

## 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 metabolismo.*

### 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.

## 49 2. RESEARCH METHODOLOGY

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

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## 56 3. OXIDATIVE METABOLISM AND APOPTOSIS

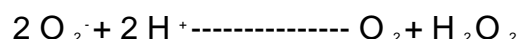
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58 When you breathe, you give all your cells the oxygen they need to produce  
59 energy through a process known as oxidative metabolism. In short, oxygen is  
60 reduced and glucose covalent bonds are broken releasing carbon dioxide,  
61 water and energy. The main cell organelle involved is the mitochondria, where  
62 several enzymes are responsible for catalyzing the stages of this process. In  
63 each of these steps there is the formation of byproducts that are mostly  
64 beneficial. However, approximately 5% may be toxic to the cell at high  
65 concentrations. Oxygen, for example, during electron transport in mitochondria  
66 can be partially reduced by generating reactive oxygen species (ROS), such as  
67 superoxide anion (O<sub>2</sub><sup>-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and hydroxyl radical (OH-  
68 ). **When failure** the balance between ROS production and elimination failure,  
69 which is called oxidative stress, occurs, damage to DNA, RNA, lipids and  
70 proteins can occur. In addition to DNA fragmentation, the ROS can cause  
71 malfunction of the DNA repair system, contributing to the development of  
72 diseases, including cancer [ 3 ].

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

82 **Superoxide dismutase** (SOD) has been reported as an important antioxidant  
83 mechanism present in eukaryotes and prokaryotes, strict aerobic and  
84 microaerophil organisms. This enzyme requires a metal as a cofactor for its  
85 functional activity, which may be copper (Cu-SOD), manganese (Mn-SOD)  
86 or iron (Fe-SOD). This enzyme acts by catalyzing the dismutation of the  
87 superoxide anion. Dismutation is a reaction in which two identical molecules are  
88 transformed into different compounds. In the case of SOD, one superoxide ion  
89 oxidizes the other, generating O<sub>2</sub> (normal) and hydrogen peroxide  
90 (H<sub>2</sub>O<sub>2</sub>). Hydrogen peroxide may be further degraded by catalase or  
91 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 phagocyted 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**

147

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,  $\alpha$ -lactalbumin,  $\beta$ -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 secretions is essential passive immunity,** prebiotic compounds and  
 160 growth factors involved in the intestinal development [ 20 ]. The colostrum  
 161 intake is critical to the survival and health of the mammals offspring [ 21 ].

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

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

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

182

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

COMPONENT	ACTIONS
<b>Lactoferrin</b>	Antibacterial, antifungal, antiviral, antiparasite and antitumor.
<b>Casein</b>	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.

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

185

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

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

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

221 Colostrinin also stimulates the activity of natural killer cells (NK cells), leading to  
222 activity up to 10 times higher than normal, much higher than any other known  
223 substance. Considering that NK cells along with the cytotoxic T cells are the

224 main immune cells to attack cancer cells and virus-infected cells, its potential  
225 effects protectors in cases of these diseases are evident [ 33 ].

226

## 227 5. CONCLUSION

228

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

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

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

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

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