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Bovine Colostrum: An Effective Prophylactic and Therapeutic against Diarrhoeal Infections: A Review

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ABSTRACT

Diarrhoea is one of the top five causes of death among paediatric and geriatric population in India. Bacterial, viral and protozoal pathogens contaminating the food and water, or even opportunistic commensal microbes can lead to diarrhoeal infections. A number of anti- infective and antiparasitic agents are available for treating these infections. However, they come along with their distinct side effects. Alternative systems of medicine suggest treatments that come from natural sources like plants, minerals and animals. Bovine colostrum is one such animal-derived product recommended by Ayurveda to boost immunity and treat infections in human beings. is a rich source of immunoglobulins such as IgG1, IgG2, IgA and IgM. These antibodies along with other immune factors such as lactoferrin, lactoperoxidase, lysozymes, lactalbumins, oligosaccharides present in colostrum provide an excellent passive protection against infections of bacterial, viral and protozoal origin. A long track record of safe use and several *in vitro*, preclinical and clinical studies have established bovine colostrum as a safe and effective remedy in the prevention and treatment of diarrhoea. We present a mechanistic review of application of bovine colostrum against primary and secondary diarrhoeal infections.

Key words: Bovine colostrum, Clinical trials, Growth factors, Immunoglobulins, Infectious diarrhoea, Secondary diarrhoeal infections.

The process of colostrogenesis gives rise to the colostrum or 'Elixir of Life'. It is a yellowish white creamy substance produced by all mammalian mothers for 0-72 hours post parturition. Loaded with a large number of nutrients, growth factors, immune factors and bioactive components (more than 90 types have been identified); colostrum is of crucial importance to the new-borns. Not only is it a source of energy and nutrition, but also of essential passive immunity giving factors (Kumar and Kumar, 2020). Colostrum from cows, or bovine colostrum (BC), is highly enriched with immunity, antimicrobial and growth supporting factors. Humans, sheep, pigs and many other mammals secrete only so much colostrum as much is suckled by the babies. Cows, on the other hand produce surplus amounts of colostrum that can be collected after the calf has consumed sufficient quantities. The richer composition of BC, as compared to human colostrum and its ability to be extracted from cows makes it a suitable natural alternative for nutritional and health-beneficial products. BC has caught the attention of the scientific community worldwide which has resulted in an extensive research on its composition, extraction, packaging, stability and clinical applications (McGrath *et al*., 2016).

Composition of bovine colostrum

Bovine colostrum provides enrichment in a high concentration low volume form. The exact composition of colostrum varies with the cattle's breed, nutrition, metabolic distresses and many other genetic and environmental factors. Apart from containing appreciable quantities of various immune factors, BC has growth factors and a consortium of macro (fats, proteins, carbohydrates) and micronutrients (vitamins and minerals). Keeping in view the applications of colostrum in preventing and treating the diarrhoeal infections, it is imperative to describe the immune factors present in bovine colostrum.

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Immune factors in bovine colostrum

Immunoglobulins (Igs), together with lactoferrin, lactoperoxidase and lysozyme form the very important anti-microbial system of bovine lacteal secretions. Igs are antibodies that are synthesized by mammals in response to antigenic or immunogenic stimuli such as bacteria and viruses and thus provide protection against microbial infections. BC has IgG1 (52-87 mg/L) as the predominant immunoglobulin (80-90% of total Igs) along with IgG2 (1.6-2.1 mg/L), IgA (3.2-6.2 mg/L) and IgM (3.7-6.1 mg/L). (Mero *et al*., 1997). Their concentration decreases progressively post parturition. IgGs have a multitude of functions including opsonization, complement fixation, prevention of adhesion

of pathogenic microbes to endothelial lining, inhibition of bacterial metabolism by blocking enzymes, agglutination of bacteria and neutralization of toxins and viruses. IgA agglutinates antigens, neutralizes bacterial and viral toxins and prevents adhesion of enteropathogenic bacteria to the mucosal lining (Hurley and Theil, 2011).

Lactoferrin (1.5-5 mg/mL) is an antimicrobial glycoprotein. It has been proposed that the antimicrobial effect of lactoferrin is based on its capacity to bind iron which is essential for microbial growth and to modify the pathogen's cell walls and membranes by reacting with their lipopolysaccharides. This can be fruitfully used as a giardicidal agent against *G. lamblia*. Apart from this, lactoferrin also stimulates intestinal epithelial cells and fibroblasts. Studies show that administration of lactoferrin greatly reduces the risks of mortality, respiratory infections and colonization of various pathogens in the gut (Zarzosa-Moreno *et al*., 2020).

Lactoperoxidase (11-45 mg/L) is a heme- group and Fe^{3+} containing glycoproteinous enzyme well known for its antimicrobial properties. These block the metabolic processes of Gram positive and negative (including *Salmonella typhumurium)* bacteria by secreting reactive oxygen species by catalysing oxidation of thiocyanate in presence of hydrogen peroxide. This complex of enzymes has shown to inactivate polio and HIV-type 1 viruses during *in vitro* studies (Gomes *et al*., 2021).

Lysozymes (0.14-0.7 mg/L) are bactericidal towards Gram negative bacteria while bacteriostatic towards Gram positive. They hydrolyze the peptidoglycans present in bacterial cell wall thus ensuing cellular breakage, degradation and lysis. Their cationic and hydrophobic characteristics also contribute to this antibacterial effect. The presence of lactoferrin augments the antibacterial activity of lysozymes (Abdelsattar *et al*., 2022).

Cytokines help in the immunologic development in neonates, diminishing unwanted immune responses as well as stimulating an inflammatory response when required. A plethora of cytokines, like granulocyte, macrophage, TNFα and interleukin (IL) 1β, IL-6, IL-10, have been reported in colostrum (Struff and Sprotte, 2007).

Proline rich polypeptides (PRP) or colostrinin are effective against disproportionate inflammation. They maintain homeostasis of the immune system. Preliminary description of composition reveals a combination of 32 or more peptides with molecular weights ranging from 0.5 to 3 kDa. These are derived from fractional proteolysis of β-casein and aβ-casein. Their function is to regulate the production of cytokines and keeping a check on the reactive oxygen species. They elicit regulatory effect on the thymus gland, eradicate symptoms of allergies as well as autoimmune diseases and help control over production of lymphocytes and T cells (Playford and Weiser, 2021).

Growth factors (Godhia and Patel, 2013; Tripathi and Vashishtha, 2006) (Table 1). The primary function of the growth factors present in colostrum is to kick start the growth in the new born calf. Table 1 gives an overview of different growth factors along with their average concentrations in bovine colostrum and the functions of the same. Colostrum is the only natural source of insulin like growth factor I and II and transforming growth factors α and β.

Nutritional factors

Being the first food for the new-born, bovine colostrum is loaded with nutrients. Macronutrients of colostrum include 70-80% proteins, 5-7% of fat and 13-18% carbohydrates. Except potassium, rest of the minerals like calcium, magnesium, zinc, sodium, phosphorous, chloride, copper are three times higher than that present in the milk. Water soluble vitamins like B1, B2, B6, B12, vitamin C as well as fat soluble vitamin A, D, E and K are at 5 times higher concentration in colostrum compared to milk. Thus, BC is a rich source of nutritional factors (Mehra *et al*., 2021).

Though most of the above mentioned bioactives are peptide and protein in nature, glycoproteins such as α2 macroglobulin, α2 antiplasmin, bovine plasma trypsin inhibitors and elastase inhibitors present in BC prevent degradation of the bioactive proteins and peptides of the nature's first food upon oral administration (Marchbank *et al*., 2021).

Table 1: Functions of growth factors present in bovine colostrum.

Growth factor	Function
Insulin-like growth factor 1	Mimics insulin function and induces anabolism, enhances growth promoting effect of growth hormone.
Insulin-like growth factor 2	Prevents catabolism.
Transforming growth factor β1	Gastrointestinal growth and repair, stimulates post injury mucosal restitution, reduces acid secretion.
Transforming growth factor β2	Key component in maintaining gastrointestinal lining integrity.
Platelet-derived growth factor	Stimulates the proliferation and development of a wide range of cell types mainly fibroblasts and also helpful in healing ulcers.
Vascular endothelial growth factor	Angiogenic, mitogenic, helpful in healing of peptic ulcers.
Epidermal growth factors	Stimulates tissue repair and wound healing and maturation of the digestive tract.
Growth hormone	Stimulates the immune response-by promoting proliferation and maturation of activated T-cells.

With the plethora of the aforementioned immune components, bovine colostrum plays a highly beneficial role in prevention and treatment of a gamut of diseases including infective diarrhoea. The use of whole colostrum rather than specific immune components, has the added value of stimulating the repair process with its growth factors. The macro and micronutrients present in bovine colostrum can help replenish energy and nutrients that are otherwise compromised in a person suffering from diarrhoea (Rawal *et al*., 2008).

The ability of AIDS/HIV patients to fight infectious disease is severely compromised due to damage to the gut from chronic inflammation and infection. Recent studies report colostrum's role in the reversal of this chronic problem stemming from opportunistic infections like *Candida albicans, Cryptosporidia, Rotavirus*, *Herpes simplex*, pathogenic strains of *E. coli* and intestinal flu infections. All gut pathogens are handled well by colostrum without side effects. It is also known that bovine colostrum contains growth factors, the major forms of which, IGF-1 and TGF-b2, are identical in composition to the human forms. They can promote mucosal recovery and gut integrity in patients with severe diarrhoeal illness. Local protection in the form of immune-supplementation with bovine antibodies has been shown to be an effective means of controlling diarrhoeal disease. Current evidence suggests that bovine colostrum can effectively ameliorate HIV-associated diarrhoea, possibly due to direct antimicrobial and endotoxin neutralizing effects and the suppression of gut inflammation as well as the promotion of mucosal integrity and tissue repair (Playford *et al*., 2000).

Aetiology of diarrhoea

Diarrhoea is defined as passing of 3 or more loose stools or liquid stools within a period of 24 hours. Diarrhoea is usually caused due to an infection in the gastrointestinal tract by a diverse range of bacteria, viruses and parasitic organisms. (Hodges and Gill, 2010).

Diarrhoea is the leading cause of morbidity and mortality in not only children but also adults. In low- income-developing countries, contaminated food and water, poor hygiene and sanitary conditions are the major sources through which infectious diarrhoea spreads. (Diarrhoeal Disease-WHO).

As per National Family Health Survey of India, diarrhoea led to a death of 6322,344 people from all age groups, with a mortality rate of 45 per 1,00,000 in 2019 (National Family Health Survey, 2019-21). The maximum deaths have been recorded in the age group of above 70, with an astonishing mortality rate of 682 per 1,00,000. The most notorious pathogen to ensue diarrhoeal death was noted to be *Campylobacter* (Behera and Mishra, 2022). In 2019, diarrhoea accounted for roughly 9% of all deaths worldwide amongst the children under the age of five years, this indicates that around 484,000 children a year, of which 7% were from India (Diarrhoea-UNICEF DATA). Fig 1 summarizes the findings of the National Family Health Survey of 2019-22 on the prevalence of diarrhoea among children across various states of India. Overall, there has been a hike in childhood diarrhoea from 9 to 9.2% from 2016 to 2020. Diarrhoea is one of the top five causes of death among infants and under-five children in India, with mortality rate being 47 per 1,00,000. A majority of these deaths can be attributed to Rotavirus (Ghosh *et al*., 2021). WHO categorises diarrhoea in three major types:

1. Acute watery diarrhoea: several hours to days; less than 14 days, no blood in the stools.
2. Acute bloody diarrhoea: several hours to days; less than 14 days, also known as dysentery, possibility of presence of blood in the stools.

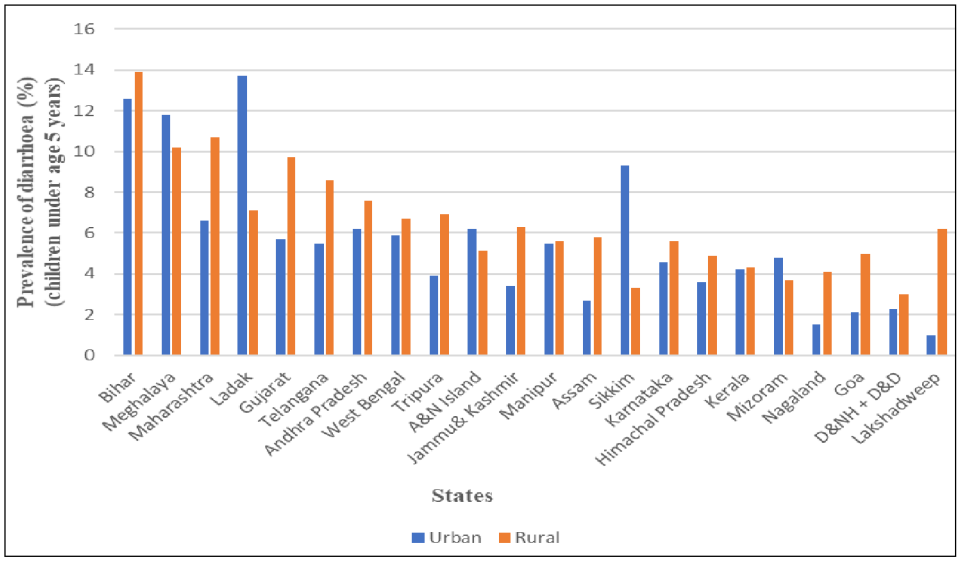


Fig 1: Prevalence of diarrhoea in children under 5 years of age in different states of India. (National Family Health Survey, 2019-21).

3. Persistent diarrhoea: more than 14 days (*Diarrhoeal Disease*, n.d.).

Diarrhoeal infections can further be classified based on the category of causative pathogens. Fig 2 gives a pictorial breakdown of the key microorganisms responsible for diarrhoea in children under 5 years of age.

Bacterial diarrhoea

A number of bacteria, including *Escherichia coli*, *Shigella, Salmonella, Campylobacter, Yersinia, Vibrio cholerae* and *Clostridium* species, cause diarrhoea. *E. coli* is the most common causative diarrhoeal agent whereas *Shigella, Salmonella* and *Campylobacter* species lead to diarrhoeal infections predominantly in children. Globally, 10-25% of diarrhoeal infections can be attributed to *E. coli*, about 10% to *Shigella* and 3-6% to *Campylobacter* species (Li *et al*., 2021).

Viral diarrhoea

Viruses are the most common cause of gastroenteritis leading to acute episodes of community acquired diarrhoea. *Rotavirus, Norovirus, Sapovirus, Astrovirus* and enteric adenovirus are some of the causative pathogens in this category. Of these, *Rotavirus* accounts for about 30-70% of infections in children, whereas *Norovirus* is the leading cause of community-acquired diarrhoea (Shah *et al*., 2012).

Parasitic diarrhoea

Entamoeba histolytica, Giardia lamblia and *Cyptosporodium parvum* commonly lead to parasitic diarrhoea. Other examples include *Cyclospora cayetanensis, Isospora belli*, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis, Blastocystis hominis, Strongyloides. G. lamblia* followed by *C. parvum* are the most common pathogens responsible for traveller's diarrhoea (Florén *et al*., 2006).

HIV associated diarrhoea

The immune-compromised condition of patients suffering from HIV make them vulnerable to various secondary infections including diarrhoea. HIV-associated diarrhoea is usually caused by the opportunistic pathogens such as *Cryptosporidium, Microsporidia, Entamoeba histolytica, Clostridium difficile, Campylobacter, Salmonella* and *Shigella* (https://plus.google.com/+UNESCO, 2016).

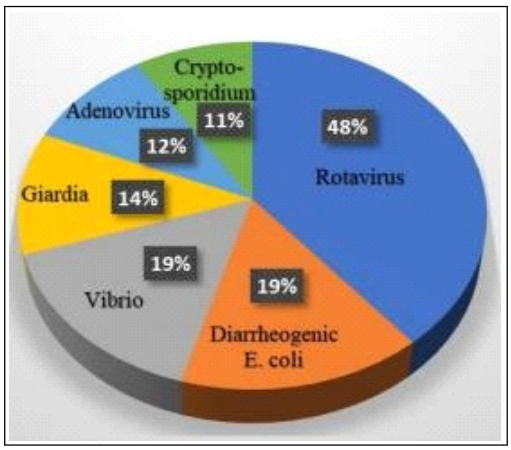


Fig 2: Most common pathogens causing acute diarrhoea in children and their prevalence rate (Shah *et al*., 2012).

Drug- induced diarrhoea

Antibiotics, antidepressants, antacids, proton pump inhibitors and many chemotherapeutic agents cause diarrhoea. This is known as drug-induced diarrhoea. The most common antibacterial drugs to cause diarrhoea are cephalosporins like cefpodoxime and cefdinir, penicillin like amoxicillin and ampicillin, ciprofloxacin, levofloxacin, azithromycin *etc*.

Since diarrhoeal infections occur mostly due to consumption of contaminated food and water, proper and regular hand washing, safe and sanitized food preparation, access to clean water can effectively prevent the acute diarrhoea. There are several drives and programs initiated by the global health organizations, Government of India and several non-profitable organizations (NGOs) to spread awareness about prevention and management of diarrhoea and water sanitization methods. "The Global Pathogen Project" is one such plan initiated by the UNESCO in association with The Bill and Melinda Gates Foundation. WHO in collaboration with UNICEF provides essential supplements and care packages delivered to different parts of the world where acute diarrhoea is one of the biggest reasons for fatalities amongst children. The Ministry of Health and Family Welfare of India has initiated a series of activities primarily aiming towards hygiene and sanitation to prevent and control the number of deaths that are caused due to diarrhoea and dehydration all across the country. India is working closely with United Nations towards eradicating diarrhoea by 2030 (Shah *et al*., 2012).

Remedies for diarrhoea

Infectious diarrhoea can last from 1-2 days to several weeks depriving the body of water, salts and electrolytes necessary for one's survival. Severe dehydration and loss of electrolytes is a major reason for death due to diarrhoea. Hence, the treatment focus is mainly on preventing and treating dehydration. Oral rehydration salt solution (ORS) is one of the best remedies to restore the fluids and electrolytes balance. ORS can be made at home by mixing half a tea spoon of salt with 6 teaspoons of sugar and dissolving it in one litre of water. This helps the intestine to absorb the fluids more effectively. Commercially available ORS formulations contain the right proportion of the electrolytes such as sodium, potassium, chloride, bicarbonate as well as glucose which aid in quick recovery from the fatigue and weakness. Probiotic use may abbreviate the term of sickness by flourishing the necessary gut microbiota and curbing the pathogen colonization (Oral Rehydration Therapy in the Second Decade of the Twenty-First Century - PMC, n.d.).

Anti-infective agents are often used in the treatment of intense, acute diarrhoea, traveller's diarrhoea and protozoal

infections. However, the major side effects associated with anti-infective treatments include sizable reduction in the natural probiotic fauna of the gut. This leads to disturbance in the natural balance of the gut further precipitating diarrhoea and pseudomembranous colitis. The anti-infective agents may cause acid reflux and gastrointestinal discomfort. They also compromise the body's natural tendencies of making antibodies thus weakening the overall immunity. Moreover, problem of antibiotic resistance is often encountered when used frequently. This may cause more harm than good and hence alternative treatment options provided by natural remedies for example, bovine colostrum, are important to tackle the diarrhoeal infections (Poonia and Shiva, 2022).

Pathophysiology (Barr and smith, 2014; Li *et al*., 2021)

The small intestine has an enormous capacity to absorb around 8-9 litres of fluid and electrolytes, from which approximately 100-200 mL is excreted through stools, under normal conditions. However, the balance towards the net secretion can be altered by enteric pathogens leading to diarrhoea. Three classes of infectious agents causing infectious diarrhoea are: bacteria, viruses and parasites.

Bacterial diarrhoea is the leading cause of infectious diarrhoea, of which *Vibrio cholerae* releasing cholera toxin remains a threat until today. The cholera toxin enters the body activating the cystic fibrosis transmembrane conductance regulator (CFTR) which leads to an increased secretion of Cl^- and a decreased absorption of Na^+ causing a decreased activity of both apical sodium transporters. Both these mechanisms add up to the increase of NaCl levels in the intestinal lumen and this increases the secretions causing secretory diarrhoea.

The most common cause of nosocomial diarrhoea is *Clostridium difficile*. It is also the most common cause of pseudomembranous colitis in which an adherent inflammatory membrane overlays the site of injury.

Another class of bacteria, called *Shigella*, causes an infection called shigellosis. This infection leads to invasive and inflammatory diarrhoea. *Shigella* species act on the M-cells of the epithelial layer destroying the macrophages. This causes an initial release of interleukin-1β, which attracts polymorphonuclear leukocytes (PMNs). PMN's activation leads to loss of absorptive function through the destruction of the epithelial layer causing greater colonization, inflammation and haemorrhage causing severe diarrhoea. Secretory diarrhoea is majorly caused by several species of pathogenic *E. coli*, *Enterohemorrhagic E. coli* (EHEC) being the deadliest. EHEC is transferred to humans through the infected cattle *via* their faeces. Shiga toxin secreted by EHEC damages the lining of the intestinal wall leading to haemorrhagic diarrhoea.

Diarrhoea among children is majorly caused by Rotaviruses. It does not cause any notable intestinal inflammation but infects the villi of the intestine causing watery diarrhoea. *Norovirus* in adults causes villi blunting, reducing the number of cells that form villi, decreasing the total surface area available for absorption and hence causing diarrhoea.

Diarrhoea caused by parasites like *G. lamblia* and *E. histolytica* has slow onset and can be present for months. It is very difficult to eradicate parasites due to their similarity to the host cells secreting chemicals which activate Ca^{2+} dependent Cl^- secretion in the small intestine. The parasite mediated destruction and inflammation reduces absorption and disrupts intestinal barrier function.

Pre-clinical studies of bovine colostrum against diarrhoeal pathogens

Various components of bovine colostrum contribute, in their own characteristic way, to its antimicrobial activity. Several *in vitro* and preclinical studies have suggested potential role of aforementioned immune components of colostrum in inactivating causative pathogens of diarrhoea.

Igs are the most predominant immune components present in the BC. Igs contain a region for antigen binding to the Fc region. Once an antigen is bound, the Fc region activates the immune system releasing the immune effector cells, such as NK cells, phagocytes, $CD4^+$, T lymphocytes by binding to the Fc receptors. Igs directly present the pathogens to macrophages for destruction stimulating T cell and B cell activation, preventing pathogens from host cell binding. In neonates, the IgG in bovine colostrum protects the intestinal mucosal surface against enteropathogenic *E. coli* (EPEC) inhibiting bacterial adhesion to epithelial cells (Korhonen and Marnila, 2009; Pakkanen and Aalto, 1997).

Igs from bovine colostrum have shown to bind to bacterial toxins such as Shiga or cholera toxin which is effectively recognised by phagocytic cells. This could possibly block the entry of the toxins into the host cells. Igs effectively inhibit bacterial metabolism and enzyme production by structural alterations leading to inhibition of the toxin production by the bacteria causing bacteriostatic activity. IgM binds to bacterial flagellae and effectively prevents the migration of the bacteria to the host cells. It also agglutinates the antigens and neutralises the toxins. Colostral Igs have also shown to act against viral infections by blocking the receptor mediated internalisation and subsequent prevention of viral replication in the host cells. In an *in vitro* study, whey protein fraction containing IgG as a major component inhibited rotavirus. Further, it prevented the infection of two of the human intestinal cell lines against four variants of rotavirus strains. This same fraction of protein showed effectiveness against rotavirus in an *in vivo* mouse experiment too (Rathe *et al*., 2014).

Lactoferrin is an iron-binding protein with a potent antibacterial and antiviral activity. The cDNA of bovine lactoferrin is homologous to the human lactoferrin, an 80 kDa iron-binding glycoprotein present in the colostrum and human transferrin, an iron-binding protein present in serum. In an *in vitro* study, 31 strains of bacteria were examined for the inactivation properties of lactoferrin B. The results suggested that 99.9% of the cells were killed in the presence

of lactoferrin peptide within an exposure of an hour. Organisms like *Campylobacter jejuni* and *Listeria monocytogenes* were killed within 10 minutes of treatment, whereas probiotic organisms like *Bifdobacterium bifidum* showed no detectable reduction in viability even after 60 mins of treatment. Lactoferrin B shows bactericidal activity against a number of pathogens causing gastrointestinal diseases like *E. coli, Salmonella enteritidis, Yersinia enterocolitica* and *C. jejuni* and common agents of food poisoning such as *Staphylococcus aureus, B. cereus* and *Clostridium perfringens*. These antibacterial activities showed by lactoferrin B are time, concentration and pH dependent. Lactoferrin disrupts the essential functions of the cytoplasmic membrane to exhibit its lethal effects. In a study conducted to compare the antibacterial activities of different components of bovine colostrum, three types of preparations were made, one containing casein-concentrated colostrum, second containing Ig-concentrated colostrum and third lactoferrin-concentrated colostrum. The experiment concluded that the preparation that contained lactoferrin-concentrated colostrum was the most active against bacteria and reduced endotoxin levels in the plasma. This experiment was cross verified by another study in murine model wherein the animals were protected against *E. coli* infection by intravenous preparations of lactoferrin (Bellamy *et al*., 1992; Seifert *et al*., 2002).

Entamoeba histolytica, a human parasite that causes amoebiasis, is a protozoal infection that affects humans worldwide. *E. histolytica* trophozoites also require iron (Fe) for its metabolic function and growth. Bovine lactoferrin was shown to exert a promising anti-amoebic effect *in vitro*, killing parasites in culture. Oral treatment of 20 mg/kg daily for 7 days in a murine model suppressed the intestinal *E. histolytica* infection by up to 63%. Lactoferrin- derived peptide Lfampin has shown to kill other protozoa, such as *Leishmania donovani* or *Giardia intestinalis* during *in vitro* studies. The peptide exerts a toxic stimulus on the parasitic trophozoites that overwhelms their homeostatic balance, committing the cells to an uncontrolled death by likely disturbing the hydrophobic interphase of the lipid bilayer. Its high affinity binding to the amoebic plasma and intracellular membranes through cholesterol causes loss of membrane integrity ultimately leading to lysis. Lfampin showed reduction in the number of amoebas and lysis which was evidenced at the end of 24 hours. This opens the possibility of using bovine lactoferrin-derived peptides as therapeutic agents for the treatment of amoebiatic infections in humans (Díaz-Godínez *et al*., 2019).

The lipid fraction of BC has been shown to contain an anti-infectious effector system against *Helicobacter pylori*. It is able to block the binding of *H. pylori* to phosphatidylethanolamine (PE) and gangliotriaosyl ceramide in mucosa cells and, although it lacks detectable antibodies, when determined using immunoblotting, to *H. pylori*-surface proteins (adhesins), colostral lipid residues contain PE and lyso-PE that bind to *H. pylori in vitro*. Colostral lipids thus have the capacity to inhibit the interaction of *H. pylori* and other pathogens expressing adhesin, with their target tissues. A study showed that the IgGs blocked over 90% attachment of *H. pylori* to the human mucosal walls *in vitro*.

Cryptosporidium parvum, a parasitic infection, is the most common cause of diarrhoea in immunocompromised patients due to T lymphocyte dysfunction special in cases of HIV or AIDS. A study conducted by Fayer and co- workers demonstrated that treatment with bovine colostral whey proteins in BALB/c mice reduced number of *C. parvum* notably after oral inoculation with live oocytes. The study further showed that colostral whey neutralised the sporozoites in mice in a time dependent manner. In humans too, colostrum showed to neutralise the sporozoites in the gut lumen when the pathogen was ingested orally. Patients treated with bovine Igs concentrate powder formulation also experienced a significant reduction in stool weight and frequency of stools passed per day (Rawal *et al*., 2008).

Overview of clinical trials of bovine colostrum

A long-standing track record of safe and healthy consumption of bovine colostrum has been supplemented with scientific reports establishing its broad-spectrum antimicrobial activity. This has led to conductance of several clinical trials to evaluate therapeutic benefit of colostrum supplementation in patients suffering from primary and secondary diarrhoeal infections. A brief account of the clinical studies has been given below:

Patel and Rana conducted an open-label, non-comparative study of 3 g of daily bovine colostrum supplementation in 551 children in the age group of 1-8 years in India. The population was selected on the basis of at least 6 months of recurrent diarrhoeal infection requiring frequent hospitalization. A powder formulation of BC was consumed by the subjects for the period of 12 weeks. The number of diarrhoea episodes was observed to be suppressed by 35.6%, 64.3% and 71.3% at the end of 4, 8 and 12 weeks of BC therapy respectively in comparison with the episodes prior to the therapy. The frequency of hospitalization was also found to reduce by 75.95%, 89.05% and 92.32% at the end of 4, 8 and 12 weeks respectively. The overall well-being of the subjects was improved significantly during and post bovine colostrum treatment (Patel and Rana, 2006).

In a double blind, placebo -controlled trial in 30 children, 3 daily doses of 7g bovine colostrum concentrate powder were given before meals to the treatment group subjects for 14 days. The study subjects suffered from diarrhoea caused by *E. coli*, specifically Shiga toxin-producing *E. coli* (STEC) and *E. coli*-expressing intimin and enterohemorrhagic *E. coli*-hemolysin (EHEC). During treatment with BC, median stool frequency decreased from three stools per day to one, whereas during treatment with placebo, the median stool frequency remained constant during the observation period. The treatment period required for a reduction in stool frequency of at least 50% was shorter in patients treated with BC. Antibiotics are not recommended

in infections with STEC since antibiotic treatment may increase Shiga toxin production may be ineffective in children with STEC-associated enteritis and may increase the risk of development of hemolytic uremic syndrome (HUS). With such a background, it is reassuring to note that the bovine colostrum treatment not only controlled the diarrhoea by eliminating the pathogens but also prevented HUS. The results of this study are clinically important as therapy of EHEC with antibiotics is controversial and an alternative safe therapy other than BC is unavailable (Huppertz *et al*., 1999).

Florén *et al.* (2006), conducted an open label, non-randomized and observational study in Nigeria on 30 HIV patients, out of which 7 were HIV-type 2 positive. They were the first to use the product ColoPlus, which is bovine colostrum incorporated in porridge form. The subjects were asked to dissolve 50 g ColoPlus powder in 100 mL warm water and to consume it as their first and last meals of the day for a total of 4 weeks. Stool microscopy results identified the main pathogens as cysts of *Cryptosporidium* and *Entamoeba histolytica*, ova of Ascaris, Hookworm and Cryptosporidium, yeast cells, Trichuris and *Strongyloides*. The mean number of stool frequency diminished from 7 in week 1 to 1.6 in week 5 (1 week after stopping the treatment). This further reduced to 1.3 in week 7. The self-reported fatigue levels stifled by 81% from 8.76 in week 1 to 1.7 in week 7 of the trial. The mean CD4+ count boosted from 153 cells/µl in the beginning of the trial to 310 cells/l at the end of the trial. Out of the 21 subjects who had a count of less than 200 CD4+ cells/µl in week 1, only 3 patients' count remained below this mark, rest all were AIDS free (by definition) (Florén *et al*., 2006).

Another study was done using ColoPlus by Kaducu and researchers in Uganda in 2011. Patients with HIV- linked diarrhoea were studied. Out of 87 patients, 42 were given standard anti-diarrhoea treatment while the others received standard treatment + 50 g of bovine colostrum-based supplement twice a day for 4 weeks. The mean stool frequency of colostrum supplemented patients dwindled from 7.5 to 1.3 (79%) while in the other group, only 58% reduction was achieved. Similarly, the BC aided group's self-reported fatigue levels contracted by 85% as compared to 43% in their counterparts. The control group's average CD4+ levels decreased by 12%, whereas they increased by 14% in the group consuming colostrum (Kaducu *et al*., 2011).

Rump and co-workers conducted a trial on 37 immunodeficiency patients out of which 29 were HIV positive. The bovine colostrum product, Lactobin (Biotest Pharma, Dreieich, Germany), was a casein-precipitated, fat free, spray- dried powder and was rich in Igs. It was given orally, 10g/day for 10 days. Out of the 29, 21 HIV-infected patients showed long lasting (more than four weeks) normalization of stool frequency, while 8 did not showcase any response. The mean stool frequency astoundingly decreased from 7.4 in the beginning to 2.2 per day at the end of regimen. 19 patients did not succumb to diarrhoea for at least 4 weeks, while 12 patients did face recurring diarrhoea within 4 weeks. Not only have these clinical trials displayed the exceptional antimicrobial and preventive powers of bovine colostrum, but also confirmed its harmless nature towards the human body. (Rump *et al*., 1992).

Pletenberg *et al.* (1993) also used Lactobin immunoglobulin (10 g/day) in an open, uncontrolled study in 25 HIV-infected patients with chronic diarrhoea with either *Cryptosporidiosis* (n= 7) or no demonstrable pathogen (n= 18). Among the 7 patients with cryptosporidiosis, the treatment led to complete remission in 3 (43%) and partial remission in 2 (28.5%) patients. The frequency of diarrhoea in these 7 patients fell from 9.4 to 3.7. Among the 18 patients with diarrhoea and negative stool culture, complete remission of diarrhoea was obtained in 7 (39%) and partial remission in 4 (22%). The frequency of diarrhoea in the 18 patients fell from 5.6 to 3.1. In the remaining 2 (28.5%) patients with cryptosporidiosis and the 7 (39%) patients with diarrhoea but no demonstrable pathogens treatment produced no significant improvement or only less than 50% reduction of the diarrhoea. Subsequent doubling of the Lactobin dose (2 × 10 g daily) in 8 of the non-responders led to complete remission in one case and at least partial remission in 4 patients. During a follow-up period of 4 weeks after withdrawal of Lactobin therapy, repeated diarrhoea occurred in only 1 of 7 patients with negative stool cultures and in none of the 3 patients with cryptosporidiosis. Apart from mild flatulence and nausea, no other side effects were observed (Plettenberg *et al*., 1993).

Table 2 further accounts for the various noteworthy clinical trials conducted in the past 2 decades, not only against diarrhoea but other gastrointestinal and even respiratory diseases.

Dose, frequency and duration of bovine colostrum supplementation

The clinical studies hitherto indicate the beneficial effects of bovine colostrum supplementation in the treatment of diarrhoeal infections among paediatric patients as well as among the immune-compromised adults.

As evident from the tabulated clinical trial reports, colostrum supplements have been taken in highly variable doses ranging from 100-200 mg up to 50-60 g. Even the frequency and duration of administration varies over a wide spectrum. Being a food ingredient, BC has not shown any toxicity or safety concern at the highest level of consumption. There is no prescribed standard dose for this supplement. However, testimonials and anecdotal evidences suggest notable health promoting effects upon daily consumption of about 1 g of colostrum in fasting condition. Systematic clinical study is surely warranted in this regard.

FUTURE PROSPECTS

The shelf life of freshly collected bovine colostrum is only 2-3 days, but removal of water by spray drying at temperatures not exceeding 60°C or freeze drying can enhance it to 2-3 years. Moreover, the dry powder form is

Table 2: Keynote clinical trials highlighting the success of bovine colostrum as a prophylactic and therapeutic.

Trial type	No. of subjects	Dose/day	Study duration	Outcome	Reference
Double blind randomized controlled trial with children suffering from acute diarrhoea	160	One BC sachet ImmuGuard® (3 g)	1 week	Children supplemented with BC witnessed lesser vomiting and diarrhoea. (BC: 8, 69; Placebo: 57, 80 respectively)	(Barakat *et al*., 2020)
Open, multicentric, noncomparative study of children aged 1-6 with recurrent upper respiratory tract infection (URTI) and/or diarrhoea.	160	One BC sachet ImmuGuard® (3 g)	4 weeks	Instances of diarrhoea, URTI and hospital admissions during the same period of time, but a year prior to the trial was considered as reference line. Mean total infections, URTI cases, episodes of diarrhoea and hospital admissions decreased from reference line to 6 months after supplementation. (8.6 to 5.7; 8.2 to 3,8; 6.1 to 3.9; 2.2 to 1.1 respectively)	(Saad *et al*., 2016)
Randomized, placebo controlled trial involving patients undergoing surgery of GI tract	40	Lactobin® 56 g	From 3 days Pre-operative to 10 days postoperative	Notably lower serum endotoxin levels in the treatment group	(Bölke, *et al*., 2002)
Randomized, placebo controlled trial involving patients undergoing open heart surgery	60	BC Concentrate 42 g	2 days preoperative	Significant lower C-Reactive Proteins (CRP) levels in the treatment group but no appreciable difference in serum endotoxin levels between treatment and control groups	(Bölke, *et al*., 2002)
Ranomized crossover trial involving healthy males to assess Non-steroidal anti-inflammatory drugs induced GI tract permeability	7	125 mL t.i.d.	5 days	Indomethacin 50 mg t.i.d administration showed three times higher gut permeability due to damage to the lining while co-administration of BC did not lead to enhancement in permeability	(Playford *et al*., 2001)
Healthy subjects divided in three groups, one received no treatment, 2nd received only BC treatment, 3rd received both BC and flu vaccine	144	Oral BC 900 mg	60 days	Average no. of flu episodes were obviously lower and no. of days with flu were 3 times lower in BC treated group	(Cesarone *et al*., 2007)
Randomized, double blind, placebo controlled trial involving healthy male volunteers	174	60 g	56 days	No. of subjects reporting the symptoms of Upper Respiratory Tract Infection (URTI) was significantly lower in BC treatment group with no significant difference in symptom duration between the treatment and placebo group	(Brinkworth and Buckley, 2003)
Randomized, double blind, placebo controlled trial involving cyclists under going intensive training	29	10 g	56 days	Appreciable enhancement in the cyotoxic T cell counts along with prevention of drop in the serum IgG2 levels post intense exercise helped in significantly reducing the episodes of URTI among treatment group	(Shing *et al*., 2007)

easy to handle and process into various dosage forms like powder formulations, capsules and tablets.

A major constraint of manufacturing of such supplements is that the content of bioactives in colostrum can vary to a great extent depending on the breed, parity, health status of the cows, season, number of milkings and most importantly storage and processing conditions. Hence, it is crucial to standardize and regulate at least the major activities of breeding and milking at farms (Poonia and Shiva, 2022).

Bovine colostrum as a health supplement and functional food has very well been established in countries like New Zealand, Australia, USA, Austria, France, Germany. India, being world's largest dairy producer needs to unravel the tremendous potential of the nature's miracle food on priority basis. Adapting and implementing latest technologies in large scale processing of bovine colostrum would surely help the country in availing its promising benefits in the form of health supplements.

CONCLUSION

Bovine colostrum known as "*Gau Piyush*" in Ayurveda is a precious gift of Mother Nature to the mankind. Bovine colostrum is a treasure of more than 90 well- characterized bioactive compounds that offer variety of health benefits. Presence of Igs like IgG, IgM, IgA and other immunity imparting compounds like lactoferrin, lactoperoxidase, oligosaccharides, lysozymes in colostrum offer excellent passive immunity against various infections. Diarrhoeal infections caused by bacterial, viral and protozoal pathogens can lead to severe morbidity and even mortality. The number of deaths due to these infections especially among paediatric and geriatric populations is significant in many developing countries including India. The allopathic treatment options, though effective; can leave the patients with weakness, compromised gut flora and weakened immune system. These side effects could make the patients vulnerable to acquire new infections. Natural remedy in the form of colostrum can help to avoid this catch 22 situation. Through several preclinical and clinical studies, bovine colostrum has been proven to be a highly effective in the treatment as well as prevention of bacterial, viral as well as protozoal diarrhoea among paediatric and adult population alike. Being nature's first food for a new-born, it is free of any side effects and thus can be considered as one of the safest and harmless treatment options in diarrhoeal infections.

Conflict of interest

Authors declare no conflict of interest.

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