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Milk and dairy products as a source of antiviral compounds[1]

Mleko i produkty mleczne jako źródło związków przeciwwirusowych

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Abstract

Milk and dairy products are a source of numerous compounds exhibiting scientifically proven biological activity, including proteins, such as immunoglobulins, lactoferrin, lactoperoxidase and lysozyme. This activity is multifaceted, with antimicrobial (antibacterial, antiviral and antifungal) and immunomodulatory effects. The content of these proteins in the diet is one of the factors determining a normal immune response. Therefore, the aim of the study was to review the literature on this subject and present these properties. Lactoferrin has been found to be the milk protein exhibiting the highest antiviral activity. By binding and sequestering iron, it removes this element from the growth environment of microorganisms. Clinical trials have shown it to be effective in inhibiting infection with the hepatitis B and C viruses (HBV and HCV), herpes simplex virus 1 and 2, human immunodeficiency virus (HIV), human cytomegalovirus, human papilloma virus (HPV), enteroviruses, adenoviruses, influenza viruses, parainfluenza viruses, and rotaviruses, the most important aetiological agent of acute diarrhoeal disease, which is one of the major causes of mortality in infants and young children in developing countries. Furthermore, it has been found to act synergistically with antiviral drugs, including interferon, acyclovir and cidofovir, allowing the doses of drugs with high toxicity to be reduced. Moreover, peptides derived from lactoferrin, such as lactoferrampin and lactoferricin, are used in medicine as protection against viruses. The use of immunoglobulin-based supplements has also been shown to reduce the incidence of diarrhoea induced by rotaviruses in infants and children up to four years of age. In addition, lactoperoxidase inactivates HIV 1 and poliovirus. Recent years have

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seen a rapid increase in the number of viral infections, which of course is due to the virus SARS-CoV-2. It has been demonstrated that the immunopathology associated with the virus may be inhibited by certain milk proteins and probiotic strains of *Lactobacillus* and *Bifidobacterium*. Trials by the New Zealand pharmaceutical manufacturer Quantec showed that a protein complex containing lactoferrin and lactoperoxidase, obtained from fresh pasteurized cow milk, may protect human cells against COVID-19. The patented defence protein IDP exhibits anti-inflammatory, antioxidant and antimicrobial activity. To conclude, the content of these antiviral proteins in milk and dairy products was assessed in the study. Milk and dairy products are readily available, and the scientifically proven properties of milk proteins should encourage their inclusion in the diet.

Keywords

milk proteins, lactoferrin, lysozyme, immunoglobulins, antiviral activity

Streszczenie

Mleko i produkty mleczne są źródłem wielu związków wykazujących naukowo udowodnioną aktywność biologiczną, w tym białek, takich jak immunoglobuliny, laktoferyna, laktoperoksydaza i lizozym. Ta aktywność jest wielopłaszczyznowa, ma działanie przeciwdrobnoustrojowe (przeciwbakteryjne, przeciwwirusowe, przeciwgrzybicze) i immunomodulujące. Zawartość tych białek w diecie jest jednym z czynników warunkujących prawidłową odpowiedź immunologiczną. Dlatego celem pracy było dokonanie przeglądu literatury przedmiotu i przedstawienie tych właściwości. Stwierdzono, że laktoferyna jest białkiem mleka wykazującym najwyższą aktywność przeciwwirusową. Wiążąc i sekwestrując żelazo, usuwa ten pierwiastek ze środowiska wzrostu mikroorganizmów. Badania kliniczne wykazały, że jest skuteczny w hamowaniu zakażenia wirusami zapalenia wątroby typu B i C (HBV i HCV), wirusem opryszczki pospolitej 1 i 2, ludzkim wirusem niedoboru odporności (HIV), ludzkim wirusem cytomegalii, ludzkim wirusem brodawczaka (HPV), enterowirusami, adenowirusami, wirusem grypy, wirusem paragrypy i rotawirusami, stanowi ponadto ważny czynnik etiologiczny ostrej biegunki, która jest jedną z głównych przyczyn śmiertelności niemowląt i małych dzieci w krajach rozwijających się. Ponadto stwierdzono, że działa synergistycznie z lekami przeciwwirusowymi, w tym interferonem, acyklowirem i cydofowirem, umożliwiając zmniejszenie dawek leków o wysokiej toksyczności. Ponadto peptydy pochodzące z laktoferyny, takie jak laktoferrampina i laktoferryna, są stosowane w medycynie jako ochrona przed wirusami. Wykazano również, że stosowanie suplementów na bazie immunoglobulin zmniejsza częstość występowania biegunki wywoływanej przez rotawirusy u niemowląt i dzieci w wieku do czterech lat. Ponadto laktoperoksydaza inaktywuje HIV 1 i wirusa polio. W ostatnich latach nastąpił szybki wzrost liczby infekcji wirusowych, co jest oczywiście spowodowane wirusem SARS-CoV-2. Wykazano, że immunopatologia związana z wirusem może być hamowana przez niektóre białka mleka i probiotyczne szczepy *Lactobacillus* i *Bifidobacterium*. Badania nowozelandzkiego producenta farmaceutycznego Quantec wykazały, że kompleks białkowy zawierający laktoferynę i laktoperoksydazę, pozyskiwany ze świeżego pasteryzowanego mleka krowiego, może chronić ludzkie komórki przed COVID-19. Opatentowane białko obronne IDP wykazuje działanie przeciwzapalne, przeciwutleniające i przeciwbakteryjne. Podsumowując, w badaniach oceniano zawartość tych białek przeciwwirusowych w mleku i produktach mlecznych. Mleko i produkty mleczne są łatwo dostępne, a potwierdzone naukowo właściwości białek mleka powinny zachęcać do ich włączenia do diety.

Słowa kluczowe

białka mleka, laktoferyna, lizozym, immunoglobuliny, aktywność przeciwwirusowa

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Introduction

Milk and its products belong to one of the food groups that should be included in the daily diet of every human being. They are a source of many bioactive compounds, including proteins such as immunoglobulins, lactoferrin, lactoperoxidase and lysozyme, with immunomodulating properties[2,3,4,5,6]. Due to the dynamic turnover of recent medical events, i.e. the emergence of the SARS-CoV-2 virus, a wide group of specialists and scientists from various fields from around the world are seeking an antidote to the coronavirus (COVID-19)[7]. According to the study of Watson *et al.* (2020)[8], proteins and peptides, including those from milk, aroused the greatest interest among researchers, because of their antiviral properties.

The aim of the study was to review the literature on the antiviral properties of compounds contained in raw milk and dairy products.

Milk proteins

The discussed raw material and its products are a valuable source of proteins and peptides[9].

Casein fractions constitute as much as 80% of cow's milk proteins. Among them, fractions α (αs1, αs2), β and κ can be distinguished. Particularly important in the context

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of health is β-casein, which has analgesic properties, but also peptides that prevent hypertension[10]. Moreover, casein phosphopeptides have the ability to increase the production of immunoglobulin A and interleukin-6[11]. Moreover, research in recent years has shown that β-casein micelles have the ability to transport nutraceuticals[12,13].

The main components of whey proteins include α-lactalbumin, β-lactoglobulin, bovine serum albumin, lactoferrin, immunoglobulins, lactoperoxidase, glycomacropeptides and lysozyme[14,15]. They are a source of bioactive peptides easily accessible to the body, thus the body can easily acquire them from dairy products during digestion through enzymatic hydrolysis, but also from the products of fermentation processes[16].

Antiviral properties of milk proteins and peptides

Milk and dairy products are among foods, whose main components are compounds showing, i.a. antiviral effects. Among milk proteins, casein, whey proteins and individual peptides derived from them are responsible for the immune response of the body[17,18,19].

Most milk proteins, especially lactoferrin and certain peptides, exhibit antiviral properties (Table 1). They have the ability to bind to the surface of the virus, inhibit

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replication of its genome or protein synthesis. Binding of milk proteins to the structure of the virus inhibits its division, which is a protective element for the human system[20,21].

Table 1. Antiviral properties of milk and dairy products[22,23,24]

Milk proteins or their peptides	Virus type	Protein function
Lactoferrin, lactoperoxidase	Herpes simplex virus	Binding to the cellular receptor (heparan sulfate) of the virus, preventing its further divisions
Lactoferrin	Human hepatitis C virus	Binding of milk protein to the virus envelope protein
Lactoferrin, lactoferricin	Human cytomegalovirus	Antiviral activity against pathogens through the process of cellular interference
Lactoferrin, lactoperoxidase	Human immunodeficiency virus	Impaired absorption and multiplication of the virus
Lactoferrin, κ-casein fraction	Influenza virus	Binding to virus surface spike proteins
Lactoferrin	Hantavirus	Limiting virus replication
Lactoferrin	Human papillomavirus	Heparan sulfate binding
Lactoferrin, human lactadherin, mucin	Rotavirus	Preventing erythrocyte aggregation
Lactoferrin	Vesicular stomatitis virus	Stimulation of interferons to inhibit viral division
Lactoferrin	Coxsackie virus	Competing with the virus for membrane receptors
β-lactoglobulin, α-lactalbumin	Adenovirus	Competing for membrane receptor binding sites

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B-lactoglobulin accounts for more than half of all whey proteins. It has the ability to bind vitamin A and modulate lymphatic response[25]. In addition, this protein is resistant to hydrochloric acid which allows to use it in drug envelopes, including antiviral ones[26].

A-lactalbumin constitutes the second largest amount of whey protein. It has antioxidant and antiradical properties, i.e. it reduces iron (FRAP) and chelates iron (FCA)[27]. A-La exhibits antibacterial and antifungal[28] activity, and inhibits proteases and integrases of HIV-1, as well as its methylated form of herpes simplex virus (HSV)[29].

Bovine serum albumin (BSA) is an excellent ligand carrier. It is presumed that due to its drug-albumin binding capacity, BSA can form complexes with HIV protease inhibitors, which in turn will affect the bioavailability of the target drug in the body[30,31].

Bovine lactoferrin (bLf), also known as lactotransferrin, is the key whey protein in terms of antiviral activity[32]. It is a glycoprotein with outstanding iron-binding capacity. Due to the presence of trypsin and similar enzymes, lactoferrin exhibits incredible degradation resistance depending on the degree of iron saturation[33]. Lactoferrin exhibits immunostimulatory and anti-inflammatory properties thanks to the inhibition of free iron utilization by bacteria[34]. Compounds such as lactoferrin, lactadherin and glycomacropeptide interfere with the multiplication of some viruses by binding to viral receptor

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sites *in vitro* by attaching directly to viral particles or blocking viral receptors[35]. Furthermore, Lf regulates humoral and cellular immune responses. It promotes the transformation of precursor T cells into T helper lymphocytes and influences the B cell maturation. Additionally, Lf helps regulate cell growth and differentiation and shows antioxidant properties[36]. Due to these abilities, bLf shows protective properties for the organism against many viruses. One of them is the acquired immunodeficiency virus (HIV) – Table 1. Lf inhibits the activity of reverse transcriptase, protease and integrase, HIV-1 enzymes which allow its replication in the cell[37]. Human papillomavirus (HPV) is another virus that is counteracted by lactoferrin. This virus can use heparan sulfate on the surface of a target cell as a receptor that Lf blocks by binding to it. Hadidi *et al.* (2018)[38] showed that transferosomal bLf may be an innovative and non-invasive method of treating HPV infections. Research proves that lactoferrin prevents infection with human hepatitis C (HCV) and human hepatitis B[39]. Recently, there have also been many reports regarding human noroviruses (HuNoVs). Studies have indicated that bovine lactoferrin inhibits viral replication in vitro and induces an innate human interferon response[40]. Cytomegalovirus is a β-herpes virus that has a limited species range and a slow replication cycle. Research has indicated that lactoferrin blocks the virus from attaching to the host cell, thereby inhibiting its multiplication[41]. Recent studies have shown that lactoferrin also shows protective properties against influenza A infection. It interacts with influenza A hemagglutinin, thereby preventing infection by different H1 and H3 virus subtypes[42]. Over the last year, there have also been many scientific reports regarding the

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possible beneficial effect of lactoferrin on inhibiting the development of coronaviruses, including SARS-CoV-2[43]. The consequences of SARS-CoV-2 infection are long-term changes in the neurological, digestive, respiratory, immune and blood systems[44,45,46]. Recently, SARS-CoV-2 has been shown to have a high affinity for ACE2 and heparan sulfate proteoglycan (HSPG), serving as a connection factor with host cells[47,48]. Research by the New Zealand pharmaceutical manufacturer Quantec demonstrated that a protein complex containing lactoferrin and lactoperoxidase, obtained from fresh pasteurized cow's milk, could protect human cells against COVID-19.

Bovine immunoglobulins (bIg), mainly the IgG isotope, two subclasses – IgG1 and IgG2, have the ability to recognize and eliminate foreign pathogens. Due to the specificity of these proteins, the first reports of their antiviral properties appeared in the 1970s[49]. Moreover, bIg was shown to inhibit the multiplication of enteropathogens in the gastrointestinal tract, reduce the risk of bacterial infections and autoimmune diseases[50].

Lactoperoxidases (LPOs) are another equally important milk component. The main task of these catalysts is to decompose certain halides (bromine, iodine), consequently producing products that inhibit or inactivate bacteria. Their biological role is to protect the body against microorganisms such as viruses and to protect cells against hydrogen peroxide[51].

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In turn, lysozyme has antiviral, antibacterial and analgesic properties[52,53]. It is produced by neutrophils and macrophages and has the ability to break down murein in the cell wall of pathogens, which makes it an antimicrobial enzyme[54]. Moreover, lysozyme can regulate immune function through direct or indirect modulation of the complement system and enhance the function and proliferation of polymorphonuclear neutrophils and phagocytes[55,56].

The antimicrobial properties are also exhibited by individual milk peptides, i.e. casecidin from casein, lactoferrampin and lactoferrin or antibacterial peptides: LDT1, LDT2 S-S and LDC S-S isolated from α-lactalbumin[57,58].

Conclusions

Milk and dairy products are a valuable source of compounds with antiviral properties, mainly lactoferrin, lysozyme and lactoperoxidase, as evidenced by numerous scientific studies in this field. In the last year, it has been reported that SARS-CoV-2 virus-related immunopathology can be inhibited by milk proteins and peptides, mainly based on lactoferrin. Opportunities are seen not only in the action of single proteins, but mainly the protein complex and milk peptides. However, this requires further research.

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