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Importance of Human Milk for Health and as Antiviral Immunotherapy - A Narrative Review

Prameela Kannan Kutty [a*]

[a] *Department of Paediatrics, Faculty of Medicine and Defence Health, National National Defence University of Malaysia, Kem Sungai Besi, Kuala Lumpur, Malaysia.*

Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Background: Immunological protection against novel mucosal pathogens is crucial to us as our immunity is unable to effectively defend against specific pathogens without previous immune encounters, as experienced in the SARS-CoV-2 pandemic. However, a nursing neonate is protected from many novel infections by exclusive human milk feeding despite having a naïve immune system without much previous pathogen exposure. It is observed that SARS-CoV-2 is not transmitted to the nursing infant through human milk and that natural maternal infections produce specific antibody responses in human milk. Furthermore, maternal vaccination against SARS-CoV-2 may modify some of these responses compared to natural infections. In this setting, it was felt necessary to also explore if early, innate immunity in human milk can protect against SARS-CoV-2.To explore this hypothesis, I reviewed the pathogenic mechanisms of COVID-19 focusing on the methods of viral entry through the human mucosae, infection establishment, immune dysregulation, and disease causation, and integrated these with the early actions by human milk feeding on mucosal infections. I then extrapolated the relevant pathways of human milk immune protection as potentials to protect against SARS-CoV-2.
Methods: This was divided into three steps which firstly included a literature search, secondly a stepwise analysis and synthesis of data, and thirdly, an integration of data to form a hypothesis. The first step searched articles in two areas. In the first area, articles included were on the infection and pathogenesis of SARS-CoV-2, and in the second area, articles included were on innate immunity in human milk. In the second step, I analyzed the immunological actions in human milk against mucosal infections, on the whole, and synthesized some of these relevant actions against

**Corresponding author: E-mail: prameela.kutty@yahoo.com;*

the pathogenesis of SARS-CoV-2 infections. In the third step, I integrated human milk immune pathways that could interfere with the establishment of SARS-CoV-2 infection, viral invasion, immune dysregulation, and the progression of the disease.

Results: Infection by SARS-CoV-2 can theoretically be reduced or mitigated by the effect of early immune constituents in human milk. Human milk feeding may confer protection against all stages of the disease including the establishment of SARS-CoV-2 infection, invasion, and immune dysregulation and these actions may benefit both the individual and the community.

Limitations: The multifunctional and dynamic nature in which human milk constituents function in a nursing infant cannot be fully reproduced by studying isolated components under experimental conditions. Even when such factors can theoretically offer protection against the virus, this concept has to be further researched in large cohorts of nursing infants.

Conclusion: The role of human milk in preventing infection by SARS-CoV-2 must be explored further and if true, exclusive human milk feeding must be considered another reason for the smaller number of infections observed in children compared to adults in the pandemic. The additional counseling of human milk feeding for protection against novel pathogens, besides its established role in reducing neonatal mortality, would enhance rates of exclusive human milk feeding. General health can be developed and promoted through the potential immunotherapy provided by it.

Keywords: Human milk feeding; immunity; SARS-CoV-2; mucosal; immunotherapy.

1. INTRODUCTION

The pathogenesis of COVID-19 explains its clinical manifestations and highlights the importance of timely preventive therapy to prevent the infection or to reduce its impact.

COVID-19 is primarily a mild disease in childhood but the knowledge of its pathogenesis continues to unfold and it can involve multiple organ systems, especially the respiratory system. Its peak infectivity coincides with maximum SARS-CoV-2 load, just before or within the initial five days of symptom onset [1]. The acute disease spectrum includes acute asymptomatic, mild and, severe disease. Amongst children who develop severe disease, there are often predisposing factors such as obesity and bronchial asthma and, other immunosuppressive conditions. There is a growing body of evidence that the virus is also temporally related to a post-infective phenomenon causing a novel disease now recognized to be a separate disease entity referred to as the Pediatric Multisystem Inflammatory disease (MIS-C) which is temporally associated with COVID-19.Its manifestations are often acute, severe abdominal pain or high grade, often unremitting fevers refractory to antibiotics [1] Systemic impact can affect almost any system with the gastrointestinal, cardiac ,dermatological, renal, respiratory, hematological or neurological systems involved in the disease [1].

COVID-19 also impacts long-term health and while some children may continue to experience prolonged illness, most recover by day 56 of illness.[2]. However, despite most children having a short duration of symptoms, some who tested negative for SARS-CoV-2 had persistent illness. [2].The spectrum of the psychological impact of COVID-19 in children is well supported and suggested reasons include the fear of the illness or social isolation associated with the disease [3].

Children have different susceptibility to the illness compared to adults [1], and this is attributed due to a number of factors [4]. Lower exposures to SARS-CoV-2 and differences in innate and adaptive immune responses in children may explain this. The presence of cross- reactivity from other coronavirus infections due to previous exposures in children who have a greater frequency of upper respiratory infections is suggested. The differences noted in intestinal microbial colonization in children with a less inflammatory immune profile in the gut or the presence of higher blood levels of factors such as melatonin have been proposed as a possible cause. Moreover, nonspecific, off-target protection from live vaccination [4] may work independently or along with other factors to explain this difference.

In addition to some of these factors, this article considers the possibility that the immunological benefits of human milk feeding may partially explain the differences observed.

Human milk feeding allows every mother to provide naturally present innate immune

defenses in her milk, even without infection exposure. This may systematically hinder the steps in invasion of mucosal portals, prime targets of the SARS-CoV-2, and provide a number of antiviral defenses, protecting from early infections. At the same time, the adaptive immunity in human milk which develops after exposure to infection mainly by antibody formation is 'stimulated', bridged by innate immune factors. Maternal vaccination against the infection may further sustain and modify useful mucosal protective immune potentials.

It is noted that human milk does not transmit the SARS-CoV-2 to the nursing infant, instead, infected mothers produce specific antibodies in the milk [5], which are likely to protect. While SARS-CoV-2 ribonucleic acid (RNA)was detected on several breast swabs it was not found in any breastmilk sample in women diagnosed with COVID-19. Moreover, SARS-CoV-2-specific immunoglobulin A (IgA) and immunoglobulin G (IgG) were found correlating with SARS-CoV-2 neutralization activity [5]. Of added importance is that the vaccination of breastfeeding women against SARS-CoV-2 produced specific IgA and IgG antibodies in breast milk for 6 weeks after vaccination. IgA was detected 2 weeks after vaccination followed by a spike in IgG after 4 weeks coinciding with a week after the second given vaccine [6].

There is no evidence thus far of human milk transmission in COVID-19, hence human milk feeding is advised during maternal COVID-19. This article argues how human milk could be useful in systematic mucosal defenses against such pathogens and how its effect of anti-inflammation and immune modulation could limit the infection and preserve tissues in the systemic pathogenesis of COVID-19.

2. MATERIALS AND METHODS

The review was divided into three steps which included:

1) literature search comprising two areas of interest
2) stepwise analyses and synthesis of data
3) exploring the domain of overlap by integration and extrapolation

In the first step, articles searched were in two areas of interest. The first area included articles that focused mainly but not exclusively on the pathogenesis of SARS-CoV-2, other coronaviruses, and other comparable infective agents. The second area of interest reviewed articles on the innate immunological protection in human milk and its role against relevant mucosal diseases.

In the search of the first area of interest, articles included were clinical research articles, experimental work, expert and interim guides. Publications selected included case reports, meta-analyses, systematic reviews on human infections by coronaviruses and other mucosal pathogens with comparable pathogenicity. Articles describing the pathogenesis of SARS-CoV-2 and its impact on the pandemic were reviewed. How mucosal viruses gain entry into the human body, establish infection and go on to produce invasive disease and complications were explored. Articles that were excluded were Webpages that provide the public with questions and answers and media releases. Except for diabetes mellitus which was considered to significantly influence the unborn infant, specific underlying chronic conditions which could influence the pathogenesis of COVID-19 were excluded. The pathogenetic mechanisms of SARS-CoV-2 on geriatric patients were excluded. Specific social habits or dietary factors other than the influence by human milk feeding were excluded.

In the search of the second area of interest, articles included searches on breastfeeding and innate immunity and breastmilk immunology related to mucosal infections and SARS-CoV- 2. Publications in this section included case reports, meta-analyses, systematic reviews, clinical research articles, reviews, and experimental work on humans and animals. The articles included reviewed the impact of innate immunity in human milk on infections and focused on those that involve the mucosal systems of the respiratory and gastrointestinal tract. Articles that elucidated how human milk factors prevent the establishment of mucosal infections, can prevent mucosal invasion and,modulate immune processes were reviewed. Except for a few relevant articles that dealt with immunoglobulins in colostrum and human milk which were included, articles that only dealt with adaptive immunity in human milk or on other aspects of human milk protection that were felt not to be directly relevant to the pathogenesis of mucosal infections were excluded.

In the second step on data analyses and synthesis, the following methods were used:

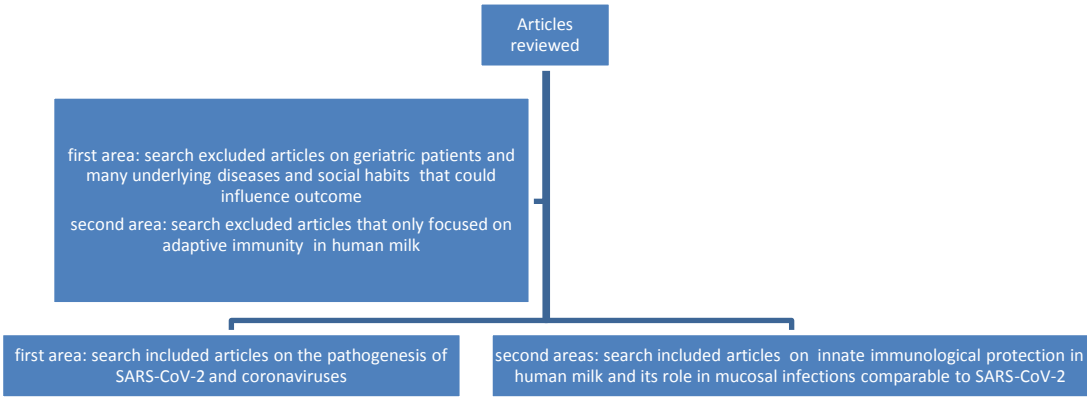

Fig. 1. Literature search areas

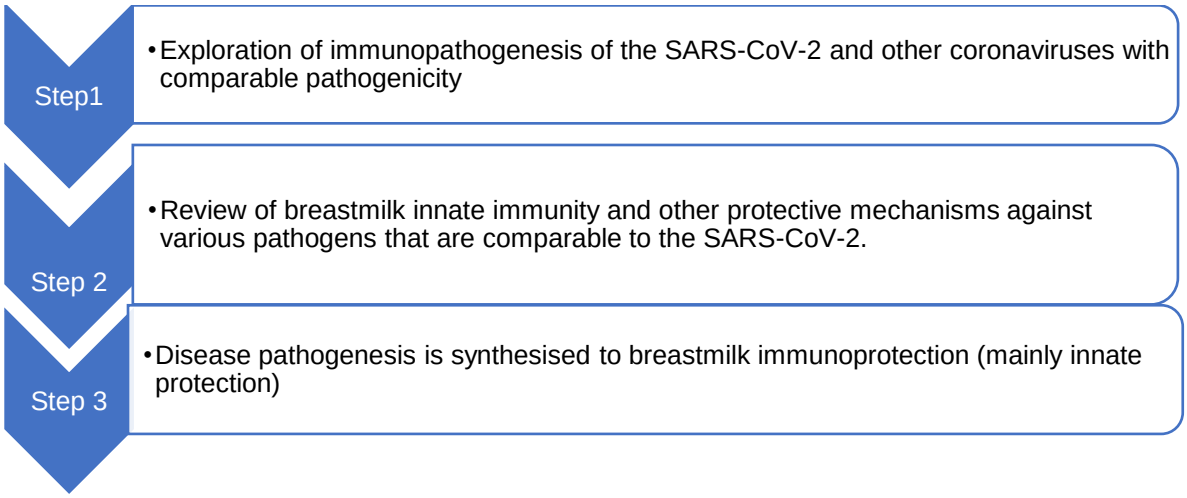

Fig. 2. Stepwise analysis and synthesis of data

Information from the pathogenesis of COVID-19 and innate breastmilk immune protection was analyzed in three steps. The first step was to explore how mucosal infections in general, and the SARS-CoV-2, specifically, infect mucosae to establish disease.

The second step analyzed the actions of breastmilk on immunity against various mucosal pathogens that were considered comparable to the SARS-CoV-2. The similarities of such pathogens included the mucosal portals of entry for disease causation, the systemic impact such as the organs affected, inflammatory responses stimulated by them, and the age of infection.

The third step synthesized some of these relevant actions against the pathogenesis of SARS-CoV-2 infections.

In the last step, the domain that overlapped between the pathogenesis of SARS-CoV-2 infection and the pathways involving actions of innate immunity in human milk against mucosal infections and immune dysregulation were integrated as a whole to form a hypothesis with practical importance.

Integration and extrapolation indicated that in theory, the pathogenicity of the disease could be reduced or halted in a systematic manner, by human milk feeding. Mucosal entry, receptor blockade, immune modulation, innate immune recognition, immune cells, and antiviral activity were protective pathways by human milk feeding against SARS-CoV-2.

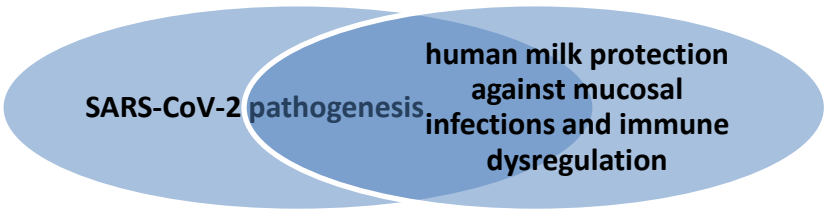

Fig. 3. Hypothesis: Protective domains in human milk feeding against the pathogenesis of SARS-CoV-2

3. RESULTS AND DISCUSSION

3.1 SARS-COV-2 Pathogenicity

SARS-CoV-2 is a large, spherical single-stranded RNA virus. It is a mucosal pathogen and genetically similar to SARS-CoV, but with a higher reproductive rate (R 0) [7]. There are four main structural proteins, the nucleocapsid protein that contains the viral genome and three envelope proteins of which the spike protein, attaches to host cells through a receptor-binding domain [7,8].

If timely clearance of the virus at the respiratory mucosae does not occur, some may go on to develop uncontrolled immune responses which could lead to acute lung injury and systemic immunopathology [8]. The virus attaches itself to target receptors which are found in many organs with hazards of widespread disease. SARS-CoV-2 binds to angiotensin-converting enzyme-2 (ACE-2) receptors and fusion with a protein on host cell surfaces internalizes the virus [7]. The virus is viable for days on smooth surfaces such as stainless steel, plastic, or glass and at lower temperatures and humidity [7]. Of note is that cellular receptors of coronaviruses belong to the same protein family, and cellular entry occurs through the co-expression of other host peptidases which activate the coronavirus spike proteins [7,8]. The transmembrane serine proteases cleave and activate the coronavirus spike proteins during cell entry [7]. Spike protein dismantling releases infective viral genome, and with proofreading mechanisms in this RNA virus, a lower mutation rate in the early stages of the pandemic was followed by the occurrence of many mutants. These mutants drive viral genetic variation that could alter viral pathogenicity leading to more infectious viruses[9]. Droplets and contact with nasal, oral, or conjunctival mucosae propagate the virus [10,11].

Fever, myalgia, headache, respiratory symptoms, and temporary anosmia with taste loss due to transient damage to olfactory cells may occur [11]. Intracellular viral replication releases infective virions which stimulate the host's innate immune responses [8,11] Viral recognition stimulates T lymphocytes and dendritic cells to the site of infection for early viral clearance. Host immunity is induced to produce inflammatory factors, macrophages, maturation of dendritic cells, and the synthesis of interferons (IFNs), all vital for eliminating the virus. Neutralizing antibodies are produced in SARS-CoV-2, possibly useful, but their exact duration and impact are yet unclear. The viral load may also be a factor in recovery [7]. Immune suppression, viral evasion, high viral load and host variables influenced by underlying conditions may contribute to more severe disease with spread to the lower airway [7,8,12]. In coronavirus infections, monocytes, macrophages, and neutrophils trigger the production of proinflammatory cytokines leading to the phenomenon referred to as a "cytokine storm" causing lung immunopathology [8]. Some develop septic shock or multi-organ dysfunction [1].Guo et al found that specific cytokines and serum markers were significantly higher in diabetic patients predisposing them to the inflammatory storm [12], with extensive tissue destruction linked to hyperferritinemia [13].

In acute severe SARS-CoV2, many children had underlying predisposing factors such as obesity, bronchial asthma, sickle cell anemia, and immunosuppression [1]. The other complication associated with the SARS -COV2 is MIS-C [1]. Clinical and laboratory observations suggest many hypotheses of the inflammatory state that occurs in the disease some 2-6 weeks following an acute illness or exposure to SARS-CoV-2. Immune dysregulation in the genesis of MIS-C resulting from an exaggerated hyperimmune response is supported by positive serology and negative PCR testing, while the antibody or T-cell recognition of self-antigens (molecular mimicry) leading to the synthesis of autoantibodies and formation of circulating immune complexes have been proposed [14]. The role of genes in the

clinical expression is suggested by differences in disease incidence in various parts of the world [14].

3.1.1 Immunobiology in children against SARS-CoV-2

Natural immunobiological mechanisms in children against the SARS-CoV-2 are more favorable than in adults and at least partially explain the relatively fewer mortalities amongst children in this disease compared to adults. The protective mechanisms include reduced expression of receptors that the virus utilizes to enter target cells or the differences in innate and adaptive immunity in this age group compared to adults which contribute to different immune dynamics. The differences in childhood immunity may preserve the pulmonary endothelial barrier and prevent acute respiratory distress syndrome (ARDS) [4,14]. Vitamin D which has anti-inflammatory and anti-oxidative properties is noted to be at lower levels in the older age groups and could also contribute to different disease patterns [4]

4. IMPORTANCE OF INNATE IMMUNITY IN HUMAN MILK

Host immune polymorphisms and viral genetic variability are likely factors for the development of Covid -19 [15]. Genetic polymorphisms can delay, diminish or exaggerate antiviral responses resulting in severe, invasive disease. Adding to this challenge is that respiratory pathogens have evolved processes to suppress or evade innate responses[16].

Evolutionarily, human nutrition provides innate protection against novel infections [17] and by so doing can indirectly prevent tissue damage. The mammary glands extract substances from maternal blood or may actively synthesize a number of immune-nutritive substances. These are present in its cellular content, in the milk fat globule membrane found in milk, in its growth factors, and in encrypted peptides within bioactive components. Many milk factors seem to have evolved for multiple functions with the capacity to adapt to the mother-infant dyad [17,18,19]. This makes human milk, on the whole, not reproducible in its immune potential, biologically responsive, and cost-effective.

Human milk through innate immunity can fortify mucosal surfaces which are sites of pathogen entry[18,19]. This early defense is mandatory in the young with relative immunodeficiency. The nursing mother can naturally protect by early innate immune responses [18,19], and further this protection if she is exposed to the infection by priming adaptive immune responses.

At sites of major antigenic challenge in the respiratory and gastrointestinal tract, innate defenses strengthen the infant's developing immunity and in some scenarios confer added individual protection. This is individually possible as the immune composition varies from mother to mother or with feeding time, in colostrum, transitional milk, and mature milk [18,19]. Colostrum is produced in the first five days after birth and is rich in white blood cells, human milk oligosaccharides (HMOs), bioactive factors such as IgA, lactoferrin, growth and colony stimulating factors (CSFs), and antioxidants. Following this, transitional milk is produced up to 2 weeks postpartum which contains gradually decreasing amounts of protein and higher lactose, fat, and, water-soluble vitamins. Mature milk is fairly constant in its nutrient content after 6 weeks postpartum. There are also differences in the milk of mothers who deliver at term compared to preterm with preterm milk containing higher proteins and specific immune factors [18].

4.1 Enhancing Physical and Chemical Barriers by Mucosal Protection

The ciliated pseudostratified columnar epithelium which lines most of the respiratory tract has special functions as a barrier to pathogens and foreign antigens, preventing infections and tissue injury [20]. Goblet cells secrete mucous and form a vital layer of vigorous innate defense through mucociliary clearance [21].

Mucociliary clearance at the airway epithelium is augmented by the formation of mucous gel, the glycosylated mucin glycoproteins, with multiple defensive roles and transmembrane mucins such as MUC1 and MUC 4 as innate defenses [21,22]. Below the mucosae, there are leukocytes that secrete antibodies, defensins, and lysozyme, for early immune defenses [22]. These substances provide dual protection, acting as a physical barrier and providing antimicrobial activity, with the capacity to opsonize microbes and clear them [22].

Inefficient mucociliary clearance or absence of sufficient mucin glycoproteins in the airway disrupts this vital, primary defense. Viruses can develop methods that interfere with early

defenses as in SARS- CoV -2 infections resulting in cell fusion, epithelial destruction, cilium shrinkage, and other pathological changes to the epithelium [23], weakening early defense.

In the infant energy-dependent processes must be conserved for growth and development and human milk is an investment towards this as nutrition is also enriched by early defences.

For instance, mucosal tissues utilize energy to produce mucins and increase their energy requirements to produce the important early defensive shield by mucin glycoproteins to fight off infections [22].

Human milk fortifies this protective shield by defensive mucous enriching factors that augment the amount of mucous in the respiratory tract or that step up early immunity by coating epithelial surfaces with mucous that prevents pathogenic viruses from entry [24, 25]. Mucins in human milk add a layer to the developing immunity in the gastrointestinal and respiratory tracts by preventing the adhesion of pathogens to the cell surface [25]. MUC1 and MUC4 competitively inhibit receptors to specific pathogenic viral interactions [24]. Sialyated human milk mucin inhibits viral binding to the infant's cell surface glycan receptor and inhibits rotavirus in the gastrointestinal tract, blocking experimental adhesion of recombinant norovirus-like particles, and such action may be emulated for immunotherapy [25,26].

Epidermal growth factor (EGF), a growth factor that is provided by amniotic fluid throughout pregnancy, is present in significant quantities in human milk and colostrum [27] and continues to nurture the gut epithelium in the postnatal period. Milk EGF may also increase mucin production by goblet cells, enhancing synthesis and secretion of mucous [28].

Trefoil factors, are cellular products that produce mucin in breastmilk and step up immunity by activating intestinal epithelial cells and healing mucosae [29]; such functions may be useful in invasive coronavirus disease. Mucosal barriers remove the virus, without the necessity of inflammation, by agglutination and expulsion through mucociliary action in the respiratory tract or peristaltic movement in the gut [30].

When pathogenic viruses are prevented from epithelial adherence and colonization, this can not only control individual infections but could also control person-to-person infection transmission. HMOs, which are found abundantly in human milk, coat epithelial surfaces and prevent pathogen contact and adherence to epithelia, an important mechanism that would otherwise permit viral replication. Soluble fucosylated and sialylated HMOs are bound by lectin receptors of fucose or sialyl-dependent pathogens, entrapping viruses so the host's innate immune system cannot recognize them. HMOs are prebiotics for commensal microbes, which also help prevent epithelial colonization by pathogenic viruses, and together, they fortify epithelia to prevent early steps of viral adherence [31]. These early epithelial protective mechanisms in human milk are argued in support of its benefits against community transmission of viral infections including infections with the coronaviruses.

4.2 Receptor Blockage

The virus that enters the cell sabotages cellular machinery for viral replication. Blocking cellular entry by interrupting viral receptors, can prevent cellular internalization of the virus. The SARS-COV-2 requires specific ACE-2 receptors [4] to enter cells while heparan sulfate proteoglycan (HSPG) receptors assist in SARS-COV-2 cell entry [32].

Human milk ingredients can function as "receptor decoys" in early infection prevention [31]. Viruses utilize cell surface glycoconjugates as receptors to enter cells, while some HMOs, abundant in early nutrition, express glycans that bind onto host cell surface lectins and prevent viral binding and invasion [33]. Not all breastfeeding mothers can effectively provide protection through this route, as specific HMO glycosylation depends on factors such as the mother's blood Lewis status, hence , a mother's blood group influences her milk HMO profiles [34].

The antiviral spectrum in human milk such as cytokines, monolaurin, Vitamin A, Tenascin C, lactadherrin, lactoferrin, and other components signify its immuno-nutritive potency. While direct nursing is optimal, where it is not feasible, milk banks may capture this by collecting milk with specific properties essential for special groups of children [35].

Lactoferrin is a multifunctional glycoprotein found abundantly in colostrum [35]. It fortifies human nutrition with direct and indirect antiviral action. Its dynamic levels were found to increase in

concentration as lactation progressed to the second year postpartum, together with IgA, total proteins, and lysozyme compared to milk bank samples, although some minerals and oligosaccharides were found to be lower [36]. Lactoferrin acts against a gamut of non-enveloped and enveloped DNA and RNA viruses through numerous mechanisms; inhibiting cellular entry, by direct attachment to the virus, or by blocking cellular receptors. Its action against human pathogens such as Herpes simplex virus, human papillomavirus, human immunodeficiency virus (HIV), and rotavirus from entering host cells, is notable at the step where these viruses enter cells utilizing common cell surface receptors such as heparan sulfate glycosaminoglycan cell receptors (HSPG) [37].

SARS-CoV and SARS-CoV-2 are similar in their sequences and receptor-binding domain structure [38], hence they are compared here when reviewing viral pathogenicity. Lactoferrin protects against SARS-CoV infection by binding to HSPGs, interrupting the initial interaction between SARS-CoV and host cells [39]. Additionally, lactoferrin may also interrupt the step of cellular entry of SARS-CoV-2 which also utilizes HSPG a cofactor, for cell anchor and entry [32].

The antiviral spectrum of lactoferrin includes fighting off infections that depend on iron. Lactoferrin interferes with the iron utilization of pathogens. Viruses may also infect iron-acquiring cells by binding to another human milk protein, transferrin receptors during cell entry. Other viruses alter proteins involved in iron homeostasis. In coronavirus infection and inflammation, lactoferrin plays a preventive role in the respiratory and gastrointestinal tract [40].

The main classes of immunoglobulins in bovine and human milk are IgG, immunoglobulin M (IgM) and IgA . The amounts of various immunoglobulin fractions differ in colostrum and milk in different species and are often unique compared with blood. In human milk, IgA represents the main immunoglobulin class [41].Secretory immunoglobulin A (sIgA), is the main antibody in mucosal secretions and in human milk.Besides its adaptive immune functions, this mucosal antibody may engage multiple innate mechanisms for early antiviral protection .It consists of two or more IgA monomers joined by a J chain in association with SC which helps transport and releases IgA into the intestinal lumen. It also protects IgA from proteolysis and anchors IgA in the mucus layer overlying the mucosal surfaces [42].

While there are specific sIgA-dominant SARS-CoV-2 antibody responses in human milk after infection, its precise function requires further study [43].However, timely innate antimicrobial protection by sIgA at intestinal mucosal sites by blocking receptor binding, immune exclusion, and interference with pathogen virulence determinants are proposed against various viral and bacterial pathogens [42]. Comparable innate functions of sIgA against SARS-CoV-2 need to be explored.

A cohort study of lactating parents compared human milk mRNA vaccination responses to responses to COVID-19 infections. This study found differences in IgA and IgG antibodies in human milk between infections and vaccinations and these differences were noted for up to 90 days. Infections were linked to variable IgA-dominant response up to 90 days after diagnosis and vaccinations were related to an IgG-dominant response. It was noted that infections and vaccinations produced neutralization activity against the live SARS-CoV-2 virus in human milk [44].

4.3 Innate Immune Recognition

Timely, selective and regulated pathogen recognition must differentiate pathogens from the plentiful commensals in the human body. The antiviral immune responses must preserve normal tissue and the commensal microbes. Cells infected with viruses must be cleared early by focused immune recognition with regulated antiviral responses. At the same time, where dysregulated immunity can cause invasive disease and tissue destruction, as in the immunopathology of invasive SARS-CoV-2 infection, the antiviral action of human milk along with its capacity for anti-inflammation and immunomodulation could be useful to counter or reduce its immunopathology.

The innate immune system recognizes pathogens by pathogen-recognition receptors (PRRs) that sense distinct pathogen-associated molecular patterns (PAMP). Toll-like receptors (TLR) are activated and signaled by RNA viruses through RNA sensors [45]. Members of the TLR family detect viruses and induce the production of interferons through several signaling proteins. Reproducing this, TLR agonists are suggested as therapy [45]. The SARS-CoV-2 activates

TLR2 signaling, which results in increased expression of proinflammatory cytokines suggested to be a mechanism of disease in severe COVID-19 [46].

Human milk components can selectively recognize pathogens and differentiate them from commensals. TLR signaling is important for such differential recognition [47,48]. In human milk there are specific TLR responses on different cellular components based on the TLR activated; such responses are not found in infant formulas [48]. TLR2, TLR3, TLR5 and soluble cluster of differentiation (sCD)14, and human β-defensin-1 (hBD-1), function as pattern recognition receptors for innate immune recognition [18]. PRRs in human milk and other bioactive substances in the intestine of the breastfed infant create an anti-inflammatory environment, while TLR responses can be modified by soluble toll-like receptors (sTLRs) and sCD14 [18,48,49].

The immunomodulation in human milk potentially fine-tunes specific TLR mediated inflammatory responses, while focusing on defenses against viruses, interacting sTLRs, and sCD14 with a spectrum of bioactive factors.

When the impact of human milk is integrated with the pathogenesis of the disease in the gastrointestinal tract which is an important organ in COVID-19 pathogenesis in children, the benefits of human milk feeding on the intestinal microbiome add to the spectrum of innate defenses. Lactoferrin, is one of a spectrum of substances in human milk, which can promote the gut milieu. It enhances the growth of enterocytes and along with anti-inflammatory and immunomodulatory actions, enriched by the trophic factors in human milk, step up mucosal immunity at the gut epithelial barrier [27,28, 38].

4.4 Immune Cells

Immune cells and their antiviral products have the potential to prevent or limit infection.

Maternal blood leukocytes pass through epithelial cell spaces to be secreted into milk, whereas blood monocytes that are secreted into milk become activated and function as motile macrophages[18,19]. The cells in human milk are involved in its dynamic immunity when required in special scenarios such as in sick infants [50]. Holistic maternal health including the health of the mother’s lactating mammary glands may be important for this.

Human milk immune cells include epithelial cells, the motile macrophage, neutrophils, lymphocytes, innate lymphoid cells (ILCs), hematopoietic progenitor cells, and stem cells [51,52]. There are epithelial cells, macrophages, neutrophils, and lymphocytes, characterized mainly by CD3+ T cells, distributed between CD4+ and CD8+ [52,53], as well as Tγδ+ cells, CD16+ NK cells , and B cells [52,54]. Some immune cells transferred in milk last in the infant for about 6 days [51], and maternal cytotoxic T lymphocytes in milk can home to the Peyer's patches of the nursing infant [55]. Human milk also contains CSFs which modify the growth and differentiation of milk neutrophils and macrophages [52]

Individualized protection is evident in the milk of mothers whose infants have severe bronchiolitis where there are increased numbers of viable cells compared to milk from mothers of healthy infants. Maternal milk cells from infants hospitalized with bronchiolitis produced a skewed cytokine profile when stimulated by the live respiratory syncytial virus [56].

Animal experiments indicate that pluripotent stem cells in human milk can multiply outside the mammary cell lineage and can integrate into distant organs. For instance, it is fascinating that human milk stem cells can reach the brain and differentiate into neurons and glial cells [57], and it is hypothesized, here, that such cells can repair damaged or injured tissue in the aftermath of invasive viral infections.

4.5 Immune Modulation

Human milk augments immune maturity and modulates immunity in the developing immune system. While there is still a lot more about immune modulation in human milk to be known, it is a dynamic process that seems to respond to the infant’s needs.

Lactoferrin, as mentioned above, is a human milk constituent with multiple antiviral actions. It binds viruses, blocks some viruses from attaching to target cells, and can suppress intracellular viral replication. Lactoferrin receptors are found in many immune cells such as monocytes and lymphocytes. Lactoferrin activates antigen presenting cells (APC) and can link innate to adaptive immune functions. The anti-inflammatory action of lactoferrin on leukocytes that are stimulated with lipopolysaccharides

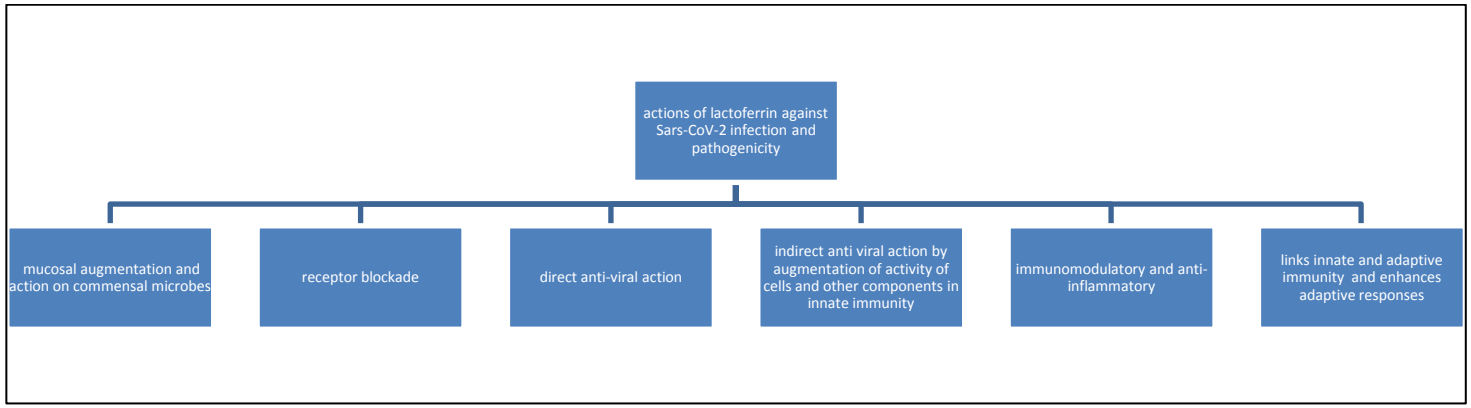

Fig. 4. Possible and postulated actions by lactoferrin in human milk in COVID-19

(LPS) is associated with its ability to regulate various signaling proteins. [58]. High lactoferrin levels in the milk of mothers of preterm infants are especially useful against early and late sepsis which preterm infants are at high risk of [38], emphasizing how human milk can be specifically utilized in special groups of children.

During the replication of SARS-CoV-2, there is the production of type 1 interferon and proinflammatory cytokines. There is increased free iron resulting from iron dysregulation in COVID-19 which could exacerbate oxidative damage. Hypercoagulable states in Covid -19 are possibly linked to iron overload [59].

Experimentally, infected bronchial cells are protected from inflammation and cell necrosis by lactoferrin [59]. Lactoferrin is an iron scavenger and modulates signaling pathways. It also helps reduce inflammation and oxidative damage [59].

In the gastrointestinal tract, lactoferrin transports iron and deprives iron of iron-dependent microbes, reducing their infectivity [58,59]. Lactoferrin also stimulates effective immune responses by recruiting APCs to enhance adaptive immunity [58,59].

When these effects are extrapolated to the nursing infant, lactoferrin, in human milk, through its action on iron, may similarly have a protective role in the hyperferritinemia associated with COVID-19. In human milk, through the action on iron, lactoferrin could be useful in the hypercoagulable state, recognized in COVID-19

Human milk lactoferrin could likewise be hypothesized to reduce immune dysregulation in the “cytokine storm” recognized as a complication of SARS-CoV-2, through anti-inflammatory impact, and by this, also reduce lung damage.

However, extrapolating the actions of a single substance present in milk must be considered in the light of the multifunctionality of human milk as a whole , and requires much further research.

At the microscale, human milk is also dynamically regulated. Human milk micro ribonucleic acids (miRNAs) are mainly produced in the mammary gland, while small amounts are drawn from maternal blood with lactation-specific regulatory functions. Cells, exosomes, and fat globules protect milk miRNA and transfer them to the infant’s bloodstream [60]. A study found that while the total miRNA provided to the nursing infant is constant in the first six months of lactation, the miRNA concentrations are altered in the fourth month compared to the second and sixth month. The authors suggest that this may be due to an adaptation to the infant’s feeding trends [60].

Xeno-miRNA (XenomiRs) are subtypes of miRNAs found in external sources and may affect a mother through her diet to influence gene expression. It has been proposed that these substances, at the microscale, may modulate a nursing infant’s immunity through regulatory information present in mother's milk [61].

A plant miRNA that can enter the human body through the gastrointestinal tract has an effect on influenza A subtypes [62].

Immunomodulatory activity in human milk is supported by reduction to allergies and immune - related diseases in later life in the breastfed [63]. A “mother-microbe-infant-microbe” link initiated and supported by human milk feeding contributes to its benefits against acute and long-term diseases [64,65]. Some maternal factors influence milk microbial composition through stages of lactation, lifestyle and dietary factors, methods of milk expression, and a mother’s body mass index (BMI) [64].

5. CONCLUSION

It is of interest that the integration of the pathogenesis of COVID-19 with the immunological actions of human milk feeding supports a theoretical possibility for stepwise protection by human milk feeding against the virus.

Many basic principles and novel developments in vaccinology [66] are potentially available in the incomparable safety profile and in the innate immune constituents of human milk.

While innate immune protection in human milk potentially protects the mucosae against viral entry, viral invasion, and disease complications, studies indicate that human milk responses may be modified by maternal vaccination in SARS-CoV-2 infections. This may be a strategy that could enhance human milk immune protection against SARS-CoV-2.

By preventing mucosal pathogens from gaining entry into the body and by protecting epithelia, human milk decreases person-to-person and community transmission of the virus.

Through timely prevention, there is reduced infective load which naturally prevents severe infection and its consequences acting as primary and secondary prevention.

While much research in this area is needed, it is important to continue to emphasize exclusive human milk feeding is a modifiable variable that promotes infection protection and holistic health.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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