Bioactive nutrition

The role of biological and functional components of milk on infant development

Ryan Carvalho
Breastfeeding is the ideal way to feed an infant.

Respiratory
- Upper respiratory tract infection
- Lower respiratory tract infection
- Asthma
- RSV bronchiolitis

Gastrointestinal
- Necrotizing enterocolitis (NEC)
- Gastroenteritis
- Celiac disease
- Inflammatory bowel disease

Other
- Otitis media
- Atopic dermatitis
- Type 1 and 2 diabetes
- Obesity
- Childhood leukemia
- SIDS
Learning from mother’s milk for infant nutrition and health

Breastfeeding is associated with lower risk of:¹–³

- Respiratory and gastrointestinal infections
- Obesity and diabetes
- Possibly allergies, but needs clarification

⁴. Forest plot drawn from indicated publications

Suggests involvement of breast milk-specific components
Components of Human milk : Nutritive and Functional

- Human milk is uniquely suited to the human infant, both in its nutritional composition and in the non-nutritive bioactive factors that promote survival and healthy development.
- Varied bioactive factors, which include cells, anti-infectious and anti-inflammatory agents, growth factors, and prebiotics.
- COLOSTRUM
  - Colostrum, produced in low quantities in the first few days postpartum, is rich in immunologic components such as secretory IgA, lactoferrin, leukocytes, as well as developmental factors such as epidermal growth factor.
  - lactose, indicating its primary functions to be immunologic and trophic rather than nutritional.
Functional benefits of bioactive components in milk

These components provide enzymatic activity; inhibit proteolytic enzymes; stimulate neonatal intestinal, immune, and brain development; shape the microbiome; and protect the infant from infection.

The diversity of human milk proteins differentiated and significantly wider. Some of these differentially expressed proteins with greater abundance in human milk, including lactoferrin, polymeric immunoglobulin receptor, alpha-1antichymotrypsin, vitamin D-binding protein, and haptocorrin.

Importantly, the functions of proteins that were more abundant in human milk were associated with development of the gastrointestinal tract, the immune system, and the brain.
Nutrition components of human milk

- US, Danish, Australian cohort
- Variability
  - Maternal factors
  - Duration post partum
  - Gestational age
  - Collection factors

<table>
<thead>
<tr>
<th>Author (year), n</th>
<th>Protein Mean (± 2 SD)</th>
<th>Fat Mean (± 2 SD)</th>
<th>Lactose Mean (± 2 SD)</th>
<th>Energy Mean (± 2 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term infants, 24-hour collection, mature milk</td>
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<tr>
<td>Nunnosen et al (1991), n=58</td>
<td>1.2 (0.9, 1.5)</td>
<td>3.6 (2.2, 5.0)</td>
<td>7.4 (7.2, 7.7)</td>
<td>70 (57, 83)</td>
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<td>Donor human milk samples</td>
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<td>Wojcik et al (2009), n=115</td>
<td>1.2 (0.7, 1.7)</td>
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<td>7.8 (6.0, 9.6)</td>
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<td>Michaelien et al (1990), n=2553</td>
<td>a 0.9 (0.6, 1.4)</td>
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<td>a 7.2 (6.4, 7.6)</td>
<td>a 67 (50,115)</td>
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<td>Representative values of mature milk, term infants</td>
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<td>Reference standard</td>
<td>0.9</td>
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<td>Preterm, 24-hour collection, first 8 weeks of life</td>
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<td>Bauer &amp; Geerts (2011)</td>
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<td>Born ≤29 weeks, n=52</td>
<td>2.2 (1.3, 3.3)</td>
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<td>7.6 (6.4, 8.8)</td>
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<td>Born 32-33 weeks, n=20</td>
<td>1.9 (1.3, 2.5)</td>
<td>4.8 (2.8, 6.8)</td>
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<td>Preterm donor milk</td>
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<td>Hartmann (2012), n=47</td>
<td>1.4 (0.8, 1.9)</td>
<td>4.2 (2.4, 5.9)</td>
<td>6.7 (5.5, 7.9)</td>
<td>70 (53, 87)</td>
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Macronutrient (g/dL) and energy (kcal/dL) composition of human milk from specified references.
## More recent breast milk composition

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<tr>
<th>Author (year), n, location</th>
<th>Protein (g/100 mL) mean ± S.D.</th>
<th>Lipids (g/100 mL) mean ± S.D.</th>
<th>Lactose (g/100 mL) mean ± S.D.</th>
<th>Energy (kcal/100 mL) mean ± S.D.</th>
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<td><strong>Term infants, mature milk, single breast full collection</strong></td>
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<tr>
<td>Thakkar et al., (2013), + Lee et al., (2016) 50, Singapore</td>
<td>1.38 ± 0.30</td>
<td>4.65 ± 2.10</td>
<td>6.44 ± 0.69</td>
<td>70.24 ± 22.00</td>
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<td>Yang et al., (2014), 540, China</td>
<td>1.10 ± 0.20</td>
<td>3.50 ± 1.60</td>
<td>7.20 ± 0.30</td>
<td>62.00 ± 14.00</td>
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<td>Fischer Fumeaux et al., (2010) 25, Switzerland</td>
<td>1.70 ± 0.30</td>
<td>1.65 ± 0.60</td>
<td>5.80 ± 0.10</td>
<td>53.10 ± 8.80</td>
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<td><strong>Preterm infants, mature milk, single full breast collection</strong></td>
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<tr>
<td>Fischer Fumeaux et al., (2010) 25, Switzerland</td>
<td>1.50 ± 0.50</td>
<td>1.63 ± 0.53</td>
<td>5.90 ± 0.20</td>
<td>58.70 ± 10.20</td>
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</table>
Nutritive components of human milk

- The most abundant proteins are casein, α-lactalbumin, lactoferrin, secretory immunoglobulin IgA, lysozyme, and serum albumin.
- Human milk fat is characterized by high contents of palmitic and oleic acids, the former heavily concentrated in the 2-position and the latter in the 1- and 3-positions of the triglycerides. The fatty acid profile of human milk varies in relation to maternal diet, particularly, in the long chain polyunsaturated fatty acids (LCPUFAs). LCPUFA intake in the Western world is skewed towards the omega-6 fatty acids, with sub-optimal intake of omega-3 fatty acids.
- The concentration of lactose in human milk is the least variable of the macronutrients, but higher concentrations of lactose are found in the milk of mothers producing higher quantities of milk.
- Micronutrients vary in human milk depending on maternal diet and body stores including vitamins A, B1, B2, B6, B12, D, and iodine. Regardless of maternal diet, Vitamin K is extremely low and Vitamin D also occurs in low
Bioactive components of human milk

- Bioactive components of food are defined as elements that “affect biological processes or substrates and hence have an impact on body function or condition and ultimately health”
  - some are produced and secreted by the mammary epithelium,
  - some are produced by cells carried within the milk,
  - others are drawn from maternal serum and carried across the mammary epithelium by receptor-mediated transport.
### Components of Human milk : Functional

<table>
<thead>
<tr>
<th><strong>Oligosaccharides &amp; glycans</strong></th>
<th><strong>HMOs</strong></th>
<th>Prebiotic, stimulating beneficial colonization and reducing colonization with pathogens; reduced inflammation</th>
<th>Newburg, 2005; Morrow, 2005; DeLeo, 2012; Marcoba, 2012; Kunz, 2012; Kusak, 2012; Bode, 2012</th>
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<tbody>
<tr>
<td><strong>Gangliosides</strong></td>
<td></td>
<td>Brain development, anti-infectious</td>
<td>Wang, B, 2012</td>
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<td><strong>Glycoaminoglycans</strong></td>
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<td>Anti-infectious</td>
<td>Coppa, 2012; Coppa, 2011</td>
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<td><strong>Macrons</strong></td>
<td>MUC1</td>
<td>Block infection by viruses and bacteria</td>
<td>Ruvooen-Closet, 2006; Liu, 2012; Sande, 2009; Saeland, 2009; Yolken, 1992</td>
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<tr>
<td></td>
<td>MUC4</td>
<td>Block infection by viruses and bacteria</td>
<td>Ruvooen-Closet, 2006; Liu, 2012; Q.</td>
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**Hormones**

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<tr>
<th><strong>Calcitonin</strong></th>
<th>Development of mural network</th>
<th>Srau, 2002; Wockley, 2012</th>
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<tr>
<td><strong>Somatostatin</strong></td>
<td>Regulation of gastric epithelial growth</td>
<td>Cho, 1999; Ranz, 1999; Guerra, 1996</td>
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</table>

**Anti-microbial**

<table>
<thead>
<tr>
<th><strong>Lactoferrin</strong></th>
<th>Acute phase protein, chelates iron, anti-bacterial, anti-oxidant</th>
<th>Adsmski, 2012; Sherman, 2004; Mazzone, 2009; Hiortan, 2008; Bucșogeanu, 2007; Valenta, 1999</th>
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<tr>
<td><strong>Lactadherin/ MFC E8</strong></td>
<td>Anti-viral, prevents inflammation by enhancing phagocytosis of apoptotic cells</td>
<td>Ghibbi, 1999; Kurokura, 2012; Aaziz, 2010; Shi, 2004; Chopes, 2013; Bologh, 2013; Peterson, 1999; Newburg, 1998; Bui, 2012; Mafa, 2006; Kurnar, 2009; Mafa, 2009; Wu, 2012; Matsumi, 2011; Salvatore, 2015</td>
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**Metabolic hormones**

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<th><strong>Adiponectin</strong></th>
<th>Reduction of infant BMI and weight, anti-inflammatory</th>
<th>Martin, 2006; Newburg, 2010; Wao, 2009; Wao, 2012; Lay, 2013; Doudna 2016; Ozers, 2012; Savino, 2008; Weyrauch, 2006</th>
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<tr>
<td><strong>Leptin</strong></td>
<td>Regulation of energy conversion and infant BMI</td>
<td>Savino, 2008; Savino, 2012a; Savino, 2012b; Fredon, 2009; Weyrauch, 2006</td>
</tr>
<tr>
<td><strong>Ghrelin</strong></td>
<td>Regulation of energy conversion and infant BMI</td>
<td>Savino, 2008; Savino, 2012; Doudna 2010</td>
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</table>

**Wyeth Nutrition Science Center**

Human Milk: Nutrients and Bioactive Factors
## Components of Human milk: Functional

<table>
<thead>
<tr>
<th>Components</th>
<th>Function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>Protection against infection, T-cell activation</td>
<td>Jarvenen, 2003; Yagi, 2010; Inshikawa, 2003</td>
</tr>
<tr>
<td>Stem cells</td>
<td>Regeneration and repair</td>
<td>Indumathi, 2012</td>
</tr>
<tr>
<td>IgA and IgG</td>
<td>Pathogen binding inhibition</td>
<td>Van de Peer, 2012; Cassan, 1999; Brandtzaeg, 2010; Recknor, 2007; Gaedke, 2009; Harley, 2011; Agarwal, 2010; Castellote, 2011</td>
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<tr>
<td>IgG</td>
<td>Anti-microbial, activation of phagocytes (IgG1, IgG2, IgG3); anti-inflammatory, response to allergens (IgE)</td>
<td>Cassan, 1999; Agarwal, 2010</td>
</tr>
<tr>
<td>IgM</td>
<td>Apoptosis, complement activation</td>
<td>Brandtzaeg, 2010; Van de Peer, 1993; Agarwal, 2010</td>
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<td>Cytokines</td>
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<tr>
<td>IL-6</td>
<td>Stimulation of the acute phase response, B-cell activation, pro-inflammatory</td>
<td>Ustunoglu, 2001; Meki, 2003; Menon, 2012; Agarwal, 2010; Castellote, 2011</td>
</tr>
<tr>
<td>IL-7</td>
<td>Increased thymic size and output</td>
<td>Aspinall, 2011; Nguyen, 2004</td>
</tr>
<tr>
<td>IL-8</td>
<td>Recruitment of neutrophils, pro-inflammatory</td>
<td>Cimai, 2003; Ustunoglu, 2005; Meki, 2003; Machocharwani, 2005; Machocharwani, 2005; Manti, 2012; Agarwal, 2010; Castellote, 2011; Mehta, 2011</td>
</tr>
<tr>
<td>IL-10</td>
<td>Regulating Th1-type inflammation, induction of antibody production, facilitation of tolerance</td>
<td>Mehta, 2005; Agarwal, 2010; Castellote, 2011; Mehta, 2011</td>
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<td>INFγ</td>
<td>Pro-inflammatory, stimulates Th1 response</td>
<td>Holc, 2012; Agarwal, 2018</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Anti-inflammatory, stimulation of T cell phenotype switch</td>
<td>Penna, 2010; Kalinowski, 1999; Satte, 1999; Nakamura, 2009; Letterman, 1994; Anso, 2007; Ozawa, 2009; Dassen-Hogendoorn, 2000; Vaidhavan, 2008; Vaidhavan, 2010; Penna, 2003; Vaidhavan, 2010; Okumoto, 2005; Penna, 2006; Peroni, 2009; McPherson, 2011; Eweschnik, 2011; Castellote, 2011</td>
</tr>
<tr>
<td>TNFα</td>
<td>Stimulates inflammatory immune activation</td>
<td>Rudloff, 1992; Ustunoglu, 2005; Ebrahimi, 2005; Meht, 2003; Agarwal, 2010; Castellote, 2011</td>
</tr>
</tbody>
</table>

### Chemoattractants
- **GM-CSF**: Trophic factor in immune cells.
- **MIF**: Macrophage Migratory Inhibitory Factor; Promotes macrophage movement, increases anti-pathogen activity of macrophages.
- **TNFRI and TNFII**: Inhibition of TNFs, anti-inflammatory.

### Growth Factors
- **EGF**: Stimulation of cell proliferation and maturation.
- **HB-EGF**: Protective against damage from hypoxia and ischemia.
- **VEGF**: Promotion of angiogenesis and tissue repair.
Factors that influence bioactive components in breast milk

**Maternal factors**
- Maternal genotype
- Maternal diet
- Maternal physiologic state
- Mode of delivery
- Infant gestational age
- Lactation stage
- Underlying medical conditions
- Maternal medication use
- BMI maternal

**Infant clinical parameters**
- Infectious morbidity
- Allergies
- Growth and body composition
- Cognitive development
- Gastrointestinal developments
- Immune system maturation
- Metabolism

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*Quantity  Quality  Composition*
Bioactive functions of human milk components.

• Intestinal maturation, and repair: Epidermal growth factor (EGF)
  EGF is critical to the maturation and healing of the intestinal mucosa.

• Growth and development of the enteral nervous system: Neuronal growth factors
  The immaturity of the newborn intestine extends to the enteral nervous system, which
  requires brain-derived neurotrophic factor (BDNF) and glial cell-line derived neurotrophic
  factor (GDNF) for its development. BDNF can enhance peristalsis.

• Tissue growth: IGF-1 may also play a role in the survival of enterocytes following intestinal damage from oxidative stress.
Bioactive functions of human milk

- Growth-regulating hormones: Calcitonin and somatostatin
- Regulating metabolism and body composition: Adiponectin and other hormones
  - Adiponectin is a large, multi-functional hormone that actively regulates metabolism and suppresses inflammation.
  - Some have proposed that adiponectin in human milk may contribute to reduced incidence of overweight and obesity in later life.
  - Adiponectin is a large, multi-functional hormone that actively regulates metabolism
Immunologic functions of milk bioatives

- Cells of human milk: Human milk contains a variety of cells, including macrophages, T cells, stem cells, and lymphocytes.
- Levels of cell differ in children with certain allergy
- About 80% of the cells in early milk are breast milk macrophages, which originate as peripheral blood monocytes that exit the bloodstream and migrate into milk through the mammary epithelium.
- Phagocytosis of human milk components transforms these monocytes into potent breast milk macrophages with unique functional features, including the ability to differentiate into dendritic cells that stimulate infant T-cell activity.89,93
- This capability provides broadly powerful protection against pathogens while stimulating development of the infant’s own immune system.
- Stem cells have also been identified in human milk; their function is under investigation
Immunologic factors in human milk

- Milk-borne TGF-β regulates inflammation and wound repair, and helps prevent allergic diseases.
- Granulocyte-colony stimulating factor (G-CSF), identified in human milk decades ago, has beneficial effects on intestinal development and the treatment of sepsis. It acts at the intestinal surface, where it increases villi, crypt depth, and cell
- The colostrum of allergic mothers contains lower IFNγ but higher Th2 cytokines IL-4 and IL-13 compared to non-allergic mothers.
Protection from Infections

Human milk sIgA-antigen complexes are taken up and processed by intestinal dendritic cells, which allows for antigen recognition while maintaining a non-inflammatory environment.

While sIgA is the predominant antibody of human milk, milk also contains IgM and IgG, the latter becoming more abundant in later.

Lactoferrin, an iron-binding glycoprotein belonging to the transferrin family, which is effective against many different bacteria, viruses, and fungi.

Lactadherin, prevents rotaviral infection in the newborn. Following infection or damage, lactadherin mediates phagocytic uptake of apoptotic cells and stimulates a signaling cascade that results in decreased inflammation and promotes healing during intestinal

Another multi-functional protein, bile salt stimulating lipase (BSSL) also protects infants from viral infection, including Norwalk.
Secretory IgA (sIgA)

sIgA is an antibody that plays a critical role in immune function in the mucous membranes. More IgA is produced in mucosal linings than all other types of antibody combined; between three and five grams are secreted into the intestinal lumen each day.

Role of sIgA

Secretory IgA (sIgA) serves as one of the early line of defense in protecting the intestinal epithelium (the gut lining) from enteric toxins and pathogenic (disease causing) microorganisms. It does this by interfering with the earliest steps in the infection process by virtue of its ability to block toxins and pathogens from adhering to the intestinal epithelium (gut lining). Ability of Secretory IgA to promote the clearance of antigens and pathogenic microorganisms from the intestinal lumen by blocking their access to epithelial receptors, entrapping them in mucus, and facilitating their removal.
Role of lactoferrin in the activation of immune cells. Lactoferrin enters in the intestinal microvilli through the help of lactoferrin receptors and transferrin receptors present on the mucosal surface of the intestinal cells. The lactoferrin molecule further boosts up the immune response due to IFN-γ, TNF-α, IL-6 and by activating NK cells, PMNs and CD3+ and CD4+ T cells. Finally the lactoferrin enters the cells by receptor mediated endocytosis where it is released within the cells once the receptors are digested by endosomes. The lactoferrin induces release of cytochrome C from mitochondria which further activates caspase 3 to cause apoptosis in tumour cells.
Lactoferrin concentration in human milk
Gross composition of breast milk

Human breast milk

- Water
- Macro- and micro-nutrients and HMO
  - Proteins (8 g/L)
  - HMOs (5-15 g/L)
  - Lipids (40 g/L)
  - Lactose (70 g/L)

Solid components

HMO

- 5 to 15 g/L in breast milk
- >130 structures described, of which about 15 make up the bulk (>80%)
- Most HMO are not generally present in farmed animal milks

(Drawn from compiled data of Austin, 2016; Sprenger, 2017; Kunz, 2017 and Austin et al. NRC unpublished data)
Production of HMOs requires "mother’s tremendous expenditure of energy", yet, 

The majority of HMOs remain intact in gut lumen and have no nutritive value.

So what do HMOs do?

And, what do BMOs do?
Summary: HMO, a multifunctional breast milk component

Mechanism of action:
- Promote bifidobacteria dominated microbiome
- Deflect pathogens
- Strenthen gut barrier function
- Educate the developing immune system
- Nuture beneficial microbiota
- Strengthen gut barrier function
- Act as trap for pathogens
- Educate the developing immune system
Osteopontin in bovine milk

The concentration in bovine milk is approximately 18 mg/l.

In human breast milk the osteopontin concentration is significantly higher.

Modification and cleavage patterns are similar in human and bovine milk.

What is the function of osteopontin in milk?

Inhibitor of calcium precipitation/crystallization?

Part of the innate immune system?

- activates the cellular immune response
- binds bacteria and induces phagocytosis of these
Osteopontin levels in human milk

High degree of variation in osteopontin content: 18-322 mg/L
Average: 138 mg/L, ~ 2.1% of total protein

<table>
<thead>
<tr>
<th>Age of mother (years)</th>
<th>Time post partum (days)</th>
<th>OPN conc. (mg/L)</th>
<th>Total protein conc. (mg/L)</th>
<th>OPN/total protein (w/w%)</th>
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<tr>
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Mean: 29.6
SD: 3.5
Osteopontin Summary of benefits

Osteopontin—
- 138 mg/ml in human milk
- activates the cellular immune system
- binds to bacteria
- binds to monocytes
- promotes monocyte migration
- induces phagocytosis of bacteria
Gangliosides

Structure

• Complex molecule with a unique structure composed of:
  – A complex carbohydrate: oligosaccharide linked to sialic acid
  – A lipid: sphingolipid (fatty acids plus sphingosine)
Effect of heat treatment and storage time on human milk gangliosides (GM3, GD3, Total, GG).

 HT effect

 Storage T effect

 Storage Time effect
Breastmilk Naturally Contains Gangliosides

The two major gangliosides found in breastmilk are GD3 and GM3¹:

GD3 is more predominant in colostrum
GM3 is more predominant in mature milk

The average ganglioside content is approximately 11 mg/L²-⁴

*Average Ganglioside Content in Chinese Human Milk*†

*Mature milk (N = 345).
†Levels are comparable to min/max values from other publications.²-⁴
Gangliosides

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**Location in the Body**
- Widely distributed throughout the body:
  - Integral to the structure and function of cell membranes
  - Abundant in the brain
  - Found in the intestinal wall of the gut
# Gangliosides

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## Source
- Produced endogenously (naturally by the body)
- Obtained from the diet, such as through breastmilk
Gangliosides Are Thought To Play An Important Role In Intestinal Immunity: Promote a Healthy Microbiota\textsuperscript{1-7}

Resist digestion and reach the intestinal tract intact\textsuperscript{8}
May guide the composition of the microbiota in the gut
Gangliosides Are Thought To Play An Important Role In Intestinal Immunity: Prevent Pathogen Adherence\textsuperscript{1-7}

- The gut is a major site of contact with pathogens as it is a frontline barrier to limit pathogenic bacteria from invading the host\textsuperscript{8-10}
- Pathogens want to attach, colonize, and invade the host—to attach, they bind to receptors in the gut\textsuperscript{1-5}

- Gangliosides may act as decoys, as they look structurally similar to the receptors, interfering with pathogen binding\textsuperscript{1-5}