory and antioxidant properties [6, 7], but their effect on hair care has not been elucidated. Here, we characterized the effect of AVEs on hair regeneration and hair loss markers

dermal papilla cells (DPCs), showing the promising use of these exosomes for hair care cosmetic products.

2. Materials and Methods

DPC were treated with AVEs (0.01%) for 24h and gene expression of hair growth markers was quantified by qPCR (real-time polymerase chain reaction).
DPC were treated with 10 µg/mL dihydrotestosterone (DHT) with or without AVE (0.01%) for 72h to simulate a senescence-like state and gene expression of senescence and damage markers was quantified by qPCR (real-time polymerase chain reaction).

3. Results

First, different genes involved in hair growth and regeneration were quantified in DPCs treated with AVEs. As shown in Figure 1, AVEs significantly upregulated growth factors (*KGF, VEGF*), Wnt pathway genes (*WNT1, CTNNB1*), Shh pathway genes (*Gli1*) and hair follicle anchor proteins (*ITGB1*).

Table 1. Gene expression changes in dermal papilla cells (DPCs) treated with aloe vera exosomes (AVE) for 24h. Results are expressed as fold change compared to control, and standard deviation is included in brackets. T-student analysis was performed to evaluate significant differences between the conditions, comparing control cells vs treated cells. * indicates $p < 0.05$; ** indicates $p < 0.01$; *** indicates $p < 0.001$.

		Control	AVE
Growth factors	**KGF**	1.00	3,38(±0,1)***
	VEGF	1.00	2,05(±0,1)**
	EGF	1.00	1,15(±0,3)
Wnt pathway	**WNT1**	1.00	3,91(±0,3)**
	CTNNB1	1.00	1,65(±0,1)***
	LEF1	1.00	0,97(±0,1)
Shh pathway	**Gli1**	1.00	1,47(±0,1)*
Hair follicle anchor proteins	**ITGB1**	1.00	1,48(±0,3)*

Next, we studied the effect of AVEs on miRNAs that have been described to regulate telogen phase and hair loss (miR-155-5p and miR-22-3p) [ref]. As shown in Figure 1, AVEs significantly downregulated the levels of both miRNAs, thus antagonizing hair loss and telogen phase processes.

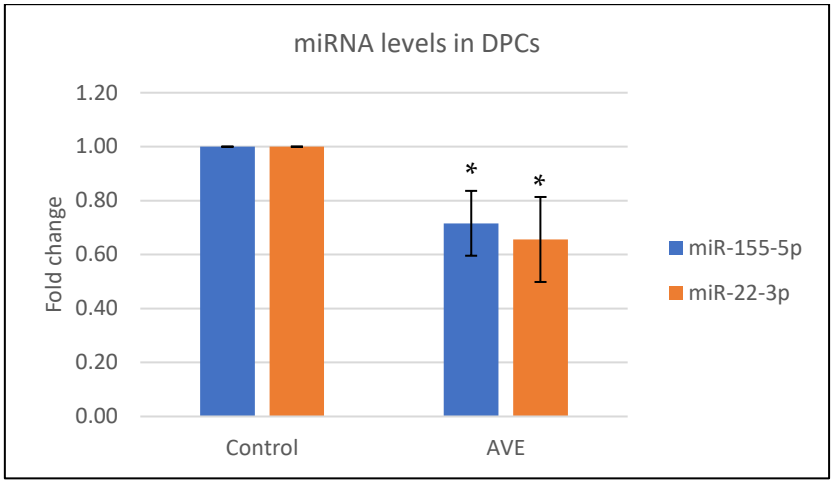

Figure 1. miRNA levels in dermal papilla cells (DPCs) treated with aloe vera exosomes (AVE) for 24h. Results are expressed as fold change compared to control. T-student analysis was performed to evaluate significant differences between the conditions, comparing control cells vs treated cells. * indicates $p < 0.05$; ** indicates $p < 0.01$; *** indicates $p < 0.001$.

In alopecia, one of the most common causes of hair loss is the detrimental effect of dihydrotestosterone (DHT) in dermal papilla cells, which induces hair follicle minituarization through increased damage and senescence in DPCs. Here, we treated DPCs with DHT for 72h to induce these markers. As shown in Table 2, genes involved in inflammation (*IL6, IL8*), senescence (*p21*), telogen phase (*TGFb1, DKK1*) and hormonal pathway (*AR*) were upregulated in DHT-treated cells. When AVEs were applied to the DHT-treated cells, all the tested genes were downregulated compared to DHT-treated cells, proving the protective effect of these exosomes on DHT-induced damage and senescence.

Table 2. Gene expression changes in dermal papilla cells (DPCs) treated with dihydrotestosterone (DHT) with or without aloe vera exosomes (AVE) for 72h. Results are expressed as fold change compared to control, and standard deviation is included in brackets. T-student analysis was performed to evaluate significant differences between the conditions, comparing control cells vs treated cells. * indicates $p < 0.05$; ** indicates $p < 0.01$; *** indicates $p < 0.001$.

	Control	DHT	DHT + AVE
DKK1	1	2,36 (±0,3)**	1,37(±0,2)*
IL-6	1	1,32 (±0,2)*	0,85 (±0,1)*
p21	1	1,43 (±0,1)**	1,05 (±0,1)*
TGF-b1	1	1,30 (±0,1)*	1,01 (±0,1)**
AR	1	2,40 (±0,2)**	1,27 (±0,1)**
IL-8	1	1,63 (±0,1)*	0,91 (±0,1)**

4. Discussion

Exosomes are nanosized vesicles that facilitate cell-to-cell communication by transporting bioactive molecules. In cosmetics, plant-derived exosomes (PDEVs) are increasingly being used based on its biocompatible, safe, sustainable and effective effect on skin conditions. Many PDEVs have been described to positively regulate skin cell pathways, but data on their effect on hair growth and loss is scarce. Here, we proved that aloe vera exosomes (AVEs) are effective targeting hair growth and regeneration through the regulation of the key pathways in healthy and DHT-damaged DPCs.

Previous research has shown that growth factors play a pivotal role in hair follicle development and cycling by promoting proliferation, angiogenesis, and survival of dermal papilla cells [8]. In addition, the Wnt/β-catenin signaling pathway is essential for the initiation of the anagen phase, contributing to hair follicle regeneration and stem cell activation. Similarly, the Sonic Hedgehog (Shh) pathway is critical for follicular morphogenesis and cycling, particularly in transitioning from telogen to anagen [9]. Dysregulation of these pathways is closely associated with hair thinning and alopecia, making them key therapeutic targets for hair loss prevention and treatment. In our experiment, we proved that AVEs upregulated different genes involved to these pathways in DPCs, thus positively regulating the hair growth response in these cells (Table 1).

Epigenetic mechanisms have also been described to regulate hair growth pathways in DPCs. Among these, miRNAs can alter gene expression levels of specific factors that can derive in altered function of DPCs. Specifically, miR-155-5p and miR-22-3p reduce the levels of growth factors and proteins that contribute to hair growth [10, 11]. Here, we showed that AVEs can effectively reduce the levels of both miRNA, which restores the physiological levels of key proteins for the development of hair follicles and impulse hair growth (Figure 1).

Dihydrotestosterone (DHT) plays a central role in androgenetic alopecia, the most common form of hair loss. Excessive action of this potent androgen on androgen receptor (AR) in DPCs causes damage and cellular senescence, which ultimately derives to hair follicle atrophy, shortening of the anagen phase and finally hair thinning and loss [12, 13]. Our results showed that DHT induced senescence (p21), inflammation (IL-6, IL-8) and telogen promoters (DKK1, TGF-b1) after 72h of treatment, as expected. When DHT and AVEs were combined, a significant downregulation in all the tested genes was observed (Table 2). These results indicate that these plant exosomes are protecting the cells against the damage and senescence induced by DHT in DPCs.

Based on these observations, we could claim that aloe vera exosomes are acting at the cross-species levels, regulating key pathways in human cells. This particular mechanism of action might be explained by the variety of proteins, lipids and phytochemicals that are included in AVEs [14]. The complexity of this type of vesicles from the biological point of view makes it difficult to mimic the described mechanism of action, and consequently plant exosomes are another interesting tool in the cosmetic ingredients list to be used for skin and hair care products.

5. Conclusion

Androgenetic alopecia is a condition where hair growth pathways and DPCs function are dysregulated, which translates in accelerated hair loss. This process is accelerated by increased levels of DHT, which induces inflammation and senescence in DPC. Here, we showed that AVEs can increase growth factors, activate key pathways such as Wnt and Shh and reduce miRNAs associated to hair loss. Besides, AVE could reduce the damage and senescence induced by increased hormone levels. Thus, AVE are a promising active ingredient to be included in galenic formulas aimed at hair care and hair loss prevention.

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