

Opinion

# Potential Effect of Bovine Colostrum on Mesenchymal Stem Cells for Regenerative Therapy

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**Abstract:** Bovine colostrum is the first mammary secretion after parturition; it is rich in Igs and bioactive compounds and could play a role in the development of naturally based products with positive effects on human health. In this discussion, we critically examine the effect of bovine colostrum on the properties of mesenchymal stem cells. Multipotent mesenchymal stem cells (MSCs) are a heterogeneous subset of fibroblast-like cells that can be isolated from various biological tissues, such as bone marrow, umbilical cord, and adipose tissues. They are characterized by their ability to self-renew and differentiate into cells of the mesodermal lineage, including adipocytes, osteocytes, and chondrocytes. Additionally, MSCs display an immunomodulatory capacity due to their ability to interact with effector cells typical of both innate and adaptive immune responses. Considering these important properties, MSCs have gained increasing attention in the field of regenerative medicine in recent decades. To date, most experimental protocols are based on cell culture media supplemented with fetal bovine serum (FBS) to promote the ex vivo expansion of MSCs while preserving their differentiative and immunomodulatory capacities. Future trends could involve the application of bovine colostrum in regenerative medicine.

**Keywords:** mesenchymal stem cells (MSCs); bovine colostrum; osteogenesis; inflammatory liver disease; regenerative therapy; functional foods; nutraceutical



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## 1. Introduction

Mesenchymal stem cells (MSCs) can be isolated from several tissues including the umbilical cord, dental pulp, breast milk, peripheral blood, endometrial polyps, nasal polyps, bone marrow, and adipose tissue. In recent decades, they have attracted increasing attention in regenerative medicine thanks to their ability to self-renew and to differentiate into a variety of cell types, including osteoblasts, chondrocytes, myocytes, hepatocytes, and adipocytes. MSCs are described as a clonal population of plastic-adherent cells and are specifically identified by a minimal phenotypic pattern, including the expression of CD73, CD90, and CD105, while lacking CD34, CD45, and HLA-DR antigens [1–3].

In recent years, new and varied reagents have been tested to improve the in vitro expansion of mesenchymal stem cells while preserving their differentiative potential. To date, most experimental activities based on the ex vivo expansion of MSCs require the integration of fetal bovine serum (FBS) into the basal medium at concentrations that do not alter the biological properties of the cells [4,5].

However, reconstituting culture media with FBS is raising ethical concerns because for its production, one million calf fetuses are euthanized annually. In addition, FBS could be a source of viruses, bacteria, and endotoxins, causing infections or allergic reactions [6].

On the other hand, dairy products, like serum, can support the proliferation and differentiation of multipotent stem cells. In a recent study by Bircan Boga and colleagues, human placental mesenchymal stem cells were cultured with a milk or whey solution at increasing concentrations and analyzed for their proliferation and differentiation capacity in comparison to FBS. Milk or whey were able to support cell proliferation as well as adipogenic and osteoblastic differentiation, albeit at lower levels than FBS [7].

A potentially appealing new substrate for promoting stem cell proliferation might be colostrum. Bovine colostrum is the “first mammary secretion after parturition” from mammary glands, consisting of a yellowish, viscous fluid rich in immunoglobulins, nutritional components, and other bioactive compounds which are all present in a highly concentrated low volume [8]. Ruminant newborns require colostrum in a timely manner to acquire passive immunity and enhance physiological processes such as gastrointestinal development, protection against infection, thermoregulation, and resistance to microbial infections [9,10]. In addition to macronutrients and micronutrient components (carbohydrates, fats, proteins, fatty acids, conjugated linoleic acid, oligosaccharides, amino acids, vitamins, and minerals), the principal constituents of ruminant colostrum are immune factors (immunoglobins IgG, IgA, and IgM), lactoferrin, lysozyme, lactoperoxidase, microRNA, glycoconjugates, B and T lymphocytes, leukocytes, interleukins, and other proline-rich polypeptides; growth factors, (IGF-I and -II), epithelial growth factors (EGFs), growth hormones, platelet-derived growth factors, fibroblast growth factor, epidermal growth factor, and low-abundance proteins [11–14].

Given the limited data available in the literature, here, we discuss the effect of bovine colostrum on the proliferative and differentiative profile of MSCs and examine the context of using colostrum and MSCs in combination for tissue regeneration. Moreover, we focus on bovine colostrum’s ability to stimulate tissue repair in rat animal models with inflammatory liver disease when administered orally in combination with MSC injections.

## **2. Bovine-Colostrum-Based Therapeutic Strategies to Achieve Tissue Regeneration and Repair**

### *2.1. Exploring the Effects of Bovine Colostrum’s Capability to Induce the Osteoblastic Differentiation of Human Mesenchymal Stem Cells and to Sustain Bone Metabolism in Rats*

Bovine colostrum’s unique composition and wide availability and the extensive number of preclinical and clinical research studies that have highlighted its therapeutic advantages [15–17] have generated significant interest in the development of naturally based products or functional foods. These products aim to impact human health positively across a broad spectrum of health indications.

Nowadays, novel therapeutic strategies to achieve tissue regeneration and repair have attracted great attention. Regenerative medicine is a growing field that applies stem cell populations or their secreted products to treat a variety of diseases.

The beneficial regenerative potential of bovine colostrum was extensively demonstrated in the skin regenerative process. Recently, Han and colleagues (2022) examined the potentially beneficial effects of bovine-colostrum-derived exosomes on UV-induced damage in three major resident skin cells (keratinocytes, melanocytes, and fibroblasts). The authors underlined how colostrum exosomes prevented the UV-induced generation of intracellular reactive oxygen species, could significantly reduce the production of the protective skin-darkening pigment melanin, and increased cell proliferation, accompanied by enhanced collagen production [18]. Bovine colostrum (BC) appears efficacious in sustaining ectoderm-derived cells.

However, a small number of scientific research studies aimed to investigate the effect of BC on mesoderm-derived mesenchymal precursors able to differentiate in skeletal and connective tissues.

So, what is the effect of bovine colostrum on mesenchymal stem cells? How does this peculiar product of animal origin impact developmental biology and the repair of damaged tissues? Here, we discuss the works currently reported in the literature which report the positive and negative effects of BC on MSCs.

Bovine colostrum is a good source of cytokines and growth factors, with a key role in the proliferation, migration, and differentiation processes of MSCs, including FGF-b, TGF, and TNF, and in 2014, Mussano et al. were pioneers in testing the effect of bovine colostrum as a possible adjuvant in bone healing. In this respect, they demonstrated the presence of the osteogenic protein BMP-2 in bovine colostrum as well as its ability to stimulate the release of several cytokines in human adipose-derived stem cells (hADSCs), including interleukin IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and VEGF, compared to cells cultured in basal conditions with 2% FBS. The authors observed a dose-dependent increase in the proliferation of MSCs when the basal culture medium was supplemented with standardized bovine colostrum derivative (SBCD) at 2.5 and 5 mg/mL, respectively. In addition, SBCD (5 mg/mL) appeared to be a powerful inducer of osteogenesis when added to an osteoblastic differentiation medium (50  $\mu$ M ascorbic acid, 10 mM  $\beta$ -glycerophosphate, and 100 nM dexamethasone), but not alone. It significantly enhanced early osteoblastic differentiation markers such as alkaline phosphatase activity and collagen I expression, as well as later osteogenic markers including calcium deposits and osteocalcin detection. Interestingly, SBCD was revealed to be able to promote *in vivo* osteogenesis. When SBCD was injected into mice in the presence of hydroxyapatite, macrophages, and stromal cells were recruited, stimulating extensive stromal calcification as early as 20 days [19].

It has been demonstrated that cow colostrum is effective in regenerating bone, particularly when it is used to treat osteoporosis [20,21].

Recently, Kydonaki, E.K. and colleagues produced ovariectomized (OVX) and orchidectomized (ORX) rat models to investigate the potential benefits of bovine colostrum (BC) on bone metabolism. Specifically, twenty-seven-week-old Wistar Han rats were divided into four groups according to the BC concentration administered: the first group corresponded to placebo control rats, the second one was exposed to BC supplementation dose 1 (BC1: 0.5 g/day/OVX, 1 g/day/ORX), the third was treated with BC supplementation dose 2 (BC2: 1 g/day/OVX, 1.5 g/day/ORX), and, finally, BC dose 3 (BC3: 1.5 g/day/OVX, 2 g/day/ORX) was supplied to the fourth group.

Following four months of BC supplementation, the bone microarchitecture was significantly improved. The cortical and trabecular bone mineral contents of the OVX rats in the BC1 group were significantly higher, whereas in the BC2 and BC3 groups, the trabecular bone mineral content was particularly higher. In ORX rats given BC dose 2, considerably higher levels of trabecular bone mineral content were reported compared to the other groups. These data were supported by high mRNA levels of bone resorption/formation markers including OPG, VEGFA, FGF2, and RANKL in the groups administered higher doses of BC. On the other hand, osteocalcin levels were noticeably higher in all ORX BC supplementation groups compared to the placebo [20].

In a second study, the authors compared the efficacy of colostrum (BC) supplementation in ovariectomized (OVX) and orchidectomized (ORX) rats with the well-known effects produced by available pharmacological and non-pharmacological agents for osteoporosis, including alendronate (ALE) and vitamin D (VD) or calcium (Ca) supplementation. The results suggested that BC supplementation may enhance the bone physiology of ORX and OVX rats by promoting the growth of new bone, albeit not to the same extent as existing ALE medication treatment for osteoporosis [21].

BC supplementation improves bone metabolism and could be a support in the treatment of bone mass loss, as well as in preventing the deterioration of bone microarchitecture typical of osteoporosis.

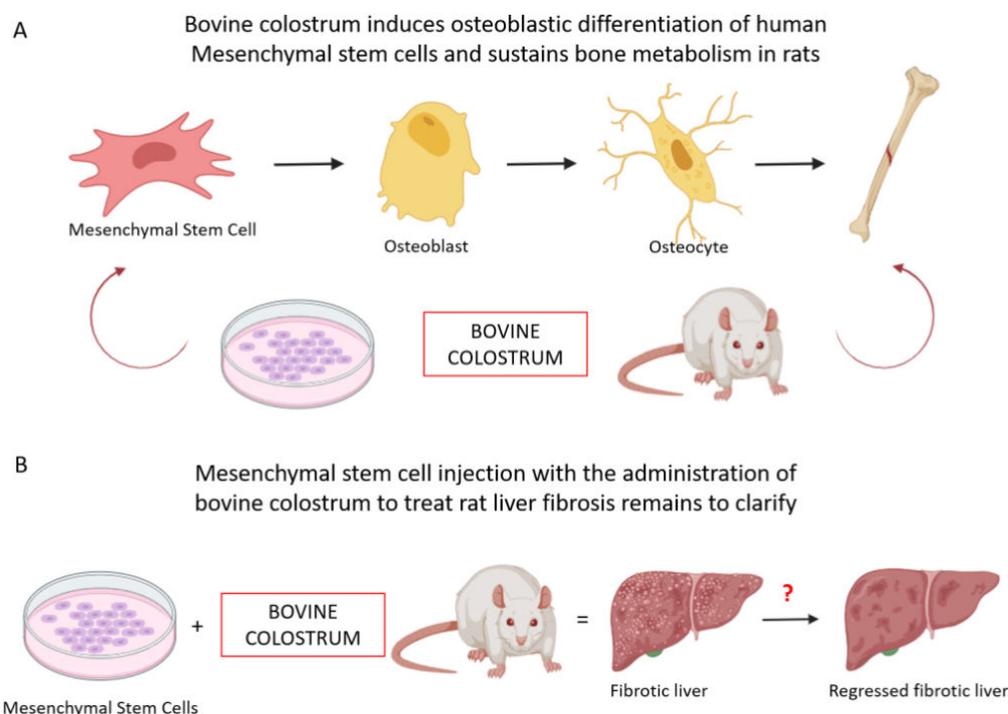
In the future, bovine colostrum could be a good source of supplementation to promote the repair of bone fractures since it seems to have an impact on the biological processes of skeletal development.

## 2.2. Investigating the Use of MSC Injection with the Administration of Bovine Colostrum to Treat Rat Liver Fibrosis

Recently, the combination of bovine colostrum and MSCs was revealed to be an intriguing tool for the treatment of liver fibrosis in rats. This liver damage can be the result of viral infections or exposure to toxic agents; it can also be generated by autoimmune, cholestatic, or metabolic diseases. Chronic inflammation induces an abnormal accumulation of the extracellular matrix (ECM) in normal parenchymal tissue; this process is continuously fed by inflammatory cytokines, the first of which is tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) [22].

In this regard, Gunadi and colleagues (2021) evaluated the effect of an MSC (1,000,000) injection associated with bovine colostrum administration at a dose of 15  $\mu$ L/g for 10 days on the liver regeneration process in 40 male Wistar rats. The animals tested had only 50% liver with liver fibrosis as they had previously undergone a resection and the administration of CCl<sub>4</sub> for 6 weeks. They found a significant reduction in TNF-alpha expression in the group of rats injected with MSCs and exposed to colostrum treatment compared to those injected with MSCs alone. On the other hand, after a 50% resection, no significant differences in the liver regenerative process were observed in rats exposed to colostrum treatment compared to the control group on days 3, 7, and 10, respectively. In addition, the combination treatment with MSCs and bovine colostrum significantly increased the number of type 2 macrophages positive for CD163 expression whose anti-inflammatory role in liver tissue is widely recognized [23]. In conclusion, the influence of bovine colostrum on the pathogenesis of liver fibrosis in rats is due to its ability to regulate the process of oxidative stress since it is rich in antioxidant elements including superoxide dismutase, GPx, catalase, vitamin E, vitamin C, and carotene [24,25]. However, these interesting data do not travel on the same wavelength as other scientific evidence reported in the literature. For example, another study by Kusumo et colleagues evaluated whether the injection of umbilical-cord-derived mesenchymal stem cells (UC-MSCs) from pregnant, single Sprague-Dawley (SD) rats in association with treatment with bovine colostrum could be effective at decreasing the expression of transforming growth factor- $\beta$  (TGF- $\beta$ ) and serum glutamic pyruvic transaminase (SGPT) in post-hepatectomy liver failure (PHLF) model animals. Indeed, TGF- $\beta$  plays an important role in the genesis of fibrosis as it activates hepatic stellate cells (HSCs) in myofibroblasts (MF), thus stimulating the production of type III collagen. In this case, eighteen Sprague-Dawley rats were injected with CCl<sub>4</sub> for eight weeks and then subjected to a 50% liver resection (LR). The authors found a significant decrease in TGF- $\beta$  and SGPT levels in both the group of animals injected with parenchymal MSCs and in the group in which the parenchymal injection of MSCs was associated with the oral administration of bovine colostrum (15  $\mu$ L/g) on the third and seventh days. Unfortunately, the combined treatment with MSCs and bovine colostrum was revealed to be no better compared to the single MSC treatment in the regenerative process of the liver tissue in the PHLF animal model [26]. These results were confirmed by Albert Eko Hendrawijaya's investigations. In this study, the authors demonstrated that co-treatment with BC and MSCs did not increase ALP and Takeda G-Protein Coupled Receptor-5 (TGR5) levels in Wistar rats post 50% hepatectomy with liver fibrosis [27]. Interestingly, in 2022 Hartanto and colleagues demonstrated that the combination of UC-MSCs (obtained from pregnant, single Wistar rats) and bovine colostrum was able to reduce  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) expression as well as the neutrophil-lymphocyte ratio (NLR) in the liver of post-resection Wistar rats by 50%. In this experiment, liver fibrosis was induced in thirty-six Wistar male rats via the injection of CCl<sub>4</sub> for 8 weeks; the animals tested then underwent liver resection. Immunofluorescence staining showed a significant decrease in  $\alpha$ -SMA, typically expressed in myofibroblasts, in the UC-MSC and bovine colostrum combination therapy group compared to colostrum or the MSC group in single therapy. These results were less evident when the neutrophil-lymphocyte ratio (NLR) was calculated. The NLR profile was similar in rats injected with MSCs alone and in those exposed to a combined treatment with MSCs and bovine colostrum (MSCs + C). The relationship between the immunosuppressive role of MSCs and the immunoregulating activity of bovine colostrum

remains to be elucidated [28]. This represents a heavy limit in the field of liver regenerative therapy, so other experimental models are required to clarify the true applicability of BC. In addition, in the future, it would be interesting to evaluate whether the administration of bovine colostrum could potentiate the effect and/or time of action of other drugs with a recognized role in the treatment of liver fibrosis [29,30] (Figure 1).



**Figure 1.** Schematic representation of the effects of mesenchymal stem cell injection and bovine colostrum administration in rats with 50% liver fibrosis (created with Biorender.com).

### 3. Conclusions

The health benefits of bovine colostrum have been extensively studied in ruminants; however, their effect on human or rat mesenchymal stem cells remains a largely unexplored field. Other studies will be needed to clarify whether and how the mix of cytokines, growth factors, and peptides that distinguish this attractive product of animal origin can impact the field of MSC-based regenerative medicine as well as systemic inflammatory and autoimmune conditions. To date, few studies have evaluated the possible beneficial effect of bovine colostrum administration together with an MSC injection to stimulate tissue regeneration in rats. A number of molecular pathways, including FGF-b, TGF, and TNF signaling, appear to be involved in the regenerative mechanism. However, some results are not yet completely clarified, so other molecular and cellular investigations are required in the future.

The studies summarized here represent a starting point for investigating the use of bovine colostrum in regenerative therapy, especially in reparative mechanisms in bone.

In addition, it would be interesting to also evaluate the impact of bovine colostrum on cancer cells; other studies have already demonstrated the pro-apoptotic effect exerted by sheep colostrum on chronic myeloid leukemia cells [16].

In the future it will be worthwhile to investigate if the incorporation of functional foods, including BC, into dietary formulations could be helpful for human health, including in the treatment of liver fibrosis.

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