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Colostrum and its benefits: a review

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Abstract

Colostrum, a nutrient-rich fluid produced by female mammals immediately after giving birth, is loaded with immune, growth and tissue repair factors. It is a complex biological fluid, which helps in the development of immunity in the newborn. It contains significant quantities of complement components that act as natural anti-microbial agents to actively stimulate the maturation of an infant's immune system. Bovine colostrum, a raw material for immune milk preparations, can be used to treat or prevent infections of the gastrointestinal tract. It is possible that colostral preparations aimed at specific consumers may play a significant role in healthcare in the future. Besides providing immune support, colostrum has remarkable muscular-skeletal repair and growth capabilities. Studies have shown that colostrum is the only natural source of two major growth factors namely, transforming growth factors alpha and beta, and insulin-like growth factors 1 and 2. These growth factors have significant muscle and cartilage repair characteristics. They promote wound healing with practical implications for trauma and surgical patients. Colostral growth factors have multiple regenerative effects that extend to all structural body cells, such as the gut.

Keywords: Human milk; Colostrum; Immunity; Wound healing; Growth factors

1. Immune system effects

1.1. Colostrum

At the closing of John Steinbeck's classic, *The Grapes of Wrath,* a woman whose newborn baby had just died saved a man dying of starvation by breast-feeding him. It was one of the

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Table 1
Cellular contents of colostrum

Cell type	Mean number ± SEM (per mm^3)	Percentage of total cells
Macrophages	2860 ± 1166	49
Polymorphs	1964 ± 855	37
Lymphocytes	675 ± 312	12
Epithelial cells	98 ± 41	2

Reprinted from Chandra RK, Breast Feeding: Immunologic and Nutritional Considerations, *Clinical Nutrition*, 2: 21–24, 1983, by permission of the publisher Churchhill Livingstone.

most highly charged moments in modern literature, and now scientific research suggests that the selfless act of this woman not only saved the man's life, it may have recharged his immune system as well [1]. The substance transferred to was colostrum (the milk produced for the first few days after birth), a rich source of nutrients, antibodies and growth factors for the suckling [2,3]. It is richer in growth factors and antibodies than ordinary milk [2,3]. Colostrum is the most potent natural immune booster known to science. It is a source of immune components and nutrients, and contains more protein, immunoglobulins (Ig), non-protein nitrogen, fat, ash, vitamins, and minerals than does milk. Because some vitamins do not cross the placental barrier, colostrum is the primary source of these nutrients for the suckling after birth [4]

This immune stimulant is a protector against a wide spectrum of bacteria and viruses [1]. Lactoferrin and immunoglobulin G (IgG) are the major glycosylated proteins in whey preparations from colostrum [5]. As reported by Mach and Pahud [6], IgG-1 is the principal immunoglobulin type in colostrum whereas IgM, IgA and IgG-2 are present in lower amounts. The concentrations of immunoglobulin A in colostrum are almost a hundred-fold higher than in milk. Calves with high serum immunoglobulin concentrations have lower mortality rates than calves with serum IgG less than 10g/L [7]. An earlier study [8] indicated that colostrum is loaded with polymorphonuclear leukocytes and macrophages, T-lymphocytes, B-lymphocytes, plasma cells, and epithelial cells (Table 1). This study revealed that the macrophages can produce lysozyme, complement components (C3 and C4), and interferon. It shows marked microbial activity, and seem to afford partial protection against the near-fatal syndrome of necrotizing enterocolitis of the newborn.

1.2. Breast milk and immunity

The anti-microbial factors present in human milk include interferons, immunoglobulins, iron-binding proteins, polymorphonuclear leukocytes, macrophages and lymphocytes [8]. Secretory IgA (sIgA) is present in large amounts in human breast milk, and represents the predominant immunoglobulin fraction [8,9]. Breast milk IgA may alter the culture characteristics of fecal pathogenic bacteria such as *E. coli.* Breast-fed infants have higher levels of sIgA than bottle-fed infants (Fig. 1).

Dallas and Rolfe [9] investigated the ability of sIgA to bind *Clostridium difficile* toxin A. It was observed that sIgA in human milk or colostrum binds to toxin A and may function as

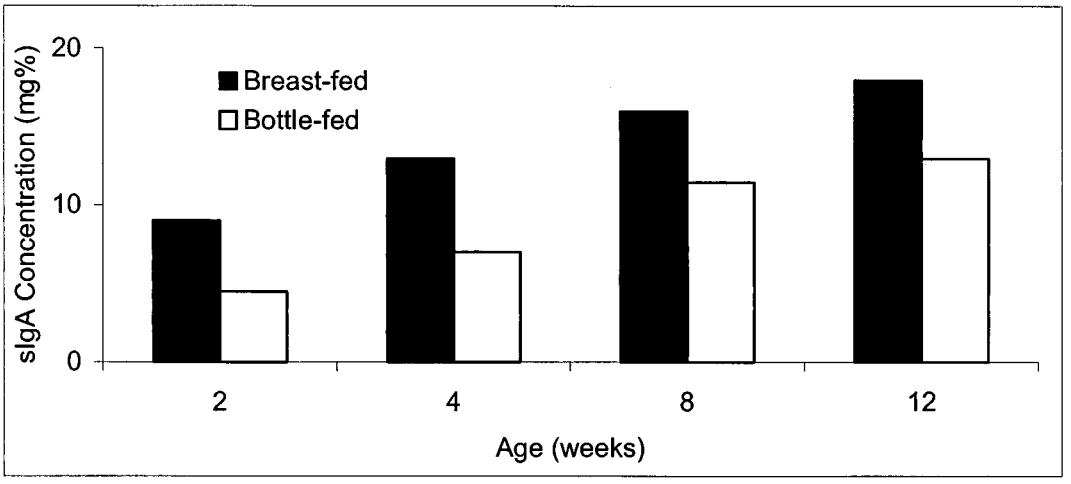

Fig. 1. Detectable secretory IgA concentration in saliva of breast- and bottle-fed infants. (Reprinted from Chandra RK, Breast Feeding: Immunologic and Nutritional Considerations, *Clinical Nutrition*, 2: 21–24, 1983, by permission of the publisher Churchill Livingstone.)

a receptor analogue to protect human infants against *C. difficile*-associated disease. Secretory IgA acts as the first line of defense against infectious agents attempting to penetrate the mucus membranes. One study [10] of Canadian infants observed a reduction in episodes of diarrhea, ear and respiratory infections among breast-fed infants. In another study [11], exclusive breast feeding for the first few weeks of life has been shown to effect a significant reduction in the development of allergic disorders, including atopic eczema and recurrent wheezing in infants with a strong family (parental) history of allergy. This is associated with lower levels of serum IgE and fewer circulating eosinophils. Human milk or colostrum contains significant quantities of complement components, C3 [8] that act as natural anti-microbial agents. Breast milk is equipped with protective factors that provide the needed specific and nonspecific passive immunity [8].

Colostral IgA is preferentially transferred to the neonate during the first 3 days postpartum [3]. At that time almost 4g of IgA is ingested by the newborn during the first day of breast-feeding. This high amount of IgA, almost equal on the first day to the total production of mucosal IgA in a normal adult [12], underscores the importance of human milk immune protection to vulnerable immature infants. According to Xanthou *et al.* [3], when an infant ingests 500 mg of polymeric IgA (pIgA), 150 mg will remain intact in the small intestine. This quantity of anti-microbial protein could make a very significant contribution to mucosal host defense. The major function of pIgA is to block the adhesion of microbial pathogens onto the intestinal epithelial surface. In one study [13], purified sIgA from colostrum and breast milk was shown to inhibit the localized adherence of enteropathogenic *E. coli* (EPEC). In the newborn rat, the concentration of DNA and the rate of DNA synthesis were greater in animals fed colostrum in comparison to animals fed mature milk. This suggests that colostrum may contain growth factors not present in mature milk or present in higher quantities in colostrum [14]. Epidermal growth factor is an example of a polypeptide found

in significantly higher concentrations in colostrum than mature milk. It increases DNA synthesis, mitotic activity and enhances brush-border membrane enzyme activity when injected into suckling mice [15].

Scientists have long known about the increased resistance of breast-fed babies to certain infections, particularly to intestinal disorders [16]. In this study, immunoglobulins A, M and G were measured in the milk of nursing mothers at the beginning of lactation and in the feces of their children. The IgA level in the human milk was very high especially during the first week of lactation. Results revealed that sIgA of human milk is stable and resistant to gastrointestinal juices and enzymes, thus gives passive immunological protection to the digestive tract of the newborn infant. A descriptive survey was conducted with infants aged 6–12 months to determine the relationship between infant feeding practices and diarrhea [17]. A guided interview was conducted with mothers of infants who attended the health facilities of Mbabane, Swaziland. Results showed that infants who were given colostrum and breast milk had fewer diarrheal attacks.

1.3. Iron-binding lactoferrin

Another immune factor present in colostrum is lactoferrin, an iron-binding protein with antibacterial and antiviral properties [1]. Chandra [8] reported that human milk contains large quantities of lactoferrin and transferrin; both are effective binders of iron. They exert their bacteriostatic effect by making iron unavailable for bacterial multiplication. Lactoferrins purified from milk and colostrum were assayed *in vitro* for their anti-HIV effects in cells and fibroblasts [18]. These lactoferrins were able to inhibit HIV-1 induced cytopathic effects. Bacteria and viruses need iron to grow and multiply. However, this iron is not made available to them because of lactoferrin's ability to bind, transport and release the iron only to the body's own cells. This gives lactoferrin the unique ability to protect humans from a wide range of harmful organisms. Other studies have shown that lactoferrin works in combination with sIgA and lysozyme [1,19]. These biochemical substances are involved in the antibacterial defense of the intestinal mucosa and are available in colostrum. Kussendrager [19] discussed the properties of colostral or milk proteins, lactoferrin and lactoperoxidase. These proteins have a role in the immune defense system, with high concentrations (6–8 g/L) found in colostrum. Both proteins demonstrated antibacterial activity. Based on the physiological and functional properties of lactoferrin, food applications include infant formulas and health foods. Potential applications of the lactoperoxidase system include functional foods, liquid milk products, cheese, meat, fish, and poultry products [19].

1.4. Immune factors in bovine colostrum

Bovine colostrum is a rich source of biological active compounds such as growth factors and essential nutrients [20]. It is richer in immune factors than human colostrum, particularly in the body's most important immunoglobulin, IgG. Bovine colostrum can supply an overtaxed body with more immunoglobulins than human colostrum [1]. Bovine colostrum contains large amounts of sIgA, which protects against viruses (e.g. poliovirus, influenza A virus and herpes simplex virus) and bacteria such as *E. coli*, salmonella and streptococcus

[21]. The protective efficacy of oral bovine immunoglobulin concentrate derived from colostrum against challenge with *Shigella flexneri* was studied in healthy adult volunteers in a randomized double-blind fashion [22]. Volunteers were given a product consisting of hyperimmune immunoglobulin concentrate with a high titer of anti-*S. flexneri* lipopolysaccharide (LPS) with sodium bicarbonate or a control preparation containing sodium bicarbonate three times a day for seven days. According to this report, the orally administered bovine immunoglobulin concentrate from colostrum protected the human volunteers from infection after they were injected with *Shigella flexneri*, a bacterium that causes dysentery epidemics. None of the volunteers who received the high-tittered hyperimmune product became ill, compared with 45% of volunteers who received the placebo. The duration of shedding of the challenge organism was decreased, and the active immune responses to *S. flexneri* LPS were less frequent and of lower magnitude in volunteers given the immunoglobulin concentrate from colostrum than in the control group. This immunoglobulin may be useful in preventing shigellosis among individuals at risk during a shigella outbreak. Similarly, Korhonen *et al.* [23] investigated the presence of natural antibacterial activity of *Helicobacter pylori* in serum, colostrum and milk from non-immunized cows. Results showed that serum and colostrum but not post-colostral milk were highly bactericidal for *H. pylori.*

1.5. Colostrum and eye infections

One study [24] assessed the antimicrobial capacity of human colostrum against *Chlamydia trachomatis*, a common agent of ophthalmia neonatorum. Results indicated that topically applied colostrum was effective in the prophylaxis of ophthalmia neonatorum of chlamydial etiology. Another investigation revealed that topically applied colostrum alleviates severe eye dryness and problematic eye lesion [25].

1.6. Colostrum and T-cells activation

In 1993, researchers discovered an immunomodulary peptide in colostrum known as proline-rich polypeptide or PRP [26]. PRP stimulates immature thymocytes to turn into functionally active T-cells. One report studied the effects of PRP, isolated from colostrum, on the kinetics of vesicular stomatitis virus (VSV) replication in resident peritoneal cells. Results revealed that the addition of PRP led to the inhibition of VSV replication [27]. Furthermore, PRP acts as an immunoregulator by changing surface markers and functions of cells [1]. Immunoregulators play important roles in homeostasis, activation of the immune response against infections, and in prevention of autoimmunity or conditions in which one's own tissues are subjected to the deleterious effects of the immune system (e.g. multiple sclerosis and rheumatoid arthritis). Colostrum and human milk contain soluble receptors and cytokine antagonists, materials that contribute to their anti-inflammatory property [28]. Colostrum has about one-half the *in vitro* inhibitory activity of gentamicin against *Staphylococcus aureus* and coliform organisms [29].

2. Colostrum as a food supplement

2.1. Functional food ingredient in healthcare

Colostrum is an excellent nutritional supplement especially for the elderly, who need to counteract the immune-suppressing effects of stress, illness, and too much "prepared" food in the diet [1]. Korhonen [30] in a recent finding suggested that hyperimmune colostral or milk preparations targeted at specific consumer groups may play a significant role in healthcare in the future, as part of a health-promoting diet and as an alternative or supplement to medical treatment regimes. Bovine Ig in colostrum has the potential to be utilized as immunological supplements to infant formula and other hyperimmune foods [31]. Similarly, an edible supplement containing processed bovine colostrum, magnesium peroxide (as a source of active oxygen), a vitamin (such as vitamin C), magnesium succinate and a bioflavonoid has been described [32]. As indicated by these scientists, the colostrum component may be used as an outer shell for a composite pill, tablet or capsule which may include an inner core containing materials of the colostrum component. In this way a wide variety of supplements may be provided in pill or capsule form, giving the advantages of colostrum, active oxygen and other materials.

The potential applications of bovine colostrum products in human clinical nutrition was examined [33], and the successful use of immune milk preparations to treat and prevent infections of the digestive tract in young children was reported. Mitra *et al.* [34] demonstrated that the ingestion of Ig having neutralizing activity against several serotypes of rotavirus prevents the occurrence of diarrhea and reduces the duration of virus excretion in infants. Thus, bovine Ig in colostrum and milk has the potential to be utilized as immunological supplements in infant formula and other hyperimmune foods [35].

2.2. Prevention of NSAID induced gut damage

Playford *et al.* [36] have used several well validated *in vivo* and *in vitro* models to investigate the potential value of defatted milk and colostrum preparations in reducing non-steroidal anti-inflammatory drug- (NSAID) induced gastrointestinal damage. NSAIDs are effective for arthritis but cause gastrointestinal injury. The efficacy of a defatted bovine colostral preparation to prevent gastric and small intestine injury induced by the NSAID indomethacin was investigated. Animal models showed that the injury caused by indomethacin could be reduced by colostrum while a similarly prepared milk solution was far less efficacious. For the *in vitro* studies, rat small intestinal and human colonic cells were used to show that these effects were not species specific.

Effects of test solutions, administered orally, were examined using an indomethacin restraint rat model of gastric damage and an indomethacin mouse model of small intestine injury. Results showed that pretreatment with 0.5 or 1 ml colostral preparation reduced gastric injury by 30% and 60%, respectively in rats. A milk preparation was much less effective. Furthermore, addition of colostrum to drinking water (10% v/v) prevented villus shortening in the mouse model of small intestinal injury. Addition of milk preparation was

ineffective. Colostrum increased proliferation and cell migration. It was concluded that bovine colostrum could provide a novel, inexpensive approach for the prevention and treatment of the injurious effects of NSAIDs on the gut and may also be of value for the treatment of other ulcerative conditions of the bowel [36]. For instance, an earlier study [37] examined the effects of colostrum on neonatal gut development and revealed that porcine colostrum increased gut growth in suckling pigs.

Indomethacin causes damage to the gastrointestinal tract by several mechanisms including reduction of mucosal prostagladin levels, reduction of mucosal blood flow, stimulation of neutrophil activation, and stimulation of apoptosis [38]. It is likely that many of these mechanisms will be influenced by the numerous growth factors present in the colostrum preparation [36]. Playford *et al.* [39] stated that some of these peptides, e.g. epidermal growth factor (EGF) and alpha-TGF, are susceptible to digestion from luminal proteases when administered alone. However, peptides involved in mucosal repair can act in a synergistic fashion if co-administered [40]. Hence, there are reasons why the use of colostrum preparation, as opposed to giving a single recombinant peptide, might be particularly beneficial.

There has been little research into the potential value of using milk or colostral fractions for adult gastrointestinal conditions. Playford *et al.* [36] revealed that bovine colostrum preparation are currently available in USA, UK and the rest of Europe as "over the counter" health food supplements. They contain large amounts of potent growth factors, which have been shown [36] to influence cell growth and migration *in vitro* and reduce indomethacin-induced gut injury *in vivo*. When an acute mucosal injury occurs, the initial phase of the repair process is the rapid migration of surviving cells over the denuded area, to reestablish a continuous epithelial layer. This begins within the first hour following injury and it is termed "restitution". It is followed by a much slower increase in cell proliferation and remodeling [41]. Nevertheless, the *in vitro* studies of Playford *et al.* [36] showed that colostrum preparation was able to stimulate both migration and proliferation.

2.3. Commercial immune milk products

Several commercial immune-milk products are available in the market [33]. They include Gastrogard (Northfield Laboratories, Oakden, Australia), a product used to prevent diarrhea caused by rotavirus in young children and PRO-IMMUNE 99 (GalaGen Inc., Minnesota, USA), a product used on young calves to prevent scours caused by *E. coli*. Furthermore, Biotest Pharm GmbH (Frankfurt, Germany) produces Lactimmunoglobulin Biotest, a product for human subjects, which contains immunoglobulins from colostrum of non-immunized cows. It has been tested in the treatment of severe diarrhea in AIDS patients [42]. Viable Bioproducts Ltd. (Turku, Finland) produces Bioenervi, a sterile-filtered colostrum-based product, which is designed to provide growth and antimicrobial factors during strenuous physical activity, e.g. training of athletes [43].

3. Growth and tissue repair factors

3.1. Wound healing capability

Besides providing excellent immune support, colostrum has remarkable muscular-skeletal repair and growth capabilities. Studies [1,44] revealed that colostrum is the only natural source of two major growth factors namely, transforming growth factors alpha and beta (TGF-A and B) and insulin-like growth factors 1 and 2 (IGF-1 and 2). These growth factors have muscle and cartilage repair characteristics that are biochemically outstanding. They promote wound healing with excellent implications for trauma and surgical healing [1]. TGF-A and B are involved in normal cell activities, such as embryonic development, cell proliferation, and tissue repair. IGF-1 has pronounced anabolic and wound-healing characteristics. It slows catabolism and it is the only growth factor that can stimulate muscle growth and repair all by itself. Its role in differentiation, repair and synthesis, as well as its interplay with other necessary growth factors, results in regenerative effects on nearly all structural cells of the body [45].

3.2. TGF-beta-like activity related to TGF-beta 2

The finding that the major TGF-beta-like activity found in bovine early colostrum is related to TGF-beta-2 is noteworthy [46]. According to this report, the TGF-beta related growth factor in colostrum could inhibit maternal cellular immune reaction to the newborn's paternal antigens. This suggests that non-cellular components in colostrum have a suppressive effect on the cytotoxic activity of monocytes [47,48]. The TGF beta-related growth factor may be one of the suppressive components [46]. Studies confirmed that crude preparations of bovine colostrum-TGF-beta-like growth factor could strongly inhibit DNA synthesis of concanavalin-A-stimulated murine thymocytes [49,50]. Although cytotoxic activities of colostrum monocytes or T-lymphocytes are reduced, colostrum and milk are considered to contribute to the defense of the newborn. The protective property of milk may be largely non-inflammatory [51] and TGF-beta-2-related growth factor may be one of the non-inflammatory agents. Another role of TGF-beta-2-related growth factor may be a positive regulator for IgA production in the mammary gland [46]. Reports indicated that TGF-beta has an inductive effect on IgA production in Peyer's patch lymphocytes and spleen lymphocytes [13,52].

3.3. Body fitness and protein synthesis

One study showed that IGF-1 infusions resulted in a significant gain in body weight and significant bone growth in rats [53]. One of the unpleasant aspects of aging is that muscles tend to waste away and fat becomes harder to lose. Colostral IGF-1 promotes the buildup of lean muscle tissue and the burning of fat for energy. Using IGF-1 while exercising muscle makes the body burn more fat due to a switch in fuel–from carbohydrate or glucose to fat [1].

3.4. Other growth factors

The presence of hepatocyte growth factor (HGF) in human milk and the contribution of HGF to the growth of neonates were investigated [54]. This study showed that human milk or colostrum contains a large amount of HGF, produced by macrophages, and this HGF induces the growth of intestinal cells. The result further suggested that HGF is one of the important factors that regulate the growth of intestinal cells in neonates after birth. Findings attest that colostral growth factors enhance DNA and protein synthesis and nutrient uptake, particularly in the muscle and cartilage.

3.5. Growth of bifidobacteria

Whey proteins isolated from buffalo colostrum were investigated for the presence of acidic glycoproteins and their influence on growth of bifidobacteria. Some of the isolated fractions were able to significantly promote the growth of *Bifidobacterium bifidus* at low concentration [55]. *B. bifidus* is known to be widely used in dairy industries. This microorganism produces acetic and lactic acids, which inhibit the growth of many gram-negative bacilli and fungal species [8].

3.6. Cell culture medium

Lehto *et al.* [56] reported that colostrum can be used as a serum substitute in mammalian cell cultures due to its growth promoting activity. Fetal bovine serum (FBS) is traditionally used in animal cell cultures to support cell growth. Similarly, bovine colostrum has been shown to support growth and monoclonal antibody (MAb) production of IgG hybridoma cell lines [57,58]. MAbs are produced in large quantities for a variety of clinical and scientific purposes [59]. According to Pakkanen *et al.* [58], cell culture media for large-scale production and purification of MAbs must fulfil several important criteria: (a) Antibody production should be continuous and reproducible. (b) Process costs should be as low as possible. (c) Risk of contamination by infectious agents and endotoxins should be eliminated. Serum is traditionally added to cell cultures to provide essential components for cellular proliferation. However, the complexity, limited availability and high cost of FBS present its greatest drawbacks. The demand for serum-free media has led to the development of several commercial formulations for the cultivation of mouse hybridomas. For most type cultured-cells, growth and synthetic activities are optimal in the presence of the multiple hormones and growth factors that serum provides [60]. Thus scientists have sought to identify a biological fluid that can supply such complex array of factors while avoiding the drawbacks and expense associated with FBS. Pakkanen *et al.* [58] revealed that bovine colostrum is a promising candidate for this purpose.

Fractions of bovine colostrum have been prepared and their ability to support the growth of mouse-mouse hybridomas in culture tested [58]. Whey was prepared from defatted colostrum by removal of casein using acid precipitation. An ultrafiltrate was obtained from cleared whey by filtration through membranes with a nominal molecular cut-off of 100 kDa. The effect of defatted colostrum, whey and ultrafiltrate as serum substitutes was examined

by cultivation of hybridoma cells in minimal essential medium containing different concentrations of the supplements. Under optimal conditions in ultrafiltrate-supplemented medium, the maximal cell concentration was 35–40% of that obtained using 10% FBS, and IgG production per cell was equal to that achieved using serum. In 1% defatted colostrum, the maximum hybridoma concentration was about 30% of that in 10% serum. At higher concentrations, hybridoma growth was significantly reduced. The growth-promoting activity of whey was low. The results showed that bovine colostrum ultrafiltrate provides a very attractive alternative to serum for production of MAbs. The study further demonstrated that hybridomas can be plated at a relatively low density (15,000 cells/mL) in ultrafiltrate without any progressive adaptation period. Antibody production correlated with cell numbers in both ultrafiltrate and FBS, indicating that the ultrafiltrate was able to support antibody synthesis. Although the cell concentrations obtained in the presence of colostrum ultrafiltrate were lower than in FBS, the cost of using colostrum ultrafiltrate compares very favorably with that of FBS [58]. However, colostrum should be fractionated before its use in cell cultures since total colostrum contains fat and protein, which may be harmful to cell cultures.

4. Conclusion

Colostrum is a rich source of nutrients and contains several biologically active molecules, which are essential for specific functions. It has the potential to help reconstitute the immune system while enhancing cell growth and tissue repair. Colostrum is an outstanding nutritional supplement, a food that protects and promotes health. The desirable properties of colostrum derivatives can be concentrated to enhance positive effects. It may be possible to combine the effective fractions of colostrum with probiotic lactic acid bacteria. It is not surprising that biotechnological companies are scrambling to clone and reproduce large quantities of the main factors that are naturally present in colostrum.

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