

## **BENEFITS AND CLINICAL USES OF COLOSTRUM IN HUMAN AND ANIMAL HEALTH. A REVIEW**

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### ABSTRACT

This paper reviews the biological role of bioactive constituents of colostrum and the use of this "first" milk in prevention and treatment of various disorders in human and domestic animals. Colostrum is a biological complex fluid richer in antimicrobial peptides, immune-regulating compounds and growth factors than the subsequent mature milk. The biological value of colostrum is documented by thousands of scientific studies and clinical trials carried out both *in vitro* than in human and animals. The main functions of colostrum include a defensive action, the modulation of immune response, the balancing of intestinal microflora and provides to the growth and repair of several tissues. Colostrum is safe, has not contraindications also to high dose levels and the reported side effects of clinical relevance are limited. Recent advances in food technology of industrial dairying allow continuous availability of ruminants colostrum. For all these reasons, unsurprisingly, pharmaceutical companies are moving in the market by producing supplements of colostrum. In conclusion, in the next future, supplements based on colostrum may have a complementary role to synthetic drugs in the prevention and treatment of several human and animals diseases.

Key words: colostrum, anti-microbial factors  
growth factors, human and animal health

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**BENEFICIILE ȘI UTILIZARE CLINICĂ A COLOSTRULUI  
PENTRU SĂNĂTATEA OMULUI ȘI ANIMALELOR. SINTEZĂ**

REZUMAT

Acest articol trece în revistă rolul biologic al constituenților bioactivi ai colostrului și utilizarea acestui „prim” lapte în prevenirea și tratamentul diferitelor disfuncții la om și animale. Rolul biologic al colostrului este documentat de mii de studii științifice și experimente clinice, efectuate atât *in vitro* cât și pe animale. Colostrul este un complex biologic lichid, mai bogat în peptide antimicrobiene, constituenți imunomodulatori și factori de creștere, decât laptele complet. Principalele funcții ale colostrului includ o acțiune de apărare, modularea răspunsului imun, echilibrarea microflorei intestinale și stimularea dezvoltării și specializării multor țesuturi. Colostrul este sigur, nu are contraindicații nici chiar în doze mari, iar efectele secundare raportate sunt limitate. Pentru toate aceste motive, companiile farmaceutice se îndreaptă spre producerea și livrarea pe piață a unor suplimente de colostru. În concluzie, în viitorul apropiat suplimentele pe bază de colostru pot avea un rol complementar ca medicamente sintetice în prevenirea și tratamentul multor boli la om și animale.

Cuvinte cheie: colostru, factori anti-microbieni, factori de creștere, sănătatea oamenilor și animalelor

Colostrum is a biological fluid produced by mammary gland after parturition, before gradually lose its characteristics and to becomes mature milk. This secretion is fundamental for the survival of mammals offspring, especially for ungulates (70). Several studies have extensively analyzed the composition of bovine, goat and human colostrum highlighting the presence of at least ninety different substances (60). Colostrum is a source of vital macro and micronutrients as proteins, fats, carbohydrates, vitamins and minerals necessary to the growth of the newborn (79,87). In addition, it contains several biologically active molecules which are essential for specific functions. The main functions of colostrum include the nutrition and growth of newborn, provide protection against pathogens, promote the development of immune system and ensure the growth, maturation and repair of several tissues either in human than in animals (18). The bioactive components in colostrum include compounds with anti-microbial activity, immuno-stimulating peptides and growth factors (11,113,132). Colostrum composition is very different from milk, in fact, some of these compounds either are missing in the milk or are present in lower concentrations (67). Anti-microbial factors provide passive immunity and protect against infections during the first period of life. The anti-microbial

activity of colostrum is due to immunoglobulins, lactoferrin, lactoperoxidase, lysozyme by a direct action on pathogen agents and to oligosaccharides, gangliosides and nucleosides that stimulate the growth of a healthy intestinal microbiota rich in bifidobacteria and lactobacilli (72). Colostrum provides signals to the immune system by inducing tolerance to food and non invasive agents antigens, avoiding the onset of immune disorders, but at the same time, promoting its maturation and an adequate immune response against pathogens (146). Some components are able to promote the maturation and modulation of the immune system either directly as colostrinin, cytokines and lactoferrin or indirectly as oligosaccharides, gangliosides and nucleosides (68). Colostrum contains growth factors as Insulin Growth Factors (IGF-I, IGF-II), Endothelial Growth Factor (EGF), Trasforming Growth Factors (TGF- $\alpha$  and TGF- $\beta$ ) that play a role in the development, maturation and repair of various tissues (108). In recent decades, bovine and goat colostrum have been used in prevention and treatment of a variety of human and animals diseases, in particular, but not only, of gastro-intestinal system (61,76). The aim of this review is to discuss the specific property of some bioactive constituents of colostrum and to assess the possible clinical uses of colostrum. This review is divided into three sections: 1) quality of colostrum; 2) constituents of colostrum and their functions; 3) clinical uses.

### **Quality of colostrums**

It must takes in consideration that not all colostrum is equal and therefore it is necessary to carry out a careful evaluation of product quality when used as supplement in human and animals. The quality of colostrum depends on the species, breed, farm management, collection period, number of parturitions and kids, animal health and processing practices. All these factors influence considerably the quality of colostrum modifying the amounts of nutritional and biological active constituents. Collection period and processing procedures are probably the most important factors that affect the colostrum quality (33,46,86). Colostrum production is limited in time, in fact, within 2-5 days from the parturition the colostrum gradually loses its characteristics and becomes mature milk. The best colostrum in terms of its composition and functional activity is produced during the first 24-48 hours after parturition. In fact, the levels of several bioactive components decrease in time-dependent manner after their concentration peak (27). Colostrum products should be manufactured in technologically-advanced facilities using low-heat pasteurization and low-pressure as processing procedures. This is important as the high temperature and high pressure denature several components of colostrum in particular those of proteic nature (65). Moreover, each batch should be analyzed prior the shipment to assure its quality, efficacy and safety.

Finally, colostrum for human and animal use should be accompanied by a certificate attesting the absence of residues as hormones, antibiotics and other

drugs, environmental chemical contaminants (pesticides, heavy metals etc.) or infectious agents. At moment, there is not a standard composition that clearly defines the colostrum to be used as a dietary supplement in human and animals. In fact, colostrum is defined as "the fluid secreted by the mammary glands during the first 3-5 days after parturition" and this is not a standard (26).

### **Constituents and their functions**

Bioactive molecules in colostrum can be divided in two classes: anti-microbial factors and growth factors.

#### **1) Anti-microbial factors.**

The anti-microbial factors are represented by compounds of different nature, which provide passive immunity, protect the host against the pathogen agents and can also modulate the immune system. Some constituents show strong antimicrobial activity as immunoglobulins, lactoferrin, lactoperoxidase, lysozyme,  $\alpha$ -lactalbumin and peptides derived from caseins as the glycomacropeptide (GMP). Oligosaccharides, gangliosides and nucleosides provide protection against pathogens acting as "false receptors" of intestinal cells. Moreover, they induce proliferation of bifidobacteria and lactobacilli that not only inhibit the pathogens proliferation but also stimulate the immune system. Others components as colostrinin (CLN), cytokines and lactoferrin have immunomodulatory functions and regulate the duration and intensity of immune and inflammatory responses.

**a) Immunoglobulins (Igs).** Colostrum Igs concentrations are very high and provide to passive immunity to the newborn during the development of its own immune system but can be useful also in the adult to give protection against infections (71,77). There are considerable differences in Igs levels depending by animal species (70,114). Colostrum contains five classes of immunoglobulins (IgA, IgG, IgD, IgE, IgM) which show different actions against pathogens. IgG are the most abundant antibodies in ruminants while IgA are higher in women than in bovine and goat colostrum (33). Igs concentrations decrease markedly during the transition from colostrum to milk in the days after parturition (75,104). Colostrum contains antibodies against several bacteria, virus, parasites and fungi (82). Igs concentrations of colostrum may be increased through specific vaccination protocols during pregnancy producing hyperimmune colostrum. Thanks to the advanced in fractionation technology the Igs can be separate and successively enriched to obtain products with high titer to use against specific pathogen agents (30,103).

**b) Lactoferrin (Lf).** Lf is a multifunctional iron-binding glycoprotein present in several exocrine fluids including colostrum. Lf concentration differ between the species and quickly declines with the milkings (49). The biological activities of Lf includes an anti-infective, anti-cancer, anti-oxidant and anti-inflammatory action, immunomodulation and control of cells growth (73). Lf is

effective against bacteria, virus, fungi and protozoa (94,99,100,145). Lf modulates immune functions as cytokine production, cytotoxicity, proliferation, maturation, migration and activation of macrophages, granulocytes, natural killer and T and B cells by binding its specific receptor (LfR) (74). Lf influences the inflammatory process regulating anti-inflammatory cytokine secretion and by its ability to bind LPS, CD 14 receptor and bacterial DNA preventing septic shock and tissue damage (45). In some conditions, Lf shows pro-inflammatory properties inducing macrophages activation (88). Lf increases proliferation and differentiation of intestinal epithelial cells and controls the composition of intestinal microflora (19,115). Lf shows anti-tumor activity decreasing cancer growth and metastasis (143). Lf can also acts as antioxidant and it is involved in the absorption of nutrients.

**c) Lysozyme.** Lysozyme is an enzyme found in various body fluids, including colostrum and milk. It has an anti-microbial action on gram negative and positive bacteria thanks its ability to split the peptidoglycan layer of bacterial cell wall determining lysis of infectious agent (119).

**d) Anti-oxidants.** Colostrum contain several compounds with both pro and anti-oxidant effect depending on physiological status (112). The compounds that can counteract the action of reactive oxygen species (ROS) are superoxide dismutase (SOD), catalase, glutathione peroxidase, vitamin A, E and C, ceruloplasmin, caseins and minerals as selenium, copper and zinc (2). Furthermore, colostrum can be also considered as a source of ROS, both because it presents macromolecules susceptible to peroxide processes as well as it contains ROS-generating systems as xanthine oxidase and lactoperoxidase whose activities contribute to eliminate infectious agents (69).

**e) Nucleotides/nucleosides.** These factors are important as metabolites but also because maintain the integrity of intestinal mucosa, modulate the immune system, influence the type of commensal flora and influence the proliferative action of growth factors (10,149).

**f) Gangliosides.** In colostrum and milk the gangliosides are associated with the membrane of fat globule and present different concentrations depending on species (102). They are involved in various fundamental cellular functions and in immune response but likewise they act as receptors for different bacteria and toxins. Ganglioides, in particular, GD3 are involved in the mechanism of proliferation, maturation and activation of lymphocytes, dendritic cells, in cytokines production and intestinal IgA secretion suggesting a their role in immune response (120). GD3 can also has a role in the development of several organs included digestive and nervous system (6). GM3 are involved in defensive mechanisms of the host given that they act as "false" receptors for toxins and adhesins of pathogens bacteria (53). Gangliosides may produce a proliferation of useful microflora as bifidobacteria and then participate indirectly in defensive mechanisms (89).

**g) Oligopolysaccharides and glycolconjugates sugars.** Colostrum contains many sugars as glycolipids, glycoproteins, cellulose, glycosaminogly-

can and mucin, in addition to lactose which is the predominant sugar (40,142).

The soluble sugars of colostrum and milk prevent the binding of bacteria and viruses to the intestinal cells acting like "false" receptors (92). Some sugars such as fructo-oligosaccharides and galacto-oligosaccharides act as prebiotics to promote the growth and maintenance of healthy intestinal microbiota rich in bifidobacteria and lactobacilli (138). This microorganism produces acetic and lactic acids during their metabolism which suppress the growth of several bacteria and fungal species (57,123). Furthermore, some bifidobacteria and lactobacilli strains have been shown to inhibit inflammatory responses in intestinal epithelial cells (62).

**h) Leukocytes.** Colostrum, contains macrophages, lymphocytes and neutrophils which give a rapid response by phagocytosis against pathogens and parasites (32,36). Furthermore, this immune cells modulating the cytokines production influence the development and the activity of the immune system of neonate (118).

**i) Proline rich polypeptide (PRP) or Colostrinin (CLN).** Colostrum and milk of several mammals are rich in CLN, but those of bovine and human have higher quantities (130). CLN consists of several peptides that contain an unusually high portion of the amino acid proline and derive from proteolysis of milk  $\beta$ -casein (68). Its biological activity is based on the action of more than one component, while the individual components alone do not have or have low activity (55). CLN regulates the secretion of other cytokines affecting both the inflammatory and immune response. CLN is an intercellular signalling molecule that has the ability to modulate the immune system regulating the proliferation and differentiation of immune cells both in vitro and in vivo (135). It stimulates the weak or unreactive immune system but can also restore the balance of immune functions when the immune system is hyperactive as in case of autoimmune diseases or allergies (14,133). CLN also plays an anti-oxidant activity by reducing the levels of intracellular reactive oxygen species (ROS) and nitric oxide (NO) suggesting a role in the treatment of neurodegenerative disease and of those in which ROS are implicated in the pathogenesis (15,150). In fact, CLN suppresses chronic microglial cells activation and shows neuroprotective function preventing the formation and increasing the disruption of  $\beta$ -amyloid peptides (37). Its immunomodulatory and neuroprotective properties can be used in spinal cord injury, traumatic and toxic brain damage and also in slowing the progression of neurodegenerative diseases like Alzheimer's disease (1,56). CLN induces the neurons growth modulating the expression of genes responsible for proliferation, differentiation and regeneration of cells in the nervous system (9) and improves cognitive function in mammals (22,111).

**l) Cytokines.** Cytokine are proteins, peptides or glycoproteins secreted by specific cells of the immune system and they are very important for the cellular communication (38). Cytokines are produced in mammary gland and then released in colostrum and milk. Colostrum contains many cytokines, as interleukins IL-1b, IL-3, IL-6, IL-8, IL-10, IL-12, IL-18, IFN- $\gamma$ , TNF- $\alpha$  and TNF- $\beta$

(44) which can regulate the development of neonate immune system, control the inflammatory response (5), allow communication between the immune cells favoring the increase of Th1 (148) and the antibodies production (129). They act in combination with other defensive components of colostrum as Igs, lactoferrin and lactoperoxidase (125).

**2) Growth factors.**

Colostrum contains several growth factors that modulate the growth, maturation, function and repair of bone, muscle, nervous, connective, cartilage, skin tissues and particularly the gastro-intestinal mucosa (108). Generally, the growth factors as the other biologically active compounds reduce their concentrations with milkings.

**a) Insulin-like growth factors (IGF-I and IGF-II)** are also known as somatomedins, are synthesized in liver under the influence of the hormone GH and their receptors are found in cells of various tissues, including those of gastro-intestinal tract (28). IGF-I shows higher concentrations than IGF-II in colostrum and both reduce their concentrations with milkings (21). Somatomedins are carried in the blood by 6 types of proteins and by their interacting with specific receptors promote the proliferation and differentiation of tissues as well as an anabolic action (12). IGF-I is associated with cell proliferation in the crypts while IGF-II controls the mechanism of cell differentiation of intestinal epithelial cells (58).

**b) Epidermal growth factor (EGF)** is a peptide present in colostrum and its functions are different in neonate and adult. EGF receptor is localized in the basolateral membrane of the enterocyte and this suggests that it acts as a peptide surveillance readily available to repair the injury site in adult (107). In neonate, the growth factor can cross the intestinal barrier and binds to receptor stimulating cellular growth (137). EGF may also prevent bacterial translocation in the gut and stimulates gut immunity (97).

**c) Transforming growth factor-  $\alpha$  (TGF- $\alpha$ )** is a peptide present in colostrum and milk but it is also synthesized in the mucosa of gastro-intestinal tract (23). Systemic administration of TGF- $\alpha$  stimulates the secretion of mucin, the cell growth, repair of wounds and inhibits acid secretion. Its physiological role is cellular differentiation and migration rather than proliferation and it is helpful in repairing and in maintaining the integrity of intestinal epithelium (106).

**d) Transforming growth factor- $\beta$  (TGF- $\beta$ )** there are 5 isoforms of TGF- $\beta$  and their binding site is the surface of the intestine (66). TGF- $\beta$  inhibits cell proliferation, is a powerful chemo-attraction for neutrophils and plays a role in repair process stimulating the migration of epithelial cells on the denuded area to re-establish epithelial continuity (31). In the intestinal mucosa regulates the inflammatory and immune response intervening in T helper lymphocytes differentiation and on IgA production (95). In children predisposed to allergy, TGF- $\beta$ 1 increases the IgG and IgA production and inhibits cell-mediated and IgE-mediated reaction against milk proteins (84).

**e) Platelet-derived growth factor (PDGF)** is a peptide derived from platelets but is also produced by macrophages. PDGF is a potent mitogen for fibroblasts and facilitates the ulcers healing (127).

**f) Vascular endothelial growth factor (VEGF)** is a peptide with potent angiogenic and mitogenic activity, which acts on vascular permeability (59). VEGF is present in colostrum and its receptor has been identified on the apical membrane of epithelial (128). These findings suggest a role of VEGF in digestive system physiology.

### **Clinical applications**

In recent decades, have been made thousands of scientific studies and clinical trials both *in vitro*, than in animals and in human using colostrum. These have led to the production of a considerable amount of scientific papers published which documenting the safety and efficacy of the use of colostrum in the treatment of a wide range of diseases (117). Moreover, colostrum may be of great benefit to maintain or recover good health during stress and convalescent periods.

**a) Diarrhoea.** The therapeutic effects of colostrum against infectious diarrhoea determined by bacteria, virus, protozoa and fungi, are due to the presence of Igs and other anti-infective factors (52,134). Colostrum and hyperimmune colostrum have been used against rotavirus (54), shigella spp. (8), *E. coli* (101), *Helicobacter pylori* (81), *Clostridium difficile* (144), protozoa as *Cryptosporidium parvum* or *Entamoeba histolytica* and fungi as *Candida albicans* in human and animal infections (3,96).

**b) Necrotizing enterocolitis, prevention and therapy.** The necrotizing enterocolitis is a serious disease characterized by severe ulceration of the small and large intestine that affects mainly children. The etiology is unclear, although it is often highlighted the presence of Enterobacteriaceae. The abnormal development of these germs is due to inadequate production of mucus, to delayed colonization of commensal bacteria and to low antibody levels and determine ulcers formation and toxins production. Colostrum reduces the bacteria multiplication and translocation and acts on mucosal repair. The use of colostrum has shown beneficial effects and therefore may represent an adjuvant therapy (13).

**c) Immune-deficiency related diarrhoea.** Chronic diarrhoea occur in children and adults who have a compromised immune system as in AIDS patients. In these patients is frequent the presence of *Cryptosporidium parvum* and bacteria. The use of colostrum in human patients has produced good results leading to an improvement of clinical conditions, with lower abdominal pain and reduction of diarrhoea (35). Furthermore, it has been identified in colostrum and intestinal mucosa of calves fed with colostrum, a lipid defined as sporozoites inhibiting the adhesion of lipid (SIL) which acts also against *Giardia* (36,122). Colostrum has been used effectively in reducing the clinical signs and elimination of oocysts in various animal species (42,90).



**d) Prevention of lesions due to non steroidal anti-inflammatory drugs (NSAIDs).** NSAIDs are among the drugs most commonly used world wide either in human than in animals (139,140). NSAIDs produces detrimental effects on several tissues but in particular on digestive system as increase in acidity, a reduction of gastric mucosal barrier, an abnormal blood flow and neutrophils activation with predisposition to mucosal ulcerations (4,80). Different models have been used to evaluate the effect of colostrum in reducing intestinal lesions caused by the use of NSAIDs (63). Colostrum reduces gastric and intestinal lesions, the permeability of the intestinal wall and shortening of villi. These effects are more evident in the acute than chronic forms (109). Colostrum may represent a novel and inexpensive approach for the prevention and treatment of intestinal ulcerative conditions.

**e) Short bowel syndrome.** This syndrome is characterized by an insufficient length of the intestine and it is associated with poor digestion and absorption. The most used therapeutic option is parenteral nutrition but other strategies are necessary to optimize the function of remained intestine. Colostrum or specific growth factors may provide benefits. Systemic administration of EGF stimulates intestinal growth in rats receiving parenteral nutrition (107). Rabbits underwent to intestinal resection showed the restoration of glucose transport as a result of oral administration of EGF (98).

**f) Mucositis induced by chemotherapy.** The treatment of cancer involving the use of high doses of chemotherapy drugs that cause side effects in various organs and tissues. Strategies to protect tissues and stimulate their recovery may increase the drugs dose and the treatment period in order to have a higher potential of healing. In this respect, EGF increases the recovery of rat intestinal mucosa damaged by methotrexate, TGF- $\beta$  improves chemotherapy-induced mucositis and some whey protein reduce methotrexate-induced intestinal lesions in mice (48,51,131). Not all studies have given satisfactory effects, EGF has only limited benefits in reducing oral ulcerations in patients undergoing chemotherapy (41). Colostrum contained antimicrobial constituents and growth factors that stimulating cell proliferation and fighting infections may be used as adjuvant to reconstitute the intestinal mucosa in combination or after chemotherapy to reduce the detrimental effects of chemotherapeutic drugs in tissues.

**g) Neurodegenerative disease.** Several studies have been conducted in Alzheimer's disease using the CNL (56). Companion animals can suffer from degenerative diseases very similar to the diseases that can strike humans (25). Neurodegenerative diseases and cognitive disfunctions are common in older pets (47,91). Neurodegenerative disorders can be caused by genetic mutations and inflammatory processes in nervous system (46). Beside to conventional therapy used also in human colostrums enriched in CLN could reduce the progression of the pathology and improve cognitive functions (85).

**h) Surgery.** Under conditions of shock, due to surgery or trauma, bacteria and endotoxins in the intestines can cross the mucosal barrier by

translocation and enter the blood and lymphatic system. Colostrum has been evaluated as a preventive treatment in pre-operative abdominal and coronary arteries surgery. In abdominal surgery reduced endotoxemia (16) while in coronary bypass surgery reduced IL-6 and C-reactive protein levels but there was not effect on endotoxemia (17). Oral treatment with bovine colostrum can reduce translocation and endotoxaemia in rats (24,64) and rabbit (39). It can be speculated that the pre-and postoperative treatment with colostrum, associated with conventional therapy, may reduce bacterial translocation and endotoxemia and thereby improve the recovery of surgical patients either human than animals.

**i) Oral cavity disorders.** The efficacy of colostrum was evaluated in oral hygiene as in Sjogren's syndrome (105), in reducing dental plaque (34) and prevention of dental caries (147). Colostrum supplements could have an effect in reducing tartar formation and bad breath in pets.

**l) Eye Disorders.** Colostrum has prophylactic and therapeutic action against Chlamydia trachomatis (116). Moreover, it has been added in the artificial tears used by people with dry eyes (78). Eye drops containing colostrum and herbal extracts could be used in the prevention and treatment of ocular infections and ulcerations also in animals.

**m) Flu.** Oral colostrum administration results more effective and safe in the prevention of flu episodes compared with antiinfluenza vaccination (93,141).

**n) Athletic Performance and body composition.** Colostrum supplementation could be effective in athletes to increase lean body mass, improve muscular strength, increase endurance capacity and speed recovery. International Olympic Committee (IOC) has accepted the colostrum as a safe dietary supplement which can be used by athletes. Several studies have examined the impact of dietary supplementation with colostrum on the body composition and exercise performance (126). The results of some studies shown an improvement in performance after several weeks of treatment (20, 124). In one study that tested the hormones, the body composition and sports performance, colostrum did not determined any significant differences (83). In elite athletes, the colostrum has improved body composition but not the sport performances (7), while on the contrary, in amateur athletes has improved performances but not body composition (50).

### **Side effects and contraindications**

In the current state of knowledge, it appears that colostrum is safe and has not contraindications also to high dose levels either in human than in animals (29). Some authors suggest a possible side-effects such as lactose intolerance, nausea (110,121) and sensitivity to milk proteins. However, additional research are necessary to confirm these data, all above, in relation to a prolonged use of colostrum and during pregnancy. Obviously, the use of colostrum is not recommended in individuals who exhibit sensitivity to milk proteins.

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## CONCLUSIONS

Colostrum is a rich source of nutrient and biologically active molecules which are essential for several specific functions. Current farming methods provide the possibility of producing large quantity of colostrum and this allows for a continuous availability of raw material. Colostrum to use for nutritional supplement must have a high quality and it is necessary a standardization of the product. Pharmaceutical companies are moving to produce commercial products containing bovine or goat colostrum while biotechnology companies are moving to clone and produce large quantities of its main components. This increasing interest in the colostrum is supported by encouraging results of the scientific studies and clinical trials although further studies are needed to confirm its potential and the long-term effects. In conclusion, in the near future, this natural biological fluid may has a complementary role to the synthetic pharmaceutical drugs, in the prevention and treatment of several diseases of human and domestic animals and it may improves the health of populations living in developing countries.

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