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Mare's milk as a source of biologically active immunoglobulins: a review of scientific data

Abstract: Mare's milk is a valuable source of biologically active immunoglobulins (Ig), which play a key role in passive immune defense. Unlike cow's milk, it contains a high concentration of IgG, IgA and secretory IgA, which makes it promising for functional nutrition and therapeutic use. Mare's milk immunoglobulins have a high affinity for pathogens, help neutralize viruses, bacteria and toxins, and modulate the immune response of the mucosa. Of particular interest is their association with lactoferrin, which enhances their antimicrobial and anti-inflammatory properties. Modern studies confirm the effectiveness of mare's milk immunoglobulins in the prevention of gastrointestinal infections, allergic reactions and inflammatory diseases. Due to its high digestibility and low allergenicity, it is considered an alternative to cow's milk for infant and dietary nutrition. Promising directions include the creation of "immune-enriched products" based on mare's milk and the use of its immunoglobulins in biomedicine, including the creation of probiotics and drugs for correcting the microbiota. This review summarizes the current knowledge on the structure, functions, and practical applications of mare's milk immunoglobulins, emphasizing their potential in nutrition and clinical practice.
Key words: mare's milk, immunoglobulins, biologically active peptides, whey proteins.

Introduction

Mare's milk has been traditionally consumed in various cultures for its health benefits and nutritional content [1]. Mare's milk is a nutrient-rich substance, containing proteins, fats, carbohydrates, phosphorus, calcium, vitamin C, and many other essential components [2-5]. Although it has a lower fat content than both human and cow's milk, it boasts a higher proportion of unsaturated fatty acids – comparable to human milk – which can help prevent high cholesterol and atherosclerosis [6]. Its protein makeup, mainly whey and casein, falls between human and cow's milk levels. The unique structure and composition of its casein micelles make mare's milk more digestible than cow's milk. Furthermore, its whey protein content is similar to that of human milk and exceeds that of cow's milk [7-10].

Mare's milk is also recognized as a functional food for humans, offering health-supporting properties [8]. It may help manage or prevent conditions like human rotavirus as a means of providing passive immunity, ulcerative colitis, gastric ulcers, severe IgE-mediated cow's milk allergy [10]. It can also support the immune system during cancer treatments [11]. Both human and mare's milk serve as primary nutritional sources for newborns in their respective species [12].

Proteins in mare's milk release bioactive peptides upon digestion, which contribute to blood pressure regulation, antimicrobial action, and anti-inflammatory effects. Most of the energy in mare's milk comes from lactose (58–70 g/kg), not fat (5–20 g/kg), resulting in lower calorie content compared to cow's milk [8]. Additionally, it acts as a prebiotic, promoting healthy gut flora by encouraging the growth of beneficial bacteria and suppressing harmful ones [13].

Mare's milk is especially valuable for human health due to its content of all nine essential amino acids and a higher level of immunoglobulin A (IgA) than in human or cow's milk. IgA plays a critical role in immune defense by identifying harmful microbes [13]. It also supports skin regeneration and protec-

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tion, offering benefits for conditions like eczema, psoriasis, and atopic dermatitis [11].

However, milk composition can vary depending on factors such as the mare's age, lactation stage, season, and breed. Various breeds – including Andalusian, Arabian, Quarter Horse, Thoroughbred, Lusitano, and Shetland – show differences in milk solids, protein, fat, and lactose content [14-20].

Besides the significance of homologous transfer of passive immunity from mother to neonate, there is growing interest in the possibility of heterologous transfer – using immunoglobulins derived from one species to confer passive immunity in another. The concept of influencing the immune status of animals through vaccination against human-related diseases, and subsequently collecting those immunoglobulins from colostrum or milk, has been recognized for some time [20, 21]. This area remains a focus of ongoing research in both animal science and human medicine [21-28].

Composition of Immunoglobulins in Mare's Milk. Mare's milk predominantly contains immunoglobulins IgG, with lesser amounts of IgA and IgM. The concentration of immunoglobulins varies throughout lactation, generally peaking in early lactation and declining thereafter. Typical concentrations reported in studies are approximately 1.0–2.5 g/L for IgG, significantly higher compared to cow's milk, which contains about 0.1–0.5 g/L [23]. Species where offspring are born without antibodies and immunity is transferred through mammary secretions (such as horses, pigs, cows, and goats). The colostral IgG concentration in many other species is usually greater than 75% of the total antibody content in bovine mammary secretions, but the high IgG concentration in colostrum decreases rapidly with each subsequent milking [29].

Structural Features: The immunoglobulins in mare's milk are mainly of the polymeric form, with IgG being the most abundant, followed by dimeric IgA and pentameric IgM. These immunoglobulins are glycoproteins capable of binding to specific antigens, thereby neutralizing pathogens.

They are divided into different types, including IgM, IgA, IgG, IgE, and IgD [14]. IgG, IgA, and IgM are the most abundant types and are found in breast milk. IgM has relatively low specificity and is not very effective in primary infections. IgA is mainly found in the secretions of the mucous membranes and helps prevent infections of the mucous membranes by causing agglutination of microorganisms. IgG is the most common immunoglobulin in colostrum and bovine milk. There are several subclasses of IgG, with IgG1 and IgG2 being the main types in the bloodstream.

Monomeric immunoglobulins have a common structural molecule consisting of two identical heavy chains and two identical light chains, with a total molecular weight of about 160 kDa [22,30]. Both heavy and light chains contain constant and variable sections. These chains are connected by disulfide bonds, which give the immunoglobulin a characteristic Y-shaped structure [31]. The class of immunoglobulin depends on the number and location of disulfide bonds. Each molecule has two antigen-binding sites located in the Fab (antigen-binding fragment), which includes variable amino acid domains. The opposite end contains an Fc (constant fragment), which has a constant amino acid sequence within each subclass and determines the specific affiliation of the immunoglobulin. The Fc region is responsible for binding to Fc receptors in different types of cells.

Polymeric immunoglobulins such as IgA and IgM consist of monomeric units linked by a covalent bond to an attached (J) chain [31,32]. As a result, dimeric forms of IgA and pentameric forms of IgM are formed. The J-chain bond also gives them certain characteristics, such as a large number of antigen-binding sites (high valence), which allows these immunoglobulins to bind bacteria effectively; a limited ability to activate the complement system, which helps prevent inflammation; and a strong affinity for the polymer immunoglobulin receptor (pIgR). This receptor facilitates the transport of IgA and IgM through epithelial cells to mucous secretions such as milk [33].

Factors Influencing Content: The immunoglobulin profile is affected by lactation stage, mare's health, diet, and environmental conditions. For example, colostrum, the first milk postpartum, contains the highest immunoglobulin concentrations.

Milk immunoglobulins come from both systemic and local resources. For example, IgG comes from blood serum [23]. Plasma IgG-producing cells are present in breast tissue, but the IgG content in colostrum is lower compared to its amount in blood. Colostrum and milk contain secretory immunoglobulins (sIgA and SIGMA), which are produced by plasma cells located in the mammary gland. Lymphocytes from the GALT system (intestinal-associated lymphoid tissue) migrate to the mammary gland, providing a direct link between the effect of antigens on the immune system of the mother's mucosa and the secretory set of breast immunoglobulins. This means that colostrum and milk from non-immunized cows may contain antibodies specific to pathogens that the

intestines and other mucous membranes of the newborn may encounter. These observations support the idea that cow colostrum can provide passive immune protection against human pathogens.

The immune link between intestinal lymphoid tissue (GALT) and the mammary gland is particularly interesting in relation to breast milk, where the main immunoglobulin is secretory IgA (sIgA), which is one of the key factors underlying the importance of breastfeeding [10].

Transepithelial transport of IgA and IgM through breast epithelial cells occurs through the polymer immunoglobulin receptor (pIgR), which binds dimeric IgA and pentameric IgM in mucosal tissues [39]. The polymeric nature of IgA and IgM is determined by their binding to the J-chain peptide [33]. Only IGA or Igg containing the J-chain have a high affinity for pIgR [40,41].

Isolation of immunoglobulins. In the milk processing, immunoglobulins are also subjected to processing – heating, exposure to acids, high pressure – as a result of which their structure and biological activity change. The methods used for the concentration or isolation of immunoglobulins are classical for the study of proteins and include salt precipitation, column chromatography [45]. Affinity chromatography methods are used to determine IgG, such as lectin-based methods [46], column chromatography of proteins A or G [47, 48], as well as recently developed methods including immobilization of protein A/G on electrospinning membranes [49], metal chelation chromatography [50, 51] and adsorption with using microparticles of polyanhydride are used [52]. Various methods for detecting and quantifying IgG include radial immunodiffusion [53], enzyme immunoassay (ELISA) [54] and newer methods such as enzyme immunoassay using heat [55] and sensors based on surface plasmon resonance [56].

Digestive enzymes action. Immunoglobulins are generally more resistant to digestion in the gastrointestinal tract than other milk proteins; for example, caseins are fermented in the stomach, which prolongs their presence, while whey proteins such as α-lactalbumin are digested quickly and β-lactoglobulin is digested more slowly. Pepsin, the main protease of the stomach, cleaves IgG into the fragment F(ab')2, which preserves two antigen-binding sites [31,57]. The activity of antibody fragments has been studied for therapeutic use [58]. Pancreatic proteases additionally break down immunoglobulins in the small intestine. The sensitivity of immunoglobulin subclasses to the action of proteolytic enzymes differs. Trypsin cleaves bovine IgG1 to a greater extent than IgM, while chymotrypsin cleaves IgM to a greater extent than IgG [59]. Bovine IgG1 is more sensitive to pepsin than IgG2, and IgG2 is more vulnerable to trypsin digestion [60]. IgG digestion in the intestine is the slowest among whey proteins, and the newborn receives fewer amino acids [61]. In vitro studies of the intestinal contents of young lambs have shown that IgA is more resistant to digestion than IgG [25].

The cleavage of immunoglobulins proceeds throughout the gastrointestinal tract [62]. In adults who consume bovine serum, about 59% of IgG and IgM are excreted from the jejunum, while only 19% are excreted from the ileum [62]. These indicators are comparable to the rate of digestion of milk proteins in adults, which are approximately 42% absorbed in the jejunum and 93% in the ileum [63], which emphasizes the relative resistance of immunoglobulins to destruction in the gastrointestinal tract. In infants who were fed bovine immunoglobulin products, about 10% of ingested IgG is found in the feces, while in adults less than 4% of ingested IgG is found in the feces [64]. Encapsulation of immunoglobulin preparations can significantly increase IgG excretion in feces, although only low levels are detected in the ileum of adults [65].

The pH of milk fluctuates during the calving period, decreasing to about 6.4, and then rising within a few days to about 6.6–6.9, which is typical for mature milk [66]. Thus, colostrum is slightly more acidic than mature milk. The effect of pH on the stability of immunoglobulins has been studied in a number of papers [67-70]. It was found that bovine IgG remains stable for several hours at a temperature of 37°C between pH 6 and 7, but decreases significantly at pH < 3 or ≥ 10 [67,68]. Acidic or alkaline conditions, especially at higher temperatures, can further destabilize IgG [69,70]. Emulsification can protect IgG from extreme pH values and proteolytic degradation, although homogenization and ultrasound treatment can reduce the residual IgG content due to shear stress [68].

Effects of heat treatment. Immunoglobulins are sensitive to high temperatures. Exposure to a temperature of 75°C can reduce the level of detectable bovine IgG by 40% within five minutes, and at a temperature of 95°C, IgG is completely denatured within 15 seconds [68]. Heating causes conformational changes that impair the antigen binding ability [69,71,72], and the antigen binding region is particularly thermolabile. Although heat treatment reduces the IgG content in colostrum, the rate of this decrease is lower than that of isolated IgG. The addition of

protectors such as sugar or glycerin can improve IgG stability when heated [73].

Many milk processing techniques involve heat treatment of colostrum, milk, or whey. Among the main immunoglobulin types in cow's milk, IgG is the most resistant to heat, while IgM is the most sensitive [74]. Standard pasteurization methods, such as those used in commercial milk and skim milk powder, preserve between 25% and 75% of the IgG found in raw milk. In contrast, milk processed using ultra-high temperature (UHT) techniques contains very little detectable IgG [75]. Despite this, antigen-specific IgG remains relatively stable under regular pasteurization conditions compared to UHT-treated milk or infant formulas made from cow's milk, which undergo more intense heat processing [76].

High-pressure processing is yet another non-thermal approach that can inactivate microbes and certain enzymes, thereby increasing product shelf life [77]. To effectively inactivate bacterial spores, high-pressure treatment must be paired with moderate heat [78]. Depending on the specific conditions, this method can lead to partial or significant loss of IgG activity in colostrum or other IgG-rich fluids [79]. However, when applied to human breast milk, high-pressure processing has shown minimal effects on IgA content [80].

Biological activities of Immunoglobulins. Several risk factors were significantly associated with foal serum IgG and mare colostrum Brix (%) in the Gallacher K. et all work. Foal serum IgG concentration was associated with colostrum Brix %, year of birth and foal birthweight. Mare colostrum IgG concentration was significantly associated with foal serum IgG concentration. The 112 colostrum samples with low Brix (<20%), 56 of these resulted in foals with serum IgG concentrations ≤8 g/L (indicating partial or complete FTPI), which suggests that further high-quality colostrum supplementation for these foals needs to happen more promptly in practice. [81]

A review of the literature showed that several constituents in mare's milk may have potential antiviral effects. Proteins of the innate immune system (lysozyme, lactoperoxidase, LF), specific immunoglobulins (IgM, IgG, and secretory IgA), lipid components, cytokines or prostaglandins help in the protection [82]

Supplementation of mare's milk has been shown to aid in the recovery of gut microbiota following intrapartum and postnatal antibiotic therapy by reducing antibiotic resistance gene load and through pre/probiotic and immunomodulatory effects. Antimicrobial and antiviral activity of mare's milk is associated with a high content of lysozyme, immunoglobulins, lactoperoxidase and lactoferrin [83,84]. Antiviral mechanisms include increased production of macrophages, increased phagocytosis, elevated production of differentiation cluster-positive IgG and IgA immunoglobulins, as well as cytokines. Mare's milk can act as an anti-inflammatory agent, reducing the expression of IL-6, IL-1, TNF-α, and γ-interferon [85,86,87]

M. Jordana Rivero et all. studied the nutritional composition, fatty acid profile, and IgG concentration of the milk produced by Chilean Corralero horse (CCH) mares from breeding farms located in southern Chile . Immunoglobulin G concentration was only affected by dietary factors and pasture composition rather than maternal parity or other known factors [88].

In our study was shown the potential bioactivity, including allergenicity, toxicity, and physicochemical properties, as well as the applicability of 56 peptides from the most active fractions of lactoferrin (LF) isolated from equine milk hydrolysate, it was determined using the Peptide Ranker online database (http://distilldeep.ucd.ie/PeptideRanker/). The studied peptides were classified as cationic (13), anionic (23), and neutral (20). The findings revealed that only the cationic and neutral peptides demonstrated significant biological activity (>0.75). Furthermore, peptide bioactivity was positively correlated with phenylalanine content. These research findings can significantly contribute to the MS-based proteomics of equine milk LF and shed light on the composition of its bioactive peptides. Further research is required to comprehensively investigate the biochemical nature and pathways of bioactive peptides responsible for the antimicrobial and antioxidant properties of LF from equine milk [89]. The products of Lactoferrin hydrolysis by trypsin contained polymeric immunoglobulin receptor, wich was confirmed at LC-MS/MS analysis.

Conclusion

Mare's milk is a unique natural source of biologically active immunoglobulins with significant therapeutic and prophylactic potential. Due to the high content of IgG, IgA, and sIgA, as well as their connection with other immunoactivity components (such as lactoferrin and lysozyme), it demonstrates pronounced antimicrobial, antiviral, and immunomodulatory properties.

Research confirms that mare's milk immunoglobulins are able to: enhance the protection of mu-

cous membranes (gastrointestinal tract, respiratory tract) due to interaction with Fc receptors; suppress pathogens by neutralizing toxins, agglutinating bacteria and blocking viral adhesion; controlling inflammatory processes, reducing the risk of allergies and autoimmune reactions.

An important advantage of mare's milk is its hypoallergenicity and high digestibility, which makes it a promising alternative to cow's milk, especially in baby and therapeutic nutrition. Prospects for further research are related to the development of immunoenriched products (mixtures, fermented drinks) based on mare's milk, the use of Ig in biomedicine, the creation of drugs for the correction of microbiota, and the prevention of infections. Also, the optimization of immunoglobulin isolation technologies to increase their stability and bioavailability.

Thus, mare's milk is not only a valuable food product, but also a multifunctional biological system that opens new opportunities for nutrition, preventive, and clinical medicine. Further study of its components will expand the scope of application in personalized nutrition and biotherapy.

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Conflict of interest

All authors are aware of the article's content and declare no conflict of interest.

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