Review

Extracellular Vesicles for Cosmetic Applications

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Abstract:
Extracellular vesicles (EVs) are nanosized membrane vesicles that carry membrane and cargo molecules inherited from their parental cells. Excellent delivery capacity, biological origin, and nanosized dimensions support the great potential of EVs as medical and cosmetic active ingredients. Many studies have already reported improved skin conditions by using EVs for skin rejuvenation, scar removal, and anti-pigmentation treatments. In this review, EVs from mesenchymal stem cells, platelets, skin microbiota, and microalgae will be considered. The most promising results come from mesenchymal stem cell (MSC) derived EVs that have impressive antiaging and wound-healing effects on the skin, but their use for medical or cosmetic purposes is not yet allowed in Europe and the United States. Autologous platelet- and extracellular vesicle-rich plasma (PVRP) is well tolerated and capable of rejuvenating the face; intradermal injections and topical applications are currently being considered in clinical and cosmetic dermatology. Symbiotic microorganisms of the human skin have many beneficial effects on the skin, but the presence of bacteria in cosmetic products is restricted; therefore, the preparation of EVs from skin-beneficial microbes is particularly relevant, and there are already many cosmetic products containing lysates from different probiotics on the market. Microalgae can produce many valuable bioactive compounds, antioxidants such as carotenoids are particularly interesting; therefore, microalgae are promising producers of EVs that could be used in cosmetic products.

Keywords: Extracellular vesicles; Skin health; Microbiota; Mesenchymal stem cells; Microalgae

1. Introduction

Human skin is an effective barrier that protects the body from the external environment. In addition to protecting the body from environmental damage, skin is also extremely important for our appearance; therefore, cosmetics have been used for thousands of years to promote our appearance more attractive. Nanotechnology is an actual strategy for the development of cosmetics formulation because nanoparticles allow more efficient penetration through the skin and effective release of ingredients, which contributes to superior technological and cosmetic effects (Santos et al., 2019). Extremely interesting nanoparticles for cosmetic use are extracellular vesicles (EVs) due to their biological origin and capability to modulate recipient cells.

Extracellular vesicles (EVs) are membrane vesicles, 40-1000 nm in size, released from the cells into their microenvironment. Normal cells of multicellular organisms, malignant cells, as well as unicellular organisms, release EVs from their surface. EVs are potent carriers of biologically active molecules because they carry membrane and cargo molecules (proteins, lipids, and nucleic acids), which inherit the molecular information from their parental cells but are enriched in specific proteins and mRNAs. Uptake of EVs by endocytosis or fusion with plasma membrane can induce activation of specific signal transduction cascades of recipient cells and thereby influence the metabolism of target cells and their physiologic state (Kharaziha et al., 2012; Gangoda et al., 2015).

EVs are released into their microenvironment continuously or they are rapidly released by the cells during cell activation. EV secretion is highly environmentally dependent and can be regulated by various stimulants such as chemical treatments, or heat, oxidative, and mechanical stress (Hahm et al, 2021; Zavec et al., 2016). For the production of EVs *in vitro*, it is important that external conditions can influence the amount of released EVs and the properties of EVs. It was found that EVs are excessively formed in connection to cell activation, high or low temperature and pH, cell starvation, pharmacologic agents, oxidative stress, electrical stimulus, electromagnetic waves exposure, and exposure to shear forces (Erwin et al., 2022; Božič et al, 2020; Yáñez-Mó et al., 2015). Besides, EVs released upon different treatments are capable of producing a spectrum of EVs with functional heterogeneity, and secreted EVs reflect the prevailing state of the cell (Kolonics et al., 2020). It was shown that the same population of neutrophils is able to generate EVs with different functional properties, EVs with pro-inflammatory or EVs with anti-inflammatory effects on neighboring cells (Kolonics et al., 2020). The characteristic of EVs to reflect the status of the environmental conditions, allows us to influence the quantity and properties of the produced EVs by changing the cell culture conditions.

The efficacy of EVs in and through the skin has not yet been thoroughly studied. EVs are similar in size and composition to liposomes but are significantly more complex. Liposomes are mostly unable to penetrate the skin (Dreier et al., 2016), so we expect that EVs also have poor penetration into the lower layers of the skin. However, the passage of both liposomes and EVs into the lower layers of the skin can be increased with microneedling (Yernen et al, 2022; Qu F et al, 2022; Kelm and Ibrahim, 2022).

Excellent delivery capacity to the cells, biological origin and nanosized dimensions support the great potential of EVs as medical and cosmetic active ingredients. EV applications have been widely investigated in aesthetic medicine and cosmetics, and many studies have already reported improved skin conditions by using EVs for skin rejuvenation, scar removal, and anti-pigmentation treatments (Kee et al., 2022). In this reflection EVs from mesenchymal stem cells, platelets, skin microbiota, and microalgae (**Figure 1**) will be reviewed.

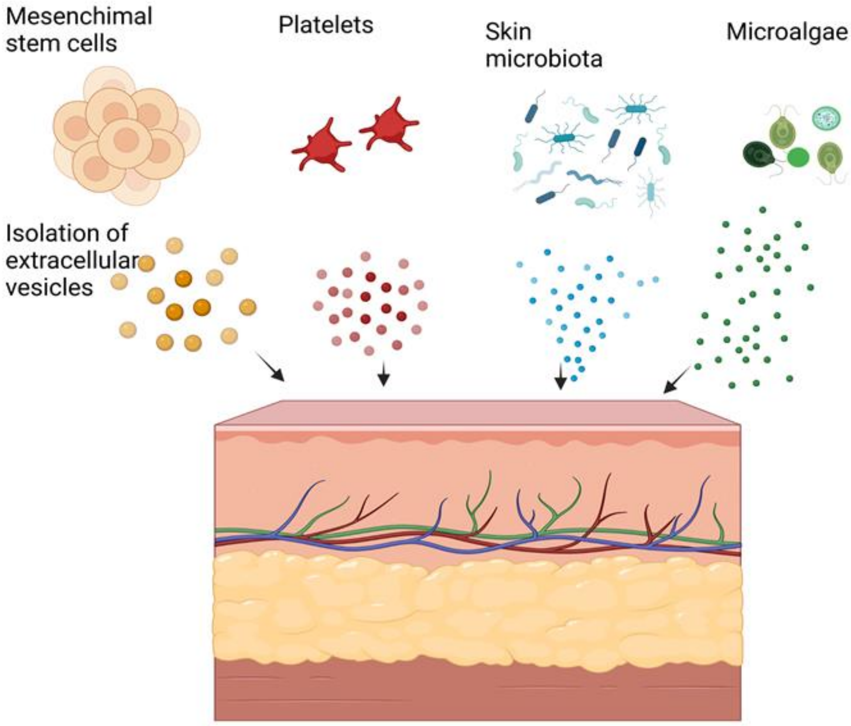

Figure 1. Schematic presentation of interaction of different types of EVs with skin.

2. Mesenchymal stem cells and their EVs

The therapeutic potential of EVs are reviewed several times, and the most promising results come from a mesenchymal stem cell (MSC) derived EVs that are transiting rapidly toward clinical applications (Wiklander et al., 2019). Mesenchymal stem cells (MSCs) are multipotent stem cells with high regenerative capacity that can be obtained from diverse sources, including bone marrow, adipose tissue, umbilical cord blood, synovium, dermis, periodontal ligament and dental pulp (Nancarrow-Lei et al., 2017). The most popular source of MSCs is adipose tissue due to its easy availability. MSCs can differentiate into a variety of mesenchymal lineages such as osteoblasts, chondrocytes, and adipocytes; therefore, they have the ability to repair specific tissues such as bone and cartilage (Song et al., 2006). Recently, MSCs have been recognized as therapeutic agents for skin regeneration and rejuvenation. MSCs have healing capacities for damaged and aged skin because they increase cell proliferation and decrease inflammation, they cause the production of collagen and elastic fibers and they cause the inhibition of metalloproteinase activation in the skin (Jo et al., 2021*).*

EVs from MSCs are studied for use in cell-free regenerative medicine, also for skin regeneration because it was shown that EVs from MSCs have antiaging and wound-healing effects on the skin. It was shown that EVs derived from amniotic cells accelerate wound healing and inhibit scar formation (Zhao et al., 2017); EVs from human adipose-derived MSCs promote the proliferation of skin fibroblasts (Choi et al., 2018a); EVs from adipose MSCs accelerate skin wound healing and reduce the cellular senescence by optimizing fibroblast properties (Li et al., 2018)

Most of the studies carried out so far are preclinical and the use of EVs is not yet allowed (in Europe and the United States) for either medical or cosmetic purposes; however, there are already preparations on the cosmetic market that contain active ingredients prepared from stem cells and their extracellular vesicles. Kimera Labs already produces such extracellular vesicles for the market, but for now only for research organizations studying the effects of EVs in various fields of medicine and cosmetics.

3. Platelet and EV-rich plasma

Platelet-rich plasma (PRP) is extensively applied as a bioactive scaffold in regeneration of different tissues. Autologous PRP is prepared from subject's own blood. Platelets are concentrated and can be exogenously activated by the addition of calcium mixtures prior to the application. Platelets contain more than 300 biologically active molecules, many growth factors, that are released upon activation and regulate the tissue regeneration process (Nurden et al., 2008); therefore, autologous PRP applications have the potential to play an important role in a variety of regenerative medicine treatments. PRP contains a specific concentration of EVs which are probably important contributors to PRPs effects; therefore the term 'platelet- and extracellular vesicle-rich plasma' (PVRP) has been suggested (Vozel et al., 2021; Troha et al., 2023).

PVPR applications have been widely investigated in clinical dermatology and aesthetic medicine for their beneficial use in skin regeneration and skin rejuvenation. It was shown that treatment with products that contain PVRP led to a significant improvement in the overall facial appearance, and biophysical measurements showed significantly improved skin elasticity (Hersant et al., 2021). It was shown that a single intradermal injection of autologous PVRP is well tolerated and capable of rejuvenating the face; the most significant results were with the correction of wrinkles of the nasolabial folds in younger subjects (Elnehrawy et al., 2017; Sclafani, 2010). Intradermal injections of PVRP cause a significant improvement in infraorbital color homogeneity, while no significant changes were observed in the crow's feet wrinkle (Mehryan et al., 2014). Intradermal injections of autologous PVRP have been shown to be an effective treatment for photodamaged skin (Díaz-Ley et al., 2015). The hyperpigmentation of melasma also significantly improved with intradermal PVRP compared with normal saline (Sirithanabadeekul et al., 2020). Topical applications of PVRP also produce favorable results, especially when combined with microneedling. Improvement in the appearance of acne scars, improvement in the appearance of hyperpigmentation, improvement in the appearance of striae on the buttocks, and improvement in the appearance of androgenetic alopecia was shown after six sessions of monthly microneedling with topical PVRP administration (Kelm and Ibrahim, 2022).

In conclusion, autologous PVPR as a therapeutic liquid is currently being considered in different fields of medicine, also in clinical and cosmetic dermatology. We anticipate that the topical application of PVRP will prevail over intradermal application in the future due to its simpler application.

4. Skin microbiota and bacterial EVs

The human microbiota is the full array of microorganisms that live on and in humans. There is a remarkably diverse array of microorganisms that includes bacteria, archaea, fungi, viruses, and some protozoans. The majority of microorganisms found in the human body live in the gut. The intestinal microbiota protects the intestinal walls from invasion by pathogens, helps in the digestion of food, and produces some vitamins (B12, K) that can not be produced by human cells. Altered intestinal microbiota can result in the development of different diseases like diabetes, asthma, and chronic gut inflammation (Motta et al., 2015).

Human skin is also inhabited by a huge number of bacteria, fungi, and viruses that compose the skin microbiota. beneficial microorganisms on the skin contribute to the first line of defense against attacking pathogens, and there are complex ecological interactions, the competition within and between microbial species is important for the development and maintenance of a healthy microbiome (Schommer and Gallo, 2013). The microbes of the skin have a significant impact on skin physiology and pathophysiology, and instability of the skin microbiota is associated with skin diseases (Byrd et al., 2018). It was shown that in patients (with atopic dermatitis, psoriasis) the microbial balance is disrupted and the skin is, therefore, more susceptible to infections with pathogenic microorganisms (Paller et al., 2019; Chen et al., 2020).

Major examples of skin microorganisms are Actinobacteria (51.8%; the most common *Corynebacteria and Propionibacteria*), Firmicutes (24.4%; the most common *Staphylococci*), Proteobacteria (16.5%), and Bacteroidetes (6.3%) (Grice et al., 2009). Microorganisms of the skin are related to microorganisms in the intestine and they can affect the entire organism through the metabolites they secrete; some of these metabolites get into the blood and affect the body's functioning via olfactory receptors (Lemoine et al., 2020). Skin microbiota varies between different sites on the skin, and between individuals, it varies according to skin type (racial diversity), social status (or skin treatment), and according to age (Kim et al., 2019). It was shown that probiotics can restore acidic skin pH, alleviate oxidative stress, attenuate photoaging, improve skin barrier function, and enhance hair quality; symbiotic microorganisms are able to slow the skin manifestations of both intrinsic and extrinsic aging (Sharma et al., 2016). Therefore, it is extremely important that our skin is inhabited by symbiotic and commensal microorganisms.

Due to legislative restrictions on the presence of bacteria in cosmetic products, currently only cosmetic products with extracts of microorganisms are present on the market, while products with live microorganisms are not yet available in Europe; therefore, the preparation of EVs from skin-beneficial microbes is particularly relevant.

Bacterial extracellular vesicles (BEVs) are membrane vesicles filled with bacteria-derived components. They are released by Gram-negative and Gram-positive bacteria, they contain diverse components originating from the cell envelope and cytoplasm, and have an important role in the interaction of bacteria with each other and with the host (Sartorio et al.,2021). BEVs have been shown to carry virulence factors and promote infection and disease development, inflammatory response, and act as immune elicitors (Deo et al., 2020; Laughlin and Alaniz, 2016). It was shown that EVs of gut bacteria are implicated in host metabolic homeostasis with their actions on the intestinal barrier, inflammation, and insulin resistance (Villard et al., 2021). The metagenomic study has shown that the composition of fecal-microbe-derived EVs and their effects on Caco-2 cells depends on the disease of the patients (Rodríguez-Díaz et al., 2023). Obviously, BEVs are important factors in the pathophysiology of metabolic diseases and could represent an interesting strategy for promoting human health. EVs of skin bacteria also carry the properties of the original bacteria and can transfer them to the host cells. It was shown that *Propionibacterium acnes*-derived BEVs promote acne-like phenotypes in the human epidermis (Choi et al., 2018b); therefore, BEVs of symbiotic bacteria of the skin microbiota can be expected to induce positive effects on the human skin.

BEVs can be obtained by isolation from the supernatant of a microbial culture, it is possible to harvest EVs sequentially, and preserve microorganisms that grow poorly in bioreactors. On the other hand, BEVs of microorganisms, easily grown in bioreactors, can be prepared in large quantities by mechanical extrusion. As regards skin microbiota, the skin genus *Staphylococcus* is cultivated more easily than *Propionibacterium* or *Corynebacterium* (Byrd et al., 2018). There are many cosmetic products containing lysates from different probiotics on the market already, and it is expected that the amount of such cosmetic products on the market will grow significantly.

5. Microalgae and their EVs

Microalgae are unicellular photosynthetic microorganisms found in marine and freshwater environments with enormous biodiversity that can produce tremendous diversity of valuable bioactive compounds. They can produce antioxidants, especially carotenoids, enzymes, fatty acids, sterols, polysaccharides, and lectins (Cardozo et al., 2007); therefore, microalgae are recognized as promising components for medical and cosmetical formulations as natural and environmentally friendly products that could replace synthetic products (Martínez-Ruiz et al., 2022). In skin exposed to UV radiation and other harmful environmental factors, the level of oxidative compounds increases. Many studies have linked reactive oxygen species (ROS) to various inflammatory skin diseases (atopic dermatitis, psoriasis, and vitiligo), skin aging, and carcinogenesis (Choo et al., 2020). However, microalgae contain many antioxidant agents that could prevent cell destabilization caused by reactive oxygen species and therefore reduce their negative impact on the skin. Antioxidant agents found in microalgae are chlorophyll, carotenoids, squalene, vitamins, flavonoids, polyphenols, and sterols (Sansone and Brunet, 2019). The genus *Chlorella, Dunaliella, Phaeodactylum*, and *Spirulina* are often used in cosmetics. It was shown that carotenoids (*Chlorella, Dunaliella*) are able to control chronic inflammation by inhibiting pro-inflammatory cytokines; astaxanthin (in most microalgae; *Haematococcus* *pluvialis* is known to produce the highest content of astaxanthin) reduces the UVB-induced production of pro-inflammatory cytokines; lutein (in *Chlorella, Dunaliella*) has strong antioxidant activity; sulfated polysaccharide from the cell walls of microalgae (*Chlorella, Phaeodactylum*) have strong anti-inflammatory activity (Choo et al., 2020). Beneficial properties of different microalgae have gained the development of microalgae-based formulations which will be resulted in more commercial products in a short period of time (Yarkent et al., 2020).

The amount of bioactive components in microalgae varies considerably among different species but also within the same species that inhabited different ecosystems. The amount of bioactive components in microalgae can be regulated by modification of cultivation conditions (temperature, nutrient availability, salinity, and lighting regime); it was shown that the production of carotenoid lutein**,** was regulated by different cultivation conditions (Schuler et al., 2020).

Microalgae release EVs that contain diverse components originating from the shedding cell as all other types of cells. It was confirmed that photosynthetic microalgae release EVs; however, some strains are better suited for the isolation of EVs (Picciotto et al., 2021). The same study also showed that microalgae are promising producers of EVs that could be used as delivery systems of biologically active compounds, which could be used for different industrial sectors such as nutraceuticals, cosmetics, or nanomedicine.

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