C H A P T E R

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Health Benefits of Bovine Colostrum in Children and Adults

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INTRODUCTION

Colostrum is the mother's first mammary secretion that all mammals provide to their newborns during the first 24–48 hours after delivery (Tokuyama et al., 1990; Stelwagen et al., 2009). Human newborns receive colostrum from their mothers during the first few hours after birth. Colostrum is secreted in more concentrated form during the first 8 hours post-parturition, and the readily available naturally produced nutrients and antibodies are delivered to the suckling newborn in a highly concentrated, low-volume format. Newborns have immature gastrointestinal (GI) and immune systems. Postnatal intake of colostrum rich in immunoglobulins and lactoferrin, growth, and antimicrobial factors provides all the important nutrients required for building their life-long immunity, promote tissue growth, and maturation of the digestive tract in neonatal animals and humans. Colostrum also has a laxative effect and therefore assists in delivering the initial stools or meconium in the newborn. It also helps in the excretion of bilirubin and reduction of neonatal jaundice (De Almeida and Draque, 2007; Cohen, 2006). Breast-fed infants have a lowered incidence of GI infections than infant-fed formula or cow's milk. Additionally, the incidence of any infection (viral, bacterial, protozoa, and other microorganisms) in very low birthweight infants is significantly lower in breast-fed infants than in infants who are given formula (Isaacs, 2001).

Fig. 1.1 shows the different constituents of colostrum found in various species of animals and humans. Colostrum contains several types of immunoglobulins, growth factors, cytokines, antibodies, lipids, lactoferrin, lysozymes, vitamins, and minerals, all of which assist in the development of passive immunity and growth of vital organs in the newborn (Morris et al., 1980, Ebina et al., 1992, Stephan et al., 1990). Colostrum and milk are not only a source of nutrients for the newborn but also a source of wide variety of protective factors, which play an important role in protecting mucosal surfaces from infections. The consumption of bovine colostrum (BC) is regarded safe in majority of the human population. Recent studies have shown that it is also well tolerated by neonates and does not show any episodes of apnea or sudden infant death syndrome (SIDS) after administration (Rodriguez et al., 2010). The minor side effects of BC ingestion include nausea, vomiting, and flatulence initially and these symptoms subside with time. Nevertheless, colostrum itself or its products should be avoided by individuals who have an allergy to milk or milk-based products.

Lactoferrin, an iron-binding protein, is present in large quantities in colostrum and breast milk. The main function of lactoferrin is nonimmune protection and regulation of iron absorption from the gut (Giansanti et al., 2016). The milk produced after few days of post-partum lacks most of the essential nutrients found in the colostrum.

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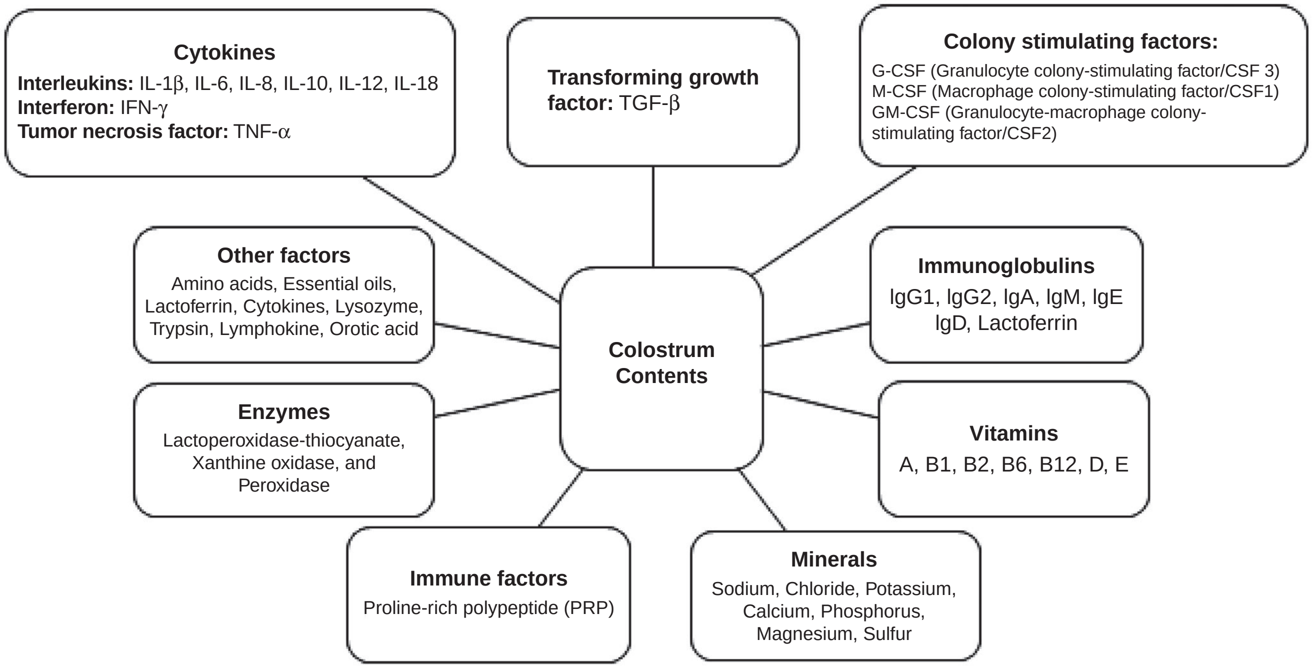

FIGURE 1.1 Overview of different constituents present in human and animal colostrum.

Historically, colostrum and milk are well known for promoting health and well-being in children and adults. The immunoglobulins and lactoferrin rich colostrum and milk of different species (e.g., cow, buffalo, goat) are readily available in large quantities making these secretions important potential sources of immune products beneficial for humans (Hurley and Theil, 2011; Giansanti et al., 2016). Research has shown that BC is more potent than the human colostrum, viz; the colostrum obtained from the cow and buffalo is 100 times to 1000 times more potent than that of the human colostrum. Therefore, BC can be consumed as a dietary supplement for its health benefits in humans (Sarker et al., 1998; Elfstrand et al., 2002).

HISTORICAL PERSPECTIVES REGARDING THE PURPORTED INDICATIONS OF COLOSTRUM

The beneficial role of mammary secretions in immune defense was deciphered by early Homo sapiens and physicians. Scientific literature in the late 19th century mentions the antibacterial properties of colostrum. The eventual findings about maternal colostrum starting from the late 19th century created a fundamental framework for the development of the discipline of immunology. Subsequently, the inherent antimicrobial and immune properties of colostrum laid the foundation for modern immunology (Isaacs, 2001). In 1892, Paul Ehrlich demonstrated experimentally where the mice immunized against plant toxins transferred the immunity to the newborn via colostrum. Further, he extended his research to the conceptual development of passive and active immunity for which he was awarded the Nobel Prize in 1908. Colostrum was shown to have a higher concentration of immunoglobulins as compared to the human milk. Smith and Little (1922) provided evidence regarding the antibacterial actions of colostrum in calves. All of 10 calves that were allowed to take colostrum after birth survived, whereas 8 out of 12 calves that did not get colostrum died. Campbell and Petersen (1963) researched extensively on the human safety profile and therapeutic benefits of colostrum from immunized cows, and colostrum was found to mitigate symptoms of arthritis and hay fever. In the 1950s, Dr Albert Sabin, father of the polio vaccine, observed that BC contained antibodies against polio virus and hence recommended its therapy in children at risk for contracting polio (Sabin and Fieldsteel, 1962).

Most of the biochemical components and their physiological roles from bovine and human colostrum were elucidated between 1970 and 1980. Lymphokines were demonstrated to stimulate immune cells in the animal models (Keller et al., 1981). Lawton et al. (1979) described the roles of cytokines, interleukins, interferon (IFN-γ), tumor necrosis factor (TNF-α), transforming growth factor (TGF-β), and colony-stimulating factors. By the mid 1980s, it

TABLE 1.1 Types of Cytokines, Interleukins, Interferon, TNF-α, and Colony-Stimulating Factors Present in the Human and Bovine Colostrum and Their Physiological Functions

Type of cytokine	Role of cytokine
Interleukins IL-1β IL-6 IL-8 IL-10 IL-12 IL-18	Stimulate production of neutrophils and macrophages, mediate communication between cells, regulate cell growth, motility, and differentiation
Interferon IFN-γ	Generates adaptive immunity, activate macrophages, inducer of Class II major histocompatibility complex (MHC), and molecular expression, is also associated with autoinflammatory and autoimmune diseases
Tumor necrosis factor—TNF-α	Involved in systemic inflammation and regulation of immune cells
Transforming growth factor—TGF-β	Controls cell growth, cell proliferation, cell differentiation, and apoptosis
Colony-stimulating factors:	
G-CSF (granulocyte colony-stimulating factor/CSF 3)	Stimulates the bone marrow to produce granulocytes and stem cells
M-CSF (macrophage colony-stimulating factor/CSF1)	Impacts hematopoietic stem cells to differentiate into macrophages
GM-CSF (granulocyte-macrophage colony-stimulating factor/CSF2)	Stimulates stem cells to produce granulocytes and monocytes

Lawton, J.W., Shortridge, K.F., Wong, R.L., Ng, M.H., 1979. Interferon synthesis by human colostral leucocytes. Arch. Disease Child. 54(2), 127–130.

was revealed that cell-mediated immunity was modulated by dietary nucleotides and nucleosides present in colostrum, which helped in the mitigation of bacterial infections in human infants. The type of cytokines, interleukins, interferon, TNF-α, and colony-stimulating factors present in the human and BC and their physiological functions are summarized in Table 1.1.

AYURVEDIC THERAPIES REPORTED ABOUT COLOSTRUM

In Hindi, colostrum is called Khees, or navadudh (खीस/नवदुगध); in Sanskrit, colostrum is termed as Gau-Piyush (गौ-पयूिष).

In India, the history of healthcare remedies based on herbal medicines and alternative therapies goes back to about 5000 B.C. Ayurveda is the ancient system of medicine in India. In Ayurvedic documentation, it was observed that BC was used for the irrigation of the eye during surgeries pertaining to the ocular region. Also, it was used in combination with the decoction of soft leaves of *Ricinus communis* or *Laghu Pancha moola* (Sanskrit: Laghu = small, Panch = five, Moola = roots). The five roots included in Laghu Pancha moola are Brihati—*Solanum indicum*, Kantakari—*Solanum xanthocarpum*, Gokshura—*Tribulus terrestris*, Shalaparni—*Desmodium gangeticum*, and Prishniparni—*Uraria picta*. Medicated eye drops (Aschyotana) were prepared with an amalgamation of goat's milk with *Glycyrrhiza glabra*, *Vitis vinifera*, *Symplocos racemosa*, and rock salt (Saindhava lavana). The application of Lepa on the eye (Enointing), consisting of *Berberis aristata*, *Zingibar officinale*, *Prunus cerasoides* ground in milk, was used for pacifying redness and eye irritation (Dhiman et al., 2010).

INTEGRAL COMPONENTS OF COLOSTRUM

Colostrum mainly consists of immune factors, growth factors, and some other nutritional components (Macy, 1949). The percentage composition of these components vary among different mammalian species. The immune factors include IgA-specific helper factor, β-lactoglobulin, secretory IgA, lactalbumin, α-1-fetoprotein, albumin, α-1-antitrypsin, α-2-macroglobulin, complements C3 and C4, and orosomucoids (Thapa, 2005). Immunoglobulins aid in building passive immunity in mammals, including humans. Therefore, they are of utmost importance during the early post-stage in neonates. BC contains IgG1, IgG2, IgA, IgM, and lactoferrin, IGg1 being the major component (Ogra and Ogra, 1978; Ahmad et al., 2013). Other nutritional components include fat-soluble vitamins, enzymes, and growth hormones (Henry and Kon, 1937; Haroon et al., 1982).

The results of a comparative study among human, cow, buffalo, and goat colostrum indicated that cow colostrum contains more nutritional constituents than other species (Ahmad et al., 2013). Also, it was found that cow colostrum has lesser amount of lactose; therefore, it could be given to patients intolerant to high concentration of lactose. The important components of colostrum are summarized in Table 1.2.

QUANTITY OF IMMUNOGLOBULINS PRESENT IN BC

Immunoglobulins are responsible for building immunity in animals and humans. The immunoglobulins present in BC are IgG1, IgG2, IgA, IgM, and lactoferrin.

IgG1, the major component, can be seen in Table 1.3.

QUANTITY OF FAT-SOLUBLE VITAMINS PRESENT IN BC

Fat-soluble vitamins (A, D, E, and K) are essential for the maintenance and promotion of good health. The content of fat-soluble vitamins remains virtually unchanged when colostrum is commercially processed. Table 1.4 shows the content of fat-soluble vitamins present in BC.

COMPARATIVE AMOUNTS OF NATURAL INGREDIENTS PRESENT IN HUMAN, COW, BUFFALO, AND GOAT MILKS

Quantitative amounts of fat, proteins, lactose, water-soluble vitamins, and minerals found in human, cow, buffalo, and goat milks are summarized in Tables 1.5–1.7 (Jenness, 1979; Ahmad et al., 2013; Eddleman, 1999). It can be noticed that the cow's milk contains far higher naturally produced nutrients than the other three species. However, the fat content is higher in the buffalo colostrum (range 11.31%–7.56%). Values depicted clearly show that the percentage of lactose in cow's milk (2.5%) is markedly lesser than that of human (6.9%–7.2%), buffalo (4.7%), and goat (4.7%) milk. Therefore, cow's milk may be used by persons having intolerance to lactose, but not by persons allergic to milk products.

THERAPEUTIC APPLICATIONS OF COLOSTRUM

Colostrum is often used as a nutritional supplement because it is rich in numerous immune modulating, growth promoting, and antimicrobial factors beneficial for health and well-being of children and adults. Some clinical trials have suggested its potential therapeutic applications described below. BC is readily available in large quantities and has great potential for making nutraceutical products for humans. It is well tolerated by neonates, children, and adults, and is considered to cause no serious adverse consequences in the human population.

BENEFITS OF TRYPTOPHAN IN CHILDREN AND ADULTS

Tryptophan is one of the essential ingredients found in the human and BC. Breast milk is the primary source of tryptophan in nursing infants. The principal role of tryptophan in the human body is synthesis of proteins and muscle tissues. It is not synthesized by the human body but can be procured from diets rich in tryptophan. Dietary sources of tryptophan in adult humans are dairy products, meats, fish, eggs, bananas, oats, pumpkin and sesame seeds, chocolate, dried dates, soy, tofu, tree nuts, including peanuts and peanut butter. Tryptophan acts as a precursor of key biomolecules such as serotonin, melatonin, niacin, tryptamine, quinolinic acid, kynurenic acid, nicotinamide adenine dinucleotide, etc. Deficiency of tryptophan can cause reduction of serotonin in the CNS and

TABLE 1.2 Components of Bovine Colostrum and Their Biological Activities

Vitamins	
A	Building of healthy immune system
B1, B2, B6	Assist in metabolizing fats and proteins
D	Intestinal absorption of calcium and other minerals
B_{12}	Maintenance of healthy nerves and red blood cells
E	Protection of brain and nervous system
Minerals	
Sodium	Maintain fluid balance, nerve transmission, and muscle contraction
Chloride	Stomach acid secretion
Potassium	Nerve transmission
Calcium	Building healthy bones and teeth, muscle functioning, immune-system development, nerve functioning
Phosphorous	Building healthy bones and teeth, maintains acid–base balance
Magnesium	Synthesizing protein, immune-system development
Sulfur	Part of protein molecule
Amino acids	Building blocks of proteins
Essential oils/lipids	Vitality and growth of the newborn
Immune factors	
Proline-rich polypeptide (PRP)	Regulates thymus gland activity
Immunoglobulins	Immunologic and neurologic properties
IgG	Neutralize toxins and microbes in the lymph and circulatory system
IgM	Bactericidal properties
IgE	Antiviral properties
IgD	Antiviral properties
Lactoferrin	Antiviral, antibacterial, antioxidant, antiinflammatory, anticancer, and regulate iron absorption in gut
Cytokines	Regulates immune response, boost T-cell activity, and immunoglobulin production
Lysozyme	Antibacterial and antiviral
Enzymes	
Lactoperoxidase-thiocyanate, xanthine oxidase, and peroxidase	Oxidize bacteria through their ability to release hydrogen peroxide
Trypsin	Prevent the destruction of immune and growth factors in colostrums
Lymphokines	Immune response mediator
Orotic acid	Prevents hemolytic anemia

(*Continued*)

TABLE 1.2 Components of Bovine Colostrum and Their Biological Activities (Continued)

Growth factors	
Growth hormone (GH)	Catalyzing the formation of DNA; cell and tissue growth and regeneration
Epithelial growth factor (EGF)	
Insulin-like growth factor-I and II (IGF-1 and IGF-II)	
Platelet-derived growth factor (PDGF)	
Fibroblast growth factor (FgF)	

Kehoe et al. (2007), Ballard and Morrow (2013).

TABLE 1.3 Immunoglobulins Present in Bovine Colostrum

Immunoglobulins	**Quantity (mg/mL)**
IgG1	35
IgG2	16
IgA	1.7
IgM	4.3
Lactoferrin	0.8

Ogra, S.S., Ogra, P.L., 1978. Immunological aspects of human colostrum and milk. J. Pediatr. 92, 550–555; Ahmad, S., Anjum, F.M., Huma, N., Sameen, A., Zahoor, T., 2013. Composition and physico-chemical characteristics of buffalo milk with particular emphasis on lipids, proteins, minerals, enzymes and vitamins. J. Anim. Plant Sci. 23, 62–74; Eddleman, H., 1999. Composition of human, cow and goat milks (B120A). Available at: ⟨http://www.disknet.com/indiana_bio lab/b120a.htm⟩ (Accessed: 30 August 2015).

TABLE 1.4 Fat-Soluble Vitamins Present in Bovine Colostrum

Fat-soluble vitamins	**Quantity (μg/g)**
Retinol (vitamin A)	4.9
Tocopherol (vitamin E)	2.9
Beta-carotene	0.7

Henry, K.M., Kon, S.K., 1937. A note on the vitamin D content of cow's colostrum. Biochem. J. 31(12), 2199; Haroon, Y., Shearer, M.J., Rahim, S., Gunn, W.G., McEnery, G., Barkhan, P., 1982. The content of phylloquinone (vitamin K1) in human milk, cows' milk and infant formula foods determined by high-performance liquid chromatography. J. Nutr. 112(6), 1105–1117; Eddleman, H., 1999. Composition of human, cow and goat milks (B120A). Available at: ⟨http://www.disknet.com/indiana_bio lab/b120a.htm⟩ (Accessed: 30 August 2015).

produce behavioral changes in children such as hyperactivity, depression, anorexia nervosa, anxiety, and behavioral impulsivity. Tryptophan isolated from BC can suppress or alleviate these conditions. It also plays an important role in induction of sleep, mood, appetite, and sensory perception (Ruddick et al., 2006). Melatonin, a byproduct of tryptophan, has a powerful free radical scavenging activity and also plays an important role in the homeostasis of circadian rhythms (Boutin et al., 2005). Recent studies have revealed the role of tryptophan in infant brain development and its improper metabolism involved in patients with autism (Boccuto et al., 2013). The 3-hydroxy kynurenine branch of the kynurenine pathway is activated in macrophages by infection and inflammation. 3-Hydroxy

TABLE 1.5 Comparison Among the Amount of Fat, Proteins, and Lactose in Human, Cow, Buffalo, and Goat Milks

Constituents	Human colostrum (%)	Cow colostrum (%)	Buffalo colostrum (%)	Goat colostrum (%)
Fat	3–5	6.7	11.31–7.56	4.1
Proteins	0.8–0.9	14.9	4.3	3.4
Lactose	6.9–7.2	2.5	4.7	4.7

Jenness, R., 1979. The composition of human milk. Semin. Perinatol. 3, 225–239; Ahmad, S., Anjum, F.M., Huma, N., Sameen, A., Zahoor, T., 2013. Composition and physico-chemical characteristics of buffalo milk with particular emphasis on lipids, proteins, minerals, enzymes and vitamins. J. Anim. Plant Sci. 23, 62–74; Eddleman, H., 1999. Composition of human, cow and goat milks (B120A). Available at: ⟨http://www.disknet.com/indiana_biolab/b120a.htm⟩ (Accessed: 30 August 2015).

TABLE 1.6 Comparison of Water-Soluble Vitamins in Human, Cow, Buffalo, and Goat Milks

Constituents	Human (mg/100 mL)	Cow (μg/mL)	Buffalo (μg/mL)	Goat (μg/mL)
Niacin	0.02	0.34	–	Approximately 0.6 μg/mL water-soluble vitamins are present
Thiamine	0.017	0.90	–	
Riboflavin	0.04	4.55	3.4	
Vitamin B12	0.03	0.60	1.59	
Pyridoxal	–	0.15	–	
Pyridoxamine	–	0.21	–	
Pyridoxine	–	0.04	3.25	

TABLE 1.7 Comparison of Mineral Content of Human, Cow, Buffalo, and Goat Milks

Constituents	Human (mg/100 mL)	Cow (mg/kg)	Buffalo (mM)	Goat (g/kg)
Calcium	33	4716	47.1	0.65
Phosphorus	13–16	4452	27.7	0.36
Magnesium	4	733	7.3	–
Sodium	50	1058	20.3	1.44
Potassium	74	2845	28.7	3.38
Zinc	0.53	38	147–728	–
Iron	0.15	5.3	42–152	–
Copper	0.04	0.3	7	–
Sulfur	–	2595	15,700	0.2
Manganese	–	0.1	38.2	–

Compiled from different sources.

anthranilic acid, a product of 3-hydroxy kynurenine, exhibits an antiinflammatory and neuroprotective role (Krause et al., 2011). L-Tryptophan degradation route of catabolism depicted by the kynurenine pathway may interfere with the pathogenesis of inflammation, infection, and neurodegenerative diseases like Huntington's disease and stroke-induced brain disease (Stone et al., 2012). A recent study was done on L-tryptophan isolated from human milk to analyze its oxygen radical absorption capacity (ORAC) and mitigation of bacterial lipopolysaccharide-induced proinflammatory cytokines (IL-6, TNF-α) using an in vitro cell based assay. Results of this study indicated that tryptophan isolated from human milk possessed nearly 99-fold higher ORAC capacity than that of whole human milk (Nayak and Buttar, 2016). Collectively, the antioxidant, antiinflammatory, antimicrobial, immunity building, and neurotransmitter properties of tryptophan and lactoferrin from colostrum and milk help in the development of CNS, the GI tract, and other organs in infants (Tsopmo et al., 2009).

IMMUNITY-RELATED DISORDERS AND ALLERGY

Hypersensitivity to the immune system leads to allergic reactions, and in some cases may cause anaphylaxis and death. Autoimmune disorders are the primary cause of hypersensitive conditions in people. The thymus gland is the central organ of the immune system and is responsible for the development of T-lymphocytes. The immature T cells also known as thymocytes, produced by the thymus have potential to remove the self-reactive immune cells. Breast-feeding plays a crucial role in the development of the thymus gland in neonates (Jackson and Nazar, 2006). A study was conducted to measure the thymic index of four-month-old neonates using an ultrasound technique. It was found that the infants who were breast-fed had a large thymic index than those who were partially breast-fed or formula-fed (Hasselbalch et al., 1996). Proline-rich polypeptide (PRP) present in colostrum acts to regulate the function of the thymus gland. It also ameliorates the pain, inflammation, and swelling caused by lymphocyte and T-cell overproduction, due to allergy and autoimmune disorders. In view of these observations, colostrum products therapy may be useful to stimulate the function of thymus gland and consequently mitigate hypersensitivity and autoimmune disorders.

CARDIOVASCULAR DISORDERS

Altered immunity is one of the underlying causes for aggravated atherosclerosis and cardiovascular diseases. Chlamydia, or immune sensitization to cardiac antigen, can cause formation of arterial plaques and coronary heart disease or stroke (Rona, 1998). The presence of PRP in colostrum may prevent the occurrence of cardiovascular diseases, as it likewise assists to prevent allergy and other autoimmune disorders. The insulin-like growth factor-1 (IGF-1) present in colostrum can elevate the level of high-density lipoprotein (HDL)-cholesterol and lower the level of low-density lipoprotein (LDL)-cholesterol, and thus help to prevent the formation of arterial atherosclerosis. Various growth factors present in colostrum may also help to repair the damaged heart muscle and promote angiogenesis (Rona, 1998).

A study was conducted to evaluate the cardioprotective effects of BC against isoproterenol-induced myocardial infarction in rats. Results showed that oral administration of BC at 500 mg/kg dose caused a significant reduction in the cardiovascular damage, but the combination dose of 500 mg/kg colostrum and 0.25 mg/kg enalapril revealed a better cardioprotective effect in rats after 28 days dosing than colostrum alone. The cardioprotective effect of colostrum was attributed to its antioxidant activity and free radical scavenging ability as well as marked inhibition of lipid peroxidation (Kaur et al., 2014). Kwon et al. (2010) reported that in an intestinal ischemia/reperfusion (I/R)-injured rat model BC can be effective against multiple organ dysfunction syndrome and systemic inflammatory response syndrome. The I/R leads to the production of various proinflammatory cytokines and free radicals, which can be attenuated by the lactoferrin present in the BC.

CEREBRAL ISCHEMIA

Neurobehavioral dysfunctions mediated by the proinflammatory cytokines can be attenuated by lactoferrin, since it is able to reverse cognitive dysfunction associated with either global cerebral ischemia or a middle cerebral artery occlusion-induced ischemic stroke (Undale et al., 2012; Choi et al., 2010). Excitotoxicity and apoptosis mediated by hemorrhage-induced *N*-methyl-D-aspartic acid (NMDA) causes hippocampal neuronal cell death. The NMDA-induced excitotoxicity and apoptosis can be mitigated by BC (Kim et al., 2012). Additionally, a reversal of partial amnesia caused by neuronal cell death was also observed after colostrum administration. It appears that BC may be effective in the attenuation of cerebral ischemia by decreasing the oxidative stress.

ANTIINFLAMMATORY EFFECT

Nonsteroidal antiinflammatory drugs (NSAIDs) are good analgesics but are prone to cause GI injury. It has been observed that BC can reduce gut permeability and thus can be used as an adjunct therapy with NSAIDs for the treatment of gastric injury. Recently, a randomized crossover clinical trial was undertaken, where indomethacin was given as a control and colostrum was coadministered. A regular dose of NSAIDs was given to both groups. It was observed that indomethacin caused threefold increase in the permeability of gut, whereas the patients in the colostrum group did not show any significant increase in the gut permeability. Therefore, colostrum can be used as a novel therapy for the treatment of drug-induced GI damage (Playford et al., 2001). Human colostrum lacks initiators and mediators of inflammation but has abundance of antiinflammatory agents. The antiinflammatory agents found in colostrum are resistant to digestive enzymes and thus can be used for oral administration for ameliorating the gastric inflammation or gastric injury (Goldman et al., 1986). Antiinflammatory activity of orally administered BC (500 mk/kg, p.o.) was determined in rats using carrageenan-induced paw edema method. BC showed moderate antiinflammatory activity by reducing oxidative stress (Yadav et al., 2016). Further studies are warranted to understand the targeted mechanism of action with regards to the antiinflammatory potential of BC before it can be recommended for therapeutic interventions in humans.

MICROBIAL INFECTIONS

As mentioned earlier, colostrum has antibacterial, antiviral, antifungal, antiprotozoal, and immunomodulatory properties, and is involved in several physiological and protective functions. The reduction of infection-induced inflammation occurring in the gastroesophageal tract of HIV patients has been observed. The repair mechanisms postulated are said to be mucosal integrity, tissue repair, and direct antimicrobial actions (Rona, 1998). Hyperimmune BC, i.e., the BC having high antibody titer, can be used for the treatment against human rotavirus (HRV) (Takayama et al., 2001) and HRV-induced diarrhea, especially in neonates (Sarker et al., 1998; Mitra et al., 1995). κ-Casein, a component detected in human and BC, is being evaluated for its antibacterial action. It is a glycosylated protein that binds directly to the viral antigens through the glycosylated residue (Inagaki et al., 2014). The antibodies can be produced naturally by vaccinating the cows rather than synthetic production of the same, which can save over 500,000 people across the world who die due to rotavirus-induced diarrhea. The strategy of increasing the potency of colostrum was done by Gunaydin et al. (2014), who attempted to surface express the IgG-binding domains of protein G (GB1, GB2, and GB3) of *Lactobacillus rhamnosus* GG. These domains bind to the colostrum-derived IgG antibodies and increase their potency against rotavirus diarrhea in mouse pups. The hyperimmune BC antibodies seems to increase the potency by 10- to 100-folds.

The intranasal administration of IgG extracted from BC to BALB/c mice increased natural killer (NK) cell cytotoxicity and improved the immune response to primary influenza A virus (H1N1) infection (Ng et al., 2010). These IgG fractions were collected from cows immunized with A/Puerto Rico/8/34 (PR8) influenza virus. The IgG was purified and administered intranasally, which reduced viral load in the mice.

Bovine κ-casein glycomacropeptide (GMP) has received worldwide attention after being recognized for inhibiting bacterial and viral adhesion. It showed positive results in suppressing the gastric secretion, modulating the immune-system responses, and promoting the growth of bifidobacteria. GMP has the ability to bind with the *Escherichia coli* and cholera enterotoxins (Brody, 2000). Kawasaki et al. (1992) demonstrated similar activity on normal Chinese hamster ovary (CHO)-K1 cells, where the cells in the normal state remain spherical, whereas the cells of the cholera-infected Chinese hamster became spindle shaped. It was observed that the cholera-infected CHO-K1 cells regained back their spherical shape after treated with GMP. This indicated that GMP was bound to the cholera toxin. Neeser et al. (1988) also demonstrated the role of GMP in preventing dental caries. Dental caries are formed when there is adhesion of the cariogenic bacteria to the oral surface. GMP plays a role in inhibiting the adhesion of the cariogenic bacteria to the teeth and the oral cavity. GMP also prevents adhesion of *Streptococcus mutans*, *S. sanguis*, and *S. sobrinus* to the saliva covered tooth model (Neeser et al., 1994). The mechanism exhibited by GMP in reducing dental caries is that it changes the microbial composition of dental plaque from *Streptococci* to *Actinomyces*, which is less cariogenic. Industrial application by incorporating GMP in toothpaste has been demonstrated by Neeser (1991a,b). The suppression of gastric secretions in rats and dogs when these animals were treated with 10–15 mg of bovine

GMP intravenously (Yvon et al., 1994). GMP showed a significant suppression of the gastric secretion and reduced the motions at the gastric fundus and the duodenum (Stan and Chernikov, 1982; Guilloteau et al., 1994). It was found that oral administration of bovine GMP to calves was more effective than the calves which were given bovine GMP intravenously (Faure et al., 1984).

Bifidobacteria present in the lower intestine is said to prevent pathogenic bacterial growth and protect the body from GI diseases. György et al. (1954) reported the presence of bifidobacterial growth promoting factors in the human colostrum. Lactoferrin from BC helps in the growth and maintenance of bifidobacterium species (Petschow and Talbott, 1991). A proliferation of splenocytes generates an inflammatory response. Inhibiting splenocyte proliferation can suppress the immune response and certain allergic reactions. Otani et al. (1992) have demonstrated the inhibition of splenocyte proliferation by the administration of casein in mice treated with mitogen *Salmonella typhimurium* lipopolysaccharide (LPS). The inhibition of B-lymphocyte and T-lymphocyte proliferation by GMP can have a down regulatory pathway for the immune system or oral tolerance (Otani et al., 1992). This can be path breaker for developing a passive defense mechanism against a broad spectrum of bacterial antigens.

SUPPRESSION OF HIV INFECTION

HIV infection drastically reduces the number of helper T cells (specifically CD4 T cells), dendritic cells, and macrophages (De Clercq, 1995). Patients suffering from AIDS have a compromised immune system and digestive system. Diarrhea is a common occurrence in AIDS patients. It has been seen that human milk elevates the levels of helper T cells in the body, thus supporting the immune system. BC supplements can help to restore the immune system and regulate the loss of T helper cells (Wirt et al., 1992). Also, it can help in protecting the mucosal integrity of the GI system, therefore preventing the leaky gut syndrome and other GI-related complications. However, a double-blind, placebo-controlled study is needed to ascertain the positive effects of BC in ameliorating the gut inflammation and suppression of the immune function associated with HIV. A study was conducted where cows were vaccinated with recombinant HIV-1 gp140 antigens, which stimulated the production of gp-140-specific polyclonal antibodies. These low-cost, large-scale source of antibodies showed broad neutralizing activity by binding to the CD4-binding sites in comparison with HIV-antibodies produced by other techniques (Kramski et al., 2012).

WEIGHT LOSS AND FITNESS PROGRAMS

Athletes and fitness trainers have a tendency to develop chronic fatigue syndrome due to a decrease in the number of T-lymphocytes and NK cells. This condition occurs due to rigorous exercise, which compromises the immune system. Colostrum has become an important dietary supplement because it provides nutrients to athletes or fitness trainers during intense training sessions. It proves beneficial for the overall development of the body and for building muscles. The supplement is generally taken in the form of powder that is mixed with milk shake supplements and other energy drinks (Mero et al., 2002). Athletes elevate the efficiency of the digestive tract by taking colostrum as a dietary supplement (Antonio et al., 2001). The compromised immune system of athletes due to physical and emotional stress endowed on them can be reversed by consumption of colostrum supplements. It can also assist in healing any injury that occurs during training sessions (Godhia et al., 2013). The increase in perspiration rate during the fitness training sessions in winters can cause bacterial infections and upper respiratory tract infections, which can be prevented by the consumption of colostrum supplement. BC was used to limit an increase in salivary bacterial load in a 12-week, randomized, placebo-controlled, double-blind study (Jones et al., 2014). In another double-blind, placebo-controlled, crossover study, it was found that BC prevented heat stroke and increased gut permeability by upregulating the antiapoptotic protein Bcl-2 and HSP70 and downregulating the proapoptotic Baxα and apoptosis initiators Caspase-3 and 9, which maintain homeostasis during high intense trainings. BC supplement increased the proapoptotic Baxα and apoptosis initiators Caspase-3 and 9 (Marchbank et al., 2011). These supplements also enhanced the intramuscular buffering capacity and lean body mass, which is considered to increase due to elevated levels of IGF-1 in the plasma (Shing et al., 2009).

Leptin is a satiety hormone produced by the white adipose tissue cells and is responsible for suppressing hunger or reducing the desire to eat more. Colostrum also contains leptin in addition to IGF-1, which is required for the process of metabolism (Rona, 1998). Leptin and IGF-1 work in combination to decrease cholesterol and triglyceride levels in the hyperlipidemic patients (Kim et al., 2009). It also helps to increase lean body mass and reduce the fat composition of the body, thus decreasing an individual's tendency to gain more weight. BC supplement therapy can increase the chances of better fitness training and weight loss programs.

DIABETES AND WOUND HEALING

Juvenile diabetes (type-1 or insulin dependent diabetes) is an autoimmune disorder where the pancreatic cells fail to produce insulin naturally; therefore, insulin injections are given to the patient regularly. As it was alluded to earlier, BC contains factors that can suppress autoimmune disorders and other allergic reactions. It also contain IGF-1, which binds both to insulin and IGF-1 receptors. Studies carried out in alloxan-induced diabetic rats confirmed the reduction of blood glucose and malondialdehyde levels, which transcend the use of BC in diabetic patients (Jahantigh et al., 2011). β-Cell regeneration and peroxisome proliferator-activated receptor-α (PPARα)-like actions of conjugated linoleic acid (CLA) were seen after the BC's administration, which possibly contributes to the insulin release from pancreatic cells (Pan and Liu, 2008). The healing of wounds in patients afflicted with diabetes is problematic, as diabetic neuropathy occurs, where, due to an uncontrolled blood glucose level, there is a loss of sensation of nerves. Due to this loss of sensation, the patient cannot feel any injury, which delays wound healing. BC helps in the reduction of blood glucose and, therefore, initiates wound healing in diabetic patients (Kim et al., 2009). Nucleotides, epidermal growth factor (EGF), transforming growth factor (TGF), and IGF-1 present in BC promote wound healing and DNA, RNA damage repair. BC also promotes growth of nerve cells, skin, cartilage, muscle, and bone. A study conducted with fibroblasts-populated collagen gel culture subjected to BC showed collagen gel contraction, which mimics the in vivo wound healing process (Takayama et al., 2001). BC was found to reduce gastric injury in animals and humans, mainly caused by the NSAIDs, by enhancing the growth of intestinal villi due to the action of IGF and TGF-β. Growth factors and lactoferrin are potentially the compounds present in BC that promote wound healing (Aalto et al., 1995). A patent has been granted for topical application of colostrum in the wound healing process (Aalto et al., 1995). Skin damage results from transepidermal water loss and epidermal thickening, which can be decreased by oral administration of 1600 mg/kg lactoferrin. A study has shown that lactoferrin is capable of safeguarding the skin from ultraviolet B (UVB)–induced photo damage in hairless mice (Murata et al., 2014). Quite recently, an elegant review was published outlining the nutraceutical and pharmacological properties of lactoferrin (Giansanti et al., 2016). For oral administration, large amounts of cost-effective lactoferrin can be produced for therapeutic applications from bovine milk.

To create a large physiological interface between the wound surface and external environment that is impermeable to microbes, newer type of wound dressings known as biological dressings impregnated with colostrum powder and collagen granules are used for wound healing (Singh et al., 2011). For repairing tissues like the skin, muscle, cartilage, and bone, colostrum powder dressings have certain advantages over conventional dressings because colostrum powder contains many antiinflammatory, antimicrobial, and growth factors that promote cell growth in wound repair. Also, due to the antiinflammatory action and assistance in the formation of healthy granulation tissue, the colostrum powder, and collagen granule wound dressings promote quick healing and reduce pain (Guben et al., 2010; Barry, http://www.icnr.org/blog.). A comparative study was done to evaluate the safety and efficacy of colostrum powder dressing with conventional dressing in the management of deep wounds. It was found that the colostrum dressing group not only required fewer dressing changes, but also showed rapid healing, a short healing time, and decreased pain compared to the conventional dressing group. The results suggest that colostrum powder dressings are safe and effective for healing deep wounds, and may be used as an adjunct therapy for the management of deep wounds (Kshirsagar et al., 2015).

LEAKY GUT SYNDROME

Leaky gut syndrome is generally linked to autoimmune diseases like diabetes, chronic fatigue syndrome, multiple sclerosis, and inflammatory and irritable bowel disease (Fasano, 2012). Body systems produce antibodies in response to stressors and attach to the tissues all over the body and cause inflammation (Mass et al., 2008). Auto-antibodies progressively result into chronic inflammatory disorders. The immune system boosters present in colostrum have revealed beneficial effects against GI tract infections and chronic pain disorders. BC helps to maintain the gut mucosal integrity and immunological status (Bölke et al., 2002). Colostrum not only possess antiinflammatory effects but also enhance nutrient bioavailability and leads to the prevention of leaky gut syndrome (Thapa, 2005). The underlying mechanism that prevents the leaky gut syndrome is the sealing of intestinal mucosae that hinder the permeability of exo- and endo-toxins. This intestinal sealing occurs due to the induction of an intestinal barrier produced by cytokine TGF-β (Bodammer et al., 2013). This mechanism was elucidated when BC-mediated induction in claudin-2 expression was observed. Claudin-2 is a tight junction protein that generates cation-selective intestinal pores causing increase in intestinal permeability and lower transepithelial electrical resistance (TER) (Rosenthal et al., 2010). Instead of decrease in TER, there is reduced intestinal permeability and high TER because of TGF-β, which balances the claudin-2 over expression.

BOVINE COLOSTRUM FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

A clinical trial on the application of BC enema was conducted for treating the distal colitis or inflammatory bowel disease (IBD). Colostrum enemas (100 mL of 10% solution) were administered to 14 patients suffering from mild to moderately severe distal colitis. Albumin solution was used as placebo. Both groups also received mesalazine (1.6 g/day). After four weeks, both groups showed moderate reduction in symptoms of IBD, whereas the improvement in histological score was greater in the colostrum group. The results suggested that colostrum enema may have potential as a novel therapy for the treatment of distal colitis (Khan et al., 2002). Additional well-designed studies with a larger number of patients are needed to substantiate the findings of this investigation.

CANCER THERAPY APPLICATIONS OF MOLECULES AND COMPOUNDS ISOLATED FROM BOVINE COLOSTRUM AND MILK

Uncontrolled cell proliferation and metastasis are the significant markers of neoplastic diseases. Current anticancer drugs cause a plethora of adverse effects. Lactalbumin present in BC can induce apoptosis in the cancerous cells. Lactoferrin is considered to be one of the natural anticancer substances. A patent has been granted to metal ion-saturated lactoferrin, which has been shown to possess anticancer properties by stimulating the Th-1 and Th-2 activation and erythrocytosis (Kanwar et al., 2005). NK cells have proven to be helpful in resisting cancer tumors and metastasis. Knekt et al. (1996) has demonstrated an inverse corelation between milk intake and incidences of breast cancer. There are also some studies showing positive or no corelation between consumption of milk and incidences of various cancer types (Jain, 1998; Ewertz and Gill, 1990; Mettlin et al., 1990). However, the rodent models of tumorigenesis have displayed a protective effect against cancer after the consumption of milk (Klurfeld et al., 1983). Some experimental models indicated that fats fed to rodents from a milk source and polyunsaturated vegetable oils exhibited contradictory results (Gill and Cross, 2000). Rats fed with polyunsaturated vegetable oils showed more prevalence for tumor growth, whereas the animals fed with fats refined from milk showed no evidences of tumor growth, which suggests that the fats obtained from milk either protect actively from cancer or are least harmful without any undesirable effects (Yanagi et al., 1993). Conjugated linoleic acids (CLA) present in milk is a potent anticarcinogen unlike other linoleic acids present in the vegetable oils, which show signs of carcinogenicity (Ip and Scimeca, 1997). Sphingomyelin and its metabolites are known to mediate transmembrane signaling mechanisms that control cell proliferation and differentiation as well as aid in cell signaling in tumor biology and apoptosis (Merrill, 1991). One-third of total milk phospholipids consist of sphingomyelin, which accounts for its anticancer properties. The low-fat milk test was conducted on carcinoma-induced mice. It was observed that the mice fed on milk-derived sphingomyelin had half the tumor incidences as compared to the control mice (Dillehay, 1994). Proteins like casein also possess anticancer properties. When casein was fed to 1,2-dimethylhydrazine (DMH)-induced rats, it showed lower incidences of colorectal cancers as compared to the rats fed with other sources of proteins (McIntosh et al., 1995). Bovine lactoferrin has been shown to reduce the incidences of colon adenocarcinomas in F344 rats (Tsuda et al., 1998). Yoo et al. (1997) reported the inhibition of metastasis of primary tumors when an iron-free form of lactoferrin was injected subcutaneously to cancer-bearing mice. Bovine serum albumin (BSA) and mammary-derived growth inhibitor (MDGI) have anticancer properties for human breast cancer MCF-7 cell line and neoplasms in the intestinal epithelium, respectively (Laursen et al., 1989; Zavizion et al., 1993; Yang et al., 1994). According to Wargovich et al. (1991), consumption of high dietary calcium obtained from bovine milk decreases the risk of colorectal cancer. While many molecules and compounds isolated from BC and milk have been tested for their promising anticancer properties, further research is needed to substantiate the potential applications of compounds and biologically active molecules derived from BC or milk as an adjunct therapy or alternate therapy for the treatment of cancer.

POLYAMINES-INDUCED CELLULAR DIFFERENTIATION AND GROWTH

Polyamines are involved in cell growth and cell differentiation cascades. The physiological relationship between intracellular and dietary polyamines for the growth of organ systems is well established (Pegg and McCann, 1982; Tabor and Tabor, 1984; Seiler, 1990). Polyamines are also involved in carcinogenesis and tumor growth (Pegg and McCann, 1982; Tabor and Tabor, 1984; Pegg, 1988). They stimulate and regulate the synthesis of DNA, RNA, and proteins along with the modulation of cell membrane functions (Pegg and McCann, 1982; Tabor and Tabor, 1984; Pegg, 1988; Seiler, 1990). In rats, dietary polyamines showed a significant role in the maturation of intestine (Dufour et al., 1988; Buts et al., 1993; Wild et al., 1993; Kaouass et al., 1994; Wery et al., 1996). Polyamines like spermine and spermidine when administered orally accelerated the mucosal maturation and proliferation in the neonatal rat intestine (Dufour et al., 1988; Buts et al., 1993; Wild et al., 1993; Kaouass et al., 1994; Wery et al., 1996). Human colostrum contains larger amounts of polyamines as compared to the BC, with the highest concentration occurring during the first few days of post-partum and subsequently decreasing two weeks after delivery (Romain et al., 1992; Dorhout et al., 1996). The amount of polyamines in the human colostrum depends on a number of factors such as the mother's age, ethnic origin, genetic influence, nutritional status, duration of lactation, dietary polyamine intake, and environmental influences (Buts et al., 1995; Motyl et al., 1995). The reason that BC contains a less amount of polyamines as compared to the human colostrum is that BC contains higher amounts of diamine oxidase (DAO) and polyamine oxidase (PAO), both of which are responsible for the biodegradation of polyamines in the BC. It appears that neonatal intake of polyamines present in the colostrum play a pivotal role in development, the structural maturation of intestinal cells, and enzyme ontogeny during early postnatal life.

COLLECTION OF BOVINE COLOSTRUM

Cows and buffalos can provide readily available immune rich colostrum and milk in large quantities. The cows and buffalos used for the production of colostrum should not be treated with exogenous hormones or antibiotics. In addition, their grazing fields should be free from herbicides, pesticides, or insecticides. The possibility of excreting trace amounts of hormones, antibiotics, and toxicants in colostrum and milk may cause adverse reactions in people consuming the colostrum supplements. The solid form of colostrum is more stable than the liquid form. Further, liquid colostrum has a high water content that increases the possibility of microbial growth (Jenny et al., 1984; Foley and Otterby, 1978). Proteins are the fundamental and integral components of colostrum. Nutritionally, they are a source of energy and amino acids, which are essential for growth and health maintenance. Colostrum should not be processed at high temperatures, as proteins tend to denature or coagulate at higher temperatures (Korhonen et al., 1998). Colostrum manufacturing is done using low-heat pasteurization and indirect steam drying (Godden et al., 2006; Seth and Das, 2011). Fats and lactose are extracted from the colostrum to make it edible to obese and lactose intolerant people (Elfstrand et al., 2002). Synthetic colostrum can either be produced by combining milk, egg, cod liver oil, and sugar together or by formulating carbohydrates, amino acids, fats, vitamins, and trace elements in exact proportions (Christensen, 2010). The synthetic products can be administered to the newborn baby when the mother is unable to produce sufficient colostrum for feeding. However, the prolonged use of synthetic colostrum should be discouraged, since it does not contain antibodies, bioactive components, and growth factors present in natural colostrum. Instead, BC products should be promoted as nutraceuticals for children and adults.

MANUFACTURING OF COLOSTRUM AND ITS INDUSTRIAL APPLICATION

Colostrum products are upscale nutraceuticals that are dispensed and formulated into capsules, tablets, and powder by leading nutraceutical industries. APS BioGroup manufactures tablets and powder made from BC. Biostrum Nutritech Pvt. Ltd and Mt. Capra Wholefood Nutritionals manufactures tablets and powder from buffalo and goat colostrum, respectively (Table 1.8).

The utilization of lactoperoxidase (LP) system as a natural bio-preservative in food-related products and cosmetics is high these days (Hoogendoorn, 1985). Therefore, extraction of LP from the BC is increasing considerably. LP is added to the pasteurized milk for the production of yogurt, which is free from bacterial acid. LP not only produces

TABLE 1.8 Some Colostrum Product Manufacturing Companies

Types of colostrum	Colostrum powder manufacturer	Colostrum capsule manufacturer
Cow colostrum	APS BioGroup	APS BioGroup
Buffalo colostrum	Biostrum Nutritech Pvt. Ltd	Biostrum Nutritech Pvt. Ltd
Goat colostrum	Mt. Capra Wholefood Nutritionals	Mt. Capra Wholefood Nutritionals

an acid-free yoghurt but also extends the storage life of yogurt for about two weeks (Nakada et al., 1996). LP systems have also been added in the toothpastes and other dental care products for reduction of acid formation by the oral microorganisms, thus preventing further dental caries. It has shown a reduction of plaque accumulation, early carious lesions, gingivitis, and aphthous lesions (Hoogendoorn, 1985).

Bovine κ-casein or κ-caseino GMP is found in whey. When bovine κ-casein is treated with chymosin during cheese making, the protein is hydrolyzed into para-κ-casein (residues 1–105), which remains with the curd, and GMP residues 106–169 are removed with the whey. GMP has the ability to bind with cholera and *E. coli* enterotoxins, inhibit bacterial and viral adhesion, suppress gastric secretions, promote bifidobacterial growth, and modulate immune-system responses. Because of its several biological activities, bovine κ-casein GMP has promising applications for functional foods and dietary supplements (Brody, 2000).

CONCLUSIONS

Human and BC is involved in several important physiological and protective functions in the newborn. The immunity, growth, and antimicrobial factors present in colostrum promote tissue growth and the maturation of the digestive tract and other organs in neonatal mammals and humans. The immunoglobulins and lactoferrin in colostrum are known to build natural immunity in newborns, which helps to reduce the mortality rate in this population. Lactoferrin from milk and colostrum regulates iron absorption from the bowel. It also has promising applications to be a natural anticancer substance. Breast milk is the primary source of tryptophan in nursing infants. Tryptophan is the precursor of serotonin, melatonin, niacin, tryptamine, quinolinic acid, kynurenic acid, nicotinamide adenine dinucleotide, etc. Deficiency of tryptophan can cause a reduction of serotonin in the CNS and can produce behavioral changes in children.

As opposed to milk, BC contains a smaller amount of lactose and therefore may be suitable for patients suffering from lactose intolerance. A limited number of human and animal studies done with colostrum itself or its supplements are indicative of future prospects for helping in curing diseases like AIDS, cardiovascular disorders, diabetes, IBD, leaky gut syndrome, infectious diseases, wound healing, and certain cancers. The biologically active molecules and compounds isolated from colostrum or milk may serve as an adjunct or alternative therapy for the treatment of cancer.

Immunoglobulins present in colostrum have the potential to enhance the immune function and well-being of healthy persons and patients. Immunity-related disorders are one of the leading causes of morbidity worldwide. Colostrum products intake may be useful to stimulate the function of the thymus gland and consequently mitigate hypersensitivity and autoimmune disorders.

Since colostrum has several naturally occurring important nutritional components, well-designed, double-blind, placebo-controlled studies with colostrum products are needed for exploring their multimodal effects and to widen their therapeutic role in children and adults. People in developing countries, for example, are desperately looking for alternative remedies for health care because synthetic drugs are very expensive, and so colostrum indeed seems to be a treasure trove that, if tapped, could eventually reveal many health benefits and cost-effective cures in humans.

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