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Exploring hematopoietic stem cell population in human milk and its benefits for infants: A scoping review

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ABSTRACT

Objective: To comprehensively explore hematopoietic stem cells (HSCs) in human milk, understanding their molecular markers, isolation methods, benefits for infants, and potential medical applications.

Methods: We conducted a scoping literature review following the PRISMA-ScR guidelines. This review included studies investigating HSCs in human milk, utilizing molecular markers such as CD34⁺, CD113⁺, and CD117⁺ for characterization. Both *in vitro* and *in vivo* studies exploring the morphology, function, and clinical implications of these cells were considered. The diverse range of papers reviewed were indexed in PubMed, Science Direct, Scopus, Sage Journals, and Google Scholar, published between 2010 and 2023.

Results: This scoping review explored 577 articles and selected 13 studies based on our inclusion criteria, focusing on HSCs in human milk. Most studies dilute samples prior to HSC isolation, followed by detection using markers such as CD34⁺, CD113⁺, and CD117⁺, with flow cytometry serving as the primary analysis tool, focusing on their isolation and detection methods. While no definitive benefits have been conclusively established, there is a strong belief in the potential of HSCs to positively impact infant immunity, growth, and tissue repair.

Conclusions: This review presents significant evidence supporting the presence of HSCs in human milk, identified by markers such as CD34⁺, CD113⁺, and CD117⁺. These cells show considerable potential in enhancing infant health, including immunity, tissue repair, cognitive development, and gastrointestinal health. Despite methodological variations in isolation and detection techniques, the collective findings underscore the potential clinical relevance of HSCs in human milk. Moreover, this review highlights the non-invasive accessibility of human milk as a source of HSCs and emphasizes the need for further research to unlock their therapeutic potential.

KEYWORDS: CD34⁺; Cellular components; Hematopoietic stem cells; Human milk; Stem cells

1. Introduction

Mother's milk is the product of mammary glands and provides essential nutrition for infant growth and immunity[1]. Recent research identifies stem cell-like populations within mammary glands, expressing unique markers and capable of differentiation into various cell types[2]. Nestin-positive stem cells found in human milk demonstrate the potential to differentiate into nerve, bone marrow, pancreatic, and epithelial cells across organs[3]. Understanding these cellular properties is clinically relevant and offers insights into development and regeneration in breast-fed infants.

Hematopoietic stem cells (HSCs) are a potential stem cell population in human milk crucial for maintaining and producing diverse blood cell lineages throughout life. Initially emerging in embryonic organogenesis, HSCs primarily reside in adult mammalian bone marrow[4]. Like other stem cells, remaining in a quiescent state while retaining the ability to divide as needed[5]. Analysis *via* flow cytometry reveals a higher concentration of HSCs in colostrum compared to mature human milk[6]. These cells, identifiable by surface markers like CD34⁺ and additional markers such as CD113⁺, CD117⁺, CD150⁺, CD244⁺, and CD48⁺, can differentiate into various blood cell phenotypes and can mobilize in response to disorders affecting different organ systems, particularly the vascular system[2,7,8].

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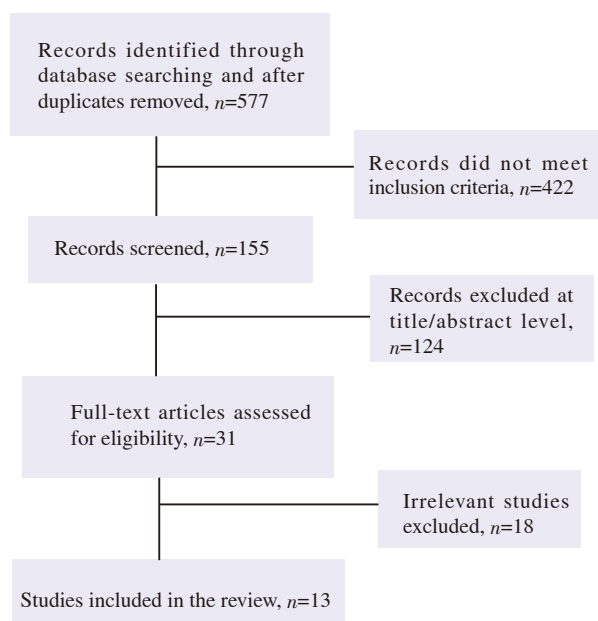


Figure 1. Flowchart of literature retrieval process.

Human milk stem cells offer potential as an alternative source for hematopoietic stem cell (HSC) transplantation, addressing the limitations of traditional sources like bone marrow. However, research primarily focuses on mesenchymal stem cells (MSCs) rather than HSCs[9–11]. Further investigation into HSCs in human milk is needed to understand their role in infant development and therapeutic applications.

2. Methods

This scoping review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines[12], systematically exploring studies about the presence and characteristics of HSCs in human milk. Inclusion criteria involved studies using molecular markers (e.g., CD34⁺, CD113⁺, and CD117⁺) for HSCs characterization, covering both *in vitro* and *in vivo* assessments of morphology, function, and clinical implications. A comprehensive literature search spanned databases such as PubMed, Science Direct, Scopus, Sage Journals, and Google Scholar, targeting only English-language articles published between 2010 and 2023. Data extraction used various keyword combinations, including 'human milk', 'breast milk', and 'stem cells'. Articles were evaluated based on title or abstract, with relevant studies included. Quality assessment followed PRISMA-ScR guidelines, considering study design and reporting clarity without excluding studies based on quality. Ethical considerations were maintained. This method aims to provide a comprehensive understanding of HSCs in human milk.

3. Results

3.1. Review of the literature

We identified a total of 577 articles, removing duplicates. Initially, 155 articles met the criteria. From these, 31 scientific papers offered information on the molecular diagnostics of HSCs in human milk. Ultimately, 13 studies provided the necessary information for our review. Figure 1 presents the PRISMA flowchart.

3.2. Human milk components and its benefits for infants

Mother's milk is a complex fluid with over 200 components, including lactose, fats, proteins, hormones, enzymes, growth factors, immunoglobulins, and cytokines[1,2]. Macronutrients energy is estimated at 65 kcal/dL to 70 kcal/dL[13], and micronutrient consist of essential vitamins such as A, B1, B2, B6, B12, D, and iodine[14]. The composition of a mother's milk varies among women, influenced by factors such as lactation stage, mammary gland fullness, breastfeeding frequency, infant growth rate and requirements, maternal health, and environmental factors[15]. Concentrations vary with each feeding to meet changing needs, offering a balanced array of macro and micronutrients essential for healthy growth and development. Human milk serves as a vital source of passive immunity, transmitting antibodies, immunoglobulins, and other immune-boosting factors that bolster the infant's immune system, thereby offering protection against allergies. Additionally, microbiota present in human milk play a crucial role in the development of gut microbiota[16], thereby reducing susceptibility to infections and diseases.

Beyond its physiological effects, breastfeeding fosters emotional bonding between the mother and baby through skin-to-skin contact, promoting feelings of comfort and security. Moreover, breastfeeding supports proper jaw and tooth development. Furthermore, breastfeeding has been linked to improvements in cognitive function and provides psychological benefits, emphasizing its crucial role in promoting overall infant health and well-being.

Human milk not only contains diverse bioactive elements like cellular components, immunological factors, and growth factors but also includes recently discovered constituents such as stem cells, commensal bacteria, and beneficial microorganisms like lactic acid-producing bacteria and bifidobacteria[17].

3.3. Stem cells in human milk

Over the past decade, evidence has emerged indicating that human milk contains stem cells and progenitor cells in addition to

Table 1. Mammary cells and expressed markers.

Mammary cells	Markers	References
Myoepithelial cells	Smooth muscle actin (SMA), cytokeratin 14 (CK14)	Sani <i>et al</i> [19]
Myoepithelial cells membrane	CK5, CK14, CK18	Kaingade <i>et al</i> [9]
Myoepithelial luminal cell molecule	Epithelial cell adhesion molecule (EPCAM)	Witkowska-Zimny <i>et al</i> [13]
Myoepithelial alveolar cells (lactocytes)	Cytokeratin 18 (CK18)	Sani <i>et al</i> [19]
Precursor mammary cell cytokeratin	Integrin 6 (CD49f) and 5 (CK5)	Twigger <i>et al</i> [20]
Leukocyte	CD45	Trend <i>et al</i> [21]
Mammary stem cells	Nestin	Sani <i>et al</i> [19]

the immune cell population[13]. Stem cells, identified by specific markers, can differentiate into various cell types and tissues *in vivo*, influenced by specific conditions. Advanced methods like multicolor flow cytometry enable precise evaluation of stem cell composition in human milk[15].

Previous hypotheses suggested the presence of stem cells and progenitor cells in the mammary glands and human milk based on the structural changes observed during pregnancy and breastfeeding[18]. Human milk stem cells, expressing embryonic stem cell markers like octamer-binding transcription factor 4 (OCT4), Y-box sex-determining region (SOX2), and homeobox (NANOG), can differentiate into ectoderm, mesoderm, and endoderm germ layers. While demonstrating colony morphology and phenotype similar to embryonic stem cells *in vitro*, they do not form teratomas when transplanted *in vivo* into immunosuppressed animals[13]. The precise origin of stem cells in human milk, particularly HSCs, is not definitively established. One hypothesis proposes that these stem cells originate from the mother's blood circulation. Cells in human milk can be categorized into two groups: those derived from blood, including immune cells and HSCs, and those from the mammary gland, including lactocytes and myoepithelial cells[15]. Further details regarding mammary cells and their markers[9,13,19–21] are provided in Table 1.

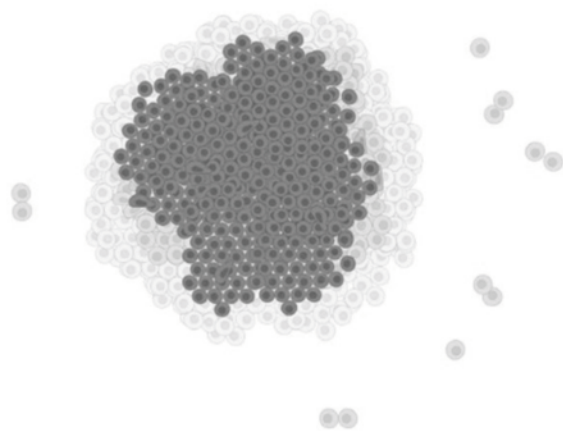


Figure 2. Graphic illustration of human mammary stem cell colonies that form mammosphere after eighth-day isolation (Adapted from Witkowska-Zimny M *et al*, *Cell Mol Biol Lett*[13]).

Several studies have provided evidence that human milk contains MSCs, which exhibit characteristics similar to embryonic stem cells, as well as mammary gland stem cells. These mammary stem cells are known to contribute to the formation of mammary gland tissue during late pregnancy and early lactation. They originate from the fetal circulating blood and are transferred to human milk after delivery. These stem cells express specific markers, including CD90, CD105, and CD73. Therefore, human milk comprises a heterogeneous population of cells, including lactocytes (milk-producing cells), myoepithelial cells derived from the ducts and alveoli of the mammary glands, as well as progenitor cells and stem cells. Freshly isolated epithelial cells from human milk have demonstrated the ability to form colonies with distinct morphologies, which can be maintained through multiple *in vitro* culture passages (Figure 2). The cellular content and proportion of human milk composition can be influenced by various factors, including infant feeding, maternal health, and the lactation stage[13].

3.4. Nature and therapeutic potential of HSCs

Fetal development in vertebrates undergoes various hematopoietic maturation stages, as depicted in Figure 3, regulated by the hematopoietic system[22]. HSCs, the primary source of adult blood and immune cells and give rise to multipotent progenitors (MPPs)[23]. These cells were first identified in the 1950s. This discovery led to the recognition of macroscopic, detectable, and serially transplantable multilineal colonies on the splenic surface 1 to 2 weeks post-transplantation[24]. Multiple studies conducted on identifying HSCs using "cell niche", as molecular marker[25], or using advance marker system such as Polylox Express Barcoding[26,27].

Any disruptions in HSC function can lead to a range of blood abnormalities, including aplasia and leukemia[28]. Currently, HSCs are the only definitive source for the treatment of malignant and non-malignant blood diseases caused by vertebral insufficiency. Bone marrow transplant or hematopoietic stem cell transplant (HSCT), aim to restore bone marrow function *via* intravenous HSC infusion. Donors can be the patient (autologous), others (allogeneic), or

Hematopoiesis

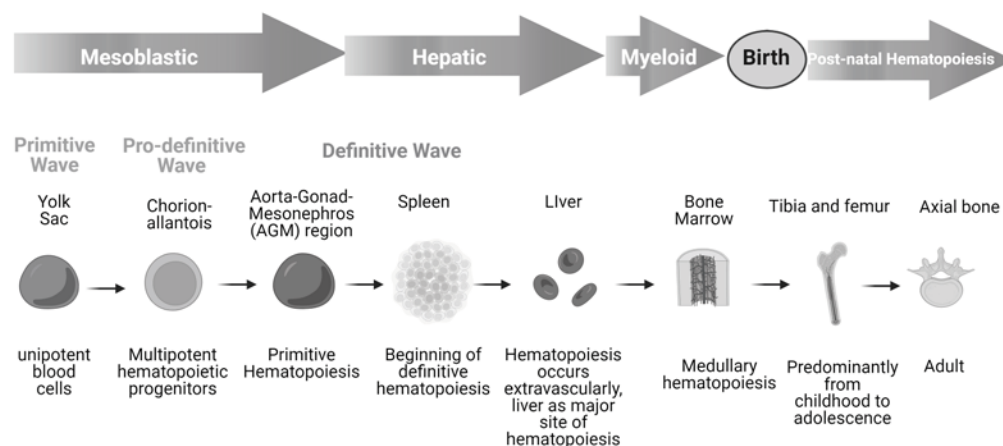


Figure 3. Graphic illustration of hematopoietic development throughout the prenatal and postnatal period reveals that cell differentiation begins as cells enter the fetal liver during the hepatic phase, while hematopoiesis in the myeloid phase occurs in the spinal cord during the third trimester of pregnancy (Adapted from Dzierzak *et al*, *Cell Stem Cell*[4]).

identical twins (syngeneic). HSCs are typically sourced from bone marrow, peripheral blood, or umbilical cord blood, with rare cases involving fetal liver collection.

3.5. HSCs identification in human milk

Identification of HSCs in human milk has emerged as an important area of study regarding the origin of stem cells. Multiple studies have provided evidence that certain subpopulations of stem cells in human milk share a common origin with HSCs. The presence of other blood-derived cells in human milk indirectly supports this notion. Commonly utilized markers for HSCs derived from peripheral blood samples include CD34 and CD45, which are recognized as universal surface antigens for HSCs[21]. Additional markers such as CD113, CD117, and CD133 have also been employed to further characterize and distinguish subsets of HSCs within human milk samples (Table 2). In a study by Valverde-Villegas *et al*, the marker CD34 was used to identify and characterize these stem cells[29]. The researchers observed that colostrum and early lactation human milk contain a high population of CD34^{dim/+} cells, indicating the presence of HSCs. These CD34^{dim/+} cells are considered HSCs. Additionally, as lactation progresses, the number of CD34⁺ cells increases, which represent other types of stem cells besides HSCs. This suggests that as lactation continues, the proportion of other types of stem cells in the milk becomes more prominent compared to HSCs[30,31]. However, the precise mechanism by which these cells are delivered into human milk and the physiological role of hematopoietic stem/progenitor cells in newborn development remain unknown[32].

The presence of HSCs and their progenitor cells (HPC) in

human milk has been demonstrated by Indumathi *et al* using flow cytometry. The main surface markers for HSCs were CD34, while CD113 and CD117 were used as markers for HPCs[7]. In contrast to bone marrow-derived HSCs, CD34, CD90, and CD45 were used as markers[33]. The study's results showed that the predominant expression of hematopoietic stem/progenitor cells in human milk, in terms of mean±SEM, was CD113⁺[(43.1±2.1)%] and CD117⁺[(23.2±1.51)%], followed by CD34⁺ stem cells [(13.07±2.0)%][33]. Similar observations were made in the study by Goudarzi *et al*, which showed that the hematopoietic markers in colostrum were higher than in mature milk using marker CD34 (1.39±0.69 *vs.* 0.45±0.23)[6]. The difference in the percentage population of CD34⁺ cells may affect the lactation stage and also the evidence of the dependability to the lactation days.

Another investigation focusing on HSCs within the bone marrow of healthy adult individuals, utilizing the CD34 marker, revealed a prevalence of approximately (1.05±0.44)%[34,35]. The study revealed a noteworthy similarity in the percentage of HSCs in human milk and CD34⁺ cells in bone marrow. This correlation is accentuated using a less invasive isolation technique for human milk-derived HSCs.

This correlation highlights human milk's potential as a convenient source of HSCs, enabling non-invasive research and applications in stem cell biology and therapy. However, human milk HSCs exhibited decreased expression after cell culture, differing from the increased expression in bone marrow-derived HSCs. Further investigation is needed to understand these implications for regenerative medicine and cellular therapies.

Table 2. Procedure for isolation and identification of hematopoietic stem cells (HSCs) in human milk and its potential benefits for infants.

Isolation	HSCs marker	Detection methods	Potential benefit for infants	Reference
Diluted with DMEM-LG, centrifuged at 400 <i>g</i> , and washed with PBS	CD34, CD133, CD117	Flow cytometry	Immunity, growth, and cognitive development	Indumathi <i>et al</i> [7]
Centrifugation at 400 <i>g</i> , washed with RPMI	CD34, CD133, CD45 and Nestin	RT-PCR; Flowcytometry; Immunofluorescence	Alternative sources for stem cell therapy	Fan <i>et al</i> [2]
Centrifugation at 1200 <i>g</i> at 4 °C for 15 min	CD 45, CD 34, and CD13	Flowcytometry	Angiogenesis, vasculogenesis, and brain development	Valverde-Villegas <i>et al</i> [30]
Diluted with an equivalent volume of phosphate-buffer saline (PBS), centrifuged at 400 <i>g</i> , at 25 °C for 15 min, and washed with PBS	CD 33, CD 34 and CD45	Flowcytometry	Immunity, tissue repair, gastrointestinal health, and brain development.	Goudarzi <i>et al</i> [6]
Centrifugation at 1200 <i>g</i> at 4 °C for 15 min	CD34 and CD 133	Flowcytometry	Neuroprotective, immunomodulatory effects, and long-term developmental benefits	Valverde-Villegas <i>et al</i> [29]
Diluted with an equivalent volume of Dulbecco's phosphate-buffer saline (DPBS), centrifuged at 810 <i>g</i> , at 20 °C for 20 min, and washed with DPBS twice	CD45, CD34, CD133, and CD117	Immunocytochemistry and electron microscopy	Regenerative potential, immunomodulatory effect, neuroprotective, and gut health	Coni <i>et al</i> [36]
Diluted and centrifugated	CD34, CD117, CD133	Flowcytometry	Tissue development and repair	Wu <i>et al</i> [37]
Density gradient centrifugation and immunomagnetic separation	CD34, CD38, CD45, and CD133	Flowcytometry, immunofluorescence staining, PCR	Not discussed	Witkowska-Zimny <i>et al</i> [13]
Not mention	CD34, CD271	Flowcytometry	Development and maturation immune system through micro chimerism	Ninkina <i>et al</i> [32]
Diluted with an equivalent volume of PBS, centrifuged at 800 <i>g</i> , at 20 °C for 20 min, and washed twice with PBS	ESRRB and CK5 (Cytokeratin 5)	qRT-PCR; Flowcytometry; Immunostaining	Immunity, tissue repair and regeneration	Twigger <i>et al</i> [20]
Diluted with 1:2 volume of Dulbecco's modified Eagle's medium (DMEM), centrifuged at 300 <i>g</i> , at 25 °C for 15 min, and washed with DPBS twice	Nestin	Flowcytometry	Supporting the infant's immune system and blood cell production	Kaingade <i>et al</i> [9]
Centrifugation at 600 <i>g</i> at 25 °C for 15 min, lipid removed and washed with PBS twice	CD45 and CD19	Flowcytometry	Enhance the infant's immune response	Trend <i>et al</i> [21]
Diluted, centrifugated and washed	CD34, CD133, CD117	Flowcytometry	Immunity, tissue repair and regeneration.	Syaidah <i>et al</i> [38]

3.6. Isolation technique and HSC culture from human milk

Various methods[2,6,7,9,13,20,21,29,30,32,36–38] can be used to isolate and extract HSCs from human milk and their potential benefits, explained in Table 2. Generally, the cellular components of human milk can be easily extracted using a simple method of dilution and centrifugation. Centrifugation speeds range from 50 to 3000×*g* for about 10-20 minutes. The specific method involves variable solution choice and centrifugation speed. Common solutions include Dulbecco's Modified Eagle Medium with Low Glucose (DMEM-LG), phosphate-buffered saline (PBS), or fetal bovine serum (FBS). Aseptic collection and prompt processing within 2-4 hours are crucial to minimizing variables. Separated

cell pellets undergo centrifugation and are diluted in equal PBS or media volumes[38]. Human milk HSCs were cultured by discarding the supernatant, followed by implantation of the cell pellet onto a tissue culture treatment plate containing DMEM medium. To enhance growth, 10% heat-inactivated human umbilical cord blood serum was added to the culture medium. Medium replacement occurs every other day to facilitate optimal cell proliferation. Upon reaching maximal confluence, cells were passaged using trypsin-ethylenediamine tetraacetic acid (EDTA)[39]. Immunofluorescence, quantitative reverse transcription-polymerase chain reaction (qRT-PCR), flow cytometry, and immunocytochemistry staining are commonly used methods for analyzing the cellular components of human milk.

3.7. The role of HSC content in mother's milk for breastfed children

Each mammal produces specific milk components to meet the nutritional needs of its newborn. The beneficial effects of breastfeeding on a child's physical and intellectual development in the short and long term have been recognized for centuries, but the underlying mechanism remains elusive[15]. The role of human milk HSCs in breastfed children is still a subject of inquiry. HSCs with CD34⁺ cell markers are present in the blood of term infants at various time points after birth, with a gradual decrease of less than 30% every 2 hours within 24 hours. HSC/HPC (CD34⁺, CD133⁺) have also been found in premature and term umbilical cord blood, believed to be derived from the mother's bloodstream while in the womb. However, the process of absorption of HSCs from human milk in the baby's digestive tract still needs to be investigated[29,36,40].

According to existing hypotheses, stem cells present in human milk may promote tissue homeostasis and regeneration in various parts of the child's body, including the brain[2]. Based on this hypothesis, a study analyzed the effect of uninterrupted breastfeeding without fasting and sternal closure in infants undergoing cardiac surgery, which significantly reduced the incidence of infection and postoperative complications. This effect may be attributed to microchimerism, where the mother's milk stem cells circulate in the child's bloodstream, aligning with the previous hypothesis[37].

Studies on experimental animals have shown that most lymphocytes from human milk congregate in the Peyer patch area of the small intestine, with the highest proportion being T lymphocytes and cytotoxic T cells (CTL). It has also been observed that CD8 T cells derived from human milk exhibit stronger cytolytic and inflammatory mediator effects compared to CD8 T cells produced by infants themselves. This finding is supported by the presence of CTL in Peyer's patches, which suppresses the infant's immature adaptive immune system to protect against the risk of oral infection during early life[31].

Additional potential of HSCs are as a primary therapy for high-risk childhood cancers using HSC transplantation (HSCT)[41]. Breastfeeding during HSCT therapy, with proper cleanliness of human milk, may support healing and extend lifespan[42]. However, more research is needed to understand these benefits fully.

4. Discussion

The scoping review presented here sheds light on the presence and identification methods of HSCs in human milk, hinting at their significant role in bolstering various aspects of infant health, including immunity, tissue repair, and overall developmental

processes. However, further research is needed to fully elucidate the mechanisms through which HSCs in human milk influence infant health. Standardization of isolation and detection techniques for HSCs will be crucial for ensuring reproducibility and comparability across studies.

In addition to HSCs, human milk offers numerous benefits for infant health and development. Breastfeeding provides optimal nutrition, conferring passive immunity against infections and allergies, and supports healthy growth and emotional bonding. Moreover, breastfeeding is associated with a reduced risk of chronic diseases later in life and promotes optimal jaw and tooth development. Overall, breastfeeding plays an integral role in infant nutrition and health, offering short-term and long-term benefits that contribute to the well-being of both the infant and the mother.

However, it is essential to acknowledge the limited depth of analysis in this research. Scoping reviews primarily aim to summarize existing literature with various study designs and methodologies, providing an overview of studies, identifying research gaps, and guiding future research.

In conclusion, currently, the main source of HSCs is bone marrow, which has limited availability. The identification of HSC/HPC content in human milk provides an alternative and relatively easy method for HSC isolation compared to bone marrow. Research on the potential of HSCs derived from human milk and their application in various clinical scenarios is still limited. However, this discovery opens a new field of potential research on the benefits of HSCs derived from human milk, with implications for cancer and stem cell studies beyond lactation itself.

Conflict of interest statement

There are no conflicts of interest in this study.

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Authors' contributions

Ghaniyyatul Khudri and Dewi Sukmawati put forward conception and design; Ghaniyyatul Khudri performed data collection, analysis, and interpretation, and article drafting; Dewi Sukmawati carried out

analysis and critical revision of the article; Ghaniyyatul Khudri and Dewi Sukmawati made final approval of the article.

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