

# Breastmilk—Old but Not Obsolete: from the Safety of Breastfeeding During the Coronavirus Disease 2019 Pandemic to Broad Antiviral Drug Development

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a major threat to global health. The high mortality rate reported during the early stage of the COVID-19 pandemic resulted in panic among patients, including lactating mothers.<sup>1–3</sup> The detection of SARS-CoV-2 RNA in breastmilk raised great concerns regarding the possibility of mother-to-child transmission (MTCT) of the virus.<sup>4</sup> According to several reports on the presence of SARS-CoV-2 in breastmilk, some experts suggested that breastfeeding should be conducted with caution, while others recommended that, infants should be separated from their mother and breastfeeding should be discontinued.<sup>5–7</sup>

Is it necessary to adopt such strict measures for the prevention of MTCT of SARS-CoV-2? Firstly, although some studies reported the presence of SARS-CoV-2 RNA in breastmilk, others did not detect any viral RNA.<sup>4,8–10</sup> Therefore, additional detection methods (e.g., viral protein detection) are required to confirm the presence or absence of SARS-CoV-2 in breastmilk. Secondly, even if SARS-CoV-2 RNA is detected, it is unknown whether breastmilk contains live virus. Thus far, infectious viruses have not been isolated from breastmilk, and MTCT of SARS-CoV-2 via breastmilk has not been reported.<sup>4,8</sup> Thirdly, it is not possible to culture the infectious viral particles isolated from the breastmilk of mothers with ongoing SARS-CoV-2 infection, regardless of the detection of viral RNA in breastmilk.<sup>11,12</sup> Therefore, there is a low probability for the presence of infectious SARS-CoV-2 particles in breastmilk. Moreover, several national and international guidelines revised their recommendations

on breastfeeding and clearly stated that breastmilk is safe and could be directly used to feed infants.<sup>13–15</sup> To avoid possible transmission via other routes, such as the respiratory tract, an expert consensus on breastfeeding in case of maternal infections suggests that infants born to mothers with influenza virus or SARS-CoV-2 can be fed with expressed breast milk without requirement for sterilization.<sup>13</sup>

Is SARS-CoV-2 infectious when mixed into the breastmilk? The presence of SARS-CoV-2 infectious viral particles in breastmilk is currently unknown. Nonetheless, there is an urgent need to investigate whether the virus remains infectious when mixed with breastmilk. Fan *et al.*<sup>16</sup> reported that, although SARS-CoV-2 or pangolin coronavirus (GX\_P2V) can be easily cultured in vero-E6 and Huh7.5 cells, exposure to various concentrations of human breastmilk collected prior to the emergence of COVID-19 completely blocked the infectivity of these viruses. In addition, this activity is not associated with the presence of IgA antibodies in milk. Moreover, the investigators found that lactoferrin possesses significant anti-SARS-CoV-2 activity, and whey protein isolated from breastmilk has markedly higher capacity to block the infectivity of SARS-CoV-2 compared to lactoferrin. According to the results of that study, breastmilk may contain other antiviral components that play an important role in inhibiting SARS-CoV-2 infection.

Breastmilk is rich in nutrients and various bioactive molecules, such as cytokines, growth factors, immune cells, antibodies, and other components that can inhibit different types of viral infection.<sup>17</sup> It was reported that breastmilk has antiviral activity against various viruses, such as influenza virus, Zika virus, hepatitis B virus, human immunodeficiency virus, etc.<sup>18,19</sup> It is well established that antibodies with specific neutralizing activity to SARS-CoV-2 are typically induced by SARS-CoV-2 infection or vaccination. Breastmilk contains high level of antibodies (e.g., IgA) after viral infection or vaccination, which is an effective approach to inhibiting SARS-CoV-2.<sup>20</sup> In addition, other components such as lactoferrin, mucin 1 (MUC1), MUC4, and lactalbumin, have shown high antiviral activity. Interestingly, SARS-CoV-2 can also be inhibited by these components.<sup>16</sup> Lai *et al.*<sup>21</sup> revealed that lactoferrin, MUC1, and lactalbumin showed significant activity against SARS-CoV-2 and its variants. Mechanistically, these factors could inhibit viral attachment through interference with the interaction between heparan sulfate proteoglycan and viral protein, as well as block viral replication by inhibiting viral RNA-dependent RNA polymerase activity.

Based on the broad antiviral activity of human breastmilk, its components offer promise for the development of antiviral drugs in the future.<sup>22–24</sup> The 3-hydroxyphthalic anhydride

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modified  $\beta$ -lactoglobulin LG (3HP- $\beta$ -LG), an active component in anti-human papillomavirus (HPV) biological dressing (JB01-BD), has been used in clinics since 2013 to block cervical infection by HPV. Hua *et al.*<sup>25</sup> reported that 3HP- $\beta$ -LG via intravaginal application also showed high anti-SARS-CoV-2 activity. Hence, this component of breastmilk was successfully used as a drug to inhibit HPV. Similarly, other components (e.g., lactoferrin, MUC1, and lactalbumin) that have exhibited broad and high activity against SARS-CoV-2 and other viruses can be used to design new antiviral drugs.<sup>16,19,21</sup> Importantly, climate change and intense globalization have created favorable conditions for viral transmission. Therefore, there is a pressing need to design drugs with broad antiviral activity for overcoming outbreaks of emerging infectious diseases. Currently, the World Health Organization has prioritized eight viral diseases (including COVID-19, Ebola, and Zika) for which research and development is urgently warranted.<sup>26</sup> Drug development using common targets against a bundle of representative highly pathogenic viruses, particularly those that have caused epidemic in the last decades, will assist healthcare professionals in the fight against emerging viruses in the future.

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## Conflicts of Interest

None.

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