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Potential benefits of colostrum in gastrointestinal diseases

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TABLE OF CONTENTS

1. ABSTRACT

This paper reviews the composition of colostrum and the potential preventive and therapeutic use of this “first milk” for treating various gastrointestinal disorders in humans. Colostrum is a complex biological liquid that is richer in antimicrobial peptides, immune-regulating compounds and growth factors than the subsequent

mature milk. The main functions of colostrum are to provide essential nutritional components, strengthen the natural defense system, modulate immune response, balance intestinal microbiota and enhance the growth and repair of several tissues. Several studies and clinical trials carried out both *in vitro* and *in vivo* on humans and animals suggest the clinical benefits of bovine colostrum (BC) supplementation in gastro-intestinal diseases. Despite the encouraging results, further well-designed studies are required in order to confirm these effects, the dose and duration of treatment. Colostrum is safe since there are no contraindications regarding high dose levels and few side effects of clinical relevance have been reported. In conclusion, in the near future, colostrum-based supplements may play a complementary role to synthetic drugs in the prevention and treatment of various gastrointestinal disorders.

2. INTRODUCTION

Colostrum is a biological fluid produced by the mammary gland after parturition, before it gradually loses its initial characteristics and to becomes mature milk. This secretion is fundamental for the survival of mammal offspring, especially for ungulates (1). Colostrum provides nutrition of newborns, enhances protection against pathogens, promotes the development of immune system and ensures the growth, maturation and repair of several tissues (2,3). Several studies have extensively analysed the composition of bovine, goat and human colostrum highlighting the presence of at least ninety different biologically active substances essential for specific functions (4). The bioactive components of colostrum include: i) anti-microbial factors, ii) immune-stimulating peptides and iii) growth factors (5). Anti-microbial factors provide passive immunity and protect against infections, especially during the first weeks of life. The anti-microbial activity of colostrum can be direct on pathogen agents or indirect by stimulating the growth of a healthy intestinal microbiota rich in Bifidobacteria and Lactobacilli (6,7). Colostrum provides signals to the immune system by inducing tolerance to food and non-invasive antigens, thus avoiding the onset of an abnormal immune response while promoting its maturation and an adequate immune response against pathogens at the same time (8). Some components are able to promote the maturation and modulation of the immune system either directly as colostrinin, cytokines and lactoferrin, β-lactoglobuline, α-lactalbumin and glycomacropeptide or indirectly as oligosaccharides, gangliosides and nucleosides that favour the development of beneficial bacteria species (2,3,9). Furthermore, colostrum contains growth factors that play important roles in the development, maturation and repair of various tissues (10). In recent decades, BC have been used for the prevention and treatment of a variety of human and animal diseases, especially but not only of the gastro-intestinal system (11,12). The aim of this review is to discuss the specific properties of some of the bioactive components of colostrum and to assess the potential clinical uses of colostrum in the prevention and treatment of various gastrointestinal disorders. This review is divided into three sections: 1) quality of colostrum; 2) constituents of colostrum and their functions; 3) clinical uses.

3. QUALITY OF COLOSTRUM

It is important to note that BC composition can vary and therefore product quality must be carefully evaluated when it is used as a supplement for humans and animals. The quality of BC depends on various factors: species, breed, farm management, collection period, number of parturitions and kids, animal health and processing practices. All these factors can influence the quality of BC by affecting the amounts of nutritional and biological active constituents, yet the most important factors affecting quality are probably collection period and processing procedures (13,14). In terms of composition, the best quality BC is produced during the first 24-48 hours after parturition. In fact, the levels of several bioactive components decrease in time-dependent manner (15). BC products should be manufactured in technologically advanced facilities using low-heat pasteurization and low-pressure processing procedures in order to avoid the denaturation of components especially those from protein nature (16). Finally, BC for human and animal use should be accompanied by a certificate attesting its quality, efficacy and safety e.g. absence of drug residues, environmental contaminants and contagious infectious agents. At present there is no standard composition that clearly defines the BC to be used as a dietary supplement in human and animals.

4. CONSTITUENTS AND THEIR FUNCTIONS

4.1. Anti-microbial and immune-stimulating factors

Are represented by compounds of various natures that, which provide passive immunity, protect the host against the pathogenic agents and can also modulate the immune system both directly and indirectly thus favouring the growth of beneficial bacteria. Immunoglobulins, lactoferrin, lactoperoxidase, lysozyme, α-lactalbumin and peptides derived from caseins such as glycomacropeptide (GMP) and whey proteins show high antimicrobial activity. Oligosaccharides, gangliosides and nucleosides provide protection against pathogens by acting as “false receptors” of intestinal cells. Moreover, they induce the proliferation of bifidobacteria and lactobacilli that not only inhibit the proliferation of the pathogens modulating the intestinal environment but also stimulate the immune system. Other components such as lactoferrin, colostrinin (CLN), cytokines and leucocytes have immune-modulatory functions.

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4.1.1. Immunoglobulins (Igs)

Concentrations in colostrum are very high and provide passive immunity to newborns during the development of their own immune systems but can also be useful for providing adults with protection against infection (17,18). Colostrum contains five classes of Igs: IgA, IgG, IgD, IgE, IgM that prove to be effective in defending the body against bacteria, virus, parasites and fungi (19). There is a rapid decrease in the Igs concentration levels of the milkings in the days following parturition (1). By following specific vaccination protocols to cows during pregnancy, it is possible to increase the Igs levels of colostrum thus producing hyperimmune colostrum that can be used against specific pathogens (20).

4.1.2. Lactoferrin (Lf)

Is a multifunctional iron-binding glycoprotein present in several exocrine fluids including colostrum. Lf concentration differs among species and rapidly decreases with subsequent milkings (21). The biological activities of Lf include anti-infective, anti-oxidant, proliferative and immune-modulatory actions (22). Lf is directly effective against several bacteria, virus, fungi and protozoa species but could also have the indirect effect of modulating intestinal microbiota (23,24). Moreover, Lf increases the proliferation and differentiation of intestinal epithelial cells (25). Lf influences the immune functions such as cytokine production, cytotoxicity, proliferation, maturation, migration and activation of macrophages, granulocytes, natural killer and T and B cells by binding its specific receptor (22). In some conditions, Lf proves to have pro-inflammatory properties that induce macrophage activation (22).

4.1.3. Lysozyme

Is an enzyme that has anti-microbial action on gram negative and positive bacteria thanks to its ability to split the peptidoglycan layer of the bacterial cell wall thus causing the lysis of infectious agents (26).

4.1.4. Anti-oxidants

Colostrum contains several compounds with both pro and anti-oxidant effect depending on physiological status (27). The compounds that are able to counteract the action of reactive oxygen species are superoxide dismutase, catalase, glutathione peroxidise, vitamin A, E and C, ceruloplasmin, caseins and minerals as selenium, copper and zinc (28). Colostrum can be also considered to be a source of reactive oxygen species, since it presents macromolecules susceptible to peroxide processes as well as containing reactive oxygen species-generating systems such as xanthine oxidase and lactoperoxidase whose activities help to eliminate infectious agents (27).

4.1.5. Nucleotides/nucleosides

Are important as metabolites but also because they maintain the integrity of intestinal mucosa and influence the type of commensal flora as well as the proliferative action of growth factors (29,30).

4.1.6. Gangliosides

In colostrum and milk are associated with the membrane of fat globules at various concentrations depending on species (31). They are involved in various fundamental cellular functions and in immune response but also act as receptors for various bacteria and toxins. Gangliosides, in particular disialoganglioside 3 (GD3) are involved in the proliferation, maturation and activation of lymphocites, dendritic cells, in cytokine production and intestinal IgA secretion thus suggesting an involvement in immune response (32). GD3 can also affect the development of several organs including the digestive and nervous systems. Monosialoganglioside 3 (GM3) is involved in the defensive mechanisms of the host since they act as “false” receptors for toxins and adhesins of pathogens bacteria (33). Gangliosides may also stimulate the proliferation of useful microbiota such as bifidobacteria and therefore participate indirectly in host defensive mechanisms (34).

4.1.7. Oligopolysaccharides and glycolconjugate sugars

Colostrum contains many sugars such as glycolipids, glycoproteins, cellulose, glycosaminoglycan and mucin, in addition to lactose which is the main sugar (35,36). The soluble sugars of colostrum prevent the binding of bacteria and viruses to the intestinal cells by acting as “false” receptors (37). Some sugars such as fructo-oligosaccharides and galacto-oligosaccharides act as prebiotics in order to promote the growth and maintenance of healthy intestinal microbiota rich in Bifidobacteria and Lactobacilli (38). This beneficial bacteria produces several substances during its metabolism that inhibit the growth of harmful bacteria but also butyric acid which is used by intestinal epithelial cells (39). Furthermore, some Bifidobacteria and Lactobacilli strains can inhibit inflammatory responses in intestinal epithelial and immune cells (38).

4.1.8. Proline rich polypeptide or colostrinin (CLN)

The colostrum of several mammalian species is rich in CLN yet the largest amounts are found in bovine and human colostrum (40). CLN consists in several peptides that contain an unusually high portion of the amino acid proline and derive from the proteolysis of milk β-casein. Its biological activity is based on the action of more than one component and therefore poor activity levels are observed in the case of single components (41). CLN regulates the secretion of cytokines affecting both inflammatory and immune response. CLN is an intercellular signalling molecule that is able to modulate the immune system by regulating the proliferation and differentiation of immune cells both *in vitro* and *in vivo* (40). It stimulates weak or unreactive immune systems but can also restore the

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balance of immune functions when the immune system is hyperactive as in the case of autoimmune diseases or allergies (42,43). CLN also plays an anti-oxidant role by reducing the levels of intracellular reactive oxygen species (ROS) and nitric oxide (NO) suggesting that it is able to control inflammatory response and those in which ROS are implicated in the pathogenesis (44). CLN has proved to have powerful immunomodulatory and neuroprotective properties that suppress chronic microglial cell activation and prevent the formation and increase the disruption of β-amyloid peptides (45). CLN induces the growth of neurons by modulating the expression of the genes responsible for the proliferation, differentiation and regeneration of cells in the nervous system and improves cognitive function in mammals (46,47).

4.1.9. Cytokines

Are proteins, peptides or glycoproteins secreted by specific cells of the immune system which are essential for cellular communication (48). Cytokines are produced in the mammary gland and then released in colostrum. Colostrum contains numerous cytokines, in particular with anti-inflammatory activity that can regulate the development of the neonate immune system, and control inflammatory response and the production of antibodies (49,50). They act in combination with other defensive components of colostrum such as Igs, lactoferrin and lactoperoxidase (51).

4.1.10. Leukocytes

Colostrum contains macrophages, lymphocytes and neutrophils that destroy the pathogens and parasites via phagocytosis (52). Furthermore, these immune cells modulating cytokine production can influence the development and the activity of the immune system of neonates (53).

4.2. Growth factors

Colostrum contains several growth factors that modulate the growth, maturation, function and repair of bone, muscle, nervous, connective, cartilage, skin tissues and particularly the gastro-intestinal mucosa (10).

4.2.1. Insulin-like growth factors I and II (IGF-I and IGF-II)

Also known as somatomedins are synthesized in the liver under the influence of the GH hormone and their receptors are found in the cells of various tissues, including the tissues of the gastro-intestinal tract (54). Somatomedins are carried in the blood by 6 types of proteins and promote the proliferation and differentiation of tissues as well as anabolic action by interacting with specific receptors (55). IGF-I is associated with cell proliferation in the crypts while IGF-II controls the mechanism of cell differentiation of intestinal epithelial cells (56).

4.2.2. Epidermal growth factor (EGF)

Is a peptide present in colostrum and its functions differ in neonates and adults. The EGF receptor is located in the basolateral membrane of the enterocyte and this suggests that it acts as readily available peptide surveillance for repairing injury sites in adults (57). In neonates, the growth factor can cross the intestinal barrier and binds to the receptor stimulating cellular growth (58). EGF may also prevent bacterial translocation in the gut and stimulates gut immunity (59).

4.2.3. Transforming growth factor-α (TGF-α)

Is a peptide present in colostrum and milk but it is also synthesized in the mucosa of the gastro-intestinal tract (60). Systemic administration of TGF-α stimulates the secretion of mucin, cell growth, wound healing and inhibits acid secretion. Its physiological role is cellular differentiation and migration rather than proliferation and it is useful for repairing and maintaining the integrity of intestinal epithelium (61).

4.2.4. Transforming growth factor-β (TGF-β)

Includes 5 isoforms of TGF-β and their binding site is the surface of the intestine (61). TGF-β inhibits cell proliferation, is a powerful chemo-attraction for neutrophils and plays a role in the repair process by stimulating the migration of epithelial cells on the denuded area to re-establish epithelial continuity (62). It regulates the inflammatory and immune response in the intestinal mucosa by intervening in T helper lymphocytes differentiation and IgA production (62,63).

4.2.5. Platelet-derived growth factor (PDGF)

Is a peptide obtained from platelets but is also produced by macrophages. PDGF is a potent mitogen for fibroblasts and facilitates the healing of ulcers (64).

4.2.6. Vascular endothelial growth factor (VEGF)

Is a peptide with potent angiogenic and mitogenic activity, which acts on vascular permeability (65). VEGF is present in colostrum and its receptor is located on the apical membranes of epithelial cells (66). These findings suggest a role for VEGF in digestive system physiology.

5. CLINICAL APPLICATIONS

This section of the review reports the effects of colostrum on various disorders of the gastro-intestinal tract, in particular those accompanied by inflammatory processes, by referring to relevant *in vitro* and *in vivo* studies (67-69). It is also important to note that some of these studies were of poor methodological quality therefore the results could not be confirmed by other researchers. BC may provide insights into the prevention and treatment of gastro-intestinal disorders, but further studies are required before it can be used for human beings.

5.1. Acute infectious diarrhoea

Is a common problem in developing countries and for travellers who visit them. It is usually caused by bacterial, viral, or parasitic infection. It could be

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associated with inflammation, intestinal damage, increased intestinal permeability, bacterial translocation and multiple organ dysfunctions. Supportive therapy (appropriate diet, fluid therapy) should be considered for all patients suffering from diarrhoea, while antimicrobials are not recommended as enteropathogens are often associated with self-limiting diarrhoea. Numerous *in vivo* and *in vitro* studies have shown that BC is beneficial in the prevention and treatment of infective gastroenteritis for various animal species, including human beings (70-74). Colostrum and hyperimmune colostrum are effective against a wide variety of intestinal pathogens. Rotavirus is a common cause of viral gastroenteritis in infants and children for which there is not currently an effective vaccine, therefore a new strategy is required in order to reduce the duration and severity of clinical signs. The treatment of rotavirus-infected infants with hyperimmune BC reduced the duration of diarrhoea and excretion of virus, and the passive immunization of healthy infants with colostrum antibodies reduced the incidence and duration of diarrhoea compared to the placebo group (75-77). On the contrary, the treatment of hospitalized infants with hyperimmune BC did not reduce the duration and severity of diarrhoea (78). In a mouse animal model, multiple administration of BC before the inoculation of rotavirus resulted in earlier recovery from diarrheal symptoms (74). Enterotoxigenic *Escherichia coli* commonly causes diarrhoea in travelers and infants in developing countries. Several studies have proved the effectiveness of BC in preventing infection caused by *E. coli* (79-83). Otto *et al*., reported that a tablet formulation of hyperimmune BC was more effective than placebo in protecting human volunteers against the development of diarrhoea caused by the bacteria (80). In a randomized, double-blind, controlled field trial, hyperimmune BC-fed infants showed a reduction in incidence and duration of diarrhoea compared to formula-fed infants (84). Two clinical studies showed that the administration of anti-*E. coli* IgG obtained from BC before oral challenge with enterotoxigenic *Escherichia coli* was effective in preventing clinical diarrhoea (85,86). *Clostridium difficile* is a bacterium that has proved to be the main cause of infectious diarrhoea. In gnotobiotic piglets with *Clostridium difficile* infection the administration of hyperimmune BC reduced the development of diarrhoea and colitis, in respect to control animals (20). In another study, hamsters treated prophylactically with hyperimmune BC were protected against *C. difficile* infection (87). In humans, anti-*C. difficile* hyperimmune BC was as effective as metronidazole in the prevention of bacterial infection (88). Finally, *in vitro* studies showed that hyperimmune BC inhibits the adhesion of *C. difficile* to enterocyte-like caco-2 cells and was effective in neutralizing A and B toxins in cultured tissue (87, 89). Protozoa such as *Criptospridium parvum* or *Entamoeba histolytica* and *Candida albicans* fungi can also cause acute diarrhoea (90-93). Cryptosporidium species generally cause chronic diarrhoea in immunocompromised individuals. Oral administration of hyperimmune BC in immunocompromised children and adults proved to be effective for treating cryptosporidiosis and in the prevention of cryptosporidiosis in healthy volunteers when administered before challenge with *C. parvum* spores (91,92). Immunoglobulins concentrate obtained from hyperimmune BC, was effective in treating diarrhoea in *C. parvum*-infected AIDS patients (93). The prophylactic and therapeutic effect of colostrum may be due to several compounds which can act in the various phases of the infective disease: they can eliminate the pathogens, improve the intestinal barrier functions, normalize host intestinal flora, inhibit bacterial translocation and modulate immune response by reducing the severity of inflammation (81, 94-100).

5.2. Helicobacter spp infections

Although Helicobacter species are commonly found in healthy humans and pets, this bacterium is found in 100% of the subjects presenting symptoms of chronic vomiting and malnutrition. *H. pylori* is the main species found in humans, *H. Bizzozeronii* is found in dogs while *H. felis* and *H. heilmannii* are the species most commonly found in cats (101). Helicobacter infections can cause inflammation of the tissues lining the stomach and duodenum thus causing acute and chronic gastritis, duodenitis, and peptic ulcers. The clinical signs of the infection are represented by nausea, vomiting, diarrhoea, abdominal pain, lack of appetite or anorexia and weight loss. Therapy consists in a combination of two antibiotics and an antisecretory drug, such as a proton-pump inhibitor or a H2-receptor antagonist, which shows a low percentage of eradication of the bacteria and various side effects such as diarrhoea due to intestinal dysbiosis and the selection of *Clostridium difficile* (102). Several *in vitro* and *in vivo* studies performed in mice have proved the effectiveness of BC in preventing and treating the Helicobacter infection (103,104). The beneficial effect of colostrum may have inhibited the invasive capacity of pathogen bacteria, modulation of immune response and favoured mucosal repair as highlighted by various *in vitro* studies (10,68,105-108). Daily administration of hyperimmune colostrum to adults or children for 4 weeks reduced the severity of clinical signs and inflammation but only eradicated the bacteria in few patients (109,110). However, the administration of hyperimmune colostrum to adult *H. pylori*-infected patients had no significant effect on the urea breath test or histological *H. pylori* count (111). In another study performed in *H. pylori*-positive infants colostrum was not able to eradicate *H. pylori* as assessed by the urea breath test (112). Further well-designed studies are required in order to evaluate the effectiveness of BC in preventing and treating the Helicobacter infection.

5.3. Drug-induced diarrhoea

The most common drugs that cause diarrhoea are antibiotics, chemotherapy drugs and non-steroidal anti-inflammatory drugs (NSAIDs).

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5.3.1. Antibiotics

are commonly used for treating several infectious diseases and can benefit both animal and human health. Occasionally, oral antibiotics can cause unwanted adverse effects like diarrhoea due to changes in intestinal microbiota. Dysbiosis can favour the selection of opportunistic or pathogenic bacteria such as *Clostridium difficile*, which is a frequent complication of long-term, broad-spectrum antibiotic therapy (20). Furthermore, microbial imbalance can also cause changes in intestinal homeostasis with increased permeability, bacterial translocation, abnormal immune response, and strong inflammatory reaction can occur (97-100). Colostrum and hyperimmune BC administration at the start of antibiotic treatment may reduce the risk of antibiotic-associated diarrhoea; selection of *Clostridium difficile* and it may also have a positive effect in regulating the immune system (2, 6,12,20,51,70,113). Moreover unlike conventional antimicrobials, BC favours the growth of beneficial bacterial populations by avoiding antibiotic-resistant organisms (20,95).

5.3.2. Chemotherapy

Cancer is one of the most common diseases of this century effecting both humans and animals. Most tumours are treated with chemotherapy. Chemotherapic agents have strong side effects on rapidly growing and self-renewing tissues such as intestinal and oral mucosa, bone marrow and hair follicles. Chemotherapeutic agents cause “intestinal mucositis”, a condition characterized by apoptosis and loss of cellular proliferation in the intestinal epithelium, resulting in crypt loss, villus atrophy and ulcerations that increase gut permeability, bacteria translocation and bleeding (114). Chemotherapy also induces immunosuppression increasing the risk of opportunistic infections and inflammations due to alterations in gut microbiota (115,116). One of the side effects of chemotherapy is “oral mucositis” causing pain and inflammation to the lining of the mouth (114). To date, there are no available drugs that can prevent mucositis. If severe lesions occur in the gastro-intestinal tract, it may be advisable to reduce the dose or discontinue treatment that consequently reduces the effectiveness of the chemotherapy. New strategies for protecting tissues and stimulating their recovery may increase the chemotherapy dose and the duration of the treatment (117,118). The administration of colostrum reduced gut toxicity during myeloablative chemotherapy in piglets (119). Growth factors included in BC in high concentrations as TGF-β, EGF and IGF-I aided the recovery of rat intestinal mucosa damaged by methotrexate and improved chemotherapy-induced mucositis (120,121). Satisfactory results were not obtained in all of the studies, EGF only had a minor beneficial effect in reducing oral ulcerations in patients undergoing chemotherapy (122). Colostrum contains antimicrobial and growth factors that, by fighting infection and stimulating cellular proliferation, may be used as adjuvant therapy for treating the intestinal mucosa in combination with or following chemotherapy in order to reduce the detrimental effects of chemotherapic drugs in tissues (10,12,68,94,123,124). Finally, BC can reduce body weight loss associated with the treatment (125,126).

5.3.3. Non steroidal anti-inflammatory drugs (NSAIDs)

Are among the drugs most commonly used worldwide due to their anti-inflammatory, analgesic and antipyretic effects both in human and in animals (127). However, NSAIDs are associated with a broad spectrum of side effects, mainly in the upper gastrointestinal tract. These drugs cause gastro-intestinal damage by reducing the mucosal gastric barrier and blood flow and stimulating apoptosis with predisposition to inflammation and mucosal ulcerations (109,128). NSAIDs can also alter the microbiota thus causing the overgrowth of Gram negative and anaerobic bacteria that results in the over secretion of pro-inflammatory cytokines and bacterial translocation (129,130). Current therapeutic options include coadministration of acid suppressants, prostaglandin analogues and relatively selective cyclooxygenase II inhibitors. However, none of these options are optimal and new approaches are required. It is likely that many of the mechanisms caused by NSAIDs to determine their side effects may be counteracted by the biologically active components present in BC which work in an additive or synergistic way (10,68). BC contains various growth factors that can stimulate the healing of ulcers as well as other compounds that can control inflammatory response, infections and epithelial barrier functions and are useful in the event of gastrointestinal injuries (68,131-133). Various models have been used to evaluate the effect of colostrum in reducing intestinal lesions and stimulating their repair (64,124,134-136). With regard to indomethacin-induced enteropathy, both prefeeding and postfeeding mice with BC facilitated the growth of intestinal villi, thus indicating preventive and healing effects (124). Colostrum-based supplements reduced gut damage and bacterial translocation in rats caused by diclofenac (134). In a rat model of gastric injury and a mouse model of intestinal injury, BC reduced the severity of the lesions caused by the administration of indomethacin (136). Furthermore, an *in vitro* study showed that BC increased proliferation and cell migration of RIE-1 and HT-29 cells (136). Colostrum reduces gastric and intestinal lesions, permeability of the intestinal wall, bacterial translocation and shortening of villi (124,137,138). In human volunteers, the co-administration of BC and indomethacin reduced gut permeability in respect to the control group that only received the anti-inflammatory drug (137). Kim *et al*., showed that the combined administration of BC and diclofenac in rats reduced the increase in intestinal permeability, changes of microbiota and villous damage caused by diclofenac (138). BC may prove to be useful for the prevention and treatment of intestinal ulcerative conditions.

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5.4. Immunodeficiency diarrhoea

Immunodeficiency is a state in which the ability of immune system to fight infections is compromised or entirely absent and immunocompromised subjects may be particularly vulnerable to opportunistic infections. Most infectious causes of immunodeficiency are due to viral infections (HIV in humans) that attack the immune system and reduce the number and the function of immune cells. The intestine is a common site of opportunistic infection and the main symptoms are diarrhoea associated with progressive weight loss. Diarrhoea in immunocompromised patients can be caused by common pathogens, including viruses, fungi, bacteria and protozoa, in particular *Criptosporidium parvum* and Giardia species (139). Current treatments include antibiotics, blood transfusions, corticosteroids, dietary supplements, immunomodulatory and antiviral drugs which may only help to alleviate symptoms and may cause strong side effects (140). In this regard, alternative and/or adjuvant strategies should be evaluated. Several studies have suggested that BC might improve the clinical conditions of HIV-associated diarrhoea, probably thanks to the synergic action of several biologically active molecules contained in BC (93,141,142). Good results have been obtained by administering colostrum to human patients which has improved clinical conditions by reducing abdominal pain, diarrhoea score and fatigue (91,143). In another study BC reduced daily stool frequency and increased the body weight and body mass index and CD4+ count respect to the control (144). Furthermore, a lipid defined as sporozoites inhibiting the adhesion of lipid (SIL) has been identified in colostrum and the intestinal mucosa of calves fed with colostrum, which also acts against Giardia (145). Colostrum has been used effectively for reducing the clinical signs and elimination of oocysts in various animal species (146). This suggests that BC can ameliorate HIV-associated diarrhoea, probably through direct antimicrobial and endotoxin-neutralizing effects, thus suppressing bacterial translocation and gut inflammation as well as favouring mucosal integrity and tissue repair (6,12,51,138). Further research must be carried out to confirm these findings.

5.5. Inflammatory bowel disease (IBD)

Are a heterogeneous group of chronic, multifactorial, relapsing inflammatory diseases of the gastro-intestinal tract (147). Common clinical signs observed in IBD patients are chronic diarrhoea, vomiting and weight loss associated to histopathological evidence of inflammation in various portions of GI tract. In humans, Crohn's disease (CD) and ulcerative colitis (UC) are the principal types of IBD. In pets, especially in dogs, several kinds of chronic diseases have been reported which present both differences and similarities with human IBD (148). While the exact aetiology of IBD remains unknown, several clinical studies suggest that interplay between genetic, environmental, immune factors and enteric bacteria play a critical role in the development of the disease (149). It has been suggested that atypical intestinal microbiota induces an incorrect activation of the gut immune system resulting in loss of tolerance and consequently a chronic inflammation of the digestive tract in genetically predisposed subjects (150). Intestinal microbiota confer important functions to the host including mucosal barrier, metabolic and immune regulatory functions (151). Evidence from recent molecular studies revealed differences in the intestinal microbiome between healthy individuals and IBD patients with a reduction of beneficial and an increase of potentially dangerous bacteria (152). Current therapy for treating IBD includes the administration of aminosalicylate, steroids, immunosuppressive agents and antibiotics; although it is not curative and has several side effects (153). New approaches are required for the prevention and/or treatment of IBD, and BC can represent a safe, low cost option (154). Prophylactic administration of BC reduced weight loss, decreased colon shortening and improved the histologic severity of colon inflammation in dextran sulfate sodium-induced colitis in mice. Furthermore, these beneficial effects were accompanied by the reorganisation of immunoregulatory cells (155). In the same animal model of colitis, BC therapy improved occult blood, stool consistency, and clinical recovery from colon inflammation but did not reduce body weight loss (156). BC enema resulted in the improvement of clinical signs and histological scores in human patients affected by active colitis compared to control (157). It is possible that BC components can balance intestinal microbiota thus favouring the growth of beneficial bacteria that in turn reinforce the mucosal barrier function, neutralize pathogen agents and reduce the risk of bacterial translocation (18,100,132,158). Other substances included in BC can help to modulate immune system cells and consequently the severity of inflammatory response while colostrum can induce epithelial regeneration (2,51,70,94,99,100,124).

5.6. Necrotizing enterocolitis (NEC)

Is a serious disease characterized by severe ulceration of the small and large intestine that affects infants and mainly pre-term neonates. The precise aetiology of NEC remains unknown, although several structural and functional deficiencies related to epithelial barrier integrity, digestive and absorptive capacity, intestinal mobility, gut microbiota and immunological dysfunctions are definitely involved in the development and progression of the disease (159,160). Maldigestion and intestinal stasis commonly observed in preterm infants can lead to abnormal gut microflora, bacterial translocation and sepsis, which contribute to an aberrant activation of the immune system and finally to uncontrolled inflammation (161). A feasible strategy for reducing the incidence of NEC could be to control the type of diet and feeding mode since the maturation of the gastrointestinal tract, bacterial colonization and the modulation of the immune system depend on these factors (123,162-164).

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The synergic action of biologically active components of BC may contribute to the maturation of the digestive tract, in balancing gut microbiota, modulation of the intestinal immune system and mucosal repair (2,10,12,57,124). Colostrum has proved to have beneficial effects and therefore may represent an adjuvant therapy (165-167). It was suggested that BC is effective in stimulating gut structure, function, and NEC resistance in preterm piglets (168). Animals fed with BC had a longer intestinal transit time, higher weight gain, absorptive capacity and enzyme activities compared to piglets fed with infant formula. At the same time, BC reduced NEC incidence, pro-inflammatory cytokines concentration such as IL-8 and reduced histological lesions (169). BC proved to have beneficial effects on NEC development and intestinal function in a piglet model and these data were confirmed by an *in vitro* study in which a modulatory action of colostrum proteins in cytokines secretion from bacteria-stimulated murine bone marrow-derived dendritic cells was observed (170). An *in vitro* study suggested that pretreatment with BC significantly reduced several bacteria specie (*Enterobacter cloacae, Klebsiella oxytoca, Escherichia coli, Serratia marcescens and Klebsiella pneumonia*) in attachment to HT-29 cells, although the treatment increased the levels of some pro-inflammatory cytokines (171). Intestinal function was restored by BC administration after initial formula-induced inflammation in a pig model of NEC. NEC severity and pro-inflammatory cytokine (IL-1β and IL-8) concentrations were lower, while villus height, galactose absorption, and brush-border enzyme activities increased in the intestines of the piglets fed with colostrum compared to the control (172,173). In clinical studies, the piglets fed with infant formula showed higher percentages of NEC development, structural damage, reduced functional activity and antioxidant levels and bacterial overgrowth compared to animals fed with BC (167,174). Colostrum administration may decrease clinical sepsis, inhibit secretion of pro-inflammatory cytokines and increase levels of circulating immune-protective factors in extremely premature infants (175). Nevertheless, further studies are required to confirm these encouraging results and to determine whether BC could be used as an effective substitute of mother's milk for preterm infants.

5.7. Short bowel syndrome (SBS)

Is characterized by insufficient length of the intestine due to surgical amputation and it is associated with poor digestion and absorption. The most common therapeutic option is parenteral nutrition but other strategies are required in order to improve the outcome of patients that depend on the functional adaptation of the remaining intestine. Colostrum contains immunoregulatory, antimicrobial and trophic components that can support intestinal development and function in neonates and could also enhance intestinal adaptation and functions (2,37,94,172). A possible strategy for improving conditions of patients is to decrease the intestinal transit of nutrients and allow a longer mucosal contact time for their absorption by increasing muscular adaptation. Colostrum supplement induces muscular hypertrophy increasing the muscle width and the number of cells and these changes may be mediated by the simultaneous increase of the serum concentrations of IGF-1 and IGF binding proteins after small intestinal resection in piglets (176). In a pig model of SBS colostrum induced intestinal adaptation, the piglets that underwent massive intestinal resection showed the same weight gain and greater villus length and crypt depth in the jejunum and ileum compared to the control (177). On the contrary, in a randomized controlled trial Lund *et al*., observed that in spite of it high content of bioactive factors, colostrum did not significantly increase intestinal functions, absorption and body composition compared with the control (178). Feeding the piglets with colostrum supplement increased intestinal proliferation significantly (179). Furthermore, the high levels of specific growth factors contained in colostrum may prove to be beneficial. Systemic administration of EGF stimulates intestinal growth in rats receiving parenteral nutrition (57,68). In rabbits that underwent intestinal resection, the oral administration of EGF proved to restore glucose transport (180). Therapeutic use of colostrum in SBS may be especially useful for treating children given that gut adaptation is better during the development of the gastro-intestinal tract rather than in adults. Additional research is required in order to determine whether this practice can improve the outcome of patients with SBS.

5.8. Surgery

Nosocomial infections present serious clinical issues in surgery despite the progress made in hygiene, surgical techniques and intensive care medicine. Under conditions of shock caused by injury or surgery, bacteria and endotoxins in the intestines can cross the mucosal barrier by translocation and enter the blood and lymphatic system sometimes causing a dangerous systemic inflammatory response syndrome (SIRS) and a multiple organ dysfunction syndrome (MODS) (181). In humans, bacterial translocation has a prevalence of approximately 15% in elective surgical patients and occurs more frequently in patients undergoing abdominal surgery, organ donors and intestinal obstruction, but is also evident in patients with chronic inflammatory bowel diseases, ischaemia–reperfusion injury shock, pancreatitis and immunocompromised subjects (132,182). In general, current therapeutic options include coadministration of fluids and vasopressors to preserve blood pressure, blood in the event of bleeding, antibiotics to counteract infections and bacterial translocation, corticosteroids or NSAIDs to control inflammation, painkillers or other analgesic drugs and diet control. In this context, colostrum administered before or after surgery could play a complementary role to conventional therapy with the aim of reducing the risk of complications. Colostrum has been identified as being a preventive treatment in pre-operatory abdominal and

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coronary arteries surgery. In abdominal surgery it reduced endotoxemia while in coronary bypass surgery it reduced IL-6 and C-reactive protein levels although it did not have any effect on endotoxemia (183,184). Several *in vitro* and *in vivo* studies have been carried out to evaluate the effectiveness of colostrum in preventing bacterial translocation, endotoxaemia and increasing morpho-physiological adaptation after small bowel surgery in rats and rabbits (132,138,185,186). It is believed that preoperative treatment with colostrum, associated with conventional therapy, may reduce bacterial translocation and endotoxemia thus favouring the recovery of both human and animal surgical patients (99,132,187). It contains numerous components that can directly or indirectly affect the various pathogenetic steps of the complications linked to surgery (20,97). Furthermore, the synergic activities of components present in colostrum can be useful in the postoperative period to ensure wound healing and the recovery of absorptive functions (129,162,176,188).

5.9. Side effects and contraindications

According to the current state of knowledge, colostrum appears to be safe and no contraindications are observed even when administered at high concentrations both in humans and animals (189,190). Some authors have reported lactose intolerance, nausea, flatulence, transient diarrhoea and unspecified abdominal discomfort as possible side effects while other studies specifically reported the absence of side effects (83,128,129,165,137,143,189,190). However, further research is required in order to confirm these data, and, more importantly, to evaluate the effects of colostrum when used for a prolonged periods of time and during pregnancy. Milk allergy is the most frequent food allergy in infancy and childhood. Like milk colostrum contains caseins, a-lactalbumin and β-lactoglobulin, and other minor proteins (immunoglobulins, bovine serum albumin) that are deemed to be the main allergens (191). For this reason, colostrum is not recommended for treating individuals who are sensitive to milk proteins.

6. CONCLUSION

Colostrum is a rich source of nutrients and biologically active molecules that are essential for several specific functions including defensive action, the modulation of immune response, the balancing of intestinal microbiota and the growth and repair of several tissues. The components of colostrum, acting synergistically, can intervene in various pathogenetic phases of several diseases, thus contributing to an improvement of clinical symptoms. Colostrum may also have a preventive action or reduce the side effects of several drugs that are currently used for treating various diseases of humans and animals. It may also play an important role in accelerating the recovery of health and body weight during convalescence. More generally, colostrum may be administered with the aim of maintaining a good health status, strengthening the immune system and preventing disease. Current farming methods foresee the production of large quantities of raw colostrum for continuous availability. Colostrum used as supplement must be of high quality and a standardization of the product is required. Pharmaceutical companies aim to produce commercial products containing bovine colostrum while biotechnology companies attempting to clone and produce large quantities of its main components. The growing interest in this natural biological fluid is supported by the encouraging results obtained in scientific studies and clinical trials carried out both *in vitro* and *in vivo* in humans and animals, although further research is required to confirm its potential and long-term effects. Colostrum is safe and does not have contraindications even at high dose levels and there are few reported side effects of clinical relevance. Therefore in the near future, this “first milk” may play a complementary role to synthetic pharmaceutical drugs, in the prevention and treatment of several diseases of humans and animals and it may improve the daily health of populations in developing countries.

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Abbreviations: BC, bovine colostrum; CD, Crohn's disease; CLN, colostrinin; EGF, Epidermal growth factor; GD3, Disialoganglioside 3; GM3, Monosialoganglioside 3; GMP, glycomacropeptide; IBD, Inflammatory bowel disease; IGF-I, Insulin-like growth factors I; IGF-II, Insulin-like growth factors II; Igs, Immunoglobulins; IL-6, Interleukin-6; Lf, Lactoferrin; MODS, multiple organ dysfunction syndrome; NEC, Necrotizing enterocolitis; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; PDGF, Platelet-derived growth factor; ROS, reactive oxygen species; SBS, Short bowel syndrome; SIL, sporozoites inhibiting the adhesion of lipid; SIRS, systemic inflammatory response syndrome; TGF-α, Transforming growth factor-α; TGF-β, Transforming growth factor-β; VEGF, Vascular endothelial growth factor; UC, ulcerative colitis.

Key Words: Colostrum, Anti-Microbical Factors, Immunity, Growth Factors, Intestinal Disorders, Review

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