Bovine colostrum: An emerging nutraceutical

Article *in* Journal of Complementary and Integrative Medicine · March 2015

DOI: 10.1515/jcim-2014-0039 · Source: PubMed

5 authors, including:

Leo J Philip Tharappel
SIRO Clinpharm Pvt Ltd
8 PUBLICATIONS **182** CITATIONS
SEE PROFILE

Ginpreet Kaur
Narsee Monjee Institute of Management Studies
169 PUBLICATIONS **2,478** CITATIONS
SEE PROFILE

Harpal Buttar
University of Ottawa
369 PUBLICATIONS **3,711** CITATIONS
SEE PROFILE

Siddhi Bagwe Parab
Narsee Monjee Institute of Management Studies
20 PUBLICATIONS **410** CITATIONS
SEE PROFILE

Review

Siddhi Bagwe, Leo J.P. Tharappel, Ginpreet Kaur* and Harpal S. Buttar

Bovine colostrum: an emerging nutraceutical

Abstract: Nutraceutical, a term combining the words "nutrition" and "pharmaceuticals", is a food or food product that provides health benefits as an adjuvant or alternative therapy, including the treatment and prevention of infectious diseases in children and adults. There is emerging evidence that bovine colostrum (BC) may be one of the promising nutraceuticals which can prevent or mitigate various diseases in newborns and adults. Immunity-related disorders are one of the leading causes of mortality in the world. BC is rich in immunity, growth and antimicrobial factors, which promote tissue growth and the maturation of digestive tract and immune function in neonatal animals and humans. The immunoglobulins and lactoferrin present in colostrum are known to build natural immunity in newborns which helps to reduce the mortality rate in this population. Also, the side-effect profile of colostrum proteins and possible lactose intolerance is relatively less in comparison with milk. In general, BC is considered safe and well tolerated. Since colostrum has several important nutritional constituents, well-designed, double-blind, placebo-controlled studies with colostrum products should be conducted to widen its therapeutic use. The objectives of this review are to create awareness about the nutraceutical properties of colostrum and to discuss the various ongoing alternative treatments of colostrum and its active ingredients as well as to address colostrum's future nutraceutical and therapeutic implications in humans.

Keywords: bovine colostrum dietary supplements, colostrum as nutraceutical, colostrum-induced immunity, human and bovine colostrum benefits, immunoglobulins and lactoferrin

DOI 10.1515/jcim-2014-0039
Received June 20, 2014; accepted January 29, 2015

***Corresponding author: Ginpreet Kaur,** Department of Pharmacology, SPP School of Pharmacy and Technology Management, Mumbai, Maharashtra, India, E-mail: ginpreet.aneja@gmail.com
Siddhi Bagwe, Leo J.P. Tharappel, Department of Pharmacology, SPP School of Pharmacy and Technology Management, Mumbai, Maharashtra, India
Harpal S. Buttar, Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ontario, Canada

Introduction

Immunity-related diseases are one of the major causes of morbidity and mortality worldwide. An efficient immune system results in self-healing [1]. Currently, the number of microbial agents that have developed resistance against various antibiotics is increasing, and antibiotic-induced resistance has become a major challenge in the medical world [2–6]. Nowadays, health-care practitioners have been talking a great deal about the healing properties of BC, and colostrum-derived new food supplements are intended to boost the immune systems in both healthy and chronically ill patients [7–9].

Colostrum also known as beestings, bisnings or first milk is the mammary secretion that all mammals provide for their newborns during the initial 24–48 h post-parturition [10, 11] with most species producing colostrum just prior to giving birth. Human newborns only get colostrum from their mothers during the first few hours after birth, and that creates the foundation of lifelong immunity. Human colostrum and bovine colostrum (BC) is a thick, sticky, yellowish liquid containing several antibodies at a higher concentration than that of ordinary milk [12].

Newborns have a very small and immature gastrointestinal (GI) system, and colostrum provides naturally produced nutrients in a highly concentrated low-volume form. In neonates, it proves to be a laxative and assists in the passage of the baby's initial stools called meconium, and also helps to remove excess bilirubin from the infant's body to prevent jaundice [13, 14]. Antibodies present in colostrum not only provide protection to neonates against infectious diseases [15] but also provide passive immunity and growth factors for the GI development [16–18].

Colostrum has been known for centuries for its health benefits [19]. Research has also shown that colostrum constituents from bovine (cow and buffalo) sources are 100-fold to 1,000-fold more potent than that of human colostrum. This means that even human infants can rely on cow or buffalo colostrum to gain health benefits [9, 20, 21]. In 1950, Dr Albert Sabin, who developed the polio vaccine, eventually found that BC contained antibodies against polio virus and hence recommended it for therapy in children at risk for contracting polio [22].

Colostrum derivatives were also tried against rheumatoid arthritis [23].

Colostrum is regarded to be safe in the majority of the human population. Although side effects like nausea and flatulence might occur initially, they decline with time. It seems that colostrum should be off bounds only to individuals who have an allergy to milk or milk-based products.

Colostrum should be produced organically and should be free of adulterants like pesticides, herbicides, anabolic hormones, antibiotics and other chemicals [24]. It should not be processed at high temperatures and pressures because its biological activity is decreased by such actions [25]). The highly concentrated solid dosage form of colostrum is preferred than the liquid dosage form. Colostrum has a short shelf-life and therefore addition of preservatives is a must for its storage at warm ambient temperatures. However, even the addition of preservatives cannot completely prevent the loss of active ingredients [26, 27]. Removal of fats, whey and lactose is done to create an optimum dosage form [21]. Synthetic manufacturing processes include low-heat pasteurization [28] and indirect steam drying [29].

Synthetic colostrum is termed as "fake" colostrum. Milk, egg yolk, cod liver oil and sugar are used to manufacture fake colostrum. This formulation is utilized to feed young animals if the mother is unable to produce sufficient colostrum. While it serves as a temporary substitute, chronic usage should be discouraged since synthetic colostrum lacks the antibodies present in natural colostrum [30, 31]. Synthetic colostrum manufactured for human neonates utilizes accurately measured ingredients that include carbohydrates, amino acids, fats, vitamins and trace elements [32]. This formula is used to feed neonates whose mothers are unable to produce colostrum.

Components of colostrum

The components of BC can be classified into three major categories, namely nutritional components [33], immune factors [8] and growth factors [7]. These are given in Table 1.

Other immune factors such as 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 are also present in colostrum.

Comparative study between the constituents of cow, human, buffalo and goat colostrum

A comparison was done to determine the health benefits of the constituents of human, cow, buffalo and goat colostrum. It can be noted in Tables 2–4 [34–36] that the cow's colostrum (BC) has more important natural constituents than the other three species. Values depicted in Table 2 clearly show that the percentage of lactose in cow colostrum (2.5%) is far lesser than that of human (6.9–7.2%), buffalo (4.7%) as well as goat (4.7%) colostrum. Therefore, cow colostrum may be given to a person having intolerance to lactose.

Quantity of immunoglobulins present in BC

Immunoglobulins are responsible for building the immunity in animals and humans. The immunoglobulins present in BC are IgG1, IgG2, IgA, IgM and lactoferrin. IgG1 being the major component can be seen in Table 5 [8, 35, 36].

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 fat-soluble vitamins are not reduced when colostrum is commercially processed. Table 6 shows the content of vitamins present in colostrum [35, 37, 38].

Manufacturers of colostrum-derived nutraceuticals

Colostrum is commercially processed into capsules, tablets and powder by various nutraceutical manufacturing industries. Some of these manufacturing companies are listed in Table 7 [39–41]. According to the manufacturers, colostrum is utilized after the needs of the newborn calves are fulfilled. Processing and storing at high temperatures degrades colostrum and results in the loss of nutrients, hence, these companies utilize processes like low-heat pasteurization and low-pressure processing. It is a point to be noted that only APS BioGroup have written about their manufacturing plants being FDA approved.

Table 1: Components of bovine colostrum.

Components	Uses
Nutritional components	
Vitamins (A, B_{12} and E)	Health, vitality and growth of the newborn
Minerals	
Amino acids	
Essential oil	
Immune factors	
Proline-rich polypeptide (PRP)	Regulates the thymus gland.
Immunoglobulins (A, D, E, G and M)	IgG neutralizes toxins and microbes in the lymph and circulatory system IgM destroys bacteria IgE and IgD are highly antiviral [77]
Lactoferrin	An antiviral, anti-inflammatory and antibacterial iron-binding protein with therapeutic effects in cancer, HIV, Cytomegalovirus [88], herpes, chronic fatigue syndrome, Candidiasis and other infections [77]
Cytokines	Regulates the duration and intensity of the immune response, responsible for cell-to-cell communication boost T-cell activity and the production of immunoglobulins
Lysozyme	It aids hydrolysis and boosts the immune system and is capable of destroying bacteria and viruses on contact
Enzymes	Lactoperoxidase-thiocyanate, xanthine oxidase and peroxidase oxidize bacteria through their ability to release of hydrogen peroxide
Leukocytes	Stimulates interferon production
Trypsin	Protease inhibitors – prevent the destruction of immune and growth factors in colostrum
Lymphokines	Mediates the immune response
Oligopolysaccharides and glycoconjugates	Attract and bind to pathogens preventing them from attaching or entering the mucous membranes
Orotic acid	Prevents haemolytic anaemia
Growth factors	
Epithelial growth factor (EGF)	Help in enhancing cell and tissue growth by stimulating DNA formation
Insulin-like growth factor-I and II (IGF-1 and IGF-II)	
Fibroblast growth factor (FgF)	
Platelet-derived growth factor (PDGF)	
Transforming growth factors A (TgA) and transforming growth factor B (TgB)	
Growth hormone (GH)	

Table 2: A comparison of human, cow, buffalo and goat colostrum.

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

Therapeutic applications of colostrum

Colostrum has many clinical or therapeutic applications and it may be used as a nutritional supplement, since it is well tolerated and seems to produce no adverse side effects.

Allergies and autoimmune diseases

Allergy is categorized as a hypersensitivity disorder of the immune system [42]. It occurs due to an improper immune response to harmless substances. Proline-rich polypeptide (PRP) present in colostrum functions as a regulatory substance of the thymus gland. Lymphocyte and T-cell overproduction, allergy and autoimmune

Table 3: A comparison of water-soluble vitamin content of human, cow, buffalo and goat colostrum.

Constituents	Human colostrum, mg/100 ml	Cow colostrum, µg/ml	Buffalo colostrum, µg/ml	Goat colostrum
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 B_{12}	0.03	0.60	1.59	
Pyridoxal	–	0.15	–	
Pyridoxamine	–	0.21	–	
Pyridoxine	–	0.04	3.25	

Table 4: A comparison of mineral content of human, cow, buffalo and goat colostrum.

Constituents	Human colostrum, mg/100 ml	Cow colostrum, mg/kg	Buffalo colostrum, mM	Goat colostrum, 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	–
Sulphur	–	2595	15700	0.2
Manganese	–	0.1	38.2	–

Table 5: Immunoglobulins present in bovine colostrum.

Immunoglobulin	Quantity, mg/ml
IgG1	35.0
IgG2	16.0
IgA	1.7
IgM	4.3
Lactoferrin	0.8

Table 6: 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
Cholecalciferol (vitamin D)	0.0305
Phylloquinone (vitamin K_1)	4.9 µg/l

Table 7: Manufacturers of colostrum-derived nutraceuticals.

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

disease symptoms, i.e. pain, inflammation and swelling are inhibited by PRP [43]. Also, PRP has been reported to improve or eliminate symptoms of autoimmune diseases like rheumatoid arthritis, myasthenia gravis, multiple sclerosis, lupus and allergies.

Cardiovascular diseases

Several studies suggest that atherosclerosis and cardiovascular diseases may be caused by altered immunity. One study indicated that, in over 79% of patients with

heart disease, a type of *Chlamydia* has been linked with the formation of arterial plaques [44]. Further, it seems that immune sensitization to cardiac antigen is the cause of heart disease [44]. Colostrum may have a beneficial function in the prevention of cardiovascular diseases due to the presence of PRP, the same effect as is observed in allergies and autoimmune diseases. Also, the growth hormones (GH) and growth factors like insulin-like growth factor-1 (IGF-1) in colostrum can raise the blood levels of HDL (high-density lipoprotein)-cholesterol, while lowering LDL (low-density lipoprotein)-cholesterol. Growth factors and GH also play a significant role in repairing the damage to heart muscle and promote the growth of new blood vessels in collateral coronary circulation [44].

In vitro and ex vivo studies showed that BC possesses concentration-related antioxidant activity as revealed by significant free radical scavenging ability and marked inhibition of lipid peroxidation [45]. In addition, the combined administration of 500 mg/kg colostrum plus 0.25 mg/kg enalapril showed marked cardioprotective effects in rats after 28 days dosing. Colostrum itself was also cardioprotective at doses of 500 mg/kg against isoproterenol-induced myocardial infarction in rats. Overall, the rat study results indicated that colostrum in combination with enalapril exhibited far greater cardioprotective activity when compared with enalapril or colostrum alone [45].

Reduction of blood flow or ischemia and excessive bleeding or haemorrhage may be two side effects of certain drugs, both of which could be life-threatening consequences. Fortunately, BC is considered to be effective against both disorders. BC's antioxidant and anticytokine activity as evaluated in an intestinal ischemia/reperfusion (I/R) injured rat model [46] could also be effective against systemic inflammatory response syndrome and multiple organ dysfunction syndrome since I/R results in the production of free radicals and various pro-inflammatory cytokines, namely tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6. Neurobehavioural changes mediated by these cytokines could be attenuated by lactoferrin present in BC since the aforementioned activities also seemed to be able to reverse cognitive dysfunction associated with either global cerebral ischemia or a middle cerebral artery occlusion induced ischemic stroke [47, 48]. Hippocampal neuronal cell death caused by haemorrhage-induced *N*-methyl-D-aspartic acid (NMDA)-mediated excitotoxicity and apoptosis was also attenuated by BC [49]. Additionally, short-term memory lapses caused by neuronal cell death were reversed by BC administration. Colostrinin, a PRP present in BC, is thought to be responsible for the reduction in the caspase-3-mediated apoptosis that was observed by the investigators.

Further well-designed studies are warranted to evaluate the nutraceutical potential of colostrum before it can be recommended for treating cardiovascular diseases in humans.

Viral and bacterial illnesses

It has been demonstrated that colostrum is helpful in reversing infection-induced inflammation occurring in the digestive tract of HIV patients [44], possibly through improvement of mucosal integrity, tissue repair and direct antimicrobial actions [50]. Colostrum also has antiviral, antifungal and antibacterial properties which enable it to kill different pathogens like *Escherichia coli*, rotavirus and *Cryptosporidium*. BC with a high antibody titre, i.e. hyperimmune BC (HBC) is especially useful against human rotavirus (HRV) [51] and HRV-induced diarrhoea [20, 52] in children. This action may be mediated by κ-casein, a component of human and bovine milk. κ-Casein is a glycosylated protein that was found to bind directly to the viral antigens through the glycosylated residue [53]. These residues are integral for antiviral activity since deglycosylation failed to neutralize HRV. Although natural production of antibodies by vaccinating cows is cheaper than production through synthetic means, the yield is not enough to successfully cover the global requirement since over 500,000 deaths occur across the world every year due to rotavirus-induced diarrhoea [54]. Hence, a way to reduce the BC dose was required. The path was shown by Gunaydin et al., who engineered *Lactobacillus rhamnosus* GG, a probiotic *Lactobacillus* strain, to surface express the IgG-binding domains of protein G (GB1, GB2 and GB3). These domains help in targeting rotavirus by binding to the colostrum-derived IgG antibodies and enhancing their potency. The combination therapy was found to be more effective than BC alone in a mouse pup infection model. It is said that such a combination may result in the dose of BC being reduced 10–100-fold.

It has been reported that colostrum is capable of killing opportunistic infections caused by *Candida albicans*, *Helicobacter pylori*, five types of Streptococci and *Cryptosporidium* [55]. The immunoglobulins, lactoferrin and cytokines in colostrum are reported to show strong antiviral activity [56]. However, a double-blind, placebo-controlled study to evaluate the effect of BC on viral upper respiratory tract infections in IgA-deficient children

failed to demonstrate a difference between salivary IgA levels between the control and test group, although the BC group did record a lower infection severity score [57]. Such studies remain to be conducted in similar adult patients along with elucidation of relevant mechanisms although the ones given below could be at work.

Recently, Wong et al. demonstrated that oral administration (1.0 g/kg) of BC to C57BL/6 mice increased natural killer (NK) cell cytotoxicity, improved the immune response to primary influenza A virus (H1N1) infection and lessened viral burden in the lungs compared to controls. It was hypothesized that the small intestinal epithelial cells may be stimulated by colostrum, and the interaction between colostrum and immunity may partly depend on the colostrum components with innate receptors present in the intestinal epithelium, including toll-like receptors, namely TLR-2 and TLR-4 [58]. Skimmed and concentrated bovine late colostrum (SCBLC), i.e. colostrum obtained on the 6th or 7th day after parturition [59] and processed, was also found to be effective in reducing the symptom rate of influenza virus in mice [60]. This action was demonstrated to be mediated through an SCBLC-mediated rise in NK cell activity in Peyer's patches, splenocytes and the lungs. Additionally, it was determined through experiments conducted in murine Peyer's patch cells that SCBLC also increased IL-12 and IFN (interferon). Thus, SCBLC was found to activate both systemic and local cellular immunity mechanisms. In view of these observations, BC may be a potential alternative therapy for enhancing the activity of NK cells and subsequently boosting immune response against viral infections in human subjects, especially, non-specific responders.

BC-derived fractions rich in IgG have been successful in alleviating the symptoms of influenza in pretreated BALB/c mice [61]. These fractions were collected from cows immunized with A/Puerto Rico/8/34 (PR8) influenza virus, the IgG purified and delivered intranasally to mice. The anti-PR8 IgG preparation significantly reduced the viral load in mice and also prevented weight loss and death from a lethal dose of the virus.

Weight loss programs

Colostrum contains leptin that induces satiety or feeling of fullness and reduced desire to eat more in addition to IGF-1, which is required for the metabolism of fat and energy production occurring through Krebs cycle [44]. Leptin could work in tandem with IGF-1 to reduce elevated cholesterol and triglyceride levels [62]. BC also promotes tissue repair and regeneration of lean muscle growth, consequently escalating strength and endurance. Elderly humans and type 2 diabetics seem to suffer from inadequate production of IGF-1. Thus, BC supplementation could be an attractive therapy for weight reduction, especially among diabetic and obese populations.

Athletic performance

Athletic training and competition includes strenuous exercise which can slow down the immune system, eventually decreasing the number of T-lymphocytes and NK cells. Due to these reductions, athletes are more prone to develop chronic fatigue syndrome. For many athletes, colostrum has become a popular dietary source due to its valuable nutrient contents [63]. Athletes increase the efficiency of the digestive tract by using colostrum as a dietary supplement [64]. They usually take colostrum in powdered form and add it to shakes and drinks [65].

The possibility of infections due to physical and emotional stress in athletes can be significantly reduced by the immune factors present in colostrum or colostrum supplements. Exercise especially during winter disposes the athlete to develop an upper respiratory infection. BC was found to limit an increase in salivary bacterial load in a 12-week, randomized, placebo-controlled, double-blinded study [66]. Although an inter-group difference was not found, BC displayed bacterial load control over time.

Studies show that colostrum helps athletes by burning body fat, boosting the immune system and accelerating healing of injuries [67]. It was also implicated in reversing exercise induced gut permeability and thus prevent heat stroke in a double-blind, placebo-controlled, crossover study [68], through upregulation of the anti-apoptotic protein Bcl-2 and HSP70 (important for maintaining homeostasis during stress, as is experienced during exercise) along with downregulation of proapoptotic Baxα and apoptosis initiators Caspase-3 and 9. It has been suggested that BC supplementation is most effective during periods of high-intensity training and recovery from training, possibly due to increased plasma IGF-1, improved intramuscular buffering capacity and increase in lean body mass [69]. Further placebo-controlled studies are needed to assess the influence of BC products on athletic performance and to determine the dosage regimens and intake duration of standardized BC supplements as well as the bioavailability of active ingredients present in the BC supplements.

Wound healing

Topical application of the colostrum constituents has depicted significant promotion for open wound healing [70]. It has been suggested that nucleotides, epidermal growth factor (EGF), transforming growth factor (TGF) and IGF-1 promote cellular and skin growth and also help in repairing DNA and RNA damage. Growth of nerve cells, skin, cartilage, muscle and bone are tissues where colostrum showed beneficial effects [29]. BC also promoted collagen gel contraction in a fibroblast populated collagen gel culture [71]. This in vitro model seems to mimic the wound healing process in vivo. A patent has also been granted for utilization of a colostrum fraction to accelerate wound healing [72]. Additionally, BC was found to reduce NSAID-induced gastric injury in animals [73] and probably humans [50] by enhancing the growth of intestinal villi possibly due to the action of IGF and TGF-β present in SCBLC [59]. The bioactive components such as fibroblast growth factors and lactoferrin present in BC are thought to mediate the wound healing actions [50].

Apart from wound healing, lactoferrin was also found to be capable of protecting the skin from ultraviolet B (UVB)-induced photodamage in hairless mice [74]. Oral administration of 1,600 mg/kg lactoferrin resulted in a decrease in transepidermal water loss and epidermal thickening, two markers of skin damage. The protective effect could have been due to inhibition of UVB-stimulated IL-1β production. IL-1β, IL-6 and TNF-α are implicated in recruiting inflammatory leukocytes as well as matrix metalloproteinases (MMPs) resulting in inflammation and skin damage. While the drawback of this study was the failure to measure IL-6 and TNF-α in the skin due to inadequate concentrations; nevertheless, IL-1β provided the required link between UVB and skin damage.

The leaky gut syndrome

The leaky gut syndrome is associated with many autoimmune diseases like chronic fatigue syndrome, diabetes, inflammatory and irritable bowel disease and multiple sclerosis [75]. Antibodies produced by the biological system in response to stressors can get attached to tissues throughout the body and cause inflammation [76]. Progressively generated auto-antibodies result in chronic inflammatory disorders [77]. The immune system enhancers present in colostrum have revealed markedly beneficial effects on clinical and subclinical GI infections and chronic pain disorders. Thus, BC supplements may provide GI and immunological benefits and help to improve gut mucosal integrity and immunological status [78]. Colostrum supplements not only possess anti-inflammatory properties but also appear to enhance nutrient bioavailability and prevent subclinical leaky gut syndrome in patients who use colostrum as a dietary supplement [79].

BC's ingredients may keep the intestinal mucosae sealed and make them impermeable to exo- and endo-toxins. This intestinal sealing capacity was attributed to BC mediated induction of intestinal barrier strengthening cytokine TGF-β [80]. The aforementioned mechanism was elucidated when a counteracting process to BC mediated induction in claudin-2 expression was sought. Claudin-2 is a tight junctional protein that forms cation-selective intestinal pores resulting in increased intestinal permeability and lower transepithelial electrical resistance (TER) [81]. Therefore, theoretically BC should have decreased TER but did not do so because TGF-β balanced claudin-2 overexpression resulting in reduced intestinal permeability and high TER.

Diabetes

Juvenile diabetes (type-1 or insulin dependent diabetes) is thought to occur through an autoimmune disorder, primarily initiated by an intense allergic reaction to the protein glutamic acid decarboxylase (GAD) found in cow's milk [29, 77]. Colostrum contains various bioactive factors, which can control and inhibit this autoimmune disorder and other similar allergies. The immunoglobulin IGF-1 found in colostrum can bind to both insulin and IGF-1 receptors present in target cells of human body. Additionally, BC was found to reduce glucose and malondialdehyde levels in alloxan-induced diabetes in rats [82]. A similar model adopted for mice showed that both BC and HBC were able to significantly reduce glucose and lipid levels [83] with HBC being the superior one. Apart from the obvious helpful actions of IGF-1, BC-mediated β-cell regeneration leading to insulin release and peroxisome proliferator-activated receptor-α (PPARα) like actions of conjugated isomers of linoleic acid (CLA) could be the mechanisms behind the antidiabetic actions of BC [82, 83]. The antioxidant effect of BC could be mediated by its non-enzymatic components such as lactoferrin and A, C, E vitamins.

HIV-associated immunomodulation

HIV infection suppresses vital cells in the human immune system such as helper T cells (specifically $CD4^+$ T cells) [84], many dendritic cells and macrophages, thus reducing their levels in the body. Further, diarrhoea is a

common complication in AIDS patients, and HIV-associated diarrhoea may result in discomfort and malnutrition. People with a healthy immune system do not experience this GI complication. It has been reported that intake of human milk increases helper T cells in the body, thus assisting in improving the immune system [85]. BC supplements may be useful in patients infected with HIV to restore the immune system and regulate the loss of T helper cells as well as GI system immune activation and mucosal integrity. Nevertheless, placebo-controlled studies are needed to ascertain if BC can effectively ameliorate HIV-associated gut inflammation and suppression of immune function.

To further enhance the utility of BC against HIV, Kramski et al. found that colostrum-derived IgG fractions possessed HIV-1 neutralizing activity [86]. These fractions were obtained by vaccinating cows with recombinant HIV-1 gp140 antigens, which resulted in the envelope proteins stimulating the production of gp-140-specific polyclonal antibodies. These antibodies bind to the CD4-binding site and thus grant BC its HIV-1 neutralizing action. This study provides a relatively cheap alternative for the production of anti-HIV antibodies as opposed to the expensive synthetic processes utilized today.

Anticancer properties of BC

Lactalbumin present in colostrum is responsible for inducing apoptosis (physiological cell death) of the cancerous cells [87]. Lactoferrin could prove to be beneficial as an anticancer substance [44, 77]. Indeed, metal ion-saturated lactoferrin has been granted a patent for displaying potent anticancer properties [87]. This lactoferrin increases treatment responsiveness, stimulates the immune response via Th-1 and Th-2 activation and also increases the leucocyte and erythrocyte count. Cancer metastasis could be inhibited by the growth and immune factors present in colostrum [44]. NK cells found in colostrum provide resistance against tumours; therefore, they have reduced cytotoxic properties. Based on these observations, the immunomodulatory components and anticancer factors present in BC supplements may be employed as an alternative remedy or adjunct therapy for curing some cancers besides radiation and chemotherapy.

Conclusions

It has been reported that colostrum mitigates a wide variety of diseases, and could be a promising nutraceutical in the future. The primary advantage of colostrum supplements is that they have negligible side effects and are well tolerated. As opposed to milk, BC has lesser amount of lactose, and therefore may be suitable for patients suffering from lactose intolerance. The immunoglobulins present in colostrum have the potential to enhance the immune function and well-being of healthy persons and patients. Limited number of human and animal studies done with colostrum supplements are indicative of future prospects for helping in curing diseases like AIDS, cardiovascular and GI disorders, infectious diseases, wound healing, and certain cancers. As colostrum has numerous naturally occurring important nutritional components, well-designed, double-blind, placebo-controlled studies with colostrum products need to be conducted to widen their therapeutic role. It indeed seems to be a treasure trove which if tapped could eventually reveal many health benefits and cost-effective cures in humans.

Acknowledgments: The authors would like to thank SPPSPTM NMIMS for providing the facilities utilized in this review.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Grivennikov SI, Sergei I, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
2. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev 2001;65:232–60.
3. Davies J. Inactivation of antibiotics and the dissemination of resistance genes. Science 1994;264:375–82.
4. Brown MR, Allison DG, Gilbert P. Resistance of bacterial biofilms to antibiotics a growth-rate related effect?. J Antimicrob Chemother 1988;22:777–80.
5. Neu HC. The crisis in antibiotic resistance. Science 1992;257:1064–73.
6. Demerec M. Origin of bacterial resistance to antibiotics. J Bacteriol 1948;56:63–74.
7. Pakkanen R, Aalto J. Growth factors and antimicrobial factors in bovine colostrum. Int Dairy J 1997;7:285–97.

8. Ogra SS, Ogra PL. Immunological aspects of human colostrum and milk. J Pediatr 1978;92:550–5.
9. van Hooijdonk AC, Kussendrager KD, Steijns JM. In vivo antimicrobial and antiviral activity of components in bovine milk and colostrum involved in non-specific defence. Br J Nutr 2000;84:S127–34.
10. Tokuyama H, Tokuyama Y, Migita S. Isolation of two new proteins from bovine colostrum which stimulate epidermal growth factor-dependent colony formation of NRK-49f cells. Growth Factors 1990;3:105–14.
11. Stelwagen K, Carpenter E, Haigh B, Hodgkinson A, Wheeler TT. Immune components of bovine colostrum and milk. J Anim Sci 2009;87:3–9.
12. Shah NP. Effects of milk-derived bioactives: an overview. Br J Nutr 2000;84:3–10.
13. de Almeida MF, Draque CM. Neonatal jaundice and breastfeeding. Neoreviews 2007;8:e282–8.
14. Cohen SM. Jaundice in the full-term newborn. Pediatr Nurs 2006;32:202–8.
15. Morris JA, Wray C, Sojka WJ. Passive protection of lambs against enteropathogenic Escherichia coli: role of antibodies in serum and colostrums. J Med Microbiol 1980;13:265–71.
16. Ebina T, Ohta M, Kanamaru Y, Yamamoto-Osumi Y, Baba K. Passive immunizations of suckling mice and infants with bovine colostrum containing antibodies to human rotavirus. J Med Virol 1992;38:117–23.
17. Majumdar AS, Ghose AC. Protective properties of anti-cholera antibodies in human colostrum. Infect Immun 1982;36:962–5.
18. Stephan W, Dichtelmuller H, Lissner R. Antibodies from colostrum in oral immunotherapy. J Clin Chem Clin Biochem 1990;28:19–23.
19. Hurley WL, Theil PK. Perspectives on immunoglobulins in colostrum and milk. Nutrients 2011;3:442–74.
20. Sarker SA, Casswall TH, Mahalanabis D, Alam NH, Albert MJ, Brüssow H, et al. Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovine colostrums. Pediatr Infect Dis J 1998;17:1149–54.
21. Elfstrand L, Lindmark-Månsson H, Paulsson M, Nyberg L, Åkesson B. Immunoglobulins, growth factors and growth hormone in bovine colostrum and the effects of processing. Int Dairy J 2002;12:879–87.
22. Sabin AB, Fieldsteel AH. Antipoliomyelitic activity of human and bovine colostrum and milk. Pediatrics 1962;29:105–15.
23. Nitsch A, Nitsch FP. The clinical use of bovine colostrum. J Orthomol Med 1998;13:110–18.
24. Afzal A, Mahmood MS, Hussain I, Akhtar M. Adulteration and microbiological quality of milk (a review). Pak J Nutr 2011;10:1195–202.
25. Korhonen H, Pihlanto-Leppäla A, Rantamäki P, Tupasela T. Impact of processing on bioactive proteins and peptides. Trends Food Sci Tech 1998;9:307–19.
26. Jenny BF, Hodge SE, O'Dell GD, Ellers JE. Influence of colostrum preservation and sodium bicarbonate on performance of dairy calves. J Dairy Sci 1984;67:313–18.
27. Foley JA, Otterby DE. Availability, storage, treatment, composition, and feeding value of surplus colostrum: a review. J Dairy Sci 1978;61:1033–60.
28. Godden S, McMartin S, Feirtag J, Stabel J, Bey R, Goyal S, et al. Heat-treatment of bovine colostrum. II: effects of heating duration on pathogen viability and immunoglobulin G. J Dairy Sci 2006;89:3476–83.
29. Seth R, Das A. Colostrum powder and its health benefits. In: Sharma R, Mann B, editors. Chemical analysis of value added dairy products and their quality assurance. Karnal, Haryana, India: Division of Dairy Chemistry, National Dairy Research Institute, 2011:59–67.
30. Thompson J, Rulofson F, Hansen D. Artificial rearing of lambs on milk replacer diets. Available at http://ir.library.oregonstate.edu/xmlui/bitstream/handle/1957/14277/ec1427.pdf. Accessed:29 Aug 2014.
31. Colostrum. Available at: http://aces.nmsu.edu/sheep/general_management/colostrum.html. Accessed:29 Aug 2014.
32. Christensen RD. Infant formula compositions for neonates lacking mother's own colostrum and method of making. US 20100183769 A1 (2010).
33. Macy IG. Composition of human colostrum and milk. Am J Dis Child 1949;78:589–603.
34. Jenness R. The composition of human milk. Semin Perinatol 1979;3:225–39.
35. Eddleman H. Composition of Human, Cow and Goat Milks (B120A). Available at: http://www.disknet.com/indiana_biolab/b120a.htm. Accessed:30 Aug 2014.
36. Ahmad S, Anjum FM, Huma N, Sameen A, Zahoor T. Composition and physico-chemical characteristics of buffalo milk with particular emphasis on lipids, proteins, minerals, enzymes and vitamins. J Anim Plant Sci 2013;23:62–74.
37. Henry KM, Kon SK. A note on the vitamin D content of cow's colostrum. Biochem J 1937;31:2199–201.
38. Haroon Y, Shearer MJ, Rahim S, Gunn WG, McEnery G, Barkhan P. The content of phylloquinone (vitamin K_1) in human milk, cow's milk and infant formula foods determined by high-performance liquid chromatography. J Nutr 1982;112:1105–17.
39. APS BioGroup. Available at: http://apsbiogroup.com/colostrum/. Accessed:30 Aug 2014.
40. Biostrum Nutritech Pvt Ltd. Available at: http://www.bcolostrum.com/new/obtainingcolostrum1.html. Accessed:30 Aug 2014.
41. Mt. Capra Wholefood Nutritionals. Available at: http://www.mtcapra.com/capracolostrum/. Accessed:30 Aug 2014.
42. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347:911–20.
43. Keech A. Novel immunologically active peptide fragments of a proline-rich polypeptide isolated from colostral mammalian fluids for treatment of viral and non-viral diseases or diseased conditions. US 20070212367 A1 (2007).
44. Rona ZP. Bovine colostrum emerges as immunity modulator. Am J Nat Med 1998;5:19–23.
45. Kaur G, Somaiya R, Wasim M, Buttar HS. Cardioprotective effects of bovine colostrum against isoproterenol-induced myocardial infarction in rats. J Pharmacol Toxicol 2014;9:37–45.
46. Kwon OY, Lee JS, Choi HS, Hong HP, Jang K-H, Paek JH, et al. Antioxidant and anticytokine effects of bovine colostrum in intestinal ischemia/reperfusion injured rat model. Food Sci Biotechnol 2010;19:1295–301.
47. Undale VR, Desai SS, Sangamnerkar SK, Upasani CD. Neuroprotective effect of cow colostrum and tetramethylpyrazine against global cerebral ischemia reperfusion injury. Int J Nutr Pharmacol Neurol Dis 2012;2:111–20.

48. Choi HS, Ko YG, Lee JS, Kwon OY, Kim S-K, Cheong C, et al. Neuroprotective effects of consuming bovine colostrum after focal brain ischemia/reperfusion injury in rat model. Nutr Res Pract 2010;4:196–202.
49. Kim SE, Ko IG, Shin MS, Kim CJ, Ko YG, Cho HJ. Neuroprotective effects of bovine colostrum on intracerebral haemorrhage-induced apoptotic neuronal cell death in rats. Neural Regen Res 2012;7:1715–21.
50. Rathe M, Muller K, Sangild PT, Husby S. Clinical applications of bovine colostrum therapy: a systematic review. Nutr Rev 2014;72:237–54.
51. Davidson GP, Whyte PB, Daniels E, Franklin K, Nunan H, McCloud PI, et al. Passive immunisation of children with bovine colostrum containing antibodies to human rotavirus. Lancet 1989;334:709–12.
52. Mitra AK, Mahalanabis D, Ashraf H, Unicomb L, Eeckels R, Tzipori S. Hyperimmune cow colostrum reduces diarrhoea Due To rotavirus: a double-blind, controlled clinical trial. Acta Paediatr 1995;84:996–1001.
53. Inagaki M, Muranishi H, Yamada K, Kakehi K, Uchida K, Suzuki T, et al. Bovine κ-casein inhibits human rotavirus (HRV) infection via direct binding of glycans to HRV. J Dairy Sci 2014;97: 2653–61.
54. Gunaydin G, Zhang R, Hammarstrom L, Marcotte H. Engineered Lactobacillus rhamnosus GG expressing IgG-binding domains of protein G: capture of hyperimmune bovine colostrum antibodies and protection against diarrhea in a mouse pup rotavirus infection model. Vaccine 2014;32:470–7.
55. Tzipori S, Roberton D, Chapman C. Remission of diarrhea due to cryptosporidiosis in an immunodeficient child treated with hyperimmune bovine colostrum. Br Med J (Clin Res Ed) 1986;296:1276–7.
56. Pan Y, Lee A, Wan J, Coventry MJ, Michalski WP, Shiell B, et al. Antiviral properties of milk proteins and peptides. Int Dairy J 2006;16:1252–61.
57. Patiroglu T, Kondolot M. The effect of bovine colostrum on viral upper respiratory tract infections in children with immunoglobulin A deficiency. Clin Respir J 2013;7:21–6.
58. Wong EB, Mallet JF, Duarte J, Matar C, Rita BW. Bovine colostrum enhances natural killer cell activity and immune response in a mouse model of influenza infection and mediates intestinal immunity through toll-like receptors 2 and 4. Nutr Res 2014;34:318–25.
59. Cairangzhuoma, Yamamoto M, Muranishi H, Inagaki M, Uchida K, Yamashita K, et al. Skimmed, sterilized and concentrated bovine late colostrum promotes both prevention and recovery from intestinal tissue damage in mice. J Dairy Sci 2013;96:1347–55.
60. Uchida K, Hiruta N, Yamaguchi H, Yamashita K, Fujimura K, Yasui H. Augmentation of cellular immunity and protection against influenza virus infection by bovine late colostrum in mice. Nutrition 2012;28:442–6.
61. Ng WC, Wong V, Muller B, Rawlin G, Brown LE. Prevention and treatment of influenza with hyperimmune bovine colostrum antibody. PLoS ONE 2010;5:e13622. doi:10.1371/journal.pone.0013622.
62. Kim JH, Jung WS, Choi NJ, Kim DO, Shin DH, Kim YJ. Health-promoting effects of bovine colostrum in type 2 diabetic patients can reduce blood glucose, cholesterol, triglyceride and ketones. J Nutr Biochem 2009;20:298–303.
63. Bovine colostrum. Healthline.com. Available at: http://www.healthline.com/natstandardcontent/bovine-colostrum. Accessed 21 Jan 2014.
64. Antonio J, Sanders MS, Van Gammeren D. The effects of bovine colostrum supplementation on body composition and exercise performance in active men and women. Nutrition 2001;17: 243–7.
65. Mero A, Kahkonen J, Nykanen T, Parviainen T, Jokinenen I, Takala T, et al. IGF-I, IgA and IgG responses to bovine colostrum supplementation during training. J Appl Physiol 2002;93:732–9.
66. Jones AW, Cameron SJ, Thatcher R, Beecroft MS, Mur LA, Davison G. Effects of bovine colostrum supplementation on upper respiratory illness in active males. Brain Behav Immun 2014;39:194–203.
67. Godhia ML, Patel N. Colostrum – its composition, benefits as a nutraceutical: A review. Curr Res Nutr Food Sci 2013;1:37–47.
68. Marchbank T, Davison G, Oakes JR, Ghatei MA, Patterson M, Moyer MP, et al. The nutriceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes. Am J Physiol Gastrointest Liver Physiol 2011;300: G477–84.
69. Shing CM, Hunter DC, Stevenson LM. Bovine colostrum supplementation and exercise performance: potential mechanisms. Sports Med 2009;39:1033–54.
70. Doillon CJ, Lehance F, Bordeleau LJ, Laplante-Campbell MP, Drouin R. Modulatory effect of a complex fraction derived from colostrum on fibroblast contractibility and consequences on repair tissue. Int Wound J 2011;8:280–90.
71. Takayama Y, Kitsunai K, Mizumachi K. Factors in bovine colostrum that enhance the migration of human fibroblasts in type I collagen gels. Biosci Biotechnol Biochem 2001;65: 2776–9.
72. Aalto JU, Jalkanen MT, Jalonen HG, Kanttinen AP, Laato MK, Pakkanen RA. Method for the improvement of wound healing and compositions therefore. WO1995000155 A1 (1995).
73. Playford R, Floyd D, Macdonald C, Calnan D, Adenekan R, Johnson W, et al. Bovine colostrum is a health food supplement which prevents NSAID induced gut damage. Gut 1999;44:653–8.
74. Murata M, Satoh T, Wakabayashi H, Yamauchi K, Abe F, Nomura Y. Oral administration of bovine lactoferrin attenuates ultraviolet B-induced skin photodamage in hairless mice. J Dairy Sci 2013;97:651–8.
75. Fassano A. Leaky gut and autoimmune diseases. Clin Rev Allergy Immunol 2012;42:71–8.
76. Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative Enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuroendocrinol Lett 2008;29:117–24.
77. What is colostrum good for? Center for Nutritional Research. Available at: http://www.icnr.org/arthritis/5-what-is-colostrum-good-for/23-what-is-colostrum-good-for. Accessed 21 Jan. 2014.
78. Bolke E, Jehle PM, Hausmann F, Daubler A, Wiedeck H, Steinbach G, et al. Preoperative oral application of immunoglobulin-enriched colostrum milk and mediator response during abdominal surgery. Shock 2002;17:9–12.
79. Thapa BR. Health factors in colostrum. Ind J Pediatr 2005;72:579–81.

80. Bodammer P, Kerkhoff C, Maletzki C, Lamprecht G. Bovine colostrums increases pore-forming claudin-2 protein expression but paradoxically not ion permeability possibly by a change of the intestinal cytokine milieu. PLoS ONE 2013;8: e64210. doi:10.1371/journal.pone.0064210.
81. Rosenthal R, Milatz S, Krug SM, Oelrich B, Schulzke JD, Amasheh S, et al. Claudin-2, a component of the tight junction, forms a paracellular water channel. J Cell Sci 2010;123:1913–21.
82. Jahantigh M, Atyabi N, Pourkabir M, Jebelli Javan A, Afshari M. The effect of dietary bovine colostrum supplementation on serum malondialdehyde levels and antioxidant activity in alloxan-induced diabetic rats. Int J Vet Res 2011;5:63–7.
83. Pan D, Liu H. Preventive effect of ordinary and hyperimmune bovine colostrums on mice diabetes induced by alloxan. Afr J Biotechnol 2008;7:4369–75.
84. De Clercq E. Toward improved anti-HIV chemotherapy: therapeutic strategies for intervention with HIV infections. J Med Chem 1995;38:2491–517.
85. Wirt DP, Adkins LT, Palkowetz KH, Schmalstieg FC, Goldman AS. Activated and memory T lymphocytes in human milk. Cytometry 1992;13:282–90.
86. Kramski M, Center RJ, Wheatley AK, Jacobson JC, Alexander MR, Rawlin G, et al. Hyperimmune bovine colostrum as a low-cost, large-scale source of antibodies with broad neutralizing activity for HIV-1 envelope with potential use in microbicides. Antimicrob Agents Chemother 2012;56: 4310–19.
87. Kanwar JR, Haggarty NW, Palmano KP, Krissansen GW. Methods of immune or haematological enhancement, inhibiting tumour formation or growth, and treating or preventing cancer. US20090202574 A1 (2009).
88. Harmsen MC, Swart PJ, de Béthune MP, Pauwels R, Clercq E, The TH, et al. Antiviral effects of plasma and milk proteins: lactoferrin shows potent activity against both human immunodeficiency virus and human cytomegalovirus replication in vitro. J Infect Dis 1995;172:380–8.