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Milk Oligosaccharides and Their Biological Activities : A Review

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ABSTRACT

Milk is a nutrient-rich liquid food produced by the mammary glands of mammals. It is the primary source of nutrition needed for the proper growth and development of the neonate. Milk is a source of many bioactive components, which not only help meeting the nutritional requirements of the consumers, but also play a relevant role in preventing various disorders. In addition to being a source of proteins and peptides, milk contains complex oligosaccharides that possess important functions related to newborn's development and health. Some of the health benefits attributed to milk oligosaccharides include prebiotic probifidogenic effects, anti-adherence of pathogenic bacteria, and immunomodulation. Oligosaccharides present in milk protect infants by reducing the number of pathogen infections and promoting the development of the intestinal epithelium. Milk Oligosaccharide based modified therapeutics exhibit varied biological activity such as anti-inflammatory, anti-coagulant, anti-tumor, anti-thrombotic, anti-adhesive, anti-arthritic, immuno-stimulant, anti-cancer, anti-complementary, anti-oxidant, anti-microbial, cardio-protective and immunological activities. This review focuses on recent findings demonstrating the biological activities of milk oligosaccharides towards the prevention of diseases of the 21st century.

Keywords: Biological activity, Milk Oligosaccharides.

1. INTRODUCTION

Milk is nature's designer food to fulfil the nutritional need for the growth and development of the neonate[1]. Mammalian milk or colostrum usually contains, in addition to lactose, a variety of oligosaccharides, with about 350 of them characterized[2]. The lactose was first isolated from milk in 1633, after three hundred years, *in 1933 Polonvsky and Lespagnol* first discovered the non-lactose fraction of human milk and that component was termed as **Gynolactose**, but it is now known that this fraction consists mainly of oligosaccharides. Milk oligosaccharide was first isolated and identified by *Kuhn and coworkers during 1953-1963.* Numerous oligosaccharides have been detected in the milk or colostrums of many mammalian species other than human are domestic herbivorous animal, non-human primates, marsupials, carnivores, caprines, monotremes, equines, bovine, and marine mammals. Oligosaccharides play an essential role in many molecular process impacting eukaryotic biology and diseases and exhibit varied biological activity such as anti-tumor, immuno-stimulant, anti-cancer, anti-complementry, anti-inflammatory, anti-coagulant, hypoglycemic, anti-viral and immunological activity[3]. Due to these biological activities shown by oligosaccharides, the search of a rich source of oligosaccharide started. Medicinal and pharmaceutical researches have unrevealed the importance of these oligosaccharides and the milk of various sources, which are either used in folk medicine, or their importance is reported in ancient medicinal systems (Ayurveda and Unani). The oligosaccharides isolated from various milk sources are categorized in two classes i.e. sialylated oligosaccharide and non-sialylated oligosaccharide which have been tested for their varied biological activities. A classification of milk oligosaccharides which on the pattern of excreted oligosaccharides (Secretor/Lewis) is **pattern A** (Secretory ABH/Lewis a-b+) presence of all fucosyl-transferase and fucosylated oligosaccharides; **pattern A1** (Secretory ABH/Lewis a-b-) absence of α-1,4-fucosyl-transferase and of trifucosyl-lacto-N-exaose (TFLNH), difucosyl-lacto-N-exaose (DFLNH), lacto-N-fucopentaose II (LNFP II); **pattern B** (no secretory/Lewis a+b-) absence of α-1,2-fucosyl-transferase, 2' fucosyl-lattose (2'FL) and lacto-N-fucopentaose I (LNFP I); **pattern C** (no secretory "poor"/Lewis a-b-) absence of α-1,2 and α-1,4 fucosyl-transferase, i.e. the absence of all α-1,2- and α-1,4-fucosylated oligosaccharides. A relationship between breastfeeding and health of the infant has been noted from the times of the first recorded use of human milk substitutes, going back thousands of years. As we enter the twenty-first century, Isolation of milk oligosaccharides and its biological importance has an emerged as a vigorous and challenging research area at the interface of biology and chemistry. From medical point of view, a broad range of oligosaccharide and oligosaccharide containing moieties are act as an effective drug against most of acute and chronic diseases. There is no doubt that anti-adhesive oligosaccharides will in the near future join the arsenal of drugs for the therapy of bacterial, viral and fungal diseases and open a new search world called **"Glycopathology"**.

2. FACTORS AFFECTING BIOLOGICAL ACTIVITIES IN MILK

There are number of factors due to which different milk oligosaccharides show varied biological activities. Some of the important factors Affecting Biological Activity in milk are summarized as follows.

1. Milk oligosaccharides are non-digested due to the presence of β-glycosidic linkage. So this β-glycosidic linkage plays an important role for

its pre-biotic activity[4].

2. Oligosaccharide mimics containing galactose and fucose specifically label tumour cell surfaces and inhibit cell adhesion to fibronectin[5].
3. Supplementation of milk formula with galacto-oligosaccharides improves intestinal micro-flora and fermentation in term infants[6].
4. Galactose and sialic acid present in milk oligosaccharide are required for optimal development of the infant's brain[7].
5. N-and O-linked oligosaccharide causes the release of histamine and other mediators of the allergenic response which then lead to the development of allergenic symptoms[8].
6. Human milk oligosaccharide containing α-1,2-linked fucose inhibits the stable toxin-producing Escherichia coli in vitro, and its toxin induced secretary diarrhea in vitro and in vivo[9,10].
7. Glycoconjugate found in human milk also inhibits binding by Campylobacter jejuni in vitro and in vivo and also inhibit binding by calci-viruses in vitro[9,10].
8. Specific fucosyl oligosaccharides of human milk have been observed to inhibit specific pathogens[9,10].
9. Some important enteric pathogens, for example- rotavirus, are inhibited by human milk oligosaccharide, α-1,2-linked fucosylated oligosaccharide, probably in conjugation with other families of oligosaccharide, constitute a powerful innate immune system of human milk[9,10].
10. Presence of sialic acid in human milk serves as anti-inflammatory components and reduces platelet-neutrophill complex formation leading to a decrease in neutrophill B2 integrin expression[11].
11. Sialylated human milk oligosaccharide also inhibits binding of pathogenic strains of Escherichia coli and ulcer-causing human pathogen H. pylori[11].
12. Neutral human milk oligosaccharide may protect the intestinal tract of neonates from Vibriocholera[11].
13. The ability of rotavirus to infect MA-104 cells in culture is inhibited by human milk, and this inhibition is due to a mucin-associated 46kDa milk glycoprotein named lactadherin. Lactadherin from human milk also inhibits rotavirus (EDIM strain) gastroenteritis in mice[12].

3. BIOLOGICALLY ACTIVE MILK OLIGOSACCHARIDES FROM DIFFERENT ORIGINS

S.No.	Animal Milk	Biological Activity
1.	**Cow Milk** 	Cow milk is used for the immuno- stimulant, nourishes the body tissues, acts as natural aphrodisiac, does rejuvenation and improves intelligence, in heart diseases and leucoderma, increase breast milk in feeding mother, assists in easy movement of intestine and bleeding disorders. Cow milk oligosaccharides reduce the adhesion of enterotoxic Eschererchia coli strain of the calf[13].
2.	**Buffalo Milk** 	Buffalo milk oligosaccharide induces significant stimulation of antibody, delayed type hypersensitivity response to Sheep RBC in BALB/c mice. Buffalo Milk oligosaccharides have ability to stimulate non-immunological resistance of the host against parasitic infections[14].

3.	**Donkey Milk** 	Donkey milk oligosaccharides have ability to stimulate non-specific and specific immunological resistance[15]. The orally treated animals were recognized for a six time increase in HA titre, two times increase in PFC & DTH response.
4.	**Mare Milk** 	Mare milk oligosaccharide fractions are having multifold properties such as anti-oxidant and lipid lowering activities[16]. It also has post heparin lipolytic activity.
5.	**Sheep Milk** 	Sheep milk is a rich source of fucosylated oligosaccharides which constitute a powerful innate immune system of human. The peptides present in sheep milk have their affect in cardiovascular, nervous and immune system. Sheep milk aggravates hiccup and dyspnoea. It also eliminates pitta, kapha and fat. It also contains fucose in its oligosaccharides which causes various biological activities[17].
6.	**Goat Milk** 	Goat milk containing galacto-oligosaccharides could be recommended to decrease most of infant allergy and diseases[3].Goat milk oligosaccharides have anti-inflammatory effects in rats with trinitrobenzenesulfonic (T) acid induced colitis and may be useful in the management of inflammatory bowel disease[2]. Goat milk oligosaccharides play an important role in intestinal protection and repair after damage caused by DSS (Dextron sodium sulphate) induced colitis and their implication in human intestinal inflammation[18].

7.	**Elephant Milk** 	The elephant milk oligosaccharide fraction contained a high ratio of sialyl oligosaccharides that is significant with respect to the formation of brain components such as gangliosides of suckling calves[19].
8.	**Camel Milk** 	Camel milk oligosaccharides show potent activity against gonorrhea septic and hysteric properties[20].
9.	**Yak Milk** 	Yak milk play a very important role in traditional Tibetan medicinal system and used in enema therapy as solution along with other drugs. Yak milk oligosaccharides possess anti-hypertensive and immunomudulatory properties.
10.	**Dog Milk** 	N-acetylneuraminlactosesulphate may play an important role in the nutrition of the rat pups, which is the dominant oligosaccharide in the Dog milk[21].

4. SOME PHYSIOLOGICAL FUNCTIONS OF MILK OLIGOSACCHARIDES

(A). Milk Oligosaccharides as a Pre-biotic[22]

Breast-fed infant micro biota is rich in bifido bacteria. Herein, human milk oligosaccharides (HMOS) have ability to promote the growth of bifido bacteria and to acidify their environment. Pre-biotic are non-digestible food which beneficially affect the host by selectively affecting the growth and activity of bacteria in colon and thus improve the health of host. The human intestine lacks enzymes able to hydrolyzeβ-glycosidic linkage with exception of lactose. Thus milk oligosaccharides are considered to be indigestible which reach the colon and are utilized by health promoting colonic bacteria and known as prebiotic.

(B). Milk Oligosaccharides as Immunomodulatries[23]

Milk oligosaccharides may play a physiological role in modulating cellular adhesion in vivo. The human milk derived acidic oligosaccharide fraction is found to enhance the production of certain cytokines after long-term exposure (20d) in vitro in the CD4+ as well as in the CD8+ T-cell subfraction. Significantly oligosaccharide isolated from buffalo milk possesses high degree of immunostimulant activity and proposed to be very helpful in cure of AIDS patient.

(C). Role of Oligosaccharides in Brain Development[24]

Oligosaccharides along with lactose and sialic acid play role in postnatal brain development. Gangliosides are complex glycosphingolipids, which make up 10% of the total lipid mass in the brain and contain different numbers of negatively charged sialic acid moieties. Brain tissue is unique in that the quantity of lipid-bound sialic acid exceeds that of the protein-bound fraction. Gangliosides are hybrid molecules composed of a hydrophilic sialyl oligosaccharide and a hydrophobic ceramide portion that consists of sphingosine and fatty acids. Many newborn mammals undergo a period of rapid postnatal brain development that requires large amount of glycolipid, which are components of cell membranes of neurons and myelin. Sialic acid present in human milk also contribute to the increased concentration of NeuAc, present in cerebral and cerebellar glycoconjugates of breast fed and thus play an important role in the development of the infant brain.Since elephant milk containssialylated oligosaccharides, it plays a definite role in brain development.

(D). Effect of Milk Oligosaccharides on Mineral Absorption[25]

Several studies in animals and humans have shown positive effects of non-digestible oligosaccharides (NDO) on mineral absorption and metabolism and bone composition and architecture. These include inulin, oligo-fructose, fructo-oligosaccharides, galacto-oligosaccharides, soyabean oligosaccharide and also resistant starches, sugar alcohols and di-fructose anhydride.

(E). Milk Oligosaccharides as Tumor Marker[26]

1-Monoclonal antibodies of several tumor cell lines and carbohydrate antigens have provided evidence that membrane glycoprotein or glycolipid which may function as differentiation antigens or tumor-associate antigens occur as free oligosaccharide in human milk. 2-Two newly isolated oligosaccharides B-1 and B-2 both have the sialyl Lea and Lex or Le-1 structure respectively. 3-The sialyl- Le structure in glycolipid or glycoprotein has been defined as gastrointestinal tumor associated antigen. These structures have been found in mucin type glycoprotein and glycolipid in a variety of human cancer. Oligosaccharides having the sialyl-Lea and difucosyl Le-Le structure also occur in human milk and Lea-Lex structure exhibits high affinity to an antibody directed to a human squamous lung carcinoma.

5. CONCLUSION

In recent decades, research has progressed fast with regard to the characterization of individual milk oligosaccharide structures and patterns in milk. It is known that milk contains a broad variety of complex oligosaccharides in concentrations ranging from 10 to 20 g/l. However, the quantity of these components does not only depend on the lactational stage but is also affected by the expression of specific glycosyltransferases in the mammary gland. The large amount of N-acetylglucosamine containing oligosaccharides in milk, which may favour the growth of specific micro-organisms, is still a matter of discussion. The analysis of the genome of some strains of *Bifidobacteria* indicates their evolutionary adaptation to use specific milk components preferentially, particularly milk oligosaccharide as substrates. But even today, the bifidogenic effect of milk oligosaccharide and their direct impact on the intestinal microbiota are difficult to demonstrate in humans. The same applies to other specific in vitrofunctions of milk oligosaccharidesuch as their potential to influence inflammatory and infectious processes via inhibition of the attachment of pathogens to epithelial cells, to influence leukocyte endothelial and neutrophil platelet interactions or to affect cell recognition and cell signaling, cell adhesion or neuro development. This interesting hypothesis needs further studies, both in animals and humans regarding structure-function relations and specific metabolic aspects.

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