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Review

Plant extracellular vesicles as the next frontier in skincare—A preclinical perspective

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Abstract: Extracellular vesicles (EVs) constitute a diverse group of micro- and nano- sized membranous lipid bilayer particles secreted by prokaryotic and eukaryotic cells. They are enriched with bioactive constituents, including lipids, proteins, mRNAs, and miRNAs. EVs play a crucial role in cell-cell communication and facilitate trans-membrane signaling. Particularly, plant-derived EVs exhibit excellent bioaccessibility and minimal immunogenicity and they play a significant role in maintaining cellular homeostasis. These plant vesicles are considered safe, and their efficacy in the prevention and treatment of various diseases has been well documented in preclinical studies. In this mini-review, we attempted to summarize the *in vitro* and *in vivo* research of plant EVs for skincare and regenerative management. Collectively, plant-derived EVs, including *Dendropanax morbifera*, *Panax ginseng*, Aloe vera, broccoli, *Olea europaea*, and *Physalis peruviana*, exert strong potential for depigmentation, skin protection, anti-aging, and antioxidant/anti-inflammatory effects, highlighting their promise as multifunctional bioactive agents and delivery vehicles in cosmetic and therapeutic applications. Despite the demonstrated ability of plant EVs to enter skin cells and deliver protective compounds, their utilization in the cosmetic and cosmeceutical industries is in its nascent stages. Considering their demonstrated capabilities, we emphasized the need for comprehensive clinical research and discussed the innovations, challenges, and opportunities to fully explore their potential for skincare and regenerative applications.

Keywords: plant-derived extracellular vesicles; skin diseases; skin regeneration; skin inflammation; skin aging; skincare; cosmetics; cosmeceuticals

1. Introduction

Coordinating cellular activities, maintaining tissue homeostasis, and orchestrating complex biological processes within the organism relies heavily on intercellular communication. Accordingly, cells are involved in intricate communication networks by secreting a diverse array of bioactive substances, including signaling molecules, growth factors, and extracellular vesicles (EVs) [1]. EVs are released by eukaryotic and prokaryotic cells as a mode of intercellular communication. These are membrane-bound structures exhibiting heterogeneity in size, with subpopulations including exosomes (30–200 nm), microvesicles (200–1000 nm), larger microvesicles (1000–2000 nm), and large oncosomes/apoptotic bodies (1000–10000 nm). These vesicles contain a miscellaneous cargo of bioactive ingredients, including proteins, lipids, nucleic acids, and small molecules, which mediate complex intercellular communication [2,3].

Plant cells release EVs. These membranous vesicles contain natural bioactive molecules that facilitate cell-to-cell communication. This communication plays a crucial role in plant growth and development. Furthermore, these plant EVs are involved in plant responses to environmental stimuli [4]. These vesicles have been isolated from various fresh and processed plant resources, including fluids, roots, fruits, seeds, and leaves. Plant EVs are also known by alternative terms such as plant-derived exosome-like nanoparticles and plant-derived nanoparticles. They offer several advantages as drug delivery vehicles compared to the mammalian EVs. Notably, they often exhibit higher yields, reduced immunogenicity, and enhanced thermal stability, which enable them to be suitable for medical and dermal care applications in diverse environments [5]. The isolation of plant EVs typically involves a multi-step process, including techniques such as juicing, ultracentrifugation, ultrafiltration, and co-precipitation. A comprehensive review of the content, biogenesis, extraction, and bioactive applications of plant EVs has been discussed elsewhere [6].

In this minireview, we discussed the skin health and regenerative applications and mechanism of action of plant EVs from *in vitro* and *in vivo* studies. In addition, we covered commercially available plant EV-based cosmetics, innovative technologies aimed at increasing their absorption and drug delivery, and the challenges and opportunities present in the skincare sector.

A comprehensive literature search was conducted utilizing the search terms "plant extracellular vesicles", "plant exosomes", "plant derived exosomes-like nanoparticles", or "plant exosomes-like nanoparticles" in conjunction with "skincare or skin regenerative applications", "cosmetics applications", or "cosmeceutical applications" across the PubMed, Google Scholar, and Sciencedirect databases. Our focus was on preclinical research exploring the applications of EVs derived from the plants in the context of skincare. Accordingly, studies that demonstrated the effect of plant EVs in wound healing and other disease conditions were not included in this review.

2. Skincare and regenerative effect of plant extracellular vesicles: Depigmentation effect

Lee et al. found that *Dendropanax morbifera* EVs can reduce melanin pigment production by suppressing the downstream events in Alpha-melanocyte stimulating hormone-melanocortin 1 receptor (α-MSH-MC1R) signaling pathway. This pathway is important for controlling the amount of melanin made in the skin. They reported that EVs from the stem and leaf were taken up by mouse melanoma cell lines and human skin model made up of melanocytes and keratinocytes. This increased their skin-whitening effect and reduced melanin production and tyrosinase activity. Moreover, leaf-derived EVs from *Dendropanax morbifera* decrease the production of proteins, such as microphthalmia-associated transcription factor (Mitf), tyrosinase, and tyrosinase-related proteins (TRP) [7]. Of note, these proteins are involved in melanin production as part of the α-MSH-MC1R signaling pathway. Tyrosinase is a protein that helps converting L-tyrosine into L-DOPA, which is a key step in the production of melanin. EVs derived from root and callus cells of *Panax ginseng* C.A. Meyer downregulated the levels of melanogenesis-linked proteins, such as tyrosinase and tyrosinase-related protein 2, as well as melanin synthesis in ultraviolet (UV)-irradiated human epidermal melanocytes [8]. In a similar study, EVs derived from the *Atractylodes lancea* rhizome have skin whitening effects. In B16-F10 murine melanoma cells stimulated by α-MSH, treatment with these EVs led to decreased expression of melanin, Mitf, tyrosinase, and TRP [9]. Likewise, EVs isolated from *Cannabis sativa* stems demonstrated antimelanogenic activity in B16-F10 melanoma cells by activating the ERK–Akt pathway and enhancing antioxidant enzyme expression [10]. EVs derived from *Rosa damascena* (rose) stem cells (RSC) culture media were shown to reduce melanin expression in B16-F10 cells and enhance the growth rate and collagen, a key protein responsible for skin strength and elasticity, levels in human dermal fibroblasts [11]. Interestingly, a reduction in melanocyte numbers was observed in a zebrafish model exposed to Yam Bean EVs [12]. These findings collectively suggest that plant-derived EVs exert their depigmenting effect primarily through interference with the α-MSH–MC1R signaling cascade, as illustrated in Figure 1. By suppressing upstream regulators such as MITF and downstream effectors including tyrosinase and TRPs, these EVs ultimately reduce melanocyte activity and melanin production.

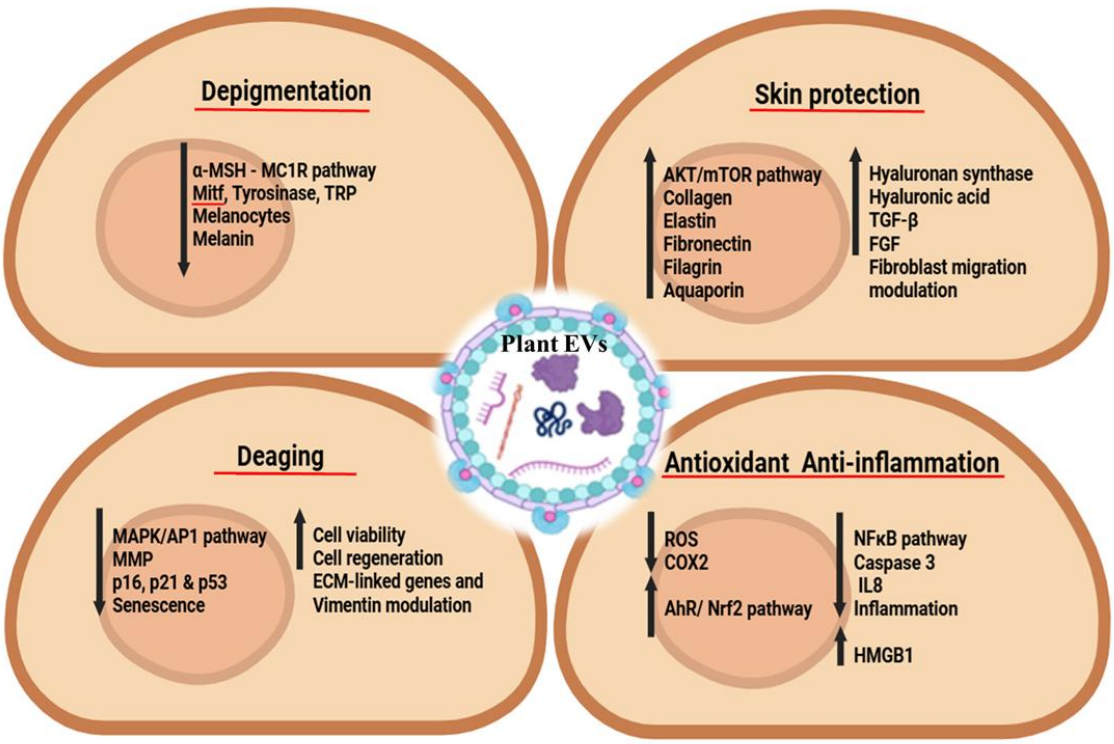

Figure 1. A pictorial overview of biochemical reactions modulated by plant EVs in preclinical models with respect to skincare effects. Upward-facing arrows indicate upregulation; and downward arrows indicate downregulation.

Altogether, plant-derived EVs show a clear ability to interfere with melanogenesis and reduce pigment formation, though the strength of evidence varies between sources. Among these, *Dendropanax morbifera* and *Panax ginseng* EVs look especially promising, since their effects were tested in cell lines and in reconstructed human skin models, with consistent downregulation of tyrosinase, TRPs, and MITF. *Rosa damascena* EVs are interesting for their combined effect on melanin reduction and collagen support, while *Atractylodes lancea*, *Cannabis sativa*, and Yam Bean EVs add further possibilities but remain at an early stage of investigation.

3. Skincare and regenerative effect of plant extracellular vesicles: Skin penetration and protection effects

Yepes-Molina et al. conducted research on broccoli root EVs to investigate their skin penetration, cellular uptake, structural integrity, and cargo retention capabilities. They used fluorescent markers to track the distribution and penetration of these vesicles through various layers of a porcine skin model and to enter into human epidermal keratinocytes and demonstrated their penetration ability. Moreover, characterization data of broccoli root EVs showed increased numbers of binding sites for glucosinolates and other bioactive molecules, and exhibited significant structural integrity due to their enrichment in aquaporins, proteins that facilitate water transport across membranes. Cosmetic stability studies revealed that EVs retained their original shape but displayed increased variability in size and protein concentration after one month, even though their membrane properties remained intact [13]. The results indicated that cosmetic formulations should contain an optimal concentration of EVs to ensure the presence of adequate protein levels, even after prolonged storage at room temperature. Other researchers reported the ability of aloe vera gel-derived EVs to penetrate the skin using *in vivo* mice model and *in vitro* mouse melanoma cell line B16-F10. Lipid analysis suggested that the presence of ceramide and glucosylceramide might facilitate their passage through the outer layer of the skin and into the dermis. They also found that the EVs were more stable than synthetic liposomes composed of phosphoglycerol, phosphocholine, and phosphoethanolamine. The authors suggested that the increased stability of these EVs could be attributed to the presence of diverse phospholipids arranged in a more ordered manner. This arrangement might contribute to their integrated membrane structure, their resistance to dissolving, and their ability to maintain their antioxidant properties over time [14]. These properties of plant-derived EVs, with or without encapsulated active ingredients, could significantly enhance the efficacy and sustainability of cosmetic formulations. A study by Yang et al. revealed that EVs derived from *Panax ginseng* can penetrate human skin cells and increase the levels of skin-related proteins such as collagen, elastin, and fibronectin. Additionally, ginseng EVs stimulated the proliferation of keratinocytes by activating the protein kinase B and mammalian target of the rapamycin (AKT/mTOR) signaling pathway [15]. Similar transdermal penetration and drug delivery properties were demonstrated for cucumber-derived EVs using a porcine skin model [16]. *Camelia sinensis* EVs showed enhanced penetration into the deep dermis compared to *Camelia sinensis* extract in an *in vivo* pigmented mouse model and reduced melanin synthesis via miR-828b targeting MYB4 through the PI3K/AKT pathway [17]. Treatment of skin fibroblasts with *Beta vulgaris*-derived EVs resulted in increased expression of collagen and hyaluronan synthase. Importantly, these EVs also suppressed fibroblast migration, suggesting a possible cosmeceutical approach for scar reduction [18]. EVs isolated from *Leontopodium alpinum* L. (Edelweiss) callus suspension culture, which was exposed to artificial light, were found to reduce oxidative stress in irradiated human HaCaT keratinocytes. In B16-F10 murine melanocytes and human fibroblasts, these EVs suppressed melanin expression and increased the expression of collagen, aquaporin, and filaggrin, respectively. The authors suggested that the increased levels of phytoconstituents like phenols and flavonoids in the EVs, resulting from the light exposure of the callus culture, might be responsible for these observed skin health related biochemical modulations [19]. EVs from ginseng callus culture were shown to stimulate the expression of genes related to collagen and angiogenesis in CCD-986sk human dermal fibroblasts. Genes such as collagen, transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), and other growth factors were upregulated after treatment with ginseng EVs [20]. Similarly, treatment with Yam Bean-derived EVs increased collagen expression in human dermal fibroblasts [12]. In 3D epidermal skin models, *Lycium barbarum* L.-derived EVs enhanced hydration by activating aquaporins and natural moisturizing factors while upregulating barrier-related proteins such as claudin-1 and filaggrin [21]. Overall, these studies indicate that plant-derived EVs contribute to skin protection primarily through activation of pro-regenerative signaling cascades, notably the AKT/mTOR pathway, and by upregulating structural and extracellular matrix components such as collagen, elastin, fibronectin, and hyaluronan synthase (Figure 1). Plant EVs may exert a dual role of bioactive agents and effective delivery vehicles within cosmetic formulations by enhancing fibroblast activity and dermal protein synthesis while maintaining stability and penetrative capacity.

Altogether, plant-derived EVs show strong potential for skin penetration and protection. Ginseng, broccoli, and Aloe vera EVs emerge as the most promising candidates for formulations, while EVs from cucumber, *Camelia sinensis*, *Beta vulgaris*, Edelweiss, Yam Bean, and *Lycium barbarum* provide complementary benefits.

4. Skincare and regenerative effect of plant extracellular vesicles: Anti-aging effect

EVs derived from *Panax ginseng* have been found to exhibit anti-skin senescence properties. EVs isolated from *Panax ginseng* root were found to reduce the expression of senescence-associated proteins, including β-galactosidase, p16, p21, and p53, in human dermal fibroblasts. Additionally, a reduction in proinflammatory IL8 and an increase in anti-apoptotic high mobility group box 1 protein (HMGB1) were observed in UV-irradiated human keratinocytes, suggesting the potential anti-aging and skin-protective benefits of these EVs. The authors suggested that the higher levels of HMGB1 in melanocytes might be caused by increased diacylglycerol in *Panax ginseng* EVs as it could activate protein kinase C, which in turn might stimulate the production of HMGB1 [8]. Another interesting study revealed that plant EVs were more effective than plant extracts. HaCaT cell lines treated with EVs from *Panax ginseng*, *Centella asiatica*, *Portulaca oleracea*, and *Camellia sinensis* exhibited significant changes in gene expression compared to their respective plant extracts. Moreover, genes associated with skin aging, growth, and hydration such as matrix metalloproteinase (MMP), FGF, and vimentin were substantially influenced by *Panax ginseng* and *Camellia sinensis* EVs compared to their extracts. It was found that cells treated with EVs or extracts from *Panax ginseng* exhibited different gene expression patterns compared to those treated with EVs or extracts from *Camellia sinensis*. This suggested that the bioactive substances contained within EVs from different plant species may have distinct biological effects [22]. Trentini et al. demonstrated the potential anti-aging and skin regenerative properties of EVs isolated from apple (*Malus domestica* sp.) fruit. In inflamed human dermal fibroblasts treated with these EVs, MMP expression was decreased, while collagen was increased. Additionally, several other extracellular matrix (ECM)-associated genes were significantly modulated [23]. Moreover, ginseng-derived EVs were found to protect cells from damage and aging, likely due to the presence of ginsenosides. These EVs reduced the expression of cell death proteins in irradiated HaCaT cells by inhibiting the mitogen-activated protein kinases (MAPK)-mediated activator protein-1 (AP-1) signaling pathway [24]. In another report, *Physalis peruviana* fruit-derived EVs were shown to exert skin cell protective effects. Human dermal fibroblasts treated with these EVs exhibited increased collagen I production while displaying reduced oxidative stress and MMP-1 levels. Moreover, these EVs augmented the proliferation and migration rate of the fibroblasts, which may assist in skin regeneration [25]. EVs derived from *Olea europaea* leaf inhibited the aging hallmarks in *in vitro* model. HaCaT and HDF-α cell lines exposed to UV-induction displayed aging-related biochemical modulations including reduced cell viability, and increased senescence associated β-galactosidase positivity, oxidative stress, and inflammation. However, cells treated with *Olea europaea* leaf-derived EVs increased the cell viability and suppressed senescence associated β-galactosidase positivity, oxidative stress, and inflammation. Moreover, these EVs enhanced the expression of collagen I and reduced the expression of MMP-1 and MMP-3 [26]. Furthermore, comparable anti-aging effects were reported for EVs from *Dendrobium officinale*, *Artemisia princeps*, and grape, which enhanced collagen and other ECM components while attenuating senescence-associated markers *in vitro* and *in vivo* models [27–29]. These data indicate that plant-derived EVs promote skin rejuvenation by suppressing MAPK/AP-1 signaling, MMPs activity, and senescence-associated proteins while enhancing cell viability, cell regeneration, and extracellular matrix components. These coordinated effects are summarized in Figure 1.

Altogether, plant-derived EVs demonstrate strong anti-aging and skin regenerative potential. Based on current evidence, ginseng, *Olea europaea*, and *Physalis peruviana* EVs emerge as the most effective candidates for anti-aging formulations, while EVs from *Camellia sinensis*, apples, *Dendrobium officinale*, *Artemisia princeps*, and grapes may provide complementary benefits.

5. Skincare and regenerative effect of plant extracellular vesicles: Antioxidant and anti-inflammatory effects

Apple EVs exhibited antioxidant and anti-inflammatory effects, as evidenced by the downregulation of mitochondrial reactive oxygen synthesis (ROS) and genes linked to the proinflammatory Nuclear Factor Kappa B (NFκB) signaling pathway [23]. Urzi et al. reported that treatment with *citrus limon* (lemon) juice EVs activated the aryl hydrocarbon receptor/nuclear factor erythroid 2-related factor 2 (AhR/Nrf2) signaling pathway in human dermal fibroblasts exposed to oxidative stress or radiation. Of note, AhR/Nrf2 activation was observed with other plant extracts known for their antioxidant properties. This study revealed increased expressions of AhR and Nrf2, along with reduced oxidative stress. Additionally, lemon EVs increased the expressions of collagen and hyaluronic acid, both important for skin integrity, and decreased the levels of the oxidative stress marker protein Cyclooxygenase-2. Furthermore, the antioxidant effects of lemon EVs were demonstrated in a zebrafish model [30]. Moreover, EVs isolated from *Platycodon grandiflorus* (Baloon flower) root were found to have similar antioxidant properties. In chemical or radiation exposed human dermal fibroblasts, these EVs decreased intracellular ROS and MMP expression [31]. Lee et al. found that *Solanum tuberosum* (potato) EVs protected skin cells from ultraviolet radiation. Irradiated HaCaT cells treated with these EVs showed increased cell viability and reduced collagen damage. These effects were not seen when cells were treated with potato protein, alcohol extracts, or EVs from

Escherichia coli. The protective effects of potato EVs were likely due to their ability to reduce the expression of MMP and proinflammatory molecules. The researchers also found that EVs obtained from *Pyrus pyrifolia* (pear), *Citrus sinensis* (citrus), and *Raphanus sativus* (radish) could modulate MMP expression. However, these effects were not as pronounced as those observed with potato EVs [32]. Cabbage and red cabbage EVs were shown to protect cells from damage. In staurosporine-conditioned HaCaT cell line and dermal fibroblasts, vesicles treatment increased cell viability and decreased the activity of proapoptotic caspase 3. Additionally, these EVs modulated inflammation and deliver drugs, such as microRNAs and doxorubicin, in murine macrophage RAW264.7 cell line and human colorectal SW480 cancer cell line, respectively [33]. Wang et al. demonstrated the anti-oxidant and anti-apoptotic effects of ginger-derived EVs in HaCaT cells and mouse dermal fibroblasts L929 exposed to UV irradiation. ROS formation was inhibited by these EVs [34]. These findings highlight that plant-derived EVs can modulate key antioxidant and anti-inflammatory pathways. Specifically, they reduced oxidative stress markers such as ROS and COX2, suppressed proinflammatory mediators, including NFκB, caspase 3, and IL-8, and enhanced antioxidant signals such as AhR/Nrf2 and the anti-apoptotic factor HMGB1 (Figure 1).

Altogether, plant-derived EVs exhibit clear antioxidant and anti-inflammatory potential. Potato EVs emerge as the most effective candidates, demonstrating strong protection against UV-induced damage, collagen preservation, and suppression of proinflammatory markers. Apple and ginger EVs provide robust antioxidant and anti-apoptotic effects, while lemon EVs offer additional benefits by enhancing collagen and hyaluronic acid and activating the AhR/Nrf2 pathway. EVs from pear, citrus, radish, cabbage, and red cabbage provide complementary protective effects and may be explored for targeted applications.

Collectively, these *in vitro* and *in vivo* findings highlight the use of plant EVs for skin rejuvenation and suggest their suitability as active ingredients or add-on components in cosmetic and cosmeceutical products. Table 1 provides a summary of the skincare effects of plant EVs.

Table 1. Skincare effects of plant EVs from preclinical studies.

S.No.	Plant extracellular vesicle (EV) source	Experimental system	Response	References
Depigmentation effect				
1	*Dendropanax morbifera* leaf and stem	*In vitro* (Mouse melanoma cell line—B16BL6)	Reduced melanin content and tyrosinase reaction; suppressed the expression of melanogenesis-linked proteins.	[7]
		In vitro (Human skin tissue model—made up of melanocytes and keratinocytes)	Inhibited melanin synthesis.	
2	*Panax ginseng*-root and callus cells	*In vitro* (human epidermal melanocytes)	Reduced melanin synthesis and melanogenesis-linked proteins; suppressed tyrosinase activity and tyrosinase-related protein 2 expression.	[8]
3	*Atractylodes lancea*-rhizome	*In vitro* (Mouse melanoma cell line—B16F10)	Reduced melanin synthesis; decreased the expression of Tyrosinase-related proteins.	[9]
4	*Cannabis sativa* stem	*In vitro* (Mouse melanoma cell line—B16F10)	Reduced melanin expression via ERK–Akt pathway activation.	[10]
5	*Rosa damascena* stem cells	*In vitro* (Mouse melanoma cell line—B16F10)	Reduced melanin expression.	[11]
6	Yam Bean	*In vivo* (Zebrafish)	Reduced the percentage of melanocytes.	[12]

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S.No.	Plant extracellular vesicle (EV) source	Experimental system	Response	References
Skin penetration and protection effects				
7	Broccoli root	*In vitro (*Porcine skin model)	EVs penetration observed through various layers of a porcine skin model. Structural integrity of EVs may be attributed to their enrichment in aquaporins.	[13]
		In vitro (Human epidermal keratinocytes)	EVs penetration observed.	
8	Aloe vera gel	*In vitro* (Mouse melanoma cell line—B16F10)	EVs penetration observed.	[14]
		In vivo (Mouse)	EV penetration observed through various layers of a mouse skin. Lipid analysis suggested that the presence of ceramide and glucosylceramide might facilitate EVs passage through the outer layer of the skin and into the dermis.	
9	*Panax ginseng*	*In vitro* (Human epidermal keratinocytes)	EV penetration observed. Increased the expression of skin-related proteins such as collagen, elastin, and fibronectin.	[15]
10	Cucumber	*In vitro (*Porcine skin model)	EV penetration and drug delivery effect observed.	[16]
11	*Camelia sinensis*	*In vivo* pigmented mouse model	Deep dermis penetration.	[17]
12	*Beta vulgaris*	*In vitro* (Skin fibroblasts)	Increased the level of collagen and hyaluronan synthase; suppressed fibroblast migration.	[18]
13	*Leontopodium alpinum* callus suspension	*In vitro* (Human keratinocytes—HaCaT)	Reduced oxidative stress.	[19]
		In vitro (Human fibroblasts and Mouse melanoma cell line—B16F10)	Inhibited melanin expression; enhanced the expression of collagen, aquaporin, and filaggrin.	
14	*Panax ginseng* callus cells	*In vitro* (Human dermal fibroblasts—CCD-986sk)	Increased the synthesis of TGF-β, FGF, and other growth factors.	[20]
15	Yam Bean	*In vitro* (Human dermal fibroblasts)	Increased collagen expression.	[12]
16	*Lycium barbarum*	*In vitro* 3D epidermal skin model	Increased aquaporin and natural moisturizing factors synthesis; enhanced hydration	[21]
Deaging and regeneration effect				
17	*Panax ginseng* root	*In vitro* (Human dermal fibroblasts)	Reduced the expression of senescence-associated proteins.	[8]
		In vitro (Human keratinocytes)	Regulated inflammation and apoptosis. Presence of diacylglycerol in the EVs may be attributed to cell protective effect.	
18	*Panax ginseng, Centella asiatica*	*In vitro* (Human keratinocytes—HaCaT)	Regulated the expression of genes associated with skin aging, growth, and hydration. Effects were high in comparison with the crude extracts.	[22]
19	*Malus domestica* fruit	*In vitro* (Human dermal fibroblasts)	Increased collagen and reduced MMP.	[23]
20	*Panax ginseng*	*In vitro* (Human keratinocytes—HaCaT)	Inhibited MAPK-mediated AP-1 signaling pathway; protected cells from damage and aging.	[24]
21	*Physalis peruviana* fruit	*In vitro* (Human dermal fibroblasts)	Increased collagen I production and reduced oxidative stress and MMP-1 levels.	[25]
22	*Olea europaea* leaf	*In vitro* (Human keratinocytes—HaCaT & Human dermal fibroblasts—HDF-α)	Increased the cell viability; suppressed senescence associated β-galactosidase positivity, oxidative stress, and inflammation. Enhanced collagen I and reduced MMP.	[26]

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S.No.	Plant extracellular vesicle (EV) source	Experimental system	Response	References
23	*Dendrobium officinale*	*In vitro* (human skin model)	Increased collagen and ECM components.	[27]
24	*Artemisia princeps*	*In vitro (*human dermal fibrablats and human 3D skin model)	Decreased β-galactosidase and MMPs.	[28]
25	Grape	*In vitro* (Epithelial cells); *In vivo* (Mouse)	Increased collagen; decreased β-galactosidase.	[29]
Antioxidant and anti-inflammatory effects				
26	*Malus domestica* fruit	*In vitro* (Human dermal fibroblasts)	Inhibited mitochondrial reactive oxygen species synthesis; suppressed proinflammatory NFκB signaling pathway.	[23]
27	*citrus limon* juice	*In vitro* (Human dermal fibroblasts)	Activated anti-oxidation-linked AhR/Nrf2 signaling pathway; increased collagen and hyaluronic acid, both important for skin integrity; reduced oxidative stress marker protein Cyclooxygenase-2.	[30]
		In vivo (Zebrafish)	Suppressed oxidative stress.	
28	*Platycodon grandiflorus* root	*In vitro* (Human dermal fibroblasts)	Decreased intracellular reactive oxygen species and MMP expression.	[31]
29	*Solanum tuberosum*	*In vitro* (Human keratinocytes—HaCaT)	Increased cell viability; reduced collagen damage; reduced MMP and inflammation.	[32]
30	Cabbage	*In vitro* (Human keratinocytes—HaCaT & Human dermal fibroblasts)	Increased cell viability; decreased proapoptotic caspase 3.	[33]
		In vitro (Mouse macrophages—RAW264.7)	Modulated inflammation.	
31	Ginger	*In vitro* (Human keratinocytes—HaCaT & Mouse dermal fibroblasts—L929)	Elicited anti-oxidant and anti-apoptotic effects.	[34]

6. Plant-derived EVs in commercial skincare products

Advancements in phytochemistry have fueled a significant increase in the utilization of plant ingredients within the skincare industry. This trend incorporates a diverse range of plant-derived materials, including crude extracts, fermented extracts, and isolated bioactive metabolites. This surge in plant-based skin health products has been driven by the escalating demand for effective natural and chemical-free approaches to skin disorder management. A comprehensive analysis of the skincare properties of the plant extracts, fermented plant extracts, and plant active metabolites have been discussed elsewhere [35–37]. Despite significant progress, a substantial lack of rigorous clinical trials and efficacy studies supporting plant EVs for skin applications persists. A few human case reports have explored plant EVs for dermatological effects, which are discussed later in this review, though dedicated clinical trials for cosmetic or skin-health applications are lacking. Nevertheless, plant EVs are being investigated in other medical contexts: Ginger-derived exosomes for inflammatory bowel disease (NCT04879810), grape exosomes for oral mucositis and colon cancer (NCT01294072, NCT01668849), and *Ecklonia cava* and *Thuja orientalis* EVs for male pattern baldness (NCT06930326). These researchers highlight the translational potential of plant EVs, suggesting that skin-focused trials may emerge in the near future. However, plant EVs have emerged as promising candidates for medical and cosmetic applications due to their unique characteristics, nanoscale dimensions, biocompatibility, and efficient cellular delivery. The potential of EVs to enhance skin health has been extensively investigated, with numerous studies demonstrating their efficacy in ameliorating skin abnormalities such as hyper-pigmentation and scar formation. While the cosmetic industry has witnessed significant advancements in the utilization of human mesenchymal stem cell (MSCs)-derived EVs, in recent times, plant-based EVs have emerged as a significant area of focus in cosmetics development. Table 2 provides a comprehensive overview of commercially and globally available skincare products incorporating plant EVs. Among several plants, EVs from *Centella asiatica* have been most widely used, followed by *Citrus reticulata* and *Rosa damascena*. Moreover, anti-aging, wrinkle reduction, collagen production, and skin cell regeneration are the primary benefits claimed by manufacturers of EVs-based cosmetics. Given the preclinical evidence for their skincare effects, EVs derived from herbs traditionally used in skincare including Indian medicine, Chinese medicine and others, may receive significant interest in the research and development of effective skin regenerative formulations.

Table 2. Commercially and globally available skincare and skin regenerative products incorporating plant EVs.

S. No.	Brand/Manufacturer	Type of skincare product	Benefits claimed	Plant name	Parts used
1	EXO SUN™	Cream	Reduction in dark spots, skin hydration, increased collagen and fibroblast production.	Aloe Vera	Leaf
2	Dr. Melaxin, Exosome Enzyme Cleanser	Cream	Anti-acne, and skin protection.	*Centella asiatica*	Leaf
3	NEOGEN DERMALOGY	Cream	Skin regeneration, wrinkle improvement, and anti-inflammation	*Centella asiatica*	Leaf
4	Cica Exosome Treatment Orb	Cream	Anti-aging, dryness relief, and revitalization.	*Centella asiatica*	Leaf
5	Ninetails	Cream	Collagen and elastin production, and cell regeneration.	*Centella asiatica*	Callus
6	MEDICUBE	Cream	Skin hydration and wrinkles reduction.	*Centella asiatica*	Leaf
7	Clarena	Cream	Fibres support, facial wrinkles reduction, and skin thickening.	*Centella asiatica*	Leaf
8	D'LEXO	Cream	Nourished and rejuvenated complexion.	*Centella asiatica*	Leaf
9	Dermaline	Cream	Skin regeneration, skin barrier strengthening, and skin health enhancement.	*Centella asiatica*	Leaf
10	Adam	Cream	Skin barrier improvement.	*Centella asiatica*	Leaf
11	Dr. Kraut	Cream	Skin regeneration, anti-inflammation, and collagen production.	*Centella asiatica*	Leaf
12	Luuv oü-BioLift Exosome	Cream	Skin repair and rejuvenation.	*Centella asiatica*	Leaf
13	RECORESERUM	Drink	Skin strength and elasticity restoration, and Skin freshness.	*Cirsium brevicaule*	Flower
14	Dr.Villy SKINCARE	Cream	Skin moisturizing, anti-wrinkle, and brightening.	*Citrus reticulata*	Fruit
15	Cosmiko	Cream	Skin regeneration, skin barrier strengthening, skin brightness, elastin and hyaluronic acid production, and wrinkles reduction.	*Citrus reticulata* and *Raphanus sativus*	Not mentioned
16	Dendrexo	Cream	Skin nutrition enhancement.	*Dendropanax morbifera*	Leaf
17	Dermafirm	Serum	Anti-inflammation and regeneration.	Eucalyptus and Perilla	Leaf

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S. No.	Brand/Manufacturer	Type of skincare product	Benefits claimed	Plant name	Parts used
18	LARA CLARA	Cream	Melanin synthesis inhibition and skin brightening.	Fermented black Garlic and Aloe vera	Tuber and gel
19	EXODROP	Cream	Skin brightening and wrinkle reduction.	Ginseng	Leaf
20	Karisma exo care	Cream	Oxidative stress reduction and anti-skin aging.	Italian fruits such as Orange, Grape, Pomegranate, Mandarin and Papaya	Fruit
21	Matrigen	Cream	Anti-aging and wrinkle improvement.	*Leontopodium alpinum*	Stem cells
22	I'M FROM	Cream	Skin protection, anti-acne and depigmentation.	Licorice	Leaf
23	Apis Natural Cosmetics	Cream	Skin elasticity, hydration and nourishment.	Marigold	Stem cells
24	HUNA	Cream	Skin hydration.	*Momordica charantia*	Fruit
25	Super star	Cream	Skin protection from free radicals, anti-aging, and skin health promotion.	Pistachio	Seed
26	P.Calm Light' Active Cream	Cream	Wrinkles reduction, Depigmentation and Skin hydration.	*Rosa damascena*	Callus
27	Exoblanc Spicule Cream	Cream	Collagen production, cell regeneration, and skin texture improvement.	*Rosa damascena*	Callus
28	Code of Harmony	Cream	Dry skin relief, skin barrier strengthening, and wrinkle reduction.	Turmeric	Stem cells
29	Beauugreen	Cream	Skin nourishment, dark circles improvement, and skin elasticity maintenance.	Yam	Tuber

7. Innovations, challenges, and opportunities

Cosmetic-grade EVs derived from MSCs are commercially available as standalone products. These EVs can be used independently or in combination with skincare peptides and other active ingredients in anti-aging serums, creams and other skincare solutions [38]. Similarly, researchers have highlighted the development of numerous innovative plant EV-based skincare formulations specifically designed to address skin aging, improve skin moisture, promote skin repair, and enhance skin regeneration. For example, Hou et al. demonstrated the drug delivery efficacy of plant-derived EVs by encapsulating active skin peptides within *Leontopodium alpinum*-derived EVs. Enhanced cellular absorption was observed in HaCaT cell line and improved uptake of skin peptide acetyl hexapeptide-8-encapsulated EVs compared to free peptides was observed in a skin penetration model [39]. This data suggested that plant EVs could be an effective and safe cargo delivery system for enhancing the skin penetration and absorption of active skincare peptides and other therapeutic ingredients. Moreover, a cosmetic ampoule formulation with *Centella asiatica* EVs and a cream formulation with apple EVs demonstrated improved skin hydration and wrinkle management with a favorable safety profile in human volunteers [40,41]. Studies on plant EVs-based gels have also received significant attention in dermal care sector to improve the delivery of the EVs and other active ingredients. When combined with hyaluronic acid-based gels, apples EVs were released more slowly at room temperature than at physiological temperature [23], suggesting the potential of plant EVs for incorporation into sustainable cosmetic gel formulations. *Physalis minima* (Golden cherry) EVs incorporated into a Natrosol polymer-based gel maintained their structural integrity and enhanced the antioxidant effect of the product [42]. Wang et al. developed a thermosensitive soluble gel incorporated with ginger-derived EVs against photo-induced skin damage model. They used poloxamer 188 and 407 as a gel base in order to optimize their gelling temperature to match the site of skin inflammation. The data indicated that the gel provided an ideal extracellular matrix-like platform for cell attachment and penetration and also enabled controlled release of the ginger EVs [34]. In a related study, *Olea europaea* leaf-derived EVs incorporated within a cross-linked hyaluronic acid and tannic acid hydrogel demonstrated a significant reduction in skin tissue aging and damage in the mice *in vivo* model of UV-induced photoaging. Notably, the expression of pro-aging markers, p21 and p53, was markedly diminished in UV-treated mice administered with *Olea europaea* leaf-derived EVs-incorporated hydrogel compared to those treated with EVs alone, suggesting a potentiation of EV bioactivity within the hydrogel-based formulation [26].

Plant EVs have exceptional demand in the development of cosmetics with or without other natural active ingredients. Despite their safety profile, low toxicity, and high biocompatibility with no documented adverse effects [43], significant challenges remain regarding their scale-up production, isolation, purification, and consistent quality. However, limited research has explored these challenges and offered novel solutions. For example, suspension and hairy root-based plant tissue culture methods have emerged as promising platforms for large-scale plant EVs production since these plant tissue culture techniques have been widely adopted in pharmaceutical and cosmetic industries for the production of active phyto-ingredients [44]. Regarding isolation, techniques such as polymer-based separation, density gradient separation, and ultracentrifugation are primarily employed for the isolation of plant EVs. Other sophisticated methods, including tangential flow filtration and immunoaffinity-based approaches in combination with size exclusion chromatography, may be considered for effective isolation as well as purification in a large-scale volume as these techniques are globally used for the isolation of EVs from animal cells [45]. Wen et al. used bead technology to remove the bacterial contamination of the EV fraction. By using Concanavalin A–imprinted magnetic beads, they have reported the removal of harmful bacteria from the solution of EVs derived from the licorice plant for purification and safety improvement [46]. The presence of EV aggregates and their variability in particle size also need to be addressed for the successful industrial and therapeutic applications. A study by Kocholata et al. investigated the application of trehalose, a non-penetrating disaccharide sugar, to prevent the aggregation of EVs isolated from the suspension culture medium of *Nicotiana tabacum* [47]. However, the data showed that trehalose was not so effective in reducing the aggregation, and the authors concluded that the inefficacy might be caused due to the trehalose saturation. On the contrary, it was demonstrated that trehalose significantly inhibited the aggregation and freeze-thaw damage of exosomes derived from mouse pancreatic beta cell lines [48]. Accordingly, much research and many development opportunities are available to reinvestigate the EV aggregation inhibition and cryoprotection effects of trehalose and other non-penetrating agents such as mannitol, sucrose, and raffinose.

A significant body of literature data describes the protective effects of MSCs and microbial EVs against skin pathological conditions like eczema and psoriasis. However, in our literature survey, we found only a few relevant research articles that demonstrated the skin protective properties of plant EVs against the above mentioned topical diseases. A case report by Lueangarun et al. described that rose stem cells (RSC)-derived EVs may ameliorate the symptoms of chronic Seborrheic dermatitis [49]. Theodorakopoulou et al. demonstrated the pigment modulation effect of RSC-derived EVs in human volunteers. They found improved synergistic effects when these rose EVs were co-administered with non-thermal microneedling treatment, which resulted in reduced facial pigmentation and photoaging [50]. In a case study-based article, the researchers discussed the promising skincare effects of RSC-derived

EVs. It was reported that these EVs were able to negatively regulate the conditions like eczema, hyperpigmentation, and scars [51]. In another interesting study, grapefruit EVs exhibited a protective effect against eczema and psoriasis in *in vivo* mice models, though in a hybrid mode. First, CX5461-loaded grapefruit EVs were synthesized by the electroporation method. CX5461 is an immunosuppressant that contains anti-proliferative property. Second, CCR6+ nanovesicles were isolated from the of bio-engineered gingiva-derived MSCs (GMSCs) membranes. Of note, CCR6 is a chemokine receptor produced by leukocytes, and CCL20 is an inflammatory protein generally associated with psoriasis, eczema, and other autoimmune conditions. Upon inflammation, epithelial cells secrete CCL20, which in turn attracts the CCR6+ Th17 proinflammatory cells and promotes severe inflammation. The authors fused the CX5461-loaded grapefruit EVs with CCR6+ nanovesicles of engineered GMSCs via the extrusion method. These grapefruit EV-CCR6+ nanovesicles hybrid modulated the chemotactic gradient of CCL20 by binding with them, which resulted in the reduced Th17 cells infiltration. Consequently, the expression of proinflammatory cytokines was significantly suppressed, and the symptoms of the eczema and psoriasis in *in vivo* models were ameliorated [52]. While numerous herbs have been traditionally utilized in Indian, Chinese, and other international medicine systems for skincare management, the number of researchers who have scientifically investigated and demonstrated the topical applications of plant EVs at the clinical level remains limited. Therefore, we postulate that significant research opportunities are available for conducting experiments to assess the properties of skin regeneration-associated plant-derived EVs at the clinical level. Drug loading and surface modification properties of plant EVs have been reported, primarily in the context of cancer therapy. A study demonstrated similar properties of EVs derived from Curcuma against senescent tumor cells. In this work, the authors engineered the Curcuma EVs to deliver the anti-cancer drug doxorubicin and to express a surface-modified antibody targeting death receptor 5, a pro-apoptotic receptor overexpressed on tumor cells. The results indicated that these engineered Curcuma EVs significantly enhanced tumor cell death [53]. The findings of this study not only underscored the potential of plant EVs in augmenting drug safety and precision drug delivery with surface modification but also suggested that similar studies involving fused plants and MSCs-derived EVs as well as fused plants and probiotics-derived EVs may hold significant promise for advancing the field of cosmetics and cosmeceuticals development.

8. Conclusion

Inventions aimed at improving the delivery methods, efficiency, and stability of plant-derived EVs, and developing hybrid EVs present significant opportunities for the successful translation of these technologies into commercial cosmetic and regenerative therapeutic products. Future advancements may involve personalized treatments utilizing plant EVs loaded with active peptides and drugs, tailored to the unique characteristics of individual skin types.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Author contributions

Conceptualization, T.S.R.; Data collection and investigation, T.S.R. and R.S.; Writing—original draft preparation, T.S.R.; Editing, T.S.R., and R.S. Both authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Authors T.S.R. and R.S. are employed by the company Hoynoza Technologies Pvt. Ltd. Hoynoza Technologies has research, development and commercial interests in extracellular vesicles. The authors declare that Hoynoza Technologies had no role in the design, execution, analysis, or interpretation of the study.

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