Exploring the Potential of Stem Cell-Based Therapy for Aesthetic and Plastic Surgery

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***Abstract*—Over the last decade, stem cell-associated therapies are widely used because of their potential in self-renewable and multipotent differentiation ability. Stem cells have become more attractive for aesthetic uses and plastic surgery, including scar reduction, breast augmentation, facial contouring, hand rejuvenation, and anti-aging. The current preclinical and clinical studies of stem cells on aesthetic uses also showed promising outcomes. Adipose-derived stem cells are commonly used for fat grafting that demonstrated scar improvement, anti-aging, skin rejuvenation properties, etc. While stem cell-based products have yet to receive approval from the FDA for aesthetic medicine and plastic surgery. Moving forward, the review on the efficacy and potential of stem cell-based therapy for aesthetic and plastic surgery is limited. In the present review, we discuss the current status and recent advances of using stem cells for aesthetic and plastic surgery. The potential of cell-free therapy and tissue engineering in this field is also highlighted. The clinical applications, advantages, and limitations are also discussed. This review also provides further works that need to be investigated to widely apply stem cells in the clinic, especially in aesthetic and plastic contexts.**

***Index Terms*—Stem cells, self-renewable, clinical applications, aesthetic medicine, grafting, plastic surgery.**

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Abbreviations

ESCs	Embryonic stem cells
BMMSCs	Bone marrow-derived stem cells
ASCs	Adipose-derived stem cells
FDA	Food and Drug Administration
iPSCs	Induced pluripotent stem cells
SVF	Stromal vascular fraction
MSCs	Mesenchymal stem cells
UBSCs	Umbilical cord blood stem cells
WJSCs	Wharton's Jelly stem cells
ISCT	International Society for Cellular Therapy
CAL	Cell-assisted lipotransfer
MSCs	Mesenchymal stem cells
CXCL5	Chemokine ligand 5
CXCL12	Chemokine ligand 12
TNF- α	Tumor necrosis factor α
IL8	Interleukin 8
PLGA	Lactic-co-glycolic acid
FGF-2 F	Fibroblast growth factor-2
PDGF	Platelet-derived growth factor
TGF	Transforming growth factor
VEGF	Vascular endothelial growth factor
GMP	Good manufacturing practices

I. Introduction

CURRENTLY, stem cell research and stem cell-based therapies are considered innovative and promising treatments for many diseases regarding their self-renewable, multipotent differentiation, and growth factor secretion properties. *In-vitro* and *in-vivo* investigations are raising support for the utilization of stem cells in therapeutic applications. The global market for stem cells was USD 7.4 billion in 2017, which is estimated to reach USD 14.8 billion by 2022, with a 14.7% compound annual growth rate (CAGR) in a period of 2017–2022 (www.bccresearch.com). Whereas, the global stem cell therapy market is USD 187 million in 2021 and estimated to reach USD 401 million by 2026 with 16.5% CAGR (www.marketsandmarkets.com).

There are 8698 studies of ongoing and completed clinical trials that were found by using "stem cell" in the database of the U.S. National Institutes of Health, which are registered in clinicaltrials.gov (accessed on 13 October 2021). Meanwhile, more than 480000 studies including "stem cell" have been published and recorded in PubMed, which are researching the characteristics, harvest, isolation, culture, storage, and applications of stem cells.

The progress in the preparation of stem cells has been developed and standardized to be safe and effective for using in clinical research [1]–[3]. Thus, despite being discovered for only two decades, stem cells have been widely used in tissue engineering and also used as immunomodulators including cardiac-related diseases, autoimmune diseases, and neurodegenerative diseases. Recently, the utilization of stem cells has become more and more common in cosmetics and plastic surgeries [1], [4], [5]. Regarding plastic surgeries, stem cells have been applied for soft tissue reconstruction and augmentation, skin rejuvenation, facial rejuvenation, scar improvement, and anti-aging therapy [6]–[8]. Traditionally, embryonic stem cells (ESCs) are described as better regenerative cells that are used for repairing damaged tissue to correct defects [9]. However, the use of ESCs is associated with ethical concerns including origin, harvest, and isolation process as well as higher cancer tumor initiation efficiency [10]. Therefore, alternative sources of stem cells, such as bone marrow-derived mesenchymal stem cells (BMMSCs), adipose-derived stem cells (ASCs), blood stem cells, and muscle stem cells have been investigated. Most investigations agreed that those adult stem cells have strongly multipotent differentiation, easy harvest, and isolation, huge amount as well as various origins and their application methods [1], [11]–[14]. The stem cell-based therapies can bring some promising results to support the application of stem cells in clinical treatment in the near future [1], [15], [16].

Stem cell therapies are over-marketed directly to consumers on the Internet and social media. [17]–[19]. There have been broadened and exaggerated claims about their ability to rejuvenate the skin as a safer, more proven, and effective alternative with reduced time treatment [17]. In 2017, 432 companies in the United States online sold unproven stem cell-based products for the treatment of unspecified skin diseases, cosmetic-related concerns, or aging improvement [20]. Additionally, there are 87% out of 243 websites advertising stem cell therapies failed to mention either the possibility or the efficiency, and 75% of websites have not demonstrated about general risks of stem cell treatment or the disapproval of the Food and Drug Administration (FDA) for many diseases [21]. Another study reported that less than 30% out of 1091 websites have reported the outcome of patients as well as side effects after treatment [22]. The support of stem cells to tumorigenesis is currently still controversial, therefore patients should be provided with all the relevant information, including benefits, risks, outcomes, and cost of therapy before deciding on treatment.

Meanwhile, Dr. Nayar and his group conducted a cross-sectional survey that addressed the attitudes and perceptions of using stem cells for aesthetic surgery [18]. The survey had been done by a list of questionnaires sent to 4592 members of the American Society of Plastic Surgeons and the American Society for Aesthetic Plastic Surgery. However, about 16.7% of responses were received. Most respondents were in solo practice (53.2%) and small group practice (18.0%). The data analysis showed that the risks and benefits of stem cell therapies are insufficient, thus current advertising of aesthetic uses of stem cells is inappropriate and unethical. During the treatment, consumers lacked informed consent, which must be provided by physicians with a scientific-based understanding of stem cell processing in aesthetic and plastic surgery [18]. Jordan *et al.* have agreed with the report from Dr. Nayar's group [17]. Regulation and standards of current aesthetic stem cell therapies do not exist, which requires the FDA and professional societies to establish a regulatory structure for stem cell preparation and their application in aesthetic and plastic surgery [18]. Among these issues, in this review, we highlight a better understanding of using stem cells and small extracellular vesicles/exosomes (types, applications, advantages, and disadvantages) for aesthetic purposes for 8 years (2014–2021) by accessing a major scientific database.

II. Types of Stem Cells for Aesthetic Uses and Plastic Surgery

Stem cells are a subset of undifferentiated cells which are characterized by self-renewable and multipotent properties [23]. Different types of stem cells are currently studied for their applications in many diseases, including aesthetic medicine and plastic surgery, especially induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs). Several studies using iPSCs as anti-aging medicines due to the stimulation of collagen and elastin synthesis (Table I and Fig. 1) [24], [25]. However, the clinical application of iPSCs in aesthetic dermatology hasn't been achieved. Therefore, MSCs are considered a better alternative source for aesthetic medicine and plastic surgery in the clinical context. Whereas MSCs are present in high amounts in several tissues, methods of isolation and expansion for each cell type as well as appropriate devices for MSCs expansion are automated [1].

MSCs are derived from bone marrow, umbilical cord, adipose tissue, muscle, cartilage, and blood [47], [48]. Stem cells from

TABLE I
CLASSIFICATION OF STEM CELLS FOR AESTHETIC USES AND PLASTIC SURGERIES

Stem cells	Stem cell origin	Aesthetic uses	Plastic surgeries
Adipose-derived stem cells	Adipose tissues	Scar reduction [26, 27] Anti-aging [28, 29] Anti-wrinkles [30] Hair loss [31]	Breast augmentation [32-34] Breast reconstruction [35, 36] Facial lipoatrophy [37] Facial augmentation [38] Gluteal augmentation [39] Bony reconstruction [40, 41]
Bone marrow-derived mesenchymal stem cells	Bone marrow	Scar reduction[42] Anti-aging [25] Systemic sclerosis (*NCT00040651**)	Bony reconstruction [43] Cartilage formation [44, 45]
Umbilical cord blood stem cells	Umbilical cord blood	Burns (*NCT02672280**) Psoriasis vulgaris (*NCT02491658**)	No application
Wharton's Jelly stem cells	Umbilical cord	Skin generation [46]	No application
Bulge stem cells	Hair follicles	Hair loss, vitiligo, and hair graying [7]	No application

Note: ∗selected studies registered on clinicaltrial.gov.

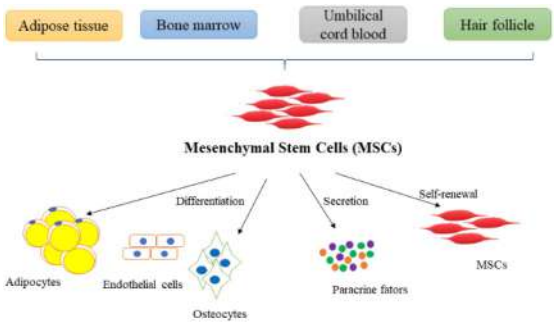

Fig. 1. Variety of stem cells used in aesthetics and plastic surgery. Mesenchymal stem cells (MSCs) can be isolated from various tissues, such as adipose tissue, bone marrow, umbilical cord, and hair follicle, and differentiated into adipocytes, endothelial cells as well as osteocytes. Besides multilineage differentiation, MSCs also exhibit self-renewal and paracrine factor secretion properties.

different origins can be used in an autologous or allogenic manner [47]. Among MSCs, ASCs are the most popular stem cells utilized in aesthetic dermatology [48]–[50]. *In-vitro*, ASCs can be used alone or co-treatment with a stromal vascular fraction (SVF) on the treatment of skin defect repair, such as reduction of facial scar, wrinkles, antioxidant and inhibition of melanin production resulting in skin whitening [26], [28], [51]–[55]. Those stem cells can be transplanted with a scaffold or injected subcutaneously to the scars. An investigation had proven that a higher number of ASCs showed higher improvement in scar reduction as compared to the low density of ASCs [48]. Besides, the use of platelet-rich plasma as an adjuvant to ASCs was supposed to enhance the proliferation and differentiation of ASCs, thus improve the autologous fat graft outcome [56], [57]. Additionally, the combination of ASCs with other methods such as carbon dioxide laser resurfacing and cultured fibroblasts demonstrated the anti-aging and skin rejuvenation properties [30], [58], [59].

Another source of MSCs frequently used in aesthetic and plastic surgery is BMMSCs. As compared to ASCs, the progress of BMMSCs preparation is reduced cost, more invasive, and harmful to patients [60]. However, BMMSCs have shown higher self-renewability, differentiation, and immunoregulation ability. After intravenous administration, BMMSCs migrate to wound sites and promote the pro-collagen synthesis within 7–8 weeks or 16–20 weeks in case of chronic wounds [42], [61].

Other stem cell sources are derived from umbilical cord blood (UBSCs), Wharton's Jelly (WJSCs), and amniotic fluid stem cells [48], [62]. Those stem cells have shown high efficiency

in skin regeneration and immune compatibility. However, it is unable to obtain a sufficient number of cells for the treatment [63]. WJSCs may stimulate skin wound healing by paracrine effects that increase gene expression which is related to cell survival, proliferation, and migration [46]. Lastly, bulge stem cells, which are relocated in hair follicles, are being investigated for the treatment of hair loss, androgenic alopecia, vitiligo, and hair graying [7].

III. The Application of Stem Cells for Aesthetic Purposes

Stem cells are well-known for their regenerative potential that is attractive for tissue engineering applications. In aesthetic medicine and plastic surgery, stem cell therapies are studied in the treatment of severe conditions such as lipodystrophy, psoriasis vulgaris, extensive burns, systemic sclerosis, epidermolysis bullosa, and radiotherapy tissue damage. Stem cells can be applied in soft tissue augmentation and rejuvenation, scar reduction, hair regeneration, and anti-aging therapies. Among MSCs, the most popular and notable used in aesthetic surgery is autologous fat grafting containing ASCs or the mixture of ASCs and SVF. The use of SVF is simple and cheap due to the lack of isolation and expansion of stem cell-based products as compared to homogenous ASCs. However, SVF is used in a single procedure and showed the unclear mechanism of the wound healing process. Even though, both concentrated ADCs population and SVF were used in many studies and shown promising results for aesthetic purposes (Table II).

A. Soft Tissue Augmentation

Soft tissue augmentation such as breast augmentation and reconstruction, gluteal augmentation, facial contouring has been reported to use autologous fat grafting. In recent years, external volume expansion of fatty tissues has shown a great aesthetic outcome and patient satisfaction after grafting. Carlo *et al.* described a simple, reliable, and inexpensive expansion system for autologous fat, that provided the environment locally for cell proliferation and angiogenesis [64]. The systematic review supported the efficacy and patient satisfaction of autologous fat injection for breast augmentation [33], [65]–[67]. Li *et al.* reported a case of 105 patients who had significant improvement in breast size, shape, and natural appearance [34]. Zheng *et al.* and Coleman SR *et al.* also agreed with the safety and efficacy of fat transplantation in breast augmentation by a long-term follow-up and revisited studies [68], [69]. The underweight women were also suitable for fat grafting procedures which showed a similar safety and success rate as compared to normal ones [70].

Breast reconstruction is more challenging than normal augmentation, especially after breast mastectomy and radiation-induced damage following breast cancer surgery. External breast expander along with autologous fat transfer is reported as a safe, economical, effective, and minimally invasive method for breast reconstruction [71], [72]. Systematic reviews also showed the oncological and radiological safety and patient satisfaction of fat grafting in breast reconstruction [35], [73], [74]. In addition, there is no increase in breast cancer recurrence rate or development potential of other cancers after lipofilling in breast reconstruction, which supports the safety of therapy [75]. Fat grafting combined with internal tissue expansion can be a promising technique for total breast reconstruction with minimal risks [76], [77]. Besides, the fat grafting technique is used for gluteal augmentation [39], [78]. A systematic review with meta-analysis showed that the subcutaneous and intramuscular injection of lipoaspirate is safe and effective to contour and reshape the gluteal region [39]. Real-time ultrasound can assist to correct the plane during gluteal fat injection, avoid injuring the deep vessels and risks of the method [79]. Another soft-tissue augmentation is facial contouring. Volume loss in the face may cause by facial lipodystrophy or aging. The injection volumes of facial fat grafting are varied regarding methods and infection sites. Only 50% of fat cells have survived after transplantation, which requires the development of efficient techniques in facial grafting [6], [80].

A systematic review with 19 articles and more than 500 participants on the average fat volume that depends on the recipient site and patient's need was reported [38]. The mean volume of fat injection was 16.9 ml [80]. A larger meta-analysis of 52 studies confirmed the safety and efficacy of autologous fat transferred for facial surgery. The study reported high patient satisfaction (91.1%) in total [81]. Some risks should be noticeable such as asymmetry, necrosis, injection, and acne formation after facial grafting [80].

B. Scar Reduction

Wound healing is a natural response process of the body in an attempt to recover the normal function and structure. Wound healing involves two overlapping processes, which are regeneration and repair, and typically results in scar formation. Promoting a more regenerative process is an effective way to reduce the scar problem [82].

Stem cell-based therapy has shown the improvement of scar reduction. Several investigations have reported the role of stem cells in the improvement of skin quality such as dermal thickness, collagen synthesis, and wrinkle reduction. Hemphill *et al.* reported human amniotic stem cells, and membrane matrix significantly decreased pain and scars after an intractably painful surgery [83]. Nano-fat which consists of ASCs can reduce the scar size, color and improve the skin [84]. Applying an ASC sheet that reduces the scar formation and promotes new skin generation which is mediated through secretion of paracrine factors such as hepatocyte growth factor and C1q/TNF-related protein 3 that decreased the recruitment of macrophages into the wound site [26]. Mechanically, mesenchymal stem cells are able to home at the injury sites and highly express wound healing cytokines such as platelet-derived growth factor, insulin-like growth factor 1, TNF-α, and IL8, resulting in regulation of inflammatory cells, downregulation fibrosis [85]. Besides, MSCs can differentiate and transdifferentiate into dermal or epidermal cells [86]. Human corneal stem cells suppress corneal scarring in the mouse model even after general cryopreservation [87].

TABLE II
THE APPLICATION OF STEM CELLS IN AESTHETIC USES AND PLASTIC SURGERY

The application	Stem cells	Aesthetic uses	Plastic surgery	Ref.
Breast augmentation	Adipose-derived stem cells		x	[34]
	Bone marrow-derived mesenchymal stem cells		x	[98]
Breast reconstruction	Adipose-derived stem cells		x	[68, 73, 74, 76, 77]
Gluteal augmentation	Adipose-derived stem cells		x	[39, 78]
Facial contouring	Adipose-derived stem cells		x	[6, 38, 80]
	Bone marrow-derived mesenchymal stem cells		x	[99]
Facial rejuvenation	Adipose-derived stem cells	x		[29, 100]
Hand rejuvenation	Adipose-derived stem cells	x		[101, 102]
Bony reconstruction	Adipose-derived stem cells		x	[40, 41]
	Bone marrow-derived mesenchymal stem cells		x	[43]
Cartilage formation	Bone marrow-derived mesenchymal stem cells		x	[44]
Scar reduction	Adipose-derived stem cells	x		[26, 84]
	Bone marrow-derived mesenchymal stem cells	x		[86, 103, 104]
	Amniotic stem cells	x		[83]
	Corneal stem cells	x		[87]
Hair growth	Adipose-derived stem cells	x		[31, 89-91]
	Bone marrow stem cells	x		[88]
	Bulge stem cells	x		[7]
Anti-aging	Adipose-derived stem cells	x		[29, 97, 105]
	Bone marrow-derived mesenchymal stem cells	x		[28, 96]

C. Hair Growth

The hair cycle is promoted by various growth factors which can be secreted by mesenchymal stem cells. BMMSCs and ASCs have successfully promoted hair growth *in-vitro* and *in-vivo* studies, which activate dermal papilla cells, increase the proliferation rate, and the conversion of the old stage to the younger stage of hair follicles [4], [88]. In 2017, a small study with 31 patients had used SVFs and SVFs-enriched fat grafts subcutaneously administered into the scalp. The study showed an increase in the number of hairs as compared to untreated patients about 31 hairs/cm^2 [31]. Similarly, another study with 20 patients using ASCs showed improvement in hair growth parameters and new hair generation rate [89]. In addition, secreted growth factors by stem cell-conditioned medium have significantly improved the hair length, hair density as compared with pre-treated values [90], [91].

D. Aging

Aging is a natural process the skin has to undergo due to the passage of time. Aging skin reduces skin elasticity, alteration of skin thickness, and collagen organization, resulting in wrinkles. Besides intrinsic aging, there are exterior factors that contribute to the acceleration of the skin aging process [92], [93]. For example, the sun-exposed area of skins experiences dyspigmentation, laxity, yellow hue, wrinkles, leathery appearance, and cutaneous malignancy due to frequent exposure to ultraviolet (UV) light [94]. Thus, UV and other extrinsic factors can cause several damages to human skin, such as irregular pigmentation, change skin color and enhance wrinkles on the skin [92], [93].

Stem cells are expected to reverse the action of these extrinsic factors on the skin [95]. Stem cells promote the regeneration of aged tissues and modulate the immune system via the secretion of growth factors, cytokines, chemokines, and angiogenic factors [7]. BMMSCs and ASCs have been studied and applied for alteration of aging [28], [29], [96], [97]. Autologous ASCs-enriched fat graft showed the decrease of elastosis, whereas increased the development of new oxytalan supported to blood vessels, which resulted in reorganizing of reticular dermis and papillary dermis [29]. Similar results were also seen by the injection of SVFs and isolated MSCs. Those effects were represented a rejuvenation potential of stem cell-based products [29]. Besides, ASC is considered an aging reverting agent [97]. Stem cells have shown high potential in the treatment of various conditions in aesthetic medicine and plastic surgery. However, there are limited preclinical and clinical data available to support the FDA for approval of the use of stem cell therapy in humans.

IV. Stem Cells Exosome in Aesthetic and Plastic Surgery

Exosomes are nano-sized extracellular vesicles (30–100 nm in diameter) that contain proteins, mRNAs, and miRNAs, metabolites, and are encapsulated in phospholipid bilayer when release into the extracellular environment. It can be found in different cell types, such as blood cells, endothelial cells, immunocytes, and stem cells [106]. Exosomes are believed to be able to regulate the bioactivities of recipient cells and act as a mode of cell communication while circulating in the extracellular space.

Stem cell-derived exosomes are commonly isolated from the conditioned medium of the culture with pre-conditioning of cells to improve the yield of exosomes. In brief, the isolation protocol of exosomes can be divided into few methods: ultracentrifugation-based techniques, size exclusion techniques, immunoaffinity binding techniques, precipitation, or microfluidic-based techniques (Fig. 3) [107]–[114]. In aesthetic medicine, exosome-mediated intercellular communication is essential to maintain cellular functions and tissue homeostasis [115], [116]. As the content of exosomes varies one from another by different sources, stem cell-derived exosomes are found to be an important factor that shows regenerative properties. Additionally, besides its shortcomings in production with large scale, cell-free therapy is supposed to easily access and to be safer with lower immunogenicity and higher stability as compared to cell-based therapy [117]. Therefore, stem cell-derived exosomes can be potential biomarkers as alternative options in regenerative medicine and aesthetics as a cell-free therapeutic solution.

A. Rejuvenation of Skin

Skin disorders, photoaging, and even wound can all contribute to skin irregularities such as wrinkles and acne scars, pigmentation changes on the face and elsewhere on the body. Kim *et al.* demonstrated that treatment using umbilical cord blood mesenchymal stem cell-derived exosomes promotes wound regeneration. The expression of collagen I and elastin are upregulated on the human skin sample. Further analysis on the exosome also reveals various growth factors content associated with skin rejuvenation such as EGF and bFGF [118].

Regarding photoaging, iPSC-derived exosomes were used to treat induced photoaged human dermal fibroblast (HDF). *In-vitro* results show that exosomes derived from iPSC were able to upregulate the expression of collagen type 1 and suppress the damages of HDFs as well as overexpression of matrix-degrading enzymes caused by UVB [119]. Another study related to photoaging treatment with human umbilical cord MSC-derived exosome showed similar regenerative effects by reducing the wrinkles, alleviating the histopathological changes, and promoting the expression of extracellular matrix constituents such as Collagen 1 and elastin [120].

The remodeling process of wound healing often led to the formation of scars that are obvious, unsightly, or disfiguring, which are affecting the appearance of the patient. Studies showed that alteration in the abundance of collagen I and collagen 3 could significantly affect the structural formation of scars [121]–[125]. Thus, there is a need of controlling the ratio of collagen content to achieve minimal scar formation. Li hu *et al.* showed that treatment of incisional wound model with adipose mesenchymal stem cell-derived exosome was enhanced collagen I and collagen III expression at the early stage to promote wound healing and inhibit collagen expression in the later stage of wound healing to reduce the scar formation [126]. Another finding supported the results aforementioned where the treatment of incisional wound model with adipose mesenchymal stem cell-derived exosome

has decreased the size of scars by reducing the collagen deposition and transition of collagen III to collagen I ratio from the scar-promoting ratio into an anti-scar ratio that was often observed in fetal wound healing [127]. Besides, MSC's ability to differentiate into endothelial lineage in order to promote the migration in a hypoxic condition, which also considerably supports tissue regeneration [128].

B. Hair Follicle Regeneration

In the study reported by Zhou *et al.*, exosomes were isolated from dermal papilla cells that were further injected on hair follicles to promote hair regeneration. Results showed that the injection of DP cell-derived exosomes triggers the upregulation of β-catenin and Sonic hedgehog (Shh) in the skin of mice. In addition to that, the anagen phase of mice was accelerated while the catagen stage was delayed [129]. Another study of Liu *et al.* co-culturing isolated ASCs with DP spheres also reported optimistic results in HF cellular arrangement for hair regeneration [130]. The Wnt/β-catenin pathway is known to be essential for HF growth and cycling, in anagen, β-catenin stabilizes and interacts with Lef/Tcf transcription factors to regulate the expression of genes that are responsible for HF growth [125], [131]. In the adult skin, Shh protein is needed for hair follicle morphogenesis and also regulating the follicular growth as well as cycling by mesenchymal and epithelial cells of the hair follicle [132].

Aside from DP cells, stem cell exosomes are gaining more attention for hair regeneration treatment as the stem cell-based treatment getting mature gradually. Wu *et al.* demonstrated that exosomes were isolated from ASCs to promote the maturation of hair follicles and trigger the growth of hair. Two-three weeks after the graft chamber assay on nude mice, significantly higher regenerated hair and hair follicles were observed. Histologically, the hair follicles in the treatment group (ASC exosome+ EC+ DC) are relatively mature as compared to the control (EC+ DC) only [133]. A similar study also reported that MSC-derived EV had enhanced DP cell proliferation and migration, intradermal injection of the exosome on mice also promotes the conversion of telogen stage into anagen stage with increased the expression of wnt3a, wnt5a, and versican [130]. In addition, a microneedle patch device was developed by Yang *et al.* delivered MSC-derived exosomes together with small molecular drug UK5099, to promote the regrowth of hair. The results showed a positive effect after two rounds of administration on mouse models, with the promotion of pigmentation and hair regrowth observed in a 6-day time [134].

V. Stem Cells Tissue Engineering in Plastic Surgery

Tissue engineering is a multidisciplinary field that combines biology, engineering, biomaterial, and clinical application to create, modify, grow, and sustain live tissue. It is indispensable for tissue engineering's strategy to supply cells with an environment regulating their proliferation as well as differentiation, which was created by biomaterial scaffolds and bioactive molecules [135]. Meanwhile, traditional surgical approaches for tissue reconstruction focused mainly on autologous and allogenic tissue transplantation or alloplastic replacement with synthetic material. Such methods are hindered by the low availability of suitable biomaterial, as well as the donor site morbidity of auto- or allogenic transplantation [136]. In tissue engineering, the lack of donor cells and tissues is a major challenge. This issue could be solved by using autologous adult stem cells in allogenic transplantation [137]. As discussed earlier, stem cells are capable of self-renewal and multilineage differentiation [138]. Hence, stem cells are particularly beneficial for aesthetic and plastic surgery (Fig. 4).

VI. Applications of Stem Cell Engineering

The practice of plastic surgery is gradually evolving. As technology advances, the materials, tools, and concepts drive the development of various applications of tissue engineering in the field of plastic surgery [139]. Both tissue-specific scaffolds and signaling molecules play an essential role in differentiating stem cells into the required cells and using them effectively to construct three-dimensional (3D) tissues. Besides, a rising number of studies have suggested that using biochemical in combination with biophysical cues as exterior stimulation has a great impact on the adherence, proliferation, and differentiation of stem cells. Biochemical cues have been used to modulate stem cell growth for years despite its difficulty of control for the long term. Growth factors and their derivatives, including VEGF, TGF β, or FGF as well as small bioactive molecules, including oxygen, nitric oxide, and metallic ions are added to the scaffold in order to create a more appropriate environment for promoting stem cell concentration and duration [140]. Compared to biochemical cues, biophysical cues such as pore size, stress relaxation, stiffness, and topography are more cost-effective and easily defined with a longer lifetime [141]. Table III has summarized the currently available biomaterials and biomolecules used in stem cell tissue engineering.

A. Adipose Augmentation

Yoshimura *et al.* [152]compared the results of breast augmentation with cell-assisted lipotransfer (CAL) to those of classic lipotransfer procedures. It was found that the CAL group had a higher breast circumference due to less graft atrophy, which they attributed to the existence of ASCs [152]. However, CAL is not considered to be universally beneficial, due to the possibility of an increase in aberrant mammographic effect [69], [153], [154]. To answers such questions, more research is required to study the long-term safety of stem cell-assisted transplantation.

Besides CAL, acellular dermal matrix (ADMs) is also a frequently employed technique in primary [138] and secondary [155] breast reconstruction. ADMs allow the surgeon to adjust the pocket to allow the expander or permanent implant to be placed precisely, resulting in ideal breast contour and landmarks [156]. ADMs also help to decrease rippling and wrinkling, provide extra tissue support, and promote the healing process.

TABLE III
CURRENTLY AVAILABLE BIOMATERIAL AND BIOMOLECULE FOR STEM CELL TISSUE ENGINEERING

Type of Biomaterials/biomolecules	Properties	Reference
Collagenous microbeads	• Allow ex vivo proliferation and differentiation on particles that are small enough to be injected	[142]
Type I collagen scaffold	• Exhibit excellent cellular compatibility and allows in vivo replacement of damaged tissue	[143]
Hyaluronic acid-based spongy scaffolds	• Stable cell carriers and have the potential to generate volume retaining tissue	[144]
Decellular matrix	• Facilitate proliferation and viability.	[145]
Injectable poly (lactic-co-glycolic acid) (PLGA) spheres	• Noninvasive soft tissue fillers.	[146]
Fibroblast growth factor-2 (FGF-2)	• Proliferation potential on human fibroblasts	[147]
Platelet-derived growth factor (PDGF)-AB	• Proliferation potential on human adipose-derived stem cells and human dermal fibroblasts.	[148]
Transforming growth factor (TGF)-beta 1	• Proliferation potential on human adipose-derived stem cells and human dermal fibroblasts.	[148]
Vascular endothelial growth factor (VEGF)	• Improves implant biocompatibility • Promotes capillary formation	[149, 150]
Granulocyte/macrophage colony stimulating factor	• Angiogenesis-related cytokine	[151]
Stromal-derived factor-l alpha	• Angiogenesis-related cytokine	[151]
Hepatocyte growth factor	• Angiogenesis-related cytokine	[151]

B. Skin Substitutes

Over the years, aside from innovations in surgical technique, the number of skin substitutes available for burn reconstruction and treatment of acute and chronic wounds has increased dramatically thanks to advances in tissue engineering [139]. Conventionally, keratinocytes and/or fibroblasts were based on natural or synthetic dermal scaffolds for drafting. Despite several skin products based on the aforementioned technology are available, the lack of self-sustaining progenitor cells has hindered the long-term clinical success of these products [157]. Recently, human ASCs were employed to create three-layered skin composites including epidermal, dermal, and hypodermal elements [158]. Results showed that appropriate epidermal formation and

stratification were observed for each type of substitute. Despite such encouraging discoveries, fully functional skin regeneration remains a long way off. Many other integumentary elements contribute to skin homeostasis by performing vital functions such as mechanosensation, thermoregulation, and pigment synthesis, and complex paracrine interactions between keratinocytes and fibroblasts are only beginning to be understood [159], [160]. Furthermore, the extracellular matrix regulates cellular activity through complex systems that must be understood to fabricate replacement skin [161], [162].

C. Artificial Skeletal Muscle

Skeletal muscle, in addition to fat and skin, plays a vital role in plastic surgery. However, the development of artificial skeletal muscle faces the challenge of recapitulating complex micro-electrical and mechanical networks [163]. Due to the limited efficacy of direct injection of donor myoblasts [164], [165], most current techniques involve myoblasts or myogenic stem cells planted onto biocompatible scaffolds. Mechanical and electrical stimulation have boosted the myogenic potential of *in vitro* constructs [165], improve the functional diversity of skeletal muscle. Researchers have used a multicultural system of myoblasts, embryonic fibroblasts, and endothelial cells for "prevascularization" *in vitro* to improve the vascularization of synthetic muscle. The artificial skeletal muscle was transplanted into immunocompromised mice, they showed better integration, survival, and vascularization than constructs maintained without one of the three starting cell types [166]. Huang *et al.* reported considerable improvement in innervated muscle when treatment with FGF9-transplanted therapy. This result was consolidated by a cross-sectional area investigation that muscle fibers were successfully re-innervated without any muscular atrophy [14].

VII. Advantages of Using Stem Cells for Aesthetic Uses and Plastic Surgery

Stem cell-based therapies are recently gained scientific attention and attraction in the field of plastic surgery that focuses on the restoration and enchantment of defective cells, tissues, or organs. Several studies have demonstrated that stem cells supported scar improvement, wound healing, skin rejuvenation, soft tissue augmentation, and hair growth [32], [37], [40], [167]–[174]. Adult stem cells such as ASCs are particularly useful due to ease of harvest with minimal invasion, similar differentiation potential to other MSCs, and have a greater proliferation rate in the expansion culture. The process of harvest, isolation, characterization, expansion, storage and transport condition of stem cell-based products were established and validated to ensure the quality of product using in clinical applications [1].

Stem cells are widely classified into totipotent, pluripotent, multipotent, oligopotent, and the last, unipotent stem cells, based on their self-renewability and differentiation potential. The developmental potency of each type of stem cell is decreased with each step of specialization, which means an iPSC is capable of differentiating into more types of cells than an MSC [175]. To achieve the unification between studies about stem cells, in 2006, the International Society for Cellular Therapy (ISCT),

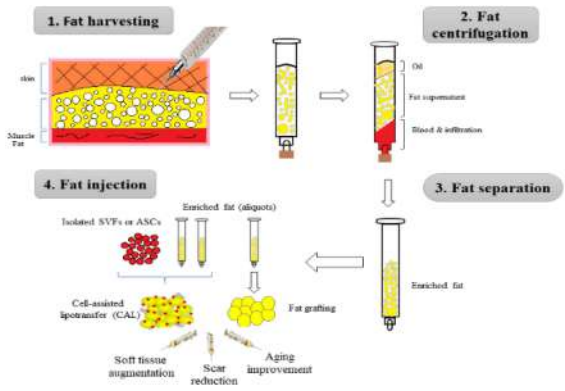

Fig. 2. Stem cell-assisted lipotransfer and fat grafting procedures for aesthetic uses and plastic surgery. SVFs- stromal vascular factions; ASCs- adipose-derived stem cells. After going through the stem cell preparation procedures including harvest, centrifugation, and separation, the autologous fat grafting containing ASCs or SVF will be used to reinject into the specific sites of the body itself for several purposes, such as soft tissue augmentation, scar reduction, and aging improvement.

Canada has released the minimal criteria for defining human MSCs based on plastic-adherence, antigen expression as well as multilineage differentiation capacity such as adipocytes, osteoblasts, chondroblasts in the presence of stimulating factors [176]. In addition, closed automated devices for large-scale isolation and expansion of stem cells were commercially developed. The protocol of BMMSCs or ASCs manufacturing process was fully described, that contributes to producing the stem cells product which satisfied the Good Manufacturing Practice (GMP) standard. Stem cell banking and storage conditions were also investigated to maximize cell viability and quality with effective costs. All those factors support the use of stem cells in clinical applications as well as in aesthetic medicine and plastic surgery [1].

Different stem cells can be applied in a variety of defect conditions. Fat grafting and CAL technique had been investigated for using in facial lipodystrophy, lower limb atrophy, breast augmentation, and reconstruction (Fig. 2) [39], [66], [67], [69]. Fat grafting was quite simple and widely used in plastic surgery. However, the lack of standard protocol, variable reabsorption rate, and partial necrosis results in the inconsistency of the long-term effects [177]. CAL consists of ASCs and SVFs, that showed enhancement of cell viability after the transplantation [36], [167]. Besides, pre-differentiated *in-vitro* stem cells can be used to decrease scar formation [27]. Co-administration stem cells by injection and fat grafting decreased the time in treatments and costs as compared to CAL. ASCs also showed high potential in the suppression of scar formation, promotion of collagen synthesis, improvement of skin color, and anti-aging ability.

Biomaterials are being developed, which are safer, more effective, biocompatible, and easily injectable into patient sites [50]. ASCs or BMMSCs were loaded on scaffolds combined with different growth factors which support cell regeneration and differentiation at the implantation site. Bone morphogenetic protein 2 or 7 and β-tricalcium phosphate together with ASCs

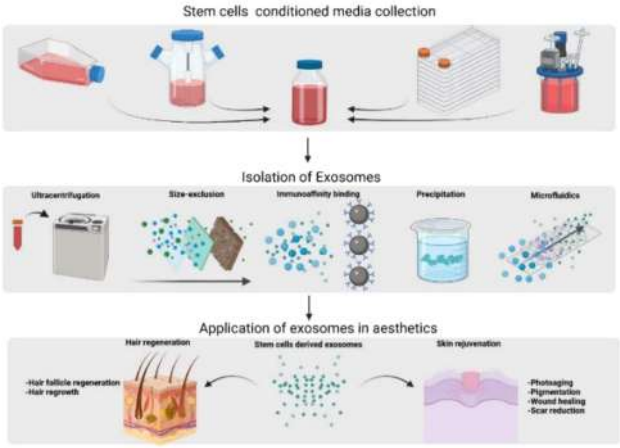

Fig. 3. Isolation and utilization process of Exosomes. Stem cells conditioned media were collected at the end of culture and proceed for downstream isolation processes. Current isolation methods of stem cell exosomes included ultracentrifugation-based technique, size-exclusion-based technique, immunoaffinity binding based technique, precipitation technique, and microfluidic-based technique. After the isolation process, the purified exosomes were then utilized as a potential alternative for cell-based treatment in aesthetic medicine and plastic surgery (Created with Biorender.com).

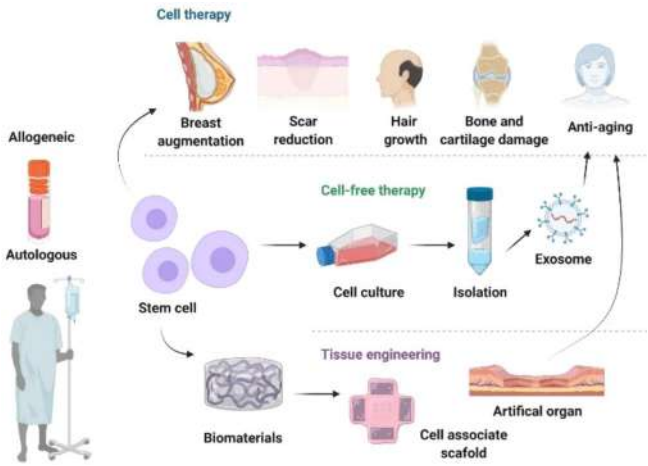

Fig. 4. Potential of stem cell-based applications in aesthetic and plastic surgery. Stem cell-based therapies include breast augmentation, scar reduction, or anti-aging. Stem cells also provide biomaterials for allogenic transplantation in tissue engineering (Created with Biorender.com).

were used for bone regeneration. Indeed, transforming growth factor-beta seeded on ASCs scaffold has been demonstrated to promote cartilage formation. Therefore, the modification and additional growth factors in the scaffold can support cell survival and drive the differentiation potential of the cells.

VIII. Limitation of Stem Cells Therapy for Aesthetic Uses and Plastic Surgery

Even though stem cell therapies have shown promising results in preclinical and clinical studies. However, there are still some limitations of stem cells for aesthetic uses and plastic surgery. Currently, the FDA has restricted the approval of stem cell-based products for aesthetic medicine and surgery due to insufficient data from animal and clinical studies. The number of clinical trials using stem cells for cosmetic treatment which are registered and available on clinicaltrials.gov is still limited. Therefore, unapproved stem cell therapies can be harmful to patients. The potential risks should be concerned, including the reactions at the administration site, rejection reaction, unexpected migration into other sites, differentiation into inappropriate cell types, non-efficiency, and risk of cancer initiation [178]–[182]. Patients can get allergies to the components containing in the culture media, such as an antibiotic (vancomycin, amikacin) or bovine serum. The abovementioned risks have restricted the use of stem cells for the treatment of diseases and conditions. There are some studies to demonstrate the link between stem cells and tumor progression and metastasis. BMMSCs released chemokines CXCL5, which increased cell proliferation and migration of breast cancer cells and colorectal cancer cells [5], [183]. Similarly, CXCL12 secreted by ASCs induced tumor growth and invasiveness in prostate cancer [184]. Marks *et al.* raised the concerns that the adverse effects of stem cell therapies are not completely investigated as most of these therapies are done outside of proper clinical trials [185]. The risks of stem cells may be more common than being acknowledged. The additional preclinical studies and controlled trials are necessary to address safety issues/side effects of stem cells in both the short term and long term [185]. Besides, the underlying mechanism of stem cells in an aesthetic application should be further ascertained.

Since aesthetic uses and plastic surgery are strongly associated with patients' satisfaction with changes in appearance and possible side effects. As such, any undesired effects from the therapies should be carefully considered in all procedures. The full and precise regulations and standards for techniques on harvesting, processing, and administration, aftercare as well as possible side effects are still being investigated. Recently, Agrawal *et al.* recommended a definitive procedure for fat grafting, that enhanced the cell quality, and cell survival after reinjecting into the area that needs to be augmented [186]. The high cost is also considered as a limitation of stem cell therapy, which highly depends on the individual financial condition and insurance of the patients. In addition, autologous stem cells are patient-specific, thus cannot be developed as a drug because of limited financial supports. All these require optimization, scale-up, and quality control of stem cell preparation and storage.

IX. Future Direction of Stem Cells in Aesthetic Applications

Even stem cell therapy has been studied and reported innovative and promising outcomes in aesthetic uses, several remaining issues need investigation before the clinical application. Firstly, stem cell processing is highly regulated. Most studies of stem cells in aesthetic medicine utilized fat grafting or SVFs which

were undefined mesenchymal stem cells, that can cause lower and more inconsistent or unexpected outcomes. Collagenase plays a key role in the isolation of ASCs enzymatically; however, an FDA-approved collagenase product is expensive. Therefore, it is necessary to optimize the protocols and procedures of stem cell preparation. GMP-grade facilities must be developed to prepare stem cells for clinical practices. Substituted collagenase sources or other effective isolation methods without using enzymes can be applied in stem cell therapy. Besides, the banking of stem cells is currently available, which is useful to preserve cells for future applications. The stability, safety, and efficacy of long-time storage cells should be carefully considered and evaluated for clinical applications.

Secondly, the regeneration and anti-aging properties of various stem cell-based products such as BMMSCs, ASCs, fat grafting, Nano-fat, SVFs, MSCs, and conditioned media have been reported. Thus, a combination of those products or biocompatible scaffolds should be studied, such as a component of scaffolds, seeding methods, cell types, and cell amount in the material. Further understanding the mechanism of stem cells in the aesthetic application is important to the next generation therapy, which is useful to understand cellular interactions, potential risks, side effects, and provide indications as well as a contraindication of this method. In addition, larger cohort group data and phase I, II, III, and IV clinical trials of using stem cell products in aesthetic uses and plastic surgery also need to be conducted in the future. A therapeutic dose of stem cells or fat amounts as well as an effective administration route should be defined for each indication. More works need to be investigated. The current literature reviews and successful results from preclinical and clinical studies will provide the primer for further researches.

X. Conclusion

By the regenerative and multipotent differentiation properties, stem cells had been investigated in the treatment of various diseases, particularly in aesthetic medicine and plastic surgery. Stem cell-based products particularly exosomes are safe and effective to augment and reconstruct the soft tissues, heal the wound and reduce the skin scar, promote hair growth; suppress and convert aging. Fat grafting and CAL technique are popularly applied to aesthetic uses to support cell survival and differentiation at the implantation sites. Currently, it is difficult to apply stem cell therapy widely on aesthetics and plastic surgery. The current preclinical and clinical studies of stem cells are limited to small subjects, standardization protocols of cell preparation and administration, which may cause the side effects and inconsistent outcomes of therapy. There are few possible risk factors and side effects that were reported in the literature review and limited studies. In addition, stem cells are directly marketed to the patients without a mention of the possible risks of the treatment. Therefore, it is necessary to optimize and standardize the processing of stem cell preparation, storage, and applications, including therapeutic dose, cell type, and effective administration route for each treatment. Besides, the FDA and government organizations should provide the regulations and guidelines to support the study and apply stem cells in clinical uses.

Declarations

1) Ethical Approval: This is a review paper, so it does not need to be approved by an Ethical Committee

2) Consent to Participate: This is a review paper, so it does not need consent from participants.

3) Consent to Publish: All authors critically reviewed and approved the publication of the final paper.

4) Authors' Contributions: Development of the idea for this work: Dinh Toi Chu. Conceptualization: Dang-Khoa Tran, Thuy Nguyen Thi Phuong, Looi Qi Hao, Benson Koh, Pau Loke Show and Dinh-Toi Chu; Literature search and data analysis: Dang-Khoa Tran, Thuy Nguyen Thi Phuong, and Nhat-Le Bui; Writing - original draft preparation: Dang-Khoa Tran, Thuy Nguyen Thi Phuong, Nhat-Le Bui, Vijai Singh, Chia-Ching Wu, Looi Qi Hao, Benson Koh, Jhi Biau Foo, Pau Loke Show and Dinh-Toi Chu; Writing - review and editing: Dang-Khoa Tran, Chia-Ching Wu, Vijai Singh, Looi Qi Hao, Benson Koh, Pau Loke Show and Dinh-Toi Chu.

5) Competing Interests: The authors declare that they have no Competing Interests.

6) Availability of Data and Materials: This is a review paper, so it does not have associated data and materials.

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Thuy Nguyen Thi Phuong, biography and photograph not available at the time of publication.

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Qi Hao Looi, biography and photograph not available at the time of publication.

Benson Koh, biography and photograph not available at the time of publication.

Ungku Mohd Shahrin B Mohd Zaman, biography and photograph not available at the time of publication.

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