

Minireview Article

Beneficial Components of Colostrum for Cancer Patients: a Mini-review Focused on Oxidative Aspects and Properties of Colostrinin

ABSTRACT

The beneficial effect of maternal colostrum and milk on the newborn as well as on the nursing mother is well known. However, many other potentially preventive and therapeutic aspects associated with the use of components of these secretions are still partially known and have sparked some research, including in the context of cancer. A narrative mini-review to present potential beneficial effects of colostrum components for cancer patients, especially focusing on oxidative aspects and potentialities of colostrinin.

Keywords: cancer; colostrum, nutraceuticals, colostrinin, oxidative metabolism, free radicals, proline rich polypeptide, alpha-lactalbumin, lactoferrin, casein.

1. INTRODUCTION

Cancer is a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and / or spread to other organs. Cancer can affect almost any part of the body and has many anatomic and molecular subtypes that each require specific management strategies. Cancer is the second leading cause of death globally and is estimated to account for 9.6 million deaths in 2018. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervix and thyroid cancer are the most common among women [1].

The incidence of cancer is growing globally at a pace that follows the aging population due to increased life expectancy. It is a direct result of the great global transformations of recent decades, which have changed the health situation of peoples through accelerated urbanization, new lifestyles, new consumption patterns [2].

The high prevalence and mortality of cancer encourages the investigation of cellular and molecular mechanisms that may contribute to more effective preventive and therapeutic means. Considering that humans are normally exposed to various cancer-inducing agents, including those obtained through diet, possible strategies involve lifestyle and diet.

There is a growing interest in research involving functional and nutraceutical foods that can positively impact people's health, especially in the context of cancer prevention and treatment. Given this, the present mini-review becomes relevant because it proposes to present potential beneficial effects of colostrum components for cancer patients, especially focusing on oxidative aspects and potentialities of colostrinin.

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50 **2. RESEARCH METHODOLOGY**

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52 This is a review of narrative literature, with theoretical and contextual
53 information plus interpretations of the researcher considering the existing
54 scientific production.

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57 **3. OXIDATIVE METABOLISM AND APOPTOSIS**

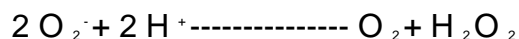
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59 When you breathe, you give all your cells the oxygen they need to produce
60 energy through a process known as oxidative metabolism. In short, oxygen is
61 reduced and glucose covalent bonds are broken releasing carbon dioxide,
62 water and energy. The main cell organelle involved is the mitochondria, where
63 several enzymes are responsible for catalyzing the stages of this process. In
64 each of these steps there is the formation of byproducts that are mostly
65 beneficial. However, approximately 5% may be toxic to the cell at high
66 concentrations. Oxygen, for example, during electron transport in mitochondria
67 can be partially reduced by generating reactive oxygen species (ROS), such as
68 superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂) and hydroxyl radical (OH⁻).
69 When the balance between ROS production and elimination, which is called
70 oxidative stress, occurs, damage to DNA, RNA, lipids and proteins can occur. In
71 addition to DNA fragmentation, the ROS can cause malfunction of the DNA
72 repair system, contributing to the development of diseases,
73 including cancer [3].

74 The body's antioxidant defense system has the primary function of inhibiting or
75 reducing the damage to cells caused by reactive oxygen species. There are a
76 wide variety of antioxidant substances, which can be classified according to
77 origin and / or location into dietary antioxidants and intra and extracellular
78 antioxidants. The mechanism of action also allows them to be classified as
79 prevention antioxidants (prevent the formation of free radicals), scavengers
80 (prevent the attack of free radicals on cells) and repair (favor the removal of
81 DNA molecule damage and the reconstitution of damaged cell
82 membranes [4].

83 SOD has been reported as an important antioxidant mechanism present in
84 eukaryotes and prokaryotes, strict aerobic and microaerophil organisms. This
85 enzyme requires a metal as a cofactor for its functional activity, which may be
86 copper (Cu-SOD), manganese (Mn-SOD) or iron (Fe-SOD). This enzyme acts
87 by catalyzing the dismutation of the superoxide anion. Dismutation is a reaction
88 in which two identical molecules are transformed into different compounds. In
89 the case of SOD, one superoxide ion oxidizes the other, generating O₂ (normal)
90 and hydrogen peroxide (H₂O₂). Hydrogen peroxide may be further degraded by
91 catalase or peroxidase [5].

92



93 Patients with neoplasia have high concentrations of oxidizing markers and low
94 concentrations of antioxidant substances. Regarding the severity of the disease,
95 it is known that the antioxidant system behaves differently according to the
96 stage of cancer. As disease progresses, lower concentrations of enzyme
97 antioxidant markers are found [6].

98 Oberley and Buettner [7] showed differences between superoxide dismutase
99 activity of cancer cells. Decreased amounts were found in many tumors
100 and they produced more superoxide.

101 Tumors possess and acquire characteristics and abilities to maintain their
102 survival and development. These include the ability to maintain proliferative
103 signaling, evade growth suppressive mechanisms, resist cell death, perpetuate
104 its replicative capacity, induce angiogenesis, and activate invasion and
105 metastasis. Underlying these characteristics are genomic instability,
106 inflammation, imbalance of cellular energy metabolism, and the ability to evade
107 immune destruction, which have been the subject of countless studies in the
108 last decade [8].

109 Tumor growth is related to a balance resulting from the sum between
110 proliferation and cell death. Combined measurement of cell death and
111 proliferation is an important weapon in the most realistic prediction of tumor
112 behavior. The genetically controlled mechanism of cell death is called
113 apoptosis, which is critical for the elimination of damaged cells. Studies have
114 shown the relevance of programmed cell death in tissue homeostasis,
115 organogenesis and tumor pathogenesis [9, 10].

116 Apoptosis is a fairly rapid cell death: cell retraction occurs which causes loss of
117 adherence with extracellular matrix and neighboring cells. Cell organelles
118 maintain their morphology, except in some cases for mitochondria, which
119 may rupture the outer membrane. The chromatin is condensed and
120 concentrated near the nuclear membrane, which remains intact. Next, the
121 membrane cell shaped extensions (" blebs ") and the core to disintegrate into
122 fragments by membrane enveloped core. Cell membrane extensions increase
123 in number and size and rupture, resulting in structures containing cell
124 content. These cell portions surrounded by the cell membrane are called
125 apoptotic bodies. Apoptotic bodies are rapidly phagocytosed by macrophages
126 and removed without causing an inflammatory process [11].

127 BCL-2 protein was originally described in 1985 [12] and since then other
128 proteins with apoptosis regulating properties have been
129 identified, currently resulting in the BCL-2 family. It is therefore a set of proteins
130 that inhibit or promote apoptosis, playing a crucial role in tissue maintenance,
131 programmed cell death during development and defense against
132 pathogens [13]. They present diverse subcellular localization, some of which
133 can be found in the cytosol, but most of them anchored in membranes, such as
134 the external mitochondrial, endoplasmic reticulum and nuclear membrane [14].
135 In the context of cancer, pro-apoptotic limbs are characterized as apoptotic
136 performers, acting as tumor suppressors while pro-survival limbs are regarded
137 as apoptosis inhibitors, acting as oncoproteins [15].

138 Apoptosis in clinical practice is a target for potential therapeutic use of
139 programmed cell death or for understanding the mechanisms of resistance to
140 radiotherapy and chemotherapy. Many alternatives seeking cancer treatment
141 are based on the induction of tumor cell apoptosis [16]. The elucidation of
142 some of the molecular mechanisms of apoptosis can generate perspectives of
143 modulation of these processes [17].

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146 **4. COLOSTRUM AND COLOSTRININ**

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148 Colostrum is defined as the first products of milk secretion, the result of the
 149 influence of lactogenic hormones, such as prolactin. It begins production at the
 150 end of pregnancy and continues until about 5 to 7 days after delivery. It is a
 151 secretion that has ten times more carotene than mature milk, which gives it
 152 a yellowish color [18].

153 Compared to milk, it has higher viscosity and is made up of blood serum
 154 components such as immunoglobulins and other serum proteins such
 155 as albumin, α -lactalbumin, β -lactoglobulin. In addition to containing many
 156 essential nutrients , in concentrations higher than those commonly found in
 157 milk , it also has several other beneficial components such as leukocytes,
 158 growth factors, hormones, cytokines and nonspecific antimicrobial factors [19].
 159 These first s Secret ions is m an essential vehicle passive immunity, prebiotic
 160 compounds and growth factors involved in the intestinal
 161 development [20]. The colostrum intake is critical to the survival and health of
 162 the mammals offspring [21].

163 The colostrum provides nutrition for newborns improves the protection against
 164 pathogens, promotes the development of the immune system and ensures the
 165 growth, maturation and repair of various tissues [22].

166 Research demonstrates that bovine colostrum can be administered to humans
 167 and other mammals since there is a compatibility of components with other
 168 bioactive species. Bovine colostrum consumption has been recommended for
 169 symptom relief in patients with diarrhea , suffering
 170 from acquired immunodeficiency syndrome , drug-induced inflammatory colitis,
 171 and acute phase responses to surgery. In addition, several published studies
 172 have shown that bovine serum proteins may have immunomodulatory,
 173 antimicrobial, antiviral, anticancer and antiulceration [23, 24, 25]. The various
 174 components of colostrum can improve immune function and well-being of
 175 healthy people, can be used as a dietary supplement, and have therapeutic
 176 perspectives for patients with various pathological conditions, such as:
 177 immunodeficiencies, cardiovascular and infectious diseases, wound healing and
 178 cancer. Also, an advantage of colostrum supplements is that they are well
 179 tolerated. Unlike milk, has a lower amount of lactose, and, therefore, may be
 180 suitable for patients suffering from intolerance to lactose [26].

181 In 2009 Kanwar [27] summarized the components of milk breast that are of
 182 particular scientific interest in the past few years (Table 1).

183

184 **Table 1.** Components and respective actions of components of colostrum and
 185 breast milk.

COMPONENT	ACTIONS
Lactoferrin	Antibacterial, antifungal, antiviral, antiparasite and antitumor.
Casein	Protective in experimental bacteremia, causing myelopoiesis. The casein hydrolysates were also protective in diabetic animals, reduced growth d and tumor and decreased symptoms of colic in babies.

Proline Rich Polypeptide	Promotion of T and NK cell activation; Protective in autoimmune disorders.
Alpha-lactalbumin	Antiviral, antitumor and anti-stress actions.
Lactoperoxidase	Antibacterial properties.
Lysozyme	Effective in treating periodontitis and preventing tooth decay.

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187 According to Menchetti et al. (2016) [28], colostrum is safe and has
 188 no contraindications, even at high doses, and , reinforce that are few are
 189 clinically relevant side effects. They emphasize their growing use in medicine
 190 and veterinary medicine as an element that may play a complementary role to
 191 synthetic pharmaceutical drugs in the prevention and treatment of various
 192 diseases. Milk proteins and peptides are well tolerated and many exhibit oral
 193 bioavailability; thus, they can complement standard therapies to increase overall
 194 success in cancer treatments. Lactoferrin, colostrum and milk-specific peptide
 195 fractions are currently being developed as clinical nutrition for cancer prevention
 196 and chemotherapy protection.

197 PRP, subsequently known as Colostrinin™, was first found in sheep colostrum
 198 as a fraction that accompanies colostrum IgG2. Later, similar polypeptides were
 199 found in human, bovine and goat colostrum. PRP is a 500 to 3000 Da molecular
 200 weight peptide complex. It contains 25% proline residues and 40% hydrophobic
 201 amino acids. It is not species specific, and is active both " in vivo" and "in
 202 vitro". Colostrinin™ has immunomodulatory properties, including effects on
 203 humoral and cellular immune responses, regulatory activity in the induction of
 204 Th1 and Th2 cytokines and has the ability to inhibit overproduction of
 205 reactive oxygen and nitric oxide species [29]. Colostrinin™ in the form
 206 of subminually administered tablets improves the clinical condition of
 207 Alzheimer's patients. The beneficial effect has been assigned to control
 208 and stress oxidative known implicated in the pathogenesis the Alzheimer's. It
 209 has been shown inhibition of overproduction of reactive oxygen species, and
 210 nitric oxide [30].

211 Still in this context, the study by Douraghi-Zadeh et
 212 al. (2009) [31], through ens tutors cytotoxicity demonstrated that pretreatment
 213 of human neuronal SHSY5Y cells with sheep colostrinina 5 microg / ml for 24
 214 hours confers neuroprotection against neurotoxicity induced by beta - amyloid .
 215 The effect of colostrinin on LPS-stimulated human peripheral blood
 216 mononuclear cells with PHA (LP) or PMA as proinflammatory activators has
 217 been the subject of research conducted by Zablocka et
 218 al. (2007) [32], inhibition was 40-60% for PMA-induced hydrogen peroxide
 219 production. The peptides also inhibited superoxide dismutase activity and
 220 induced IL-6, IL-10 and TNF-alpha. Effects are then highlighted not only on
 221 adaptive immunity as already known but also on innate immunity.

222 Colostrinin also stimulates the activity of natural killer cells (NK cells), leading to
 223 activity up to 10 times higher than normal, much higher than any other known

224 substance. Considering that NK cells along with the cytotoxic T cells are the
225 main immune cells to attack cancer cells and virus-infected cells, its potential
226 effects protectors in cases of these diseases are evident [33].

227

228 **5. CONCLUSION**

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230 The high prevalence and mortality of breast cancer prompts the investigation of
231 cellular and molecular mechanisms that may contribute to more effective
232 preventive and therapeutic means.

233 Considering that humans are normally exposed to various cancer-inducing
234 agents, including those obtained through diet, possible strategies involve
235 lifestyle and diet.

236 While fat-rich, high-fiber, industrialized foods have been linked to the onset and
237 progression of cancer, a healthy diet has been reported to be protective. Added
238 to this is the growing interest in research involving functional and nutraceutical
239 foods that can positively impact health of people, especially in the context of
240 cancer prevention and treatment.

241 Colostrin is still little explored in scientific research, but its immunomodulatory
242 role is already evident. However, in relation to cancer, its possible benefits have
243 not yet been properly evaluated, instigating in vitro and in vivo research on
244 different types of tumors.

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