Bovine Colostrum in the Treatment of Cancer

Subjects: Oncology

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Bovine colostrum (BC) has attracted the interest of numerous researchers investigating its anti-cancer potential in humans. Dressings loaded with BC are beneficial in treating chronic wounds and diabetic foot ulcers. Lactoferrin, a glycoprotein with potent anti-oxidant, anti-inflammatory, anti-cancer, and anti-microbial effects, is abundant in BC. The BC pills successfully promote the regression of low-grade cervical intraepithelial neoplasia when administered intravaginally. The biological, genetic, and molecular mechanisms driving BC remain to be determined. Oral BC supplements are generally well-tolerated, but some flatulence and nausea may happen.

bovine colostrum cancer treatment natural products

1. Role of Lactoferrin and Lactalbumin in Cancer Therapy

Lactoferrin is a glycoprotein with powerful anti-oxidative, anti-inflammatory, anti-cancer, and anti-bacterial effects. Lactoferrin increases T-helper-1/T-helper-2/anti-inflammatory cytokine immunological response and production. In children, lactoferrin has been reported to prevent stomach infections, necrotizing enterocolitis, and late-onset sepsis [1][2][3].

Lactoferrin is a highly effective immunological modulator, anti-cancer drug, and tissue regenerator. Additionally, it can prevent the synthesis of pro-inflammatory cytokines. Lactalbumin is found in whey and can significantly boost immunological response and glutathione synthesis. Lactoferrin and lactalbumin have been reported to trigger apoptosis in malignant cells [4]. Lactoferrin has been observed to increase caspase-1 and IL-18, diminishing intestinal metastatic foci. Also detected is cytotoxic T and natural killer (NK) cell apoptosis triggered by lactoferrin. In addition, lactoferrin suppresses the activation of carcinogens via the hepatic CYP1A2 enzyme [5]. Because it can pass through the blood-brain barrier, lactoferrin can be used to carry chemotherapeutic drugs. This is especially useful for treating brain tumors [6]. It suggests that lactoferrin and whey lactalbumin can be utilized to treat cancer in conjunction with chemotherapy and radiation. This strategy would improve the chemotherapeutic efficacy of medications and minimize chemo- and radiotherapy, resulting in fewer cancer patients experiencing adverse side effects.

2. In Vitro Anti-Cancer Effects of BC Components

In vitro cell culture studies are used in selected cancer cell lines as a promising tool to determine the anti-proliferative and cytotoxic effects of potential anti-cancer agents isolated from natural sources or synthesized in the laboratory. In vitro cell culture studies provide clues about the mechanism of action of anti-cancer agents toward

cancer cells. Anti-cancer effects of lactoferrin were evaluated using an MTT assay. The addition of lactoferrin in the culture medium inhibited the growth of cancer cell lines (MDA-MB-231 and MCF-7) [7].

Two milligrams per milliliter of purified lactoferrin inhibited the proliferation of esophageal cancer cell lines (KYSE-30) and HEK cancer cell lines. After 62 h, adding 500 g/mL lactoferrin to the culture medium decreased the cell viability of KYSE-30 cancer cells by 80%. The normal HEK cell line exhibited no effect. Analysis by flow cytometry revealed that lactoferrin caused apoptosis in KYSE-30 human esophageal cancer cell lines [8]. **Table 1** summarizes the findings of in vitro studies conducted to evaluate the anti-cancer properties of BC components (lactoferrin, liposomal bovine lactoferrin, bovine lactoperoxidase, lactoferrin nanoparticles, and CLA) on various cancer cell lines (such as gastric, esophageal, colorectal, liver, lung, prostate, breast, and ovarian).

Table 1. Anti-cancer effects of BC constituents on various cancer cell lines.

BC Component	Cancer Type	Dose	Result	Reference
Lactoferrin	Gastric cancer (AGS human stomach carcinoma cell)	500 µg/mL	80% cytotoxicity in AGS cell line	[9]
Lactoferrin	Human esophagus cancer cell (KYSE-30 esophageal squamous cell carcinoma)	500 µg/mL	After 20 and 62 h, the growth of azoxymethane (AOM)-induced aberrant crypt foci (ACF) was inhibited by 53% and 80%, respectively.	[8]
Lactoferrin	Lung cancer (human lung cancer cell line, A549)	0.9375–15 mg/mL	Lactoferrin lung cancer (human lung cancer cell line, A549) 0.9375 to 0.1 mg/mL Concentration-dependent suppression of VEGF mRNA and VEGF protein expression.	[10]
Liposomal bovine lactoferrin	Colorectal cancer (RKO and RCN-9 human CRC cells)	≥10 µg/mL	Significant ($p < 0.01$) inhibition of colon aberrant crypt foci growth occurred in the RKO and RCN-9 cells.	[11]
Bovine lactoperoxidase (LPO) and lactoferrin (LF) nanoparticles	Colorectal cancer (Caco-2), liver cancer (HepG-2), breast cancer (MCF-7), and prostate cancer (PC-3).	315–1388 µg/mL	NF-kB expression was inhibited by a factor of ten in Caco-2, HepG-2, and MCF-7 cells; NF-B mRNA levels were reduced by four in PC-3 cells, and Bcl-2 levels were reduced by a factor of fifteen in comparison to 5-fluorouracil treatment.	[12]
CLA	Ovarian cancer cells (SKOV-3 and A2780 cells)	7 µM CLA for 48 to 72 h	Reduction in E2F induces a ninefold increase in autophagolysosomes and a G1 cell cycle arrest in SKOV-3 and A2780 cell lines.	[10]

BC Component	Cancer Type	Dose	Result	Reference
	Breast cancer cell line (MCF-7), colon cancer cell line (HT-29), (mouse fibroblast cell line Balb/3T3)	0.1–100 µg/mL	Reduced anti-apoptotic Bcl-2 expression	[13]

3. In Vivo A…hans and Animal Models

In order to evaluate the safety, efficacy, and toxicity of anti-cancer drugs, it is necessary to conduct preclinical research on suitable animal models after obtaining information from in vitro studies. Numerous anti-cancer research involving BC supplements and key components have been conducted on rodents. Rats and mice have been treated with lactoferrin and CLA for colorectal, lung, and esophageal malignancies. In preclinical trials, a reduction in colon tumor burden and a downregulation of VEGF expression were reported [11][14]. Only a small number of clinical trials on a few patients have been conducted to understand the anti-cancer potential of BC components. Based on the promising anti-cancer benefits of CLA in preclinical models, 24 breast cancer patients participated in an open-label clinical investigation. CLA was administered orally at 7.5 g/day for 20 days. It has been discovered that CLA inhibits the expression of fatty acid synthase (FASN) and lipoprotein lipase (LPL). The decreased activity of these biomarker enzymes indicates breast tumor growth suppression [15]. Another clinical investigation revealed that CLA (3 g/day) might be advantageous for rectal cancer patients undergoing chemoradiation [16].

4. BC for Chemotherapy-Induced GI Toxicity in Acute Lymphoblastic Leukemia (ALL)

The most prevalent kind of juvenile cancer is ALL. Cure rates continue to rise, with the 5-year overall survival rate over 90% and the long-term survival rate for children exceeding 80% to 90% [17][18][19]. However, anti-leukemic treatment is exacerbated by several toxicities. During ALL therapy, 2–4% of patients die due to treatment-related complications, primarily due to therapy-induced immune suppression and infections. In addition, nearly all patients get severe infections and chemotherapy-induced mucositis [20][21]. Mucositis is commonly believed to primarily impact the oral cavity, although it can also affect the entire GI tract [22][23][24]. GI toxicity may impair vital GI functions, resulting in microbial translocation with inflammatory and infectious consequences [22][25][26][27][28][29]. Consequently, multiple studies have shown links between oral and intestinal toxicity generated by chemotherapy and unfavorable treatment outcomes, such as fever, severe infections, and overall death [21][25][30][31]. However, therapeutic and prevention strategies are now restricted to highly specialized illness scenarios and dental care procedures for youngsters [32][33][34].

In a recent randomized, double-blind, placebo-controlled clinical trial, the researchers examined the impact of BC supplementation on fever, infectious morbidity, and mucosal toxicity during ALL induction therapy [35]. They observed no statistically significant influence on the critical outcome, fever days. Similarly, there was no significant effect on other infectious morbidities, such as days with neutropenic fever, the requirement for intravenous

antibiotics, or C-reactive protein (CRP) levels. Patients in the placebo group had substantially higher peak NCI-oral mucositis scores than patients receiving the BC product, indicating a putative protective effect of BC supplementation on the oral mucosa. In a previous trial, whey protein concentrates were administered to patients undergoing hematopoietic stem cell transplantation. There was no effect found on mucositis. However, subgroup analysis suggested positive benefits on the duration and severity of oral mucositis in patients who received the highest protein supplement doses [36]. A putative protective impact of milk bio-actives on the GI mucosa is suggested by mouse experiments in which injection of components from bovine milk or whey had positive effects against chemotherapy-induced gut damage [37][38]. Most of the proposed beneficial chemicals in milk are present in greater concentration in colostrum than in mature milk, and complete BC has been recommended as a potential treatment for chemotherapy-induced mucositis [39][40][41]. Previous studies indicated that colostrum has gut-protective effects in pigs, relative to formula, in connection to chemotherapy [42][43]. However, the positive effects of increasing colostrum dosages could not be proven in pigs treated with chemotherapy and fed a normal milk diet [44], showing that both the dosing regimen and the control diet may be significant. In pre-clinical research, BC has been shown to sustain intestinal barrier function, improve nutritional absorption, and minimize intestinal inflammation [42][43].

During chemotherapy, in a previous clinical trial, most patients suffered febrile neutropenia, of which fewer than fifty percent may signify an established infection in pediatric cancer patients [45][46]. However, the origin of fever is frequently obscure and may result from systemic inflammation produced by other harmful consequences of chemotherapy. Several investigations have revealed a temporal relationship between GI damage, systemic inflammation, and fever in the absence of a detectable infection [26][47][48][49]. This is consistent with the clinical study's findings, which indicate that the peak of gastrointestinal toxicity correlates with the peak of circulating CRP levels [35]. Overall, these findings indicate that hazardous events in the GI tract may be linked to microbial translocation and systemic immune activation. Consequently, interventions with implications for mucosal barrier preservation and compounds related to the protection, homeostasis, and modulation of inflammatory responses of mucosal surfaces after chemotherapy may help ameliorate the effects of chemotherapy on the GI tract and other complications [25][32]. Although BC had a putative protective impact on the oral mucosa, there were no significant effects on fever, intramuscular infection, inflammatory response, or bloodstream infections. Thus, systemic effects of BC supplementation could not be demonstrated.

Oral mucositis incidences were equivalent to those found in past trials of anthracycline-based chemotherapy and hematological malignancies [24][50]. Daily self-reporting toxicity rating return rates were also satisfactory and comparable to earlier reports [51].

The mentioned clinical study was limited by the small sample size and concerns with supplement compliance. Although the predicted number of patients was considered in the computation of sample size, the incidence of fever was lower than anticipated. The study had sufficient power to detect a difference in the number of fever days [35]. During ALL induction therapy, the administration of prophylactic BC had no effect on fever, infectious morbidity, or inflammatory reactions in this trial. Nonetheless, these preliminary results, although not conclusive, showed that

BC supplementation may lessen the peak severity of oral mucositis, motivating additional research on mucositis to confirm these findings and evaluate its mechanism of action.

Prior studies of nutrition interventions for children with chronic conditions rarely measured compliance, and research on adults demonstrates difficulty in maintaining oral nutrition intervention adherence [52][53]. The reasons for lower adherence to oral supplements may include taste changes caused by chemotherapy, nausea, swallowing pain, and palatability concerns. In nutrition trials, it is essential to optimize the flavor, content, and texture of supplemental items and provide parents and pediatric patients undergoing chemotherapy with the proper support and instructions [53].

5. The Immunomodulatory Effects of BC on Colorectal Cancer

There is a significant interest in the inflammatory micro- and macro-environments of primary and secondary metastatic tumors in patients with colorectal cancer. The tumor's microenvironment makes it easier for cancer cells to travel to other organs and establish themselves there, such as the liver and the lungs. Colostrum polyvalent immunoglobulins administered orally promoted the expression of anti-inflammatory cytokines known as interleukin (IL)-10 and IL-13 in patient-derived peripheral blood mononuclear cells [54]. In these cells, the release of inflammatory cytokines such as IL-1, IL-6, interferon, tumor necrosis factor, and IL-12 was reduced by colostrum polyvalent immunoglobulins that were given and delivered orally [55]. When colostrum polyvalent immunoglobulins were administered orally, immune cells and cells arising from tumors were both more prone to apoptosis. Using vitamin D3 as a cofactor resulted in an even greater improvement in the anti-inflammatory effects. In addition to being administered orally, the colostrum-derived polyvalent immunoglobulins displayed beneficial ex vivo effects on inflammatory cytokine responses. They increased the apoptosis of immune cells taken from patients diagnosed with colorectal cancer. This study provides evidence for the use of polyvalent immunoglobulins derived from colostrum that is provided orally to patients with colorectal cancer to modify stage-dependent local and systemic inflammation in these patients [54]. However, there is not yet adequate evidence to suggest that BC affects the immune microenvironment of tumors; despite this, further inquiry into the topic is warranted.

6. Targeted Oral Delivery of Paclitaxel through Exosomes Derived from BC

Paclitaxel is an anti-cancer medicine frequently used in the management of lung cancer and other types of cancer at earlier and more advanced stages. Paclitaxel, derived from solvents, is an effective cancer treatment, but it is often not well tolerated and is associated with significant side effects [56]. Exosomes and other naturally occurring nanocarriers are attracting much interest as a potential way to get around these limitations. According to a recent study, a tumor-targeted oral formulation of paclitaxel employing BC-derived exosomes not only enhances the clinical efficacy against orthotopic lung cancer but also reduces or eliminates the systemic and immunotoxicity of the traditional intravenous dose [56]. This finding was made possible by using exosomes derived from breast cancer

cells. These findings will advance the exosome-mediated targeted oral delivery of paclitaxel as a therapeutic alternative to existing therapies by using the benefits of BC exosomes.

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