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Review Article

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Upcycled Mesenchymal Stem Cells: Repurposing Biological Waste Towards Sustainable Regenerative Therapies

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Abstract
Over the last two decades, the use of adult stem cells in therapy has gained significant momentum. However, stem cells are usually associated with high extraction, expansion and storage costs. This is delaying their approval into clinical practice. By repurposing medical waste tissues for stem cell harvesting, there is an opportunity to extract valuable therapeutic material without incurring additional costs associated with procuring raw materials or handling waste disposal. Harvesting stem cells from discarded tissues is a non-invasive, safe procedure that lowers healthcare costs associated with managing donor site complications. Given the dire need for stem cells in regenerative therapies, it is imperative that necessary advancements are made towards reducing the gap between the supply and the demand of such cells for therapy. The innovative concept of "Upcycled mesenchymal Stem Cells (USCs)" has been proposed to upcycle and repurpose adult mesenchymal stem cells from biowastes. Summary has been presented regarding the regenerative applications, current clinical status, potential benefits and limitations of USC-based therapies.

Keywords:
Upcycled mesenchymal stem cells; regenerative therapy; biological waste material; sustainability; clinical trials

1. Introduction

The end of the 19th century marked the beginning of the concept of stem cells with self-renewal properties. Among these, a population of adult stem cells called mesenchymal stem cells (MSCs) have proven to be the prominent cell choice for various regenerative therapies. Self-renewal, multilineage differentiation, immunomodulation and paracrine effects are some of the documented properties of MSCs that have sparked great enthusiasm to unveil the hidden potential of these cells in different therapies [1]. MSCs are known to be obtained from a diverse range of tissues such as bone marrow, adipose tissue, skin, peripheral blood, muscles, synovial membrane, dental pulp, urine, menstrual blood, and birth-associated tissues such as placenta and umbilical cord [2]. The most commonly exploited source of human MSCs is the bone marrow. However, the isolation of MSCs from bone marrow, as well as other sources such as skin, peripheral blood, and muscles, is a highly invasive procedure that is accompanied by patient discomfort and the risk of infection. Therefore, research efforts are directed toward examining the regenerative potential of MSCs from biological wastes and other sustainable sources.

Upcycling refers to the process of repurposing or transforming discarded or unused materials. In regener-

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ative medicine, the term upcycled has previously been used for umbilical cord stem cells, as the umbilical cord is considered a rich source of MSCs and other types of stem cells [3]. Likewise, in a recently published study, the cells derived from waste prenatal or postnatal tissues/products are recognised as waste-derived stem-like cells (WDS-IC) [4]. Following this, a new term has been proposed to describe sustainable or green sources of MSCs as "Upcycled MSCs or USCs" which entail MSCs isolated from either birth-associated discarded tissues or the biological waste material discharged by the human body.

The literature has been examined for sustainable sources of MSCs, summarizing the biological characteristics of USCs, their advantages over conventional MSCs, regenerative applications, and clinical status. USCs demonstrate potential to transform discarded stem cells into valuable therapeutics. For the purpose of this study, the term "conventional MSCs" refers to traditional sources of MSCs, such as those outlined in Table 1.

2. MSCs from Biological Waste Material

2.1. Birth-Associated Spare Parts

Amnion/chorion membrane: The fetal membrane consists of two main layers: the amnion, which is the outermost layer surrounding the fetus and amniotic fluid, and the chorion, the innermost layer in direct contact with the maternal decidua. The specific substances secreted by these membranes govern amniotic fluid homeostasis and the cellular physiology of the maternal tissue. Their unique structural organisation and rich proteomic profile mark them as a potential source of stem cells. The amnion is the source of amniotic epithelial cells (hAECs) and amniotic mesenchymal stem or stromal cells (hAMSCs). hAMSCs can be extracted from the inner mesodermal tissue of the amnion by mechanical or enzymatic removal of the outer amniotic epithelial layer. These cells behave like fibroblasts and express different mesenchymal markers. Significantly, hAMSCs demonstrate multilineage potential and can differentiate into adipocytes, chondrocytes, osteoblasts and myocytes, as well as ectodermal lineages [5]. Likewise, the chorion is the source of chorionic mesenchymal stem cells (hCMSCs) which exhibit fibroblast-like characteristics and can be differentiated into conventional mesodermal lineages, including osteogenic, chondrogenic and adipogenic lineages [6].

Amniotic fluid: Amniotic fluid (AF) serves as the source of exchange of nutrients and other chemicals from the mother to the fetus. Traditionally, AFMSCs can be collected from AF either by the process of amniocentesis or during cesarean deliveries [7]. Although the collection of AF by amniocentesis is an invasive process, a non-invasive way of isolation from the medical waste discarded during C-section deliveries can be explored. The fluid is collected aseptically by a syringe and processed to remove erythrocytes, yielding a heterogeneous mixture of cells. After two subsequent passages, the cells become more homogenous with fibroblast-like morphology [8]. AF-MSCs exhibit a high self-renewal capacity and retain a normal karyotype even after successive divisions. Notably, they share similar morphological characteristics with BM-MSCs. Their greater differentiation capabilities are due to the presence of the human embryonic stem cell markers, octamer-binding transcription factor-4 (Oct-4) and stage-specific embryonic antigen-4 (SSEA-4). AF-MSCs show significant pluripotency and can successfully be differentiated into adipogenic, chondrogenic, endothelial, hepatic, myogenic, neurogenic, and osteogenic lineages under requisite conditions [9].

Umbilical cord and cord blood: The umbilical cord (UC) is an extra-embryonic tissue that is traditionally discarded after birth. UC comprises two umbilical arteries, one umbilical vein and Wharton's jelly (WJ), a mucoid connective tissue. Various parts of UC have been explored as a source of MSCs including WJ, cord lining, and cord blood, in which WJ has been most widely studied. Accordingly, UC serves as a source of Wharton's jelly MSCs (WJ-MSCs), cord lining MSCs (CLMCs) and cord blood-derived MSCs (UCB-MSCs) [10]. Several methods of UC-MSC isolation have been described, including the tissue explant method, mechanical dissociation followed by enzymatic digestion, and enzymatic digestion of WJ, with or without blood vessels [11]. UC-MSCs or WJ-MSCs specifically exhibit the expression of various MSC markers and adhesion molecule markers, while demonstrating low or negligible expression of immune response-related antigens and hematopoietic stem cell-associated surface antigens [12]. Several *in-vitro* findings suggested that UC-MSCs are highly plastic and can be differentiated into osteoblasts, cartilage, endothelial cells, neurons, cardiomyocytes, hepatic, and pancreatic cells. Moreover, UC-MSCs can modulate the immune system by secretion of various immunomodulatory cytokines regulating the functioning of different immune cells [13].

Maternal decidua: the maternal uterine bed nurturing the developing embryo, called the decidua, is discarded along with the placenta after childbirth. This tissue is the source of two cell populations - decidua basalis MSC (DBMSCs) and decidua parietalis MSC (DPMSCs), both of them represent a sustainable source of MSCs. For stem cell isolation, the decidua is typically enzymatically digested using

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collagenase and DNase enzymes, followed by filtration and centrifugation to extract the cells [14]. Although little research has been done to examine the functional characteristics of decidua-derived MSCs (DMSCs), they are known to differentiate into all three germ layers. Furthermore, they can differentiate into adipocytes, osteocytes and chondrocytes, while also secreting a wide range of growth factors and bioactive molecules with diverse functions [15,16].

2.2. Adult Biological Waste Material

Extracted tooth: The tooth is a highly vascularised, mineralised soft tissue that can serve as an easily accessible noncontroversial source of dental MSCs (DMSCs). Several types of DMSCs have been identified from the human adult permanent tooth, the deciduous tooth, oral mucosas and the periodontal ligament [17]. The pulp of human exfoliated deciduous teeth from children serves as a great disposable tissue to isolate stem cells from human exfoliated deciduous teeth (SHEDs). These stem cells can be isolated by using two methods: first is the enzymatic digestion of minced pulp tissue with collagenase and dispase, and the other is the tissue explant method that allows cells to grow out from the minced pulp on culture dishes [18]. They are characterised as highly plastic DMSCs with high population doubling time and express several embryonic stem cell markers on their surfaces [19]. SHEDs are reported to be differentiated into adipogenic, chondrogenic, endothelial, myogenic, hepatic, neuro-glial, osteogenic, odontogenic and pancreatic lineages [20]. DMSCs exclusively express various cell proliferation and extracellular matrix-related genes and are useful for various regenerative applications.

Adipose tissue remnants: Subcutaneous adipose tissue serves as a rich source of stem cells that can be retrieved from liposuction procedures. The lipoaspirate is considered a biomedical waste and thus qualifies as a sustainable and easily accessible source of MSCs [21]. Adipose tissue-derived MSCs/stromal cells (AT-MSCs or ASCs) can be harvested either from liquid fat after the liposuction procedure or from solid fat retrieved from abdominoplasty. In a non-enzymatic method, a heterogeneous mixture of mature adipocytes is collected from the stromal vascular fraction (SVF) harvested after liposuction or resection by mechanical means. Besides, the enzymatic process involves collagenase digestion and centrifugation [22]. AT-MSCs are multipotent cells with high proliferation capacities with multilineage differentiation and immunosuppressive potential [23]. In studies, AT-MSCs have demonstrated the classical trilineage differentiation as BM-MSCs.

Menstrual blood: Menstrual blood is a unique, easily accessible and sustainable source of menstrual blood-derived MSCs (MenSCs). The endometrial regeneration stem cell hypothesis suggests that adult stem cells in the uterine endometrium drive the continuous regeneration of shed endometrial tissue during menstruation [24]. Isolation of endometrial MSCs (eMSCs) is an invasive surgical process, while MenSCs can be easily collected from the discharged menstrual blood. Studies have shown that about two to four-fold higher frequency (0.04% to 0.02%) of MenSCs can be achieved from menstrual blood as compared to BM-MSCs [25]. In 2007, Meng et al. achieved a breakthrough by identifying and isolating endometrial regenerative cells as a novel alternative source of stem cells from menstrual fluid. MenSCs are isolated from menstrual blood by conventional density gradient centrifugation or direct red blood cell lysis treatment [26]. These are adherent cells with fibroblast-like morphology and possess high proliferation capacity. Like BM-MSCs, they can differentiate into varied mesodermal lineages and show some superior characteristics of differentiation into cardiomyocytes, neural cells, epidermal-like cells and hepatocytes. In terms of growth profile, MenSCs have exhibited higher cellular proliferation and *in vitro* migration properties with a 3.5-fold increase in colony-forming units (CFUs) *in vitro* as compared to BM-MSCs [27].

Urine: Human urine serves as a convenient, economical and safe way of isolating cells with self-renewal and multi-differentiation potential. Urine-derived stem cells (UdSCs) can be easily harvested from a patient's voided urine samples, providing an inexpensive and minimally invasive method. These isolated stem cells express surface markers similar to those of mesenchymal stem cells (MSCs), renal cells, and other pluripotent cells [28]. UdSCs can be extracted from the urine samples by conventional centrifugation method and are generally cultured in keratinocyte serum-free media [29]. It has been evident from several studies that UdSCs have multipotent differentiation potential and can differentiate into the established MSC lineages as well as endothelial cells, neuronal cells, urothelial cells, podocytes and smooth muscle cells [30]. In addition, they secrete various angiogenic and immunomodulatory growth factors that are desirable for various therapeutic applications.

Periapical cyst/lesions: Human periapical cysts represent the most frequent oral cysts formed as an inflammatory reaction to endodontic infection. For the first time, Marelli et al. reported and characterised a new MSC population called as human periapical cysts-MSCs (hPCy-MSCs) from human periapical lesions, a biological waste material [31]. These cells are isolated from the cystic wall

by mechanical disruption followed by enzymatic digestion (collagenase and dispase) and culturing in a suitable medium [32]. The newly isolated MSCs were believed to have trilineage differentiation potential. Moreover, hPCy-MSCs express several neuronal markers and can differentiate into neurogenic-like cells. Easy harvest, self-renewal and high proliferation capacities, multipotency, proangiogenic properties and immunomodulatory actions mark them as an attractive source of dental MSCs [33].

Skin: The human skin is the largest organ of human body and serves as a source of multipotent stem cells. Human foreskin obtained during the circumcision procedure in new born babies is considered as a discarded surgical waste. Some recent studies have shown that foreskin-derived MSCs (FSK-MSCs) have multipotent and pluripotent properties and displayed multilineage differentiation and immunomodulatory actions [34]. Likewise, the excised burned human skin, which is generally discarded in routine procedures, is a host for viable burn-derived MSCs (BD-MSCs). These cells have shown comparable biological properties, including, population doubling time and colony formation with reduced differentiation potential when compared to UC-MSCs [35].

3. Clinical Status of Upcycled MSCs

As of 16 August 2024, a comprehensive evaluation of the ClinicalTrials.gov database revealed a total of 1674 trials registered for various types of mesenchymal stem cells (MSCs). For upcycled MSCs, specific search was carried out using terms such as "amniotic fluid mesenchymal stem/stromal cells", "adipose tissue mesenchymal stem/stromal cells", "umbilical cord/cord blood mesenchymal stem/stromal cells", and "Wharton's jelly mesenchymal stem/stromal cells," among others. This search yielded information on the total number of trials, clinical phases, statuses, and cell types involved. Repeated outcomes were excluded, considering only unique identifiers. The analysis showed that the majority of trials were conducted on umbilical cord-derived MSCs (UC-MSCs) and adipose tissue-derived MSCs (AT-MSCs), with no trial data available for amniotic fluid-derived MSCs (AF-MSCs), chorionic MSCs (hCMSCs), or periapical cyst-derived MSCs (hPCy-MSCs) (Figure 1A). USCs from other sources, such as exfoliated teeth, periapical cysts, menstrual blood and urine, have recently gained attention, and their clinical application is still unexplored.

Table 1: Comparison of conventional versus upcycled MSCs.

Sources	Isolation	Proliferation Capacity	Differentiation Capacity	Key Strengths	Limitations
Conventional MSCs					
Bone marrow [36,37]	BM aspirate	Mean doubling time is 40 h, senescence after passage seven	Adipogenic, chondrogenic, osteogenic	• The most extensively used stem cell source • High proliferation and differentiation • Highest clinical validation	• Isolation procedure is invasive and painful
Synovium/ synovial fluid [38]	Synovium and synovial fluid	Can proliferate up to passage ten	Adipogenic, chondrogenic, osteogenic	• High *in vitro* proliferation and differentiation • Lower yield	• Isolation procedure is invasive and painful
Skin [39]	Human skin biopsies	Doubling time is 7–8 days	Adipogenic, myogenic, osteogenic	• Useful for autologous regenerative applications	• Isolation procedure is invasive and requires skin biopsies
Muscle [40]	Skeletal muscle tissue	Doubling time is 40 h	Adipogenic, blood cells, chondrogenic, hepatogenic, myogenic, neurogenic, osteogenic	• High self-regenerative potential	• Isolation procedure is invasive and requires biopsies

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Table 1: *Cont.*

Sources	Isolation	Proliferation Capacity	Differentiation Capacity	Key Strengths	Limitations
Peripheral blood [41]	Mononuclear lymphocytes	Doubling time is 95 h	Adipogenic, chondrogenic, endothelial, osteogenic, neurogenic	• Higher amount of MSCs can be collected	• Lower chondrogenic and adipogenic potential • Isolation process in invasive
Upcycled MSCs					
Amnion/ Chorion [9]	Embryonic amnion/chorion membrane	Doubling time is 36 h	Adipogenic, chondrogenic, osteogenic	• Isolation process is non-invasive • High yield and self-renewal capacity	• Limited clinical evidence
Amniotic fluid [9]	Embryonic amniotic fluid	Doubling time is 36 h	Adipogenic, osteogenic, neurogenic	• Isolation process is non-invasive • High self-renewal capacity	• Limited clinical evidence
Placenta [42]	Placental tissue	Doubling time is 36 h	Adipogenic, endothelial, neurogenic, osteogenic	• Isolation process is non-invasive • High self-renewal capacity	• No standardized isolation protocols
Umbilical cord and cord blood [13]	Umbilical cord and cord blood	Mean doubling time is 30 h	Adipogenic, chondrogenic, endothelial-like cells, neuron-like cells, osteogenic	• Isolation process is non-invasive • Highest proliferation potential • Comparable to BM-MSC • Suitable for allogenic applications	• Genetic instability due to source and culture conditions
Adipose tissue remnants [21,43]	Waste tissue remnants from liposuction or abdominoplasty	Mean doubling time is 4 ± 1 h, faster proliferation than BM-MSCs	Adipogenic, chondrogenic, muscular, neurogenic, osteogenic	• Isolation process is non-invasive • High proliferation rates	• Inferior osteogenic and chondrogenic potential
Extracted tooth [44]	Extracted tooth	Mean doubling time is 19 h	Adipogenic, chondrogenic, hepatogenic, myogenic, neuronal, odontogenic, osteogenic	• Isolation process in non-invasive	• Limited studies available
Menstrual blood [45]	Blood from menstrual cycle	Mean doubling time is 18–36 h	Adipogenic, chondrogenic, chardiomyocyte, hepatocytes, myogenic, osteogenic	• Isolation process in non-invasive • Ideal for personalized therapies in women	• Donor variability

Table I: *Cont.*

Sources	Isolation	Proliferation Capacity	Differentiation Capacity	Key Strengths	Limitations
Urine [28,30]	Voided human urine	Mean doubling time is 20–29 h for fresh urine and 28–32 h for preserved urine	Beta-like cells, chondrogenic, endothelial, myogenic, neuronal, osteogenic, smooth muscle cells, uroepithelial	• Isolation process in non-invasive	• Lower yield • Limited studies available
Periapical cyst [31]	Dental cyst/lesion	Mean doubling time is 19 h	Adipogenic, neuronal, osteogenic	• Isolation process in non-invasive	• Limited studies available
Foreskin [46]	Excised foreskin	Mean doubling time is 20–30 h	Adipogenic, chondrogenic, osteogenic	• Isolation process in non-invasive • Low immunogenicity	• Limited studies available • Limited accessibility

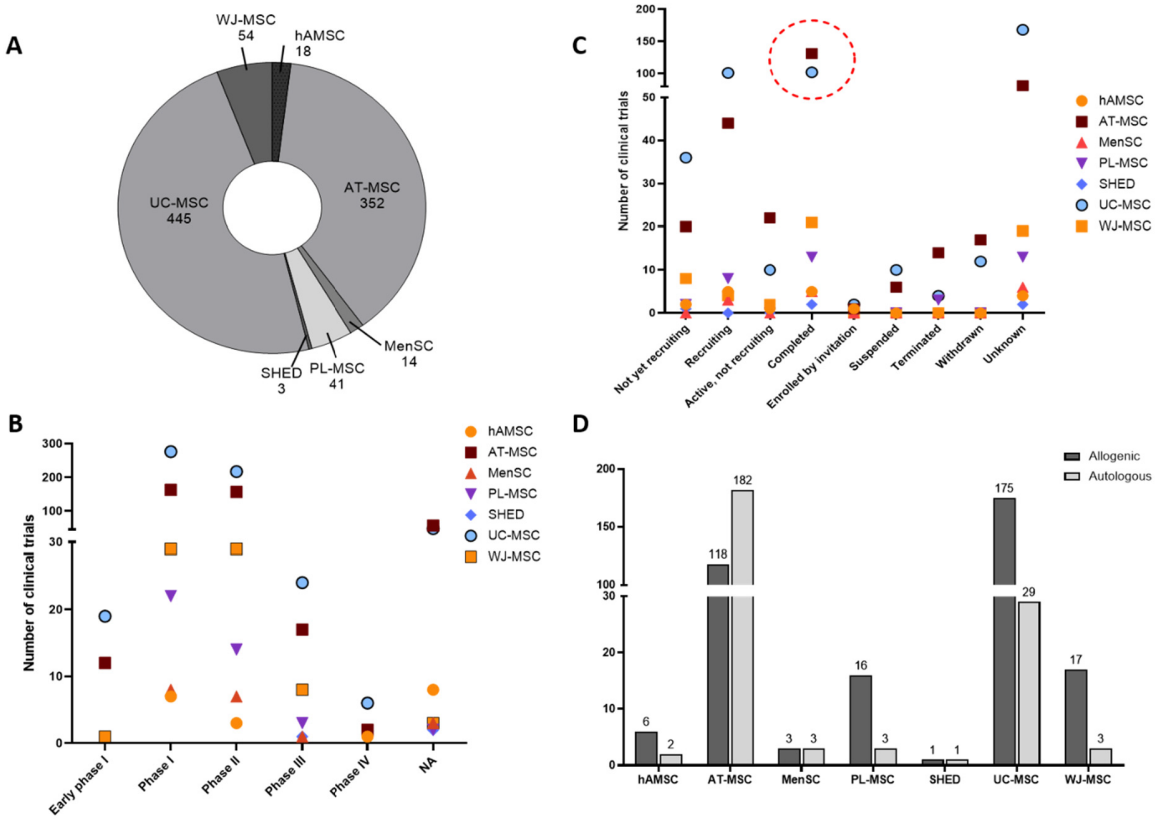

Figure 1: Representation of clinical parameters of various USCs (**A**) Number of clinical trials identified per USC source. (**B**) USCs in various phases of clinical trials (**C**) Status of the clinical trials–red dotted circle highlights the highest number of completed trials are reported with UC and AT-MSCs (**D**) Allogenic versus autologous sources of USCs.

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Among all the registered trials, most focused on phase I and II studies (Figure 1B), reflecting the early stage of clinical validation for these therapies. This analysis suggests that the long-term efficacy of MSC-based therapies remains insufficiently established, hindering broader clinical translation. Regarding trial statuses, the majority were either recruiting or completed (Figure 1C). For most clinical trials, allogenic MSCs were used, except for AT-MSCs, which are commonly employed in autologous applications (Figure 1D). Advantages of allogenic MSCs, such as low immunogenicity, ease of availability, and donor selection flexibility, position them as favourable for clinical use. However, limited data prevents definitive conclusions about the therapeutic superiority of allogenic versus autologous sources.

Despite the abundance of completed trials, few have published results, complicating the assessment of clinical efficacy. Prominent examples include the CATO trial in the U.S., which explores intravenous UC-MSCs for heart failure, outcomes [47]. The results from clinical trial NCT04355728, which assessed the efficacy of UC-MSC treatment for acute respiratory distress syndrome in COVID-19 patients, revealed positive outcomes with improved patient survival. The study demonstrated a significant reduction in inflammatory cytokines or "cytokine storm" in COVID-19 [36]. The safety and efficacy of UC-MSCs based therapies in a clinical trial (NCT03102879) for regenerative endodontic procedures (REPs) is another promising example of MSC clinical potential. In a 12-month follow-up study, patients were evaluated and shown positive pulp response and improved clinical efficacy with no adverse events [36]. The results from another clinical trial study (NCT03691909) illustrated the positive effects of autologous AD-MSC infusion in rheumatoid arthritis (RA) patients. AD-MSC treatment resulted in reduced C-reactive protein (CRP) levels in patients with significant improvement in joint symptoms, with no long-term adverse events reported [48]. The therapeutic benefits of AD-MSCs have been evaluated in another clinical trial (NCT03060551) in systemic sclerosis patients. After a 20-week follow-up period, patients with nebulised AD-MSC have shown improvement in hand edema, active ulcers and skin fibrosis with no adverse events [49]. One clinical study (NCT01385644) implemented PL-MSCs in pulmonary idiopathic fibrosis patients in a phase 1b trial. The published results revealed that the use of MSC-based cell therapy improved lung function in moderately fibrotic lung disease with a short-term safety profile [50]. In essence, although a minority of trials with upcycled MSCs have published results, the available data certainly provide an encouraging direction for further clinical investigation. A brief overview of some clinical trials for upcycled MSCs completed in 2023 is provided in Table 2.

4. Applications of USCs in Regenerative Medicine

The significant biological properties of USCs make them an ideal source for regenerative applications, including the repair and regeneration of damaged tissues. The most recent applications of USCs focus on treating bone and cartilage defects, muscle degeneration, dental problems, liver failure, neuronal degeneration, and dental defects. Over the last decade, AD-MSCs have been extensively explored for tissue repair, wound healing and organ regeneration. AD-MSC cells are primarily used in autologous transfers for facial rejuvenation, cosmetic surgeries and reversal of skin necrosis [51]. Some studies have shown the potential of bioactive substances secreted by AD-MSCs in bone tissue engineering including bone repair and regeneration [52]. Likewise, USCs from dental sources have been documented to show better osteogenic potential promoting bone regeneration and reducing inflammation [53]. It has been demonstrated that MenSCs also contribute to wound healing and blood vessel formation by secreting some cytokine signals promoting cutaneous regeneration [54]. Beyond tissue and bone regeneration, a recent study reported on the applications of USCs from various sources, including UC-MSC, WJ-MSC, and AMSC, in cell-based and biomaterial-based neural regeneration [4]. After BM-MSC, AD-MSC and UC-MSC are the most extensively studied MSCs for treating nervous system inflammation, traumatic brain injuries and neuronal regeneration [55,56]. Studies have also shown that DMSCs have remarkable neurogenic potential due to the secretion of different neurotrophic factors and specifically, SHEDs are known for their neuroprotective activity [57,58]. Moreover, several preclinical and clinical studies revealed that the immunomodulatory properties of MSCs are beneficial for promoting liver regeneration. Similar to conventional BM-MSCs, AD-MSCs [59], UC-MSCs [60] and PL-MSCs [61] have shown differentiation into hepatocyte-like functional cells in 2D and 3D cultures. For dental applications, dental tissue-derived MSCs have widely been explored for periodontal tissue regeneration, dental pulp regeneration, tooth reconstruction and other dental tissue engineering applications. Besides, other USCs like AD-MSCs and UC-MSCs have also shown success in periodontitis and other dental diseases. Emerging studies continue to uncover novel applications for USCs in regenerative medicine. Their diverse biological properties, including immunomodulation and differentiation potential, underscore their versatility.

Table 2: Examples of clinical trials with upcycled MSC completed in 2023. (Data retrieved from Clinicaltrials.gov).

NCT Number	Study Phase	Study Design	Intervention	Cell Type	Condition	Completion Date	Summary
NCT05703308	III	Non-randomised study with 180 participants	Menstrual Blood Derived-Mesenchymal Stromal Cells	Autologous	Poor Ovarian Response/Female infertility	January, 2023	MenSC treatment has shown improvement in pregnancy outcomes in women after 2 month follow-up period with no reported side effects
NCT05777213	I	Open-label interventional study with 27 participants	Conditioned Medium Wharton's Jelly-derived mesenchymal stem cells (CM-WJMSCs)	Allogenic	Ulcers	February, 2023	Study completed, results not available
NCT05279157	II	Randomised, parallel study with 15 participants	Human adipose-derived MSCs	Autologous	Corneal disease	February, 2023	Study completed, results not available
NCT04928287	II	Randomised, double-blind, single-centre study with 24 participants	Human adipose-derived MSCs	Autologous	Parkinson's disease	February, 2023	Study completed, results not available
NCT03943576	I/II	Randomised, interventional study with 25 participants	Human adipose-derived MSCs (GXCPC1)	Allogenic	Knee osteoarthritis	March, 2023	Improved pain and knee function with no reported adverse event after one year of follow-up
NCT04325594	II	Non-randomised, open-label, interventional study with 30 participants	Human umbilical cord-derived MSCs	Allogenic	Chronic heart failure	April, 2023	Study completed, results not available
NCT03308006	II	Open-label, interventional study with 18 participants	Human adipose-derived MSCs	Allogenic	Knee osteoarthritis	April, 2023	Study completed, results not available
NCT03254758	I/II	Open-label, interventional study with 21 participants	Human adipose-derived MSCs	Allogenic	Liver cirrhosis	April, 2023	Study completed, results not available

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Table 2: *Cont.*

NCT Number	Study Phase	Study Design	Intervention	Cell Type	Condition	Completion Date	Summary
NCT03183934	I/II	Open-label, observational study	Human adipose-derived MSCs ALLO-ASC-DFU	Allogenic	Dystrophic Epidermolysis Bullosa	April, 2023	Study completed, results not available
NCT04992832	I/II	Randomised, placebo, double-blind, interventional study with 0 participants	Human umbilical cord MSCs-derived secretome (PRIME-HFrEF)	Allogenic	Heart failure	April, 2023	Study completed, results not available
NCT04040348	I	Open-label, interventional study with 6 participants	Human umbilical cord MSCs	Allogenic	Alzheimer's disease	April, 2023	Study completed, results not available
NCT04530071	I/II	Randomised, double-blind, placebo study with 36 participants	Human umbilical cord-derived MSCs (CordSTEM-DD)	Allogenic	Chronic low back pain	April, 2023	Study completed, results not available
NCT04040348	I	Open label, single group assignment with 6 participants	Human umbilical cord-derived MSCs	Allogenic	Alzheimer's disease	April, 2023	Study completed, results not available
NCT05579665	I/II	Randomised, open-label, interventional study with 45 participants	Human umbilical cord MSCs-derived secretome	Allogenic	Knee osteoarthritis	May, 2023	Clinical improvement and biomarker changes in patients with mild to moderate disease with no side effects
NCT04738981	III	Randomised, open-label, interventional study with 130 participants	Human umbilical cord MSCs	Allogenic	Graft versus host disease	May, 2023	Better response after MSC therapy with no toxicity and adverse effects
NCT04208646	II	Multicentre, randomised, double blind study with 106 participants	Human adipose-derived MSCs (AlloJoin®)	Allogenic	Knee Osteoarthritis	July, 2023	Study completed, results not available

Future research should prioritize long-term clinical studies to validate efficacy and explore underutilized sources, such as MenSCs and SHEDs, for broader clinical use.

5. Advantages and Challenges of Using USCs

Considering the limitations of conventional MSC sources, interest in biological waste products has recently been increased. USCs have comparable proliferative, migratory, immunomodulatory and anti-inflammatory properties and can be isolated by non-invasive procedures. Moreover, studies have shown that isolated MSCs from fat tissues during liposuction procedure can generate an entire network of blood vessels thus supporting tissue regeneration [62]. Despite having biological and medical benefits, USCs have additional advantages based on ethical and regulatory background. USC-based therapies are sustainable and help to reduce the burden of huge biomedical waste generated in hospitals and clinics.

With each technological advancement, USC-based therapies have certain limitations and challenges. Cautions need to be considered from a safety perspective during the development of USC products. For instance, hemocompatibility, route of delivery of USC products, and potential adverse events after infusion of large cell doses should be considered. The *in vivo* phenotype of USC is still poorly defined in terms of hemocompatibility. Among USCs proposed, molecular profiling of PL-MSCs has revealed that these cells express higher levels of extravascular procoagulant factors compared to the prototypic hemocompatibility. It is proposed to perform careful hemocompatibility screening before clinical application, particularly when USCs are used systemically. Indeed, different USCs can secrete high levels of tissue factors (as shown for PL-MSCs) which might trigger coagulations. MSCs also express receptors for complement activation products that can trigger activation of the innate immune response [63]. Additional factors to be considered during studies of USCs would include effects of culture media/culture expansion, freeze-thawing, and the reconstitution buffer which might affect their phenotypes and secretion of tissues factors. Similar to the other so called conventional MSCs, it is also proposed to address USCs dosing, fitness, potency assays and careful investigation of the potential mechanism of action (might be indication dependent). Moreover, it is crucial to consider biosafety measures while isolating MSCs from biological waste material. Maintaining quality assurance and aseptic conditions, collecting in sterile containers, developing assays for testing potential contaminants during and after isolation, properly disposing of unused material, and maintaining detailed documentation are some of the essential biosafety measures to be considered. It is recommended to obtain a consent from the donors before using their biological waste for any research purpose. Additionally, complying with patient information and data privacy are critical measures to be considered to follow ethical and regulatory standards.

6. Conclusions

Repurposing of discarded tissues serves an alternate way to procure MSCs with an opportunity to overcome the additional financial burdens and reduce carbon foot print by minimising medical waste disposal. Furthermore, harvesting MSCs from discarded tissues typically involves a non-invasive procedure, in contrast to invasive approaches such as bone marrow aspiration or tissue biopsies. These surgical methods often involve huge expenditures due to anaesthesia, operating room utilisation, and postoperative care.

Moreover, traditional harvesting procedures can lead to donor site morbidity, encompassing various complications such as discomfort, pain, or even infection. In addition, researchers face limitations in the quantity of source material available for cell expansion and various cell culture assays. The utilisation of discarded medical wastes as a source of MSC might circumvent the above-mentioned issues and offer an ethically sound alternative for the integration of stem cell-based therapies. In essence, repurposing discarded tissues for stem cell harvesting provides a cost-effective alternative, overcoming the financial challenges of conventional stem cell extraction methods, and facilitating the potential integration of stem cell therapies into clinical applications. For specific diseases where patients are quite sick, have contraindications for bone marrow or adipose tissue extraction, or can't wait for the manufacturing process, the availability of the shelf cells can make the clinical journey easier.

However, the clinical success of USCs is challenged by factors such as variability and viability of isolated cells, inconsistent standardization and characterization protocols, hemocompatibility issues, reproducibility concerns, the impact of different delivery methods, and lack of extensive preclinical validations. To raise awareness within the scientific and regulatory communities, it is essential to investigate the hidden potential of various sources of USCs in experimental conditions and to translate and validate their efficacy in clinical settings.

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List of Abbreviations

AF	Amniotic Fluid
AT-MSC	Adipose Tissue-derived MSCs
BD-MSC	Burn-Derived MSC
CLMC	Cord Lining MSC
CRP	C-Reactive Protein
hAMSCs	Amniotic Mesenchymal Stem Cells
hPCy-MSC	Human Periapical Cysts-MSCs
DBMSC	Decidua Basalis MSC
DMSC	Dental-Tissue Derived MSC
DPMSC	Decidua Parietalis
FSK-MSC	Foreskin-Derived MSC
hAECs	Amniotic Epithelial cells
MSC	Mesenchymal Stem cells
MenSC	Menstrual Blood-Derived MSCs
Oct-4	Octamer-Binding Transcription Factor-4
REP	Regenerative Endodontic Procedures
SHED	Human Exfoliated Deciduous Teeth
SSEA-4	Stage-Specific Embryonic Antigen-4
SVF	Stromal vAscular Fraction
UDSC	Urine-Derived Stem Cells
USC	Upcycled Mesenchymal Stem Cells
UCB-MSC	Umbilical Cord Blood-Derived MSCs
UC	Umbilical Cord
WJ	Wharton's Jelly

Author Contributions

Conceptualization, methodology, software: D.A., J.K.B. and N.K. (Nupur Kohli); Validation, formal analysis, funding acquisition: D.A., J.K.B. and N.K. (Nupur Kohli); Investigation, resources, data curation, writing---original draft preparation, writing---review and editing, visualization, supervision, project administration: D.A., J.K.B, G.S., N.K. (Nadir Kadri) and N.K. (Nupur Kohli). All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors have no conflict of interest to declare.

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AI Declaration

The authors confirm that no AI tools were used to generate any content of this manuscript. The authors take full responsibility for the accuracy, originality, integrity, and scientific content of the manuscript.

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