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Review Article

Exosomes for skin treatment: Therapeutic and cosmetic applications

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ABSTRACT

The therapeutic potential of exosomes, which are nano-sized extracellular vesicles derived from various cell types, have drawn substantial interest in the field of dermatology. Exosomes have distinctive capabilities, including facilitating intercellular communication, delivering bioactive molecules, and modulating immune responses, which make them promising candidates for skin regeneration, wound healing, and treating dermatological disorders. Specifically, exosomes derived from the stem cells of mesenchymal and adipose cells, have numerous applications in skin repair and regeneration. Exosomes also find expanded applications in treatments and therapies related to hair. Exosomes emit signals and growth factors that impact the activity of nearby epithelial cells, encouraging their growth, specialization, and the development of hair formations. This review explores the efficacy of topical and transdermal applications of exosomes in skin and hair and highlight the transformative potential of exosome-based therapies in dermatology and pave the way for future research and clinical applications.

1. Introduction

Extracellular vesicles (EVs), which are membrane-bound particles released by cells, play roles in both physiological and pathological processes and are gaining attention for their potential therapeutic use in regenerative medicine. EVs can be categorized as exosomes, ectosomes, apoptotic bodies, large oncosomes, and exomeres. Ectosomes are vesicles ranging in size from 0.1 to 1 μm in diameter that bud directly from the plasma membrane and are released into the extracellular space. Unlike living cells, ectosomes display the phospholipid phosphatidylserine on their surface [1]. The key features of ectosomes released by various cells, such as tumor cells, polymorphonuclear leukocytes, and erythrocytes, include the expression of phosphatidylserine and the possession of anti-inflammatory and immunosuppressive properties, similar to those observed in apoptotic cells [2]. Apoptotic bodies(ApoBDs) are membrane-bound vesicles that are produced during apoptosis and arise from the disassembly of apoptotic cells. Initially considered as mere waste containers, these small sealed sacs carry information and substances from dying cells, later recognized for their ability to deliver beneficial materials to healthy recipient cells, such as autoantigens [3]. There are extracellular vesicles which are cancer-derived known as large oncosomes. Large oncosomes are a specific type of extracellular vesicle that are significantly larger than typical exosomes and microvesicles, usually ranging in size from 1 to 10 micrometers in diameter. These vesicles are shed from the plasma membrane of cancer cells, particularly those with aggressive or metastatic potential [4]. Exomeres are a newly identified subset of extracellular vesicles (EVs). Unlike other types of EVs, exomeres are characterized as non-membranous nanovesicles with a diameter of ≤50 nm. Research into the cargo of exomeres is beginning to uncover their enrichment with proteins that play roles in regulating metabolic pathways. Similar to other types of EVs, exomeres also carry nucleic acids and lipids that can be transferred to recipient cells [5]. Exosomes are nano-sized vesicles that contain a variety of biological molecules, which are secreted by most of the cells in our body. They range in size between 30 to 150 nm in diameter. Due to its features such as biocompatibility, payload capability, and reduced immunogenicity, exosomes can act as an excellent drug delivery tool [6].

In recent years, there has been a growing interest in the field of regenerative medicine and the potential of exosomes as therapeutic agents and drug delivery tools. Exosomes have emerged as powerful conciliator of intercellular communication. These tiny vesicles contain

Abbreviations: EVs, extracellular vesicles; MSC -Exo, Mesenchymal-derived Stem Cell exosomes; MiRNA, Micro RNA; Mical2, Molecule interacting Cas L2 gene; ADNV, Apple Derived exosome like Nano-vesicles; TLR4, Toll Like Receptor 4; ASCEs, Adipose-derived Stem Cell Exosomes; CM, Conditioned Media; DFb, Dermal Fibroblast; HADSC-exo, Human Adipose-Derived Stem cells -derived exosomes; PELNVS, Plant Exosomes Like Nano-vesicles; MNs, microneedles

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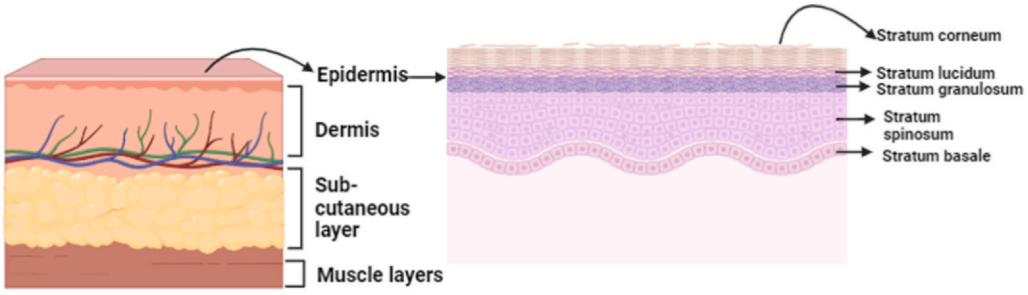

Fig. 1. Skin layers; Diagram showing various layers of skin and epidermis.

proteins, lipids, and nucleic acids, which can influence recipient cells and regulate their behavior. One area where exosomes are gathering remarkable attention is their application in skin health and rejuvenation. Topical and transdermal applications of exosomes furnish a promising route for targeted delivery of their regenerative effects directly into the skin. Drugs can penetrate the skin through several modes. The primary modes of skin penetration include paracellular, transcellular, trans-appendageal and the routes via lipid bilayers, hair follicles, and tight junction. In intercellular or paracellular route, the drug penetrates between the cells of the stratum corneum in contrast to transcellular or intracellular route where the drug crosses directly through the corneocytes of the stratum corneum. The trans-appendageal route is the most relevant for large molecules and particles including nanoparticles as it bypasses the stratum corneum and penetrates via appendages such as hair follicles, sebaceous glands and sweat glands. Penetration of small water soluble molecules can occur through the tight junctions in stratum granulosum. Entry through follicles and lipid bilayer depends on the molecular size and lipophilicity of the molecules.

After the identification of exosomes, they have been utilized as diagnostic biomarkers and potential carriers for drug delivery due to their size and ability to transport biological substances to recipient cells. Exosomes possess attributes such as biocompatibility, selective tumor homing, modifiable targeting efficiency, and robust stability, rendering them remarkable and highly effective for delivering drugs in diverse disease contexts, including cancer therapy. The capacity of exosomes to facilitate specific physiological and pathological mechanisms is harnessed to create targeted delivery of therapeutic agents, aiming to reduce systemic toxicity [7]. Over the past few years, recognizing the constraints inherent to therapeutic agents, a multitude of synthetic nano-delivery systems have emerged to amplify drug effectiveness. Among these, extracellular vesicles stand out as a class of innate nano-sized drug transporters discharged by cells. Exosomes, which are minuscule vesicles enclosed by lipid bilayer membranes, and released by various cells within the body, serve as conduits for vital signaling molecules. Consequently, their advantageous size and considerable potential in drug therapy have positioned them as a focal point of research in the fields of biomedicine and biomaterials [8].

2. Biogenesis of exosomes

The broad classes of EVs include micro vesicles, apoptotic bodies and exosomes. The biogenesis of exosomes is a biologically complex, highly regulated process that involves several sequential steps from early endosome formation to eventual release of fully mature exosomes. Early endosomes mature into late endosomes or multivesicular bodies (MVBs). The inward invagination the endosomal membrane of MVBs produces intraluminal vesicles (ILVs) in the lumen of organelles. The next critical step is to decide whether ILVs will be degraded by lysosomes or produced as exosomes. This crucial process requires numerous sorting stages. When the cell membrane is given the chance to merge with the MVBs, ILVs are eventually released by exocytosis into the extracellular environment. The vesicles that are released are called as exosome [9]. The endosomal sorting complex required for transport (ESCRT) plays a key role in ILV formation. It is an intricate protein machinery composed of ESCRT0, ESCRT I, ESCRT II, ESCRT III that work cooperatively to facilitate MVB formation, vesicle budding, and protein cargo sorting [10].The overall energy required for the entire exosome release process is provided by ATPase. A specific type of ATPase known as VpS4p/SKD1 causes constriction of the neck that facilitates release of vesicle buds from the membrane. The vesicles are released after interacting with a particular set of SNAREs or N-ethylmaleimide sensitive factor attachment protein receptors[11]. These exosomes are loaded with various cargoes such as proteins, lipids and nucleic acids (DNA, mRNA and miRNA) depending on the source. A different approach of exosome production relies on ESCRT-independent approach. This approach is said to be independent on raft-based microdomains for the lateral sorting of cargo within the endosomal membrane of MVBs. Ceramides are formed from sphingomyelinases by hydrolytic removal of the phosphocholine moiety, which are predicted to be greatly concentrated in these microdomains. In model membranes, ceramides are known to cause lateral separation of phases and the assembly of microdomains. Additionally, the endosomal membrane's natural negative curvature may result from the cone-shaped structure of ceramide, which would encourage domain-induced budding[12]. In summary, there are multiple independent pathways involved in formation, sustenance and cargo sorting of exosomes which are yet to be fully understood.

3. Skin barriers

Skin, the largest organ in the human body consists of three layers: epidermis, dermis, and hypodermis. The outermost layer of the skin is the epidermis, a thin layer that is tightly packed with epithelial keratinized cells. It is divided into 5 layers namely stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale (Fig. 1) [13]. The primary achievement of skin barrier function is largely attributed to the stratum corneum. The stratum corneum is the outermost covering of the epidermis, and consists of very tightly packed dead cells known as corneocytes. Stratum corneum acts as formidable physical, environmental, and microbial barriers protecting organisms from external invasion and homeostasis maintenance [14]. Stratum corneum, functions as an effective barrier that restricts the penetration of most drugs, making it challenging for them to cross the skin. Tight junctions, which is a part of stratum granulosum are considered to be the second largest barrier of skin [15]. Tight junctions are crucial components of the skin barrier, playing a vital role in maintaining skin integrity, preventing water loss, and protecting against the entry of pathogens, allergens, and toxins. These specialized structures are found between cells in the epidermis, particularly in the outermost layer, the stratum corneum, and the underlying layers of the epidermis.They are of significant importance due to their central location. They are composed of various proteins, including claudins, occludins, junctional adhesion molecules (JAMs), and zonula occludens (ZO) proteins. These proteins form a network of strands that seal the space between adjacent cells, creating a barrier that regulates the movement of molecules and ions through the paracellular space (the space between cells). It forms a continuous layer and prevents the passage of small molecular drugs[16].

Fortunately, there are non-invasive approaches that can substantially augment drug permeation through this barrier. The utilization of nanocarriers to expand the spectrum of drugs available for transdermal delivery has emerged as a valuable and promising alternative [17]. Exosomes, originating from endocytic membranes, facilitate the transfer of essential biomolecules in cell communication, influencing both pathological and physiological processes in skin diseases. Exosomes, with their heterogeneity and endogeneity, stand out from nanoparticles like liposomes, making them widely utilized in treating dermal diseases [18].

4. Topical application of exosomes

Exosomes have recently gathered significant attention in the cosmetic industry, emerging as a focal point of interest and research within the field. They have proven to be advantageous in skincare due to their rich composition of proteins, lipids, and various molecules that foster healing, hydration, and skin protection. These components contribute to enhancing collagen production, mitigating inflammation, and safeguarding the skin against environmental stressors [19]. The utilization of exosomes in topical creams, serums, masks, etc., has commenced due to their wide-ranging therapeutic advantages [20]. In a recent study by Kim et al., they documented the application of extracellular vesicles derived from mesenchymal stem cells (MSC-Exos) obtained from human umbilical cord blood on the skin. This topical application was performed on human skin samples ex vivo, leading to an upregulation of genes related to the skin's extracellular matrix. As a result, this approach has been found to contribute to skin rejuvenation [21].

In addition to their rejuvenating properties, mesenchymal stem cells play a pivotal role in treating sensitive skin [22]. By harnessing the regenerative capabilities of mesenchymal stem cells, medical treatments can effectively repair and soothe skin that is prone to irritation, inflammation, and other sensitivities. This makes them a versatile and crucial element in the advancement of dermatological therapies, offering hope for more effective and targeted approaches to skincare and healing.

4.1. Effect of exosomes on melanogenesis and hyperpigmentation

Melanin, responsible for skin coloration, is synthesized through melanogenesis, primarily influenced by melanosomes' quantity and distribution in the skin [23].Extracellular vesicles, in addition to their other roles, exhibit a notable capacity to counteract melanogenesis, the process by which melanin is produced in skin cells [24]. Numerous tyrosinase inhibitors, including ascorbic acid and kojic acid, have been developed for skin whitening purposes. However, their efficacy has been compromised by issues of low stability and adverse effects, leading to their limited success in practical applications [25,26]. Extracellular vesicles (EVs) derived from Korean seaweeds, specifically *Sargassum fusiform* and *Codium fragile*, exhibit anti-melanogenic properties on the skin. Studies demonstrated that EVs obtained from these seaweeds effectively diminish melanin synthesis in MNT-1 cells and downregulate the expression of crucial regulators such as MITF, tyrosinase, and TRP-1, which play pivotal roles in melanin production and in turn affect skin brightening [27]. MicroRNAs carried by exosomes also play a critical role in inhibiting tyrosinase and melanogenesis. For instance, miR-2478 derived from milk exosomes, which is overexpressed in melanocytes, suppresses Rap1a expression, leading to reduced melanin production and downregulation of melanogenesis-related genes [28]. Evidence suggests that exosomal microRNAs significantly influence melanogenesis regulation. UVB-irradiated keratinocyte-derived exosomes enhance melanogenesis in melanocytes by increasing MITF, TRP1, TRP2, and TYR expression, suggesting their potential as regulators of melanogenesis. Specific keratinocyte-derived exosomal miRNAs like hsa-miR-644a, hsa-miR-365b-5p, hsa-miR-197–5p, and hsa-miR-4281 have been selectively analyzed and shown to both promote and inhibit melanogenesis through functional assays [29,30].

Hyperpigmentation is a prevalent skin disorder caused by excessive activity of tyrosinase, which is characterized by the dark spots and patches in the skin [31]. Research has shown that stem cells and their derivatives, along with conditioned media (CM), exhibit inhibitory effects on skin pigmentation. The exosomes isolated from the CM of ASCs through tangential flow method exhibited skin-brightening efficacy in human skin. The study demonstrated that ASC-exosomes effectively lowered intracellular melanin levels in B16F10 cells without inducing significant cytotoxicity, both in the presence and absence of α-MSH. Furthermore, in a prospective, split-face, double-blind, randomized placebo-controlled study, the topical formulation containing ASC-exosomes successfully reduced hyperpigmentation [32]. Apart from that, the combination treatment of hASCs derived exosomes and fractional CO_2 laser also contributes to the treatment of atrophic acne scars[33].

4.2. Effects of exosomes on aging

Aging, particularly skin aging, is a major concern for many individuals due to its effects on appearance, health, and overall quality of life. The aging process impacts the skin by causing wrinkles, fine lines, sagging, and changes in pigmentation. Skin aging is influenced by two primary processes: intrinsic and extrinsic aging. Intrinsic aging, driven by genetic factors, naturally occurs over time, while extrinsic aging is caused by environmental factors such as oxidative stress, sun exposure, and other external influences [34].

Exosomes and extracellular vesicles have a wide range of effects on skin aging. Notably, exosomes derived from bovine milk (MK-Exo) have been found to possess anti-aging properties, impacting keratinocytes and fibroblasts, which results in wrinkle reduction and skin moisturization [35]. One of the major challenges in cosmetics is the ability of functional ingredients to penetrate the skin barrier. MK-Exo has demonstrated the capacity to cross this barrier to some extent, as indicated by its interactions with human skin. Consequently, MK-Exo is a promising candidate for improving the delivery and effectiveness of cosmetic ingredients. Exosomes isolated from the ADSC culture medium, known as ADSC-derived exosomes (ADSC-Exos), have been found to mitigate senescence in human dermal fibroblasts (HDFs) and promote their migration. Additionally, ADSC-Exos have been shown to enhance the expression level of type I collagen, reduce reactive oxygen species (ROS), and decrease senescence-associated β-galactosidase (SA-β-Gal) activity in HDFs. Furthermore, ADSC-Exos significantly inhibited the expression levels of senescence-related proteins p53, p21, and p16 and effects in anti-aging of skin[36]. In addition to natural aging, photo-aging has become a significant challenge faced by many individuals today. Chronic sun exposure leads to photoaging of human skin, characterized by clinical, histological, and biochemical changes that differ from those seen in skin that has aged naturally without sun exposure[37].It has been studied that the exosome-like nanovesicles derived from *Phellinus linteus*, a polypore mushroom that typically grows on mulberry trees, improves and resists photoaging of the skin. These exosomes possess high levels of miRNAs and the effect of the extracted RNAs on UV photoaging mouse models was studied. The miRNAs extracted from these exosomes play an anti-aging role by inhibiting the expression of Mical2 (Molecule interacting Cas L 2 gene) in human skin cells through cross-species regulation [38]. Normally, aging is characterized by the degradation of the extracellular matrix, regulated by the expression of a group of zinc-containing endopeptidases known as matrix metalloproteinases (MMPs), MMP-1 and MMP-3. The expression of MMPs increases with age[39].The human induced pluripotent stem cells(iPSCs) derived- exosome also have some remarkable effects on photoaging through the inhibition of these MMPs. The studies involving iPSC-derived exosomes on human dermal fibroblasts (HDFs) have demonstrated that these exosomes stimulate the proliferation and migration of HDFs under normal conditions. Furthermore, pretreatment with iPSCs-derived exosomes has been shown to inhibit UVB irradiation-induced damage to HDFs, as well as the overexpression of matrix-

degrading enzymes MMP-1 and MMP-3[40]. The iPSC-Exo is thought to have a variety of proteins as well as different types of RNAs like mRNAs, miRNAs, and lncRNAs, which can impact cell physiology. Therefore, the positive effects of iPSC-Exo on skin fibroblasts are likely due to the combined action of its cytokines, membrane proteins, and RNAs. Moreover, exosomes derived from adipose-derived mesenchymal stem cells (ADSC-Exos) have been shown to possess anti-aging properties in photoaged skin. These properties also include the inhibition of collagen type III and the expression of MMP-1 and MMP-3 [41]. Another study conducted with the nanovesicles isolated from the apple variety Golden Delicious proved that they exhibited anti-inflammatory effects on primary dermal fibroblasts, thereby affecting skin aging. The mode of action of ADNV seemed to involve the downregulation of the NF-κB pathway through the dimming of TLR4-induced signals. The results have shown that fibroblasts that were already in a state of inflammation displayed a more pronounced response compared to those in a non-inflamed condition, demonstrating the anti-inflammatory properties of exosomes. ADNVs also reduce extracellular matrix degradation by increasing collagen synthesis (COL3A1, COL1A2, COL8A1, and COL6A1) and by decreasing the production of metalloproteinases (MMP1, MMP8, and MMP9) [42]. Like bovine-milk exosomes, bovine-colostrum-derived exosomes also have a notable impact on aging of skin. Treatment with colostrum exosomes prevented the generation of intracellular reactive oxygen species in epidermal keratinocytes induced by UV exposure. In human dermal fibroblasts treated with colostrum exosomes, the expression of matrix metalloproteinases was suppressed, while cell proliferation increased, accompanied by enhanced production of collagen, a key component of the skin's extracellular matrix[43].

Exosomes have garnered significant attention in the field of anti-aging treatments due to their ability to influence cellular processes that contribute to aging. These extracellular vesicles, which carry proteins, lipids, RNA, and other bioactive molecules, can modulate various biological functions and potentially reverse or slow down aging-related changes in the skin and other tissues. They represent a cutting-edge approach in anti-aging treatments, leveraging their natural ability to modulate cellular processes and promote regeneration. By enhancing skin rejuvenation, reducing inflammation, and supporting tissue repair, exosome-based therapies offer promising potential for reversing or slowing down the visible and systemic effects of aging. As research continues to advance, exosome therapies may become a cornerstone of anti-aging medicine, offering innovative solutions for maintaining youthfulness and health.

4.3. Effects of exosomes on inflammations due to pathological conditions

Skin inflammation is a complex response to various disease conditions and external stimuli, characterized by redness, swelling, heat, and pain. It serves as a protective mechanism to eliminate harmful stimuli, including pathogens, damaged cells, and irritants, and to initiate the healing process. Inflammation can be categorized into two types: **acute** and **chronic**. **Acute inflammation** represents the body's immediate response to injury or infection and typically resolves within a few days. This response is marked by a rapid influx of immune cells, especially neutrophils, to the affected area, resulting in the classic signs of inflammation: redness (erythema), warmth, swelling (edema), and pain. In contrast, **chronic inflammation** is a persistent response that plays a central role in several dermatological diseases, such as psoriasis, atopic dermatitis (eczema), and rosacea etc Exosomes have been identified as effective regulators of inflammatory responses in various disease conditions.

Psoriasis is a chronic autoimmune condition that causes the rapid buildup of our skin cells, which is possessing several challenges in treatment due to the complex nature of the disease. Generally, targeted immune therapy is used for the treatment of psoriasis. Since long-term immunotherapy causes some health risks and loss of response, alternative strategies are sought after. The exosomes derived from mesenchymal/ stromal cells are potent immunomodulators, that can ease psoriasis-induced inflammations when applied topically. Fluorescent exosomes applied topically to human skin explants were mainly localized within the stratum corneum, with less than 1 % of the fluorescent material exiting the explant over a 24-hour period. Despite this limited penetration, the topical application of MSC exosomes in a mouse model of imiquimod (IuMQ)-induced psoriasis resulted in a significant reduction in IL-17 levels and induction of the terminal complement activation complex C5b-9 in the mouse skin[44,45]. The death of psoriatic keratinocytes has recently been identified as a significant amplifier in triggering the inflammatory cascade. Considering that both keratinocytes and immune cells exhibit high expression of the protein Programmed Death-1(PD-1) in psoriasis, it could be a potential therapeutic target for treating the condition. The PD-1 receptor plays a crucial physiological role in maintaining immune tolerance. By interacting with its ligands (PD-L1 and PD-L2), it helps prevent the onset of various immune-mediated diseases. Increasing evidence highlights the significant role of the PD-1/PD-L1 pathway in the pathogenesis of psoriasis [46]. In a recent study, PD-L1 positive exosomes (pri@exo) derived from tumor cells, carrying pristimerin, was used to target PD-1 expressing cells for drug delivery. It was found that they efficiently reversed induced psoriasis in mice through reduction in epidermal thickness, diminished plaque formation, and the suppression of excessive inflammations [47]. Exosomes released by keratinocytes have the ability to engage in communication with other keratinocytes and immune cells through distinctive surface biomarkers. This communication may prove effective in addressing the inflammation associated with psoriasis and its underlying pathogenesis. A group of researchers aimed to map out and study the effectiveness of an exosomal delivery system of tofacitinib (TFC), an FDA approved medication for rheumatoid arthritis, psoriasis, etc. The results have shown that drugs encapsulated by exosomes exhibit lower cytotoxicity compared to the free ones. Also, it shows high suppression of TNF a, IL-23, IL-6, and IL-15 genes which are associated with plaque-type psoriasis from which we can conclude that the exosome-based drug delivery of TFC has a significant role in enhancing the therapeutic effects[48]. In generalized pustular psoriasis, neutrophil-derived exosomes play a significant role in enhancing skin autoinflammation by activating keratinocytes. They contribute to the inflammatory process by interacting with and stimulating keratinocytes. The activation of keratinocytes by neutrophil exosomes highlights their role as key mediators in the inflammatory cascade associated with this severe form of psoriasis [49].

Facial erythema (redness) is a recently reported side effect of treatments for atopic dermatitis with 'Dupilumab', which is interlukin-4 (IL-4) receptor alpha antagonist. In a work by H. Han et al. [50]), it is reported that topical application of the adipose-derived stem cell exosomes (ASCEs) can reduce the erythema symptoms of Dupilumab. The results showed that the topical application of ASCEs in the treatment of Dupilumab Facial Redness (DFR), reduced inflammation, boosted the expression of skin barrier-related proteins, and promoted angiogenesis. A significant benefit of ASCE is its capacity to deliver therapeutic effects through topical application, a crucial feature considering that DFR typically presents as localized skin lesions [50,51].

Exosomes are powerful modulators of inflammation with significant potential for therapeutic applications in treating inflammatory diseases. Their ability to regulate immune responses, inhibit pro-inflammatory pathways, and promote tissue repair makes them a promising tool in the development of anti-inflammatory therapies. As research progresses, exosome-based treatments could offer new strategies for managing a wide range of inflammatory conditions, from autoimmune diseases to neuroinflammatory disorders.

4.4. Effect of exosomes in wound healing

Exosomes have been identified as influential contributors to processes such as angiogenesis, cell proliferation, differentiation, apoptosis, and inflammation. This discovery has sparked heightened interest

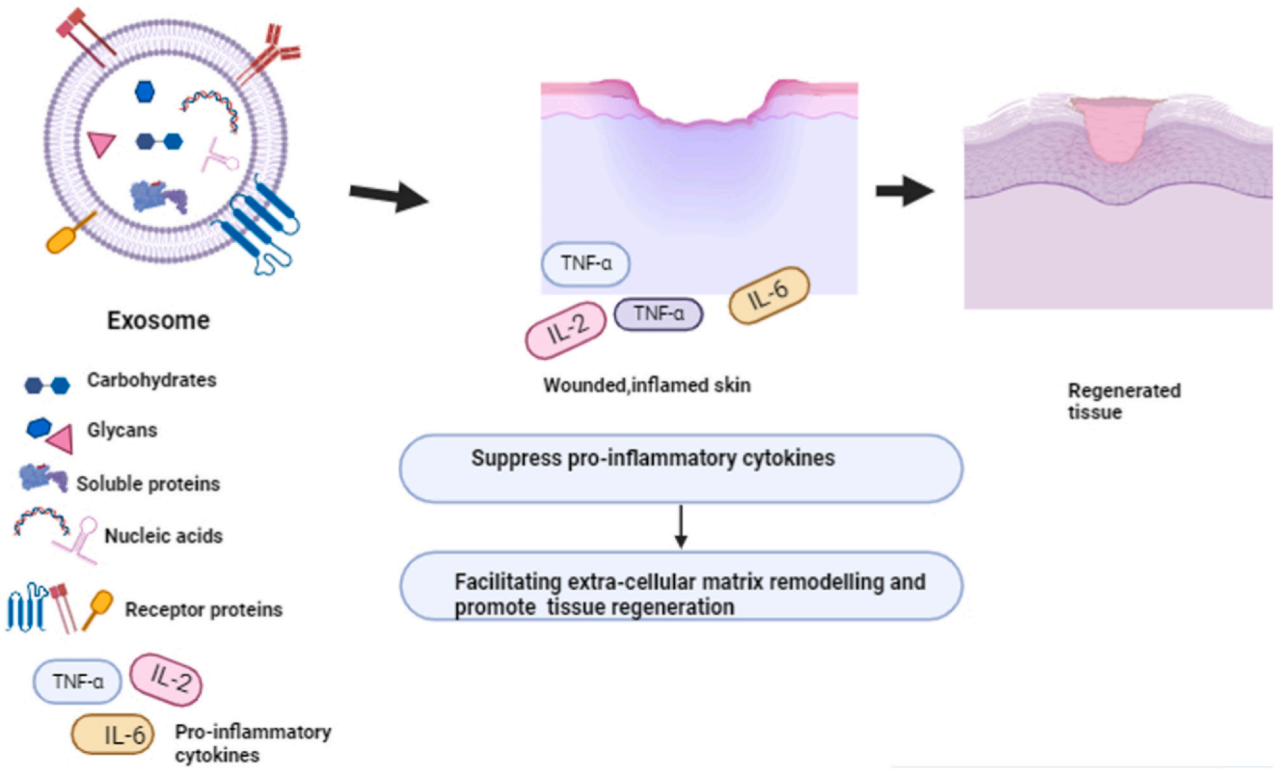

Fig. 2. Effect of exosomes in wound healing; Exosomes suppress pro-inflammatory cytokines and foster anti-inflammatory responses. It facilitates ECM remodelling and promotes tissue regeneration.

in exploring their therapeutic potential for wound healing. Exosomes derived from various sources including MSCs, keratinocytes, endothelial cells, immune cells, and several other body fluids can regulate wound healing [52]. Exosomes obtained from mesenchymal stem cells (MSCs-Exos) exhibit superior functionality and greater ease of handling compared to cell-based products [53]. These exosomes effectively suppress pro-inflammatory cytokines, fostering anti-inflammatory responses facilitating extracellular matrix (ECM) remodelling, thereby promoting tissue regeneration (Fig. 2).

Diabetic ulcer is a very serious issue in diabetes patients and its treatment still remains a challenge. The pivotal role of exosomes in healing diabetic ulcers has been observed in some recent studies. Diabetes, a prevalent medical condition within our society, notably hinders both angiogenesis and the process of wound healing. The studies by Hsu et al., proves that the adipose stem cell-derived exosomes have the ability to enhance the closure of diabetic ulcers. Exosomes from culture supernatants of adipose stem cells and dermal fibroblasts (DFb) of diabetic mice were extracted and subjected to electron microscopy and nanoparticle tracking analysis. It was observed that ASCs secreted higher amounts of exosome-associated proteins in the culture supernatant compared to DFb and also when topically administered, it is found that ASC-Exo induced faster wound closure over time compared with treatment with DFb-Exo [54]. Like ASC-Exo, Human adipose-derived stem cells also have an indispensable role in wound healing. The study involved conducting a full-thickness skin biopsy experiment on mice [55]. The integrated application of hADSC-exo by local smearing and intra-venously results in promoting wound healing, enhancing re-epithelization, reduction of scar width, increased angiogenesis, and collagen synthesis (Fig. 3).

Hyaluronic acid (HA), a primary constituent of the skin extracellular matrix (ECM), finds extensive application in wound dressings and dermal fillers. A study has been conducted to explore the impact of exosomes derived from adipose-derived stem cells (ASC-EXOs) on human dermal fibroblasts (HDFs) and evaluate their potential synergy with hyaluronic acid (HA) in *in vivo* models of wound healing and dermal filler applications. The results have stipulated that ASC-EXOs positively influence cell proliferation, migration, and gene expression associated with wound healing, potentially expediting wound closure and supporting tissue regeneration. Moreover, the combination of HA and ASC-EXOs could amplify the benefits in wound healing and tissue remodeling, suggesting potential applications in clinical and regenerative aesthetics for skin repair and regeneration [56]. In another study, it has been indicated that ADSC-Exos overexpressing H19 (long non-coding gene), may enhance the expression of SOX9 through miR-19b, thereby expediting the wound healing process in skin tissues [57].

Exosomes are integral to the wound healing process, from the initial response to injury to the final tissue remodeling stage. They are indispensable in wound healing by facilitating intercellular communication and regulating various biological processes necessary for tissue repair. They help coordinate the complex interplay between various cell types and signaling pathways, promoting efficient and effective wound healing. The therapeutic potential of exosome-based treatments is a promising area of research, particularly for enhancing the healing of chronic or severe wounds.

4.4.1. Scar formation

Hypertrophic scars and keloids are benign fibroproliferative disorders that may arise after skin injury, characterized by abnormal fibroblast proliferation and extracellular matrix (ECM) deposition [58,59]. Exosomes have shown potential in modulating the formation of these scars depending on the microenvironment and fibroblast heterogeneity at the site of injury. Exosomes modulate cell activity, reduce inflammation, promote skin cell proliferation and migration, regulate collagen production and degradation, and prevent excessive scar tissue formation or fibrosis [60]. They also promote angiogenesis, essential for proper wound healing, by carrying pro-angiogenic factors such as VEGF [61,62]. Exosomes regulate the expression and activity of MMPs, enzymes that break down ECM components, aiding in proper ECM

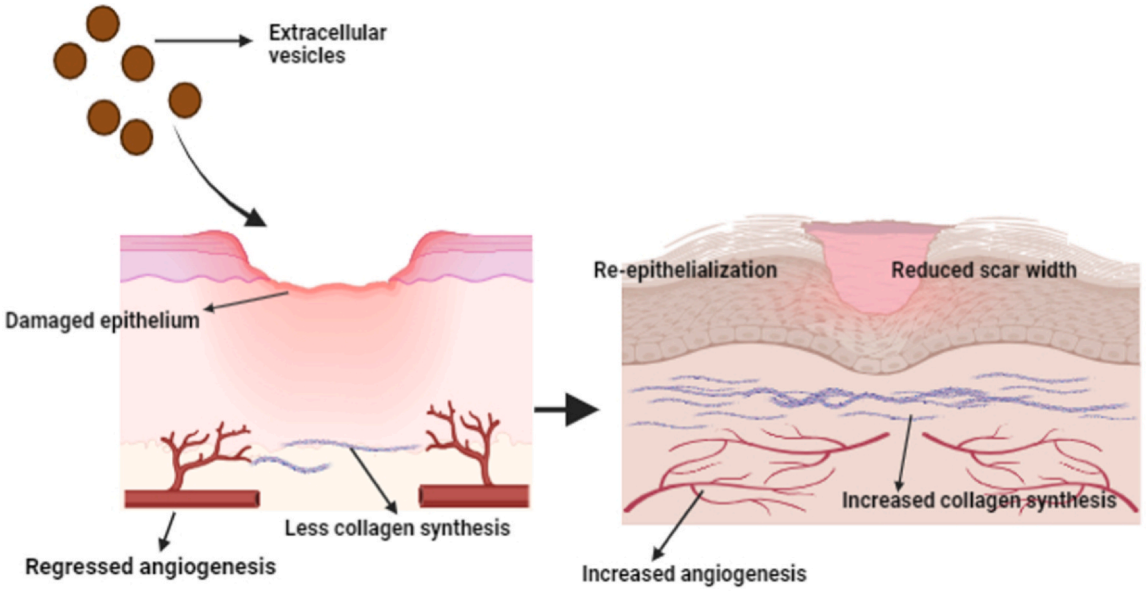

Fig. 3. Re-epithelialization of wounded skin; Application of EVs resulted in increased angiogenesis, increased collagen synthesis and there by promote re-epithelialization of wounded skin.

remodeling and preventing fibrotic scar formation [63,64]. Mesenchymal stem cell (MSC) and Adipose-derived stem cell(ADSC) exosomes have been extensively studied for their regenerative properties, including skin healing and scar reduction. Adipose-derived stem cell (ADSC) exosomes are the most commonly used for scar treatment, known to inhibit the proliferation and ECM production by keloid and hypertrophic scar fibroblasts. Human amniotic epithelial cell exosomes also suppress hypertrophic scar formation. The inhibition of lncRNA-ASLNCS5088 and LINC01605M2 macrophage-derived exosomes impairs fibroblast production, migration, and invasion [65]. Keloid fibroblast exosomes release miR21, aiding in cell proliferation and collagen production [66](Li et al., 2021). Intracellular communication via exosomes between melanocytes and fibroblasts significantly influences scar formation. ADSC-derived exosomes may inhibit the proliferation, migration, and collagen synthesis of keloid fibroblasts by inhibiting the TGF-β/Smad pathway, reducing scar formation [66]. Additionally, miR29a-modified ADSC exosome therapy attenuates collagen deposition and ECM synthesis in hypertrophic scar tissue [67]. Animal studies show that mice treated with ADSC-derived exosomes exhibit faster wound healing and less collagen deposition, indirectly regulating fibroblasts and myofibroblasts by promoting angiogenesis and inhibiting inflammation. Numerous animal studies and ongoing clinical trials demonstrate the effectiveness, safety, and efficacy of exosome-based therapies for scar treatment in humans.

5. Transdermal application of exosomes

Transdermal drug delivery is a commonly used method in contemporary medicine nowadays. It offers several advantages, including ease of use, reduced side effects, and improved patient compliance. In a transdermal drug delivery system, the drugs can penetrate the epidermis barrier and get absorbed by the skin. The drugs permeate the skin at a relatively steady pace, moving through the outermost layer known as the stratum corneum via passive diffusion. This movement occurs along a concentration gradient, progressing from the surface of the skin towards its inner layer. This process leads them to the capillaries within the dermis, from where they access the bloodstream. Consequently, these drugs can travel throughout the body, either to exert a systemic therapeutic impact or to achieve a local effect through localized microcirculation [68].

Exosomes are emerging as transdermal drug carriers with notable flexibility and exceptional permeability. They offer a means of transport for both small-molecule and large-molecule drugs, enhancing transdermal and dermal drug retention. This, in turn, elevates local effectiveness and promotes adherence to drug delivery protocols. Exosomes are employed in transdermal applications primarily due to their exceptional ability to penetrate effectively. The primary function of exosomes is to transmit information to recipient cells, thereby influencing their functions. This implies that they could play a pivotal role in facilitating cross-kingdom communication between plants and mammals, which could be a contributing factor to the enhanced penetration effectiveness of active pharmaceutical ingredients [69].

Plant Exosome Like Nano-vesicles (PELNVs) possess inherent capabilities for targeted localization within specific tissues, showcasing key attributes of an effective targeted drug delivery system. Also, they share structural similarities with liposomes and exhibit a high degree of resemblance to the surfaces of mammalian cell membranes, featuring bilayer phospholipid structures. Consequently, PELNVs can efficiently traverse the stratum corneum of the skin using both trans- and intercellular pathways, facilitated by lipid fusion interactions [70]. A broccoli-derived exosome was found to exhibit high lipophilicity and exceptional interception efficacy, making it well-suited for deep penetration into skin tissues, as reported [71]. PELNV treatment fosters the expansion and movement of fibroblasts, facilitating enhanced re-epithelialization through the stimulation of keratinocyte cell proliferation and migration. Additionally, it leads to heightened collagen synthesis while boosting the production of elastin and fibronectin. Certain pathways such as phagocytosis, macro-pinocytosis, and Clathrin-mediated endocytosis have been associated with the cellular internalization of PELNVs [72].

The nano-exosomes extracted from Aloevera bark callus have been observed as an effective cosmetic composition as they induce collagen formation and keratin improvement. By confirming it in the human skin through various application tests, they proved their efficiency as the functional material for exosome-based lotion formulation [73]. This concept proposes the development of a cosmetic and pharmaceutical formulation suitable for safe application to the skin. This formulation would have the dual benefits of preventing skin aging, promoting skin regeneration, and enhancing overall skin health. Additionally, it envisions a novel application as a transdermal delivery system, suggesting

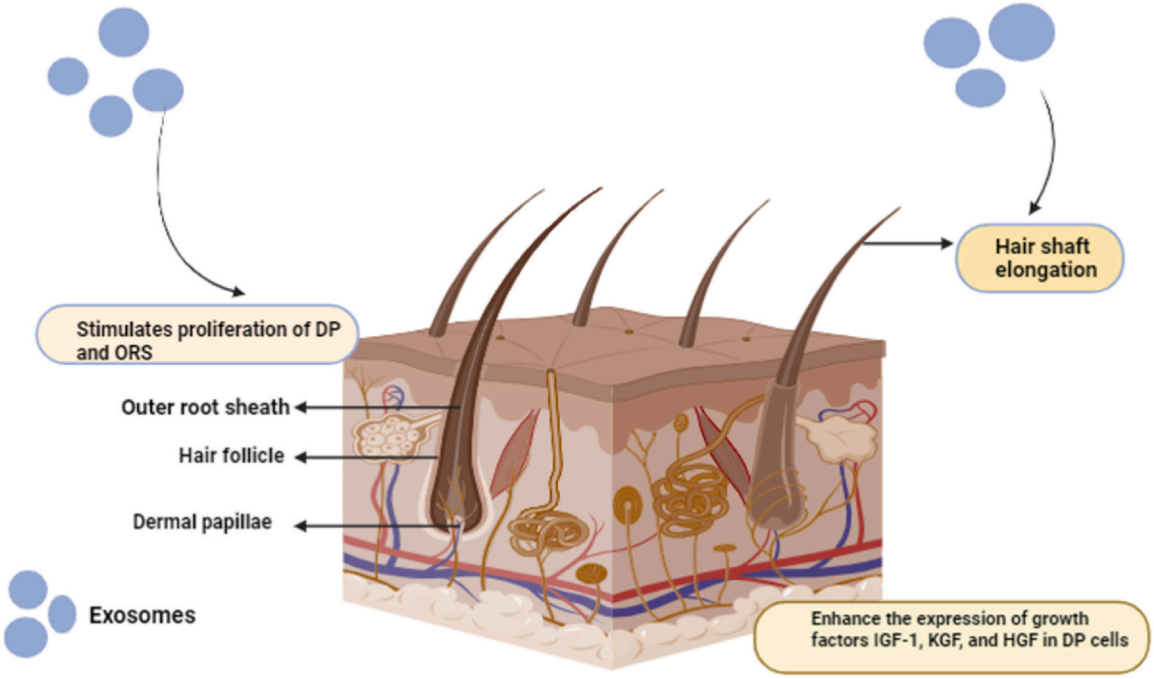

Fig. 4. Action of exosomes on hair growth; Exosomes stimulate dermal papillae and Outer root sheath, elongation of hair shaft and increase the expression of growth factors IGF-1, KGF and HGF in DP cells.

the potential to administer beneficial compounds through the skin for therapeutic purposes. This innovative approach aims to combine skincare and medical advancements into a single product.

The transdermal administration of exosomes on the skin has been shown to contribute to the process of wound healing also. Senile wound healing is complicated, as the aging process can lead to a natural slowdown in the body's ability to heal, resulting in a complete failure of repair and the emergence of chronic wounds in many instances[74]. The delayed wound healing in aging is attributed to the diminished activity of aged dermal fibroblasts (A-FBs) and disrupted local immunoreaction in the deep dermis, necessitating supplementary interventions to address the complexities of the local microenvironment. It has been introduced as an innovative double-layer microneedle patch (MNP) composed of hyaluronic acid methacrylate (HAMA) and polyvinyl alcohol (PVA), coated with exosomes derived from young fibroblasts (Y-EXOs) (Y-EXOs@HAMA/PVA MNP), for proficient deep drug delivery, enhanced healing of aged wounds, and immunoregulation. The preservation of nanovesicle bioactivity is achieved through a spraying and freeze-drying technique. This study has shown the effective dual functionality of young fibroblast-derived exosomes (Y-EXOs) in both anti-aging and anti-inflammatory responses. The Y-EXOs@HAMA/PVA microneedle patch emerges as a promising novel approach for deep drug delivery, poised to enhance the healing of challenging wounds in aged skin, with potential applications in future clinical settings [75]. Similar to Y-EXO microneedle patches, methacrylate gelatin (GelMA) microneedle (MNs) patches offer a transdermal technique for the controlled release of exosomes. The GelMA/PEGDA hydrogel-based microneedle patch preserves the biological activity of exosomes and drugs in vitro and also it shows a promising method for clinically repairing diabetic wounds[76].

6. Exosomes in hair growth

Exosomes have been employed not only in skincare applications but also for promoting hair growth. Numerous studies provide compelling evidence supporting the idea that exosomes derived from dermal papillae have the potential to stimulate hair growth. Dermal papilla cells are located at the base of the hair follicle in the dermis layer of the skin. They release signals and growth factors that influence the behaviour of adjacent epithelial cells, promoting their proliferation, differentiation, and the formation of hair structures. This reciprocal signalling between dermal papilla cells and matrix cells is pivotal in regulating the hair growth cycle and ensuring the proper development of the hair follicle [77]. Exosomes derived from three-dimensional dermal papilla (3D DP-Exos) stimulated the proliferation of both dermal papilla (DP) cells and outer root sheath (ORS) cells and also enhanced the expression of growth factors such as IGF-1, KGF, and HGF in DP cells. In addition, the treatment with 3D DP-Exos resulted in increased hair shaft elongation in cultured human hair follicles (Fig. 4) [78].

DPC-Exos also play a crucial role in regulating the cycle of hair follicles and promoting the growth of hair cells. DPC-Exos were administered through cutaneous injection at various stages of hair follicle cycles, and their impacts were assessed through histological and immuno histochemical analyses. DPC-Exos demonstrated the expression of tumor susceptibility gene 101, cluster of differentiation CD9, and CD63, and also, the administration hastened the initiation of hair follicle anagen while postponing catagen. The results have shown that DPC-Exos plays a vital role in controlling the growth and development of hair follicles, offering a potential avenue for addressing hair loss through treatment [79]. Individuals experiencing moderate hair loss often resort to topical treatments such as minoxidil, an antihypertensive potassium channel opener, and finasteride, a 5α-reductase inhibitor that suppresses dihydrotestosterone. These are the only treatments approved by the Food and Drug Administration for promoting hair regrowth. It has been found that miR-218–5p (tumor suppressor genes) was notably up-regulated in DP spheroid–derived exosomes and it is effectively stimulating the transition of the hair follicle cycle. DP spheroid–derived exosomes up-regulated β-catenin and promoting the development of hair follicles [80,81].

Stem cells obtained from adipose tissue, known as adipose-derived stem cells (ADSCs), are a significant type of stem cell characterized by their ability to undergo multilineage differentiation and self-renewal. Studies have indicated that adipose-derived stem cells play a crucial role in the process of hair regeneration. In a study by Wu et al., they effectively isolated extracellular vesicles from adipose-derived stem cells (ADSC-Exos) and showed their capability to enhance hair follicle

regeneration *in vivo*[82]. The effectiveness of mesenchymal stem cell-derived extracellular vesicle (MSC-EV) therapy in promoting hair growth was assessed in an animal model. Treatment with MSC-EVs resulted in enhanced proliferation and migration of DP cells, along with elevated levels of Bcl-2(B-cell lymphoma-2), phosphorylated Akt (Serine/threonine protein kinases) and ERK (Extracellular signal-regulated kinase). Furthermore, MSC-EV-treated DP cells exhibited heightened expression and secretion of VEGF (Vascular endothelial growth factor) and IGF-1(Insulin-like growth factors). The intradermal injection of MSC-EVs into C57BL/6 mice facilitated the transition from telogen to anagen, accompanied by increased expression of wnt3a, and wnt5a. The overall finding is that MSC-EVs possess the potential to stimulate DP cells, extend their survival, trigger the activation of growth factors in vitro, and facilitate hair growth in vivo [83,84].

Exosomes hold significant potential in the field of hair regeneration due to their ability to deliver a wide range of bioactive molecules that stimulate hair follicle cells, promote angiogenesis, reduce inflammation, and activate stem cells. As research continues, exosome-based treatments may become a key tool in the fight against hair loss, offering a novel approach to restoring hair growth and improving scalp health.

7. Future perspective and challenges

Exosomes are poised to revolutionize the cosmetic industry, offering significant potential for advancements in beauty products and treatments. Incorporated into topical creams, serums, and masks, exosomes have demonstrated a wide range of therapeutic and anti-aging advantages. Exosomes offer significant advantages in skincare due to their rich content of proteins, lipids, and various molecules that actively contribute to skin healing, hydration, and protection. These bioactive components play a pivotal role in enhancing collagen production, mitigating inflammation, and safeguarding the skin against environmental stressors. Exosomes can be packed with specific ingredients, such as antioxidants, peptides, or hyaluronic acid, and used as efficient carriers to transport these active compounds deep into the skin. This targeted delivery system can intensify the effectiveness of cosmetic products, ensuring that active ingredients reach their desired destinations. Recent studies on exosomes and advancements in the cosmetic field suggest that it may be possible to produce personalized skincare products tailored to individual skin needs. Exosome-based formulations could be adjusted based on a person's genetics, skin type, and lifestyle factors for optimal results. Exosomes are capable of supporting and repairing the skin's natural barrier function. This could be beneficial for individuals with sensitive or compromised skin, as well as those dealing with various skin barrier diseases. Exosomes can be applied through minimally invasive cosmetic procedures, such as microneedle or laser treatments, to enhance the outcomes and speed up the recovery process. Considering various ethical issues, exosomes can be taken from plants and stem cells which is a good alternative to traditional animal-derived cosmetic products. As the use of exosomes in cosmetics grows, regulatory bodies will need to establish guidelines and safety standards to ensure product safety and efficacy. Companies will need to navigate these regulations and conduct appropriate testing and clinical trials. Increasing consumer awareness and education about the benefits and science behind exosome-based products will be essential for their acceptance in the cosmetic market.

Utilizing exosomes in drug delivery systems holds great promise owing to their inherent capacity to shuttle biomolecules such as proteins, nucleic acids, and lipids across biological barriers. However, there are some challenges associated with it. Exosomes are complex extracellular vesicles derived from various cell types, and their composition may vary depending on the cell of origin and physiological conditions. This complexity makes it challenging to standardize the production and separation methods and master their precise biological mechanisms. Purifying exosomes presents another significant challenge in their utilization. Existing methods often result in heterogeneous preparations with contamination from other extracellular vesicles and proteins, affecting the reproducibility and purity of the exosome population. Exosomes are sensitive to environmental factors such as temperature and pH which can affect their stability and integrity and also possess a tendency to aggregate. Developing a method for long-term storage without compromising their biological activity is essential for practical applications and persists as a big challenge in exosome research. Exosomes originating from various cell sources might trigger immune responses in recipients, potentially resulting in adverse effects or clearance by the immune system. It is imperative to comprehend the immunogenicity profile of exosomes and devise strategies to alleviate reactions, which is crucial for their clinical application.

Author contributions

HS: Collection of information and writing, RA: Writing the manuscript, KST: Reviewing the manuscript, SD: Validating, reviewing and editing the manuscript

Ethical statement

This material is the authors' own original work, which has not been previously published elsewhere.
The paper is not currently being considered for publication elsewhere.
The paper reflects the authors' own research and analysis in a truthful and complete manner.
The paper properly credits the meaningful contributions of co-authors and co-researchers.
The results are appropriately placed in the context of prior and existing research.
All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

CRediT authorship contribution statement

Harsha Sreeraj: Writing – original draft, Data curation, Conceptualization. **Anukiruthika Rajakumar:** Data curation. **Tamilselvi K.S.:** Writing – review & editing, Project administration. **Subha Damodharan:** Writing – review & editing, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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