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.

2. RESEARCH METHODOLOGY

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

3. OXIDATIVE METABOLISM AND APOPTOSIS

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

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

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

$$2\,O_2^- + 2\,H^+ \text{---------- } O_2 + H_2O_2$$

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

Comment [FDC1]: Was this review reported following the guidelines like PRISMA for example? If yes, please include.

Comment [FDC2]: **Eligibility criteria?** Study design: nonexperimental designs (observational, cohort studies, surveys, cross-sectional and longitudinal) inclusion and exclusion criteria.

Comment [FDC3]: Primary and secondary outcomes?

Comment [FDC4]: Information sources and search strategy:
Were these articles selected from databases (Cochrane Library, Lilacs, Eric, Livivo, PubMed/Medline), without limitations regarding language or date?
It's very important include.

Comment [FDC5]: How was methodological quality assessed to minimize risk of bias?

Comment [FDC6]: How were the data analyzes conducted? What software was used to perform the analyzes of this review?
Very importante item.

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

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

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

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

BCL-2 protein was originally described in 1985 [12] and since then other proteins with apoptosis regulating properties have been identified, currently resulting in the BCL-2 family. It is therefore a set of proteins that inhibit or promote apoptosis, playing a crucial role in tissue maintenance, programmed cell death during development and defense against pathogens [13]. They present diverse subcellular localization, some of which can be found in the cytosol, but most of them anchored in membranes, such as the external mitochondrial, endoplasmic reticulum and nuclear membrane [14].

In the context of cancer, pro-apoptotic limbs are characterized as apoptotic performers, acting as tumor suppressors while pro-survival limbs are regarded as apoptosis inhibitors, acting as oncoproteins [15].

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

4. COLOSTRUM AND COLOSTRININ

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

Compared to milk, it has higher viscosity and is made up of blood serum components such as immunoglobulins and other serum proteins such as albumin, α-lactalbumin, β-lactoglobulin. In addition to containing many essential nutrients , in concentrations higher than those commonly found in milk , it also has several other beneficial components such as leukocytes, growth factors, hormones, cytokines and nonspecific antimicrobial factors [19].

These first s Secret tions is m an essential vehicle passive immunity, prebiotic compounds and growth factors involved in the intestinal development [20]. The colostrum intake is critical to the survival and health of the mammals offspring [21].

Comment [FDC7]: Adjustments

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

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

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

Table 1. Components and respective actions of components of colostrum and 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 periodentitis and preventing tooth decay.

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

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

Still in this context, the study by Douraghi-Zadeh et al. (2009) [31], through ens tutors cytotoxicity demonstrated that pretreatment of human neuronal SHSY5Y cells with sheep colostrinina 5 microg / ml for 24 hours confers neuroprotection against neurotoxicity induced by beta - amyloid .

The effect of colostrinin on LPS-stimulated human peripheral blood mononuclear cells with PHA (LP) or PMA as proinflammatory activators has been the subject of research conducted by Zablocka et al. (2007) [32], inhibition was 40-60% for PMA-induced hydrogen peroxide production. The peptides also inhibited superoxide dismutase activity and induced IL-6, IL-10 and TNF-alpha. Effects are then highlighted not only on adaptive immunity as already known but also on innate immunity.

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

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

5. CONCLUSION

The high prevalence and mortality of breast cancer prompts 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.
While fat-rich, high-fiber, industrialized foods have been linked to the onset and progression of cancer, a healthy diet has been reported to be protective. Added to this is the growing interest in research involving functional and nutraceutical foods that can positively impact health of people, especially in the context of cancer prevention and treatment.
Colostrinin is still little explored in scientific research, but its immunomodulatory role is already evident. However, in relation to cancer, its possible benefits have not yet been properly evaluated, instigating in vitro and in vivo research on different types of tumors.

REFERENCES

1. WHO. Cancer. Available: https://www.who.int/health-topics/cancer#tab=tab_1

2. INCA. Cancer. Available: https://www.inca.gov.br/numeros-de-cancer/incidencia

3. Silva CT, Jasiulionis MG. Relação entre estresse oxidativo, alterações epigenéticas e câncer. Ciência e Cultura. 2014; 66:38-42.

4. Jacob MJ. The integrated antioxidants systems. Nutrition Research. 1985; 15:755-765.

5. Yu BP. Cellular defenses against damage from reactive oxygen species. Physiological Reviews. 1994;74:139-162.

6. Mendonça PS, Carioca AAF, Maia FMM. Interações entre estresse oxidativo, terapia utilizada e estadiamento em paciente com câncer colorretal. Revista Brasileira de Cancerologia. 2014;60:129-134.

7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144:646-674.

8. Oberley LW, Buettner GR. Role of superoxide dismutase in cancer: a review. Cancer Research. 1979; 39:1141-1149.

9. Story M, Kodym R. Signal transduction during apoptosis; implications for cancer therapy. Frontiers in Bioscience. 1998; 23:365-375.

10. Villunger A, Strasser A. Does death receptor signaling play a role in tumorigenesis and cancer therapy? Oncology Research. 1998; 10:541-550.

11. Ziegler U, Groscurth P. Morphological features of cell death. News in Physiological Sciences. 2004; 19:124-128.

12. Tsujimoto Y, Cossman J, Jaffe E, Croce CM. Involvement of the BCL-2 gene in human folicular lymphoma. Science. 1985; 228:1440-1443.

13. Wang HG, Reed JC. Mechanisms of Bcl-2 protein function. Histol Histopathol. 1998; 13(2):521-530.

14. Youle RJ, Strasser A. The BCL-2 protein family: opposing activities that mediate cell death. Nature Reviews Molecular Cell Biology. 2008; 9(1):47-59.

15. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL - 2 protein family : implications for physiology and therapy. Molecular Cell Biology. 2014; 15(1):49-63.

16. Wong RSY. Apoptosis in cancer: from pathogenesis to treatment. Journal of Experimental & Clinical Cancer Research. 2011; 30(1):87.

17. Grivicich I, Regner A, Rocha AB. Morte celular por apoptose. Revista Brasileira de Cancerologia. 2007; 53:335-343.

18. Patton S. Canfield LM, Huston GE, Ferris AM, Jensen RG. Carotenoids of human colostrum. Lipids. 1990; 25:159-165.

19. Foley JÁ, Otterby DE. Availability, storage, treatment, composition, and feeding value of surplus colostrum: a review. Journal of Dairy Science. 1978; 61:1033-1060.

20. Picone G, Zappaterra M, Luise D, Trimigno A, Capozzi F, Motta V, et al. Metabolomics characterization of colostrum in three sow breeds and its influences on piglets' survival and litter growth rates. J Anim Sci Biotechnol. 2018; 9:23.

21. Langer P. Differences in the composition of colostrum and milk in eutherians refl ect differences in immunoglobulin transfer. Journal of Mammalogy. 2009; 90:332-339.

22. Lonnerdal B. Bioactive proteins in breast milk. Journal of Paediatrics and Child Health. 2013; 49:1-7.

23. He F, Tuomola E, Arvilommi H, Salminen S. Modulation of human humoral immune response through orally administered bovine colostrum. FEMS Immunololy & Medical Microbiology. 2001; 31:93-96.

24. Pan Y, Lee A, Wan J, Coventry MJ, Michalski WP, Shiell B, Roginski H. Antiviral properties of milk proteins and peptides. Int Dairy J. 2006; 16(11):1252-1261.

25. Wan ZX, Zhang F, Geng Q, Wang PY, Zhou H, Zhang YM. Effect of orally administered bovine colostrum on cytokine production in vivo and in vitro in immunosuppressed mice. Int. Dairy J. 2010; 20: 522-527.

26. Bagwe S, Tharappel LJ, Kaur G, Buttar HS. Bovine colostrum: an emerging nutraceutical. Journal of complementary & integrative medicine. 2015; 12: 175-185.

27. Kanwar JR, Kanwar RK, Xueying S, Punj V, Matta H, Morley SM, Puri M, Sehgal R. Curr. Protein Pept. Sci. 2009; 10(4):308-338.

28. Menchetti L, Traina G, Tomasello G, Casagrande-Proietti P, Leonardi L, Barbato O, Brecchia G. Potential benefits of colostrum in gastrointestinal diseases. Frontiers in Bioscience. 2016; 1:331-351.

29. Janusz M, Zabłocka A. Colostrinin: a proline-rich polypeptide complex of potential therapeutic interest. Cellular and molecular biology. 2013; 59:4-11.

30. Zabłocka A, Janusz M. Effect of the proline-rich polypeptide complex/colostrinin™ on the enzymatic antioxidant system. Archivum Immunologiae et Therapiae Experimentalis. 2012; 60:383-390.

31. Douraghi-Zadeh D, Matharu B, Razvi A, Austen B. The protective effects of the nutraceutical, colostrinin, against Alzheimer's disease, is mediated via prevention of apoptosis in human neurones induced by aggregated beta-amyloid. Journal of Nutrition Health and Aging. 2009; 13:522-527.

32. Zabłocka A, Janusz M, Macała J, Lisowski J. A proline-rich polypeptide complex (PRP) isolated from ovine colostrum. Modulation of H2O2 and cytokine induction in human leukocytes. International Immunopharmacology. 2007; 7:981-988.

33. Maher J. The Physiological Functions of Proline-Rich Polypeptides. Dynamic Chiropractic. 2007; v.25:1-4.