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Systematic Review : Immunoglobulin Concentration in Breast Milk as a Body Defense against Sars-Cov-2



Miftah Chairunnisa¹, Dewi Rahmawaty A P², Ananti Setya P P³

¹Midwifery Department, STIKes Patria Husada Blitar, Indonesia

²Nursing Department, STIKes Patria Husada Blitar, Indonesia

³Midwifery Department, STIKes RSPAD Gatot Soebrata Jakarta, Indonesia

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Abstract

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The largest cases of pneumonia occurred in Wuhan City, Hubei Province of China in December 2019, which resembles SARS-CoV as a cause of SARS (Severe Acute Respiratory Syndrome) virus infection. The number of cases reaches 3.2 million people worldwide, and among them are breastfeeding mothers. Although virus transmission occurs through direct contact with infected patients, the number of infants or young children who were infected with COVID-19 during breastfeeding was only 10%. There is no scientific evidence for vertical transmission from mother to her baby during pregnancy and breastfeeding. The content of immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) has a positive impact on the infant's body. The objective of the study was to determine the immunoglobulin concentration in breast milk against SARS CoV2. The method used a systematic review approach with the design of *Preferred Reporting Items For Systematic Reviews & Meta-Analyses* (PRISMA). The result showed laboratory clinical trials, the IgA, IgG, and IgM responses showed good results in the spread of the coronavirus into the baby's body. IgA reactivity has a higher concentration than other cells. In conclusion, Covid-19 pandemic made the public worried about their health, including breastfeeding mothers. The role of health workers is needed to provide information related to breastfeeding exclusively to their babies so that they will receive protection against virus entered their bodies. **Suggestion:** It is necessary to develop studies regarding the typical responses that come up from IgA, IgM, IgG and are able to protect infants from Covid-19 and vertical transmission between mother and her baby during pregnancy to breastfeeding.

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✉ Correspondence Address:

STIKes Patria Husada Blitar – East Java, Indonesia

Email: chmiftah8@gmail.com

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INTRODUCTION

The largest case of pneumonia occurred in Wuhan City, Hubei Province of China in December 2019, which resembles SARS-CoV as a cause of SARS (Severe Acute Respiratory Syndrome) virus infection. WHO (World Health Organization) stated that on March 11, 2020, there had been a pandemic outbreak known as SARS-CoV-2. SARS-CoV-2 is the virus that causes Covid-19 that occurs in all countries. This incident infected as many as 3.2 million people in the world and more than 220,000 people died (Fox et al., 2020).

SARS-CoV and SARS-CoV-2 have similar characteristics of 76% to 79.5%, but the difference between them is in the symptoms that arise. SARS-CoV sufferers often experience breathing problems or dyspnea, so if this condition is serious it will lead to pneumonia. The mode of transmission of SARS-CoV-2 is through droplets, and when it attacks sufferers, it generally does not cause symptoms (Jaimes et al., 2020).

During the pandemic, breastfeeding mothers are considered a risk group for transmitting Covid-19 to their babies. The study states that there is no vertical transmission from mother to her babies during pregnancy until the breastfeeding period. According to the data was obtained, only 10% of babies experience Covid-19 due to direct contact and require follow-up. It is mentioned that the pathology of Covid-19 does not correlate with the transmission and the spread in large numbers (Fox et al., 2020).

The government's program regarding breastfeeding has been stated in the Republic of Indonesia Government Regulation, The Number is 33th of 2012. This program is a priority program because of its wide impact on the nutritional and health status of toddlers. This program is also recommended by WHO (World Health Organization) and UNICEF (United Nations Children's Fund) (Nawang Swastika Raras, Ari Suwondo, Sri Wahyuni, 2016)

The high morbidity and mortality rates in children at the beginning of the first month of life are caused by several diseases such as upper and lower respiratory tract infections, gastroenteritis, sepsis, and meningitis. It is also caused by other factors, namely quantitative and qualitative deficiencies contained in the immune component or the immune system. Early breastfeeding in the neonatal period is very important because of the susceptibility of

the baby's body to large numbers of microorganisms after birth. An immature baby's immune system at birth often occurs in premature babies, so it is feared that there will be an increased risk of infection (Susi Hartati, 2012). Therefore, to protect this population from coronavirus infection, it is very important for babies to be given nutritional intake through breast milk, where the contents in colostrum and breast milk include immunoglobulin A, immunoglobulin M and immunoglobulin G have a positive impact on immunity, i.e protecting against the entry of the coronavirus into the mucosa of the respiratory tract, digestive tract, and nervous system.

The explanation above has been delivered based on existing research and it is necessary to carry out a comprehensive assessment of the concentration of the immunoglobulin response in breast milk.

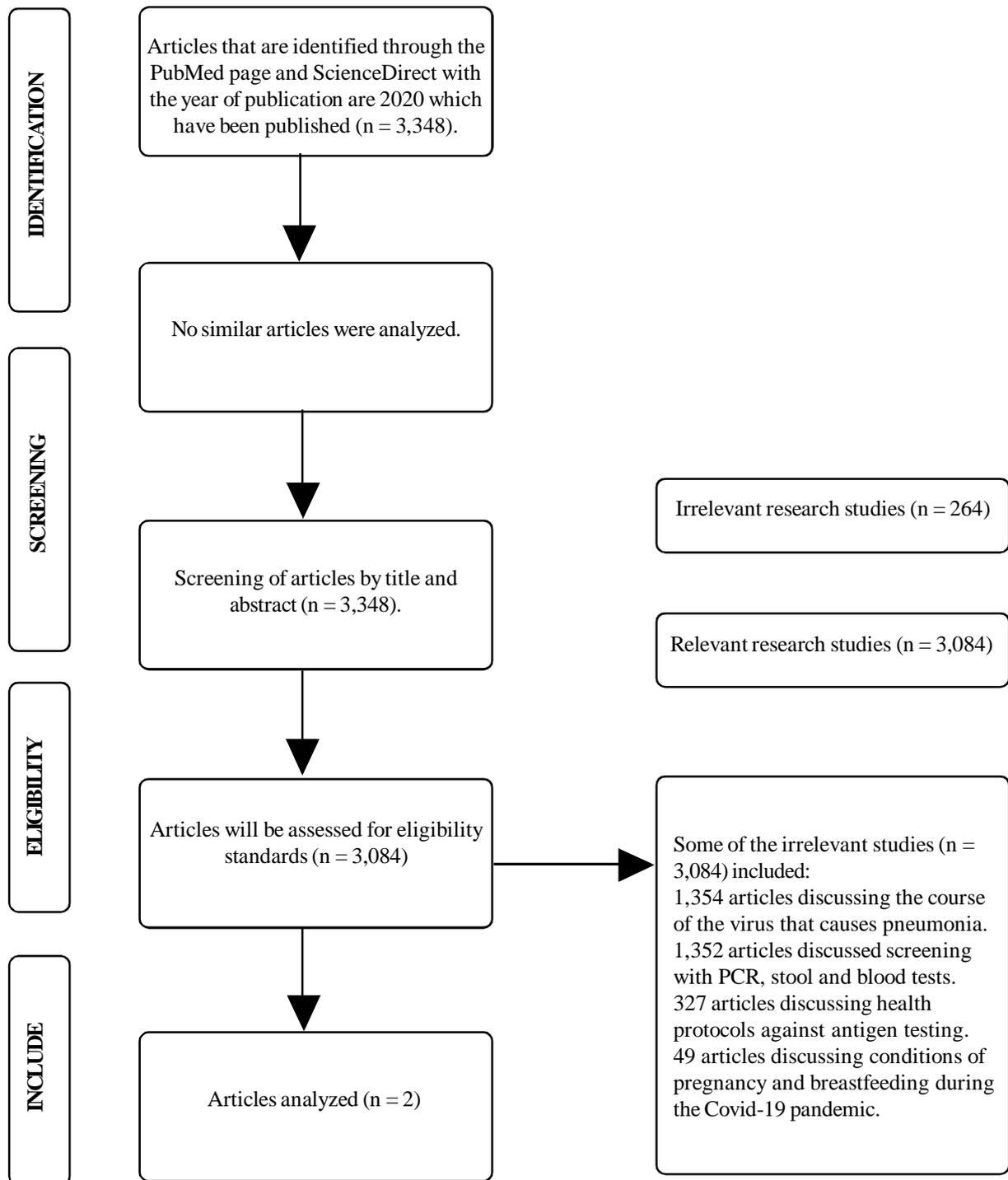
METHODS

The systematic review was used by searching for as much of the previous studies as possible in accordance with the research theme. The research design and research instrument used PRISMA (Preferred Reporting Items for Systematic Reviews & Meta-Analyses), which used a flowchart based on the 2009 PRISMA checklist. The articles obtained from Scintdirect and Pubmed, with the keywords used were "Immunology of Breast Milk" and "SARS-CoV-2". The search for the articles that matched the keywords was 2,203 and articles searched by the year of publication, i.e 2020. The articles used were based on international journals by looking for updated articles that can be analyzed based on inclusion and exclusion criteria. The inclusion criteria in this study were researchers downloading original articles about the concentrations of immunoglobulin in breast milk against SARS-CoV-2 specifically. The method used was in the form of a case-control study, and then the articles analyzed were published in 2020 on an international base. Meanwhile, the exclusion criteria were article findings in the form of reports and case studies.

The steps taken were downloading articles using existing keywords. The relevant articles found were 3,348 articles. There were 3,348 relevant articles based on the title and abstract as a whole which was divided into two categories, namely the relevant studies totaling 3,084 articles and the irrelevant ones as many as 264 articles. Then, the ar-

ticles assessed for the eligibility standard, where two articles met the requirements for analysis and 3,082 articles do not meet the eligibility standard requirements. The relevant studies found generally discussed the immunoglobulin response (IgA, IgM, and IgG) to the coronavirus and vertical transmis-

sion from mother to her baby, while the unrelated one was discussing the course of the virus that causes pneumonia, detection of examinations (fecal PCR, swab, rapid), health protocols against SARS-CoV-2 and conditions of pregnant women and nursing mothers during the Covid-19 pandemic.



RESULTS

The results of previous research about “immunoglobulin concentration in breast milk as the body’s defense against SARS-CoV-2” are presented in Table 1.

Table 1 shows the population synthesis based on the reviewed literature. The research study was obtained from two selected research articles and was conducted in New York with one article and Amsterdam with one article. The similarity of the

Table 1. Previous research of immunoglobulin-A concentrations in breast milk against the SARS-CoV-2.

No	Name, Year and Title	Research methods	Samples	Research Place	Conclusion
1	Evidence of a significant secretory-IgA-dominant SARS-CoV-2 immune response in human milk following recovery from COVID-19 Alisa Fox, Jessica Marino, Fatima Amanat, et.all	Prospective case control study	15	New York	IgA responses have very high concentrations in preventing transmission of the SARS-CoV-2 virus, relatively.
2	Breastmilk; a source of SARS-CoV-2 specific IgA antibodies Britt J. van Keulen, MD, Michelle Romijn, MD, Albert Bondt, PhD, et.all	Prospective case control study	38	Amsterdam	Breastmilk from mothers who have recovered from COVID-19 contains significant amounts of IgA against SARS-CoV-2, both before and after pasteurization.

two research studies, i.e the research design is the prospective case-control study.

The eligibility criteria contained in the two articles varied from fifteen to thirty-eight respondents. Then, research studies were published in the last 1 year, in 2020. The studies found were related to the immunoglobulin-A response to the SARS-CoV-2 virus.

A study conducted in New York showed that there were fifteen breastfeeding respondents who had been exposed to the SARS-CoV-2 virus, then tested in 3 different laboratories.

This testing experiment aimed to see the reactivity of IgA, IgG, IgM and antibody secretory types. The results of the four components assessed showed that IgA and secretory antibodies had higher reactivity than the others. The twelve samples, breast milk was shown to have reactivity against IgA. Four samples showed reactivity to IgG and IgM, then two samples showed reactivity to IgG but not IgM. In addition, one sample had IgM but not IgG reactivity, then one sample also showed reactivity to IgG but not IgA, IgM.

The study conducted in Amsterdam showed that serum and breast milk samples were tested through neutralization aimed at assessing whether they could reduce the SARS-CoV-2 virus replica. The neutralization of SARS-CoV-2 virus in this model was successful for serum samples (13%) and breast milk samples (26%). This is because it has a relatively high level of antibodies, namely IgG in serum and IgA in breast milk. Then, it is carried out by pasteurization test on breast milk, as is done with the standard method approach and high pressure heating on breast milk. The result of using both methods before and after pasteurisasi is that there is no difference in protein and IgA levels.

DISCUSSION

The emergence of SARS-CoV-2

The largest cases of pneumonia occurred in Wuhan in 2019. The agent causing the case was identified as betacoronavirus known as SARS-CoV. Coronavirus is an RNA that is included in the coronaviridae virus group, the order nidovirales,

where the virus is found in humans, mammals, and birds. The result of this virus is an infection of the respiratory tract, digestive system and nervous system. Coronavirus is a large and encased RNA that is divided into 4 genes, namely alpha, beta, delta and gamma, where covid beta and allfa are known to infect humans, called the human coronavirus (HCoV). There are four types of HCoV such as 229E, NL63, OC43, and HKU1 which cause upper respiratory tract infections in adults around 10% to 30%. In addition, two types of endemics that are considered very worrying for human life with a brief increase in the incidence of morbidity and mortality are SARS-CoV and MERS-CoV (N. Zhu et al., 2020).

Several studies state that the novel coronavirus (SARS-CoV-2) is a new virus that has similarities to the SARS virus, where the similarities between SARS-COV-2 and SARS-CoV are shown around 76% to 79.5%. This is due to the presence of the same amino acid composition in both viruses, while MERS-CoV has the same amino acid composition only 40% (Jaimes et al., 2020).

The Molkuler Ejikman Biological Institute announced that the spread of the coronavirus could be through the air in the form of aerosols. This condition has occurred in the hospital due to the use of a ventilator which is a medical procedure, which produces aerosols with small particles so that the distance of the spray is longer. Then, the coronavirus can also enter the human lungs through the respiratory tract, intestines through the mouth, and through the eyes (Nakayama et al., 2019). Transmission of the virus occurs through direct contact with someone who is infected with the virus through droplets or mouth, eye, and nose fluids. The body reacts differently to the virus when the virus enters the lungs causing difficulty breathing or shortness of breath. Then, in the intestine it causes diarrhea and in the eyes, it causes conjunctivitis (Guan et al., 2020), (Lovato & de Filippis, 2020). Viruses that successfully enter the cells of living things as hosts (host), then will spread and reproduce. This will cause some symptoms experienced by sufferers, or even cause no symptoms.

The entry of the corona virus into cells is through an endocytosis mechanism, where the virus is received by a receptor called angiotensin-converting enzyme 2 (ACE-2) which is on the surface of the cell and enters the cell (Guan et al., 2020). Protein S (Spike Protein) acts as a channel for viruses to

enter human target cells, especially in the lungs, where the lung cells are the part that is covered by the epithelium as a protector (Jia et al., 2005). Protein S will be captured by angiotensin-converting enzyme 2 (ACE-2) which is part of the receptor (Imai et al., 2005), where ACE-2 is an integral membrane composed of glycoproteins and Zn-metallo peptidase enzymes (breakdown proteins that containing zinc) (Tai et al., n.d.). Then, the ACE receptor has several cells such as lung, kidney and heart cells, generally these cells are more abundant in the lungs (Sri Sumarmi, 2020). The two receptors have binding power that affects the travel and spread of the coronavirus, where the binding power of ACE-2 to protein S in SARS-CoV-2 is around 10 to 20 times compared to protein S in SARS-CoV (Wrapp et al., 2019). This shows that the transmission of covid-19 is faster than SARS. In addition, the entry of viruses into cells is influenced by the Transmembrane Enzyme Serine Protease-2 (TMPRSS2) (Hoffmann et al., 2020). The corona virus in living cells will respond to other cells, where RNA will be released from the nucleocapsid into the cell cytoplasm, then transitioned by the host cell to produce new viruses. The viral replication mechanism in the host cell takes place so fast, that it causes one of the cells to become infected and causes the cell to be damaged. Then, the emergence of a new virus will spread in large numbers to attack and host human lung cells. The development of these millions of viruses is accompanied by an attack in the lungs causing T lymphocytes to secrete cytokines that act as defense forces in large numbers. This event is called a cytokine storm or cytokines release syndrome, where the production of pro-inflammatory cytokines is excessive and causes hyperinflammation which increases the permeability of blood vessels and the failure of the body's organs to work properly (Mehta et al., 2020). This condition is possible as a cause of death for people with Covid-19 (Sri Sumarni, 2020).

Given that the transmission of the corona virus is so fast, breastfeeding mothers are a risk group for exposure to Covid-19 because generally they are prone to stress which causes the immune system to decline. Research studies in China regarding vertical transmission from mother to fetus that show the transmission of geminal cells or placental blood during pregnancy, childbirth or during the postpartum period of breastfeeding, found no coronavirus in the baby's body. However, what was

found was transmission from mother to baby through direct contact accompanied by the presence of small particles or droplets. Reducing the spread and transmission of the corona virus in the body is important to increase the body's immunity for people with Covid-19 and those who are not infected. The strategy is to fulfill the basic principles of increasing immunity to the corona virus (H. Zhu et al., n.d.).

Increasing immunity to fight the entry of the corona virus can be done in several ways including 1) taking vitamins and supplements, 2) exercising regularly is an easy alternative, where exercising can stimulate the performance of antibodies and activate white blood cells to circulate quickly, 3) avoid dehydration which causes the body to feel tired and decreased immunity, 4) avoid stress (Amalia et al., 2020).

Immunoglobulins A, G and M in breast milk

Breastmilk is a dynamic source of nutrients and bioactive factors for optimal development and growth for babies and children. Breast milk is the secretion of human breasts that changes in hormonal, nutritional composition and developing active factors (Permanyar et al., n.d.). In breast milk also contains antibodies that have various active pathogens for protection or to increase the body's resistance to disease. Most of the antibodies have a high enough protein content that is secreted in the first days of breastfeeding. During breastfeeding, the immunoglobulin concentration decreases, but the amount of immunoglobulin received by the child does not change (Cacho & Lawrence, 2017).

During the growth period, babies get nutritional intake through breast milk (breast milk), where this intake will determine the survival of the baby in the future. Babies who are not maximal in getting breast milk (breast milk) are often susceptible to disease because the formation of immunity in the body is not yet perfect. Another aspect can also be seen from the history of exclusive breastfeeding which shows that breastfeeding babies who are not given exclusively will have a 4.47 times greater risk of developing pneumonia (Susi Hartati, 2012). Given the current cases of pneumonia and the SARAS-CoV-2 outbreak in the spotlight, because the increase everyday makes breastfeeding mothers worry about giving breast milk to their children.

Colostrum and breast milk contain several types of immunoglobulins, one of which is secretory IgA

which has an important role in concentration and biological properties. In addition, IgA also plays a role in the defense of mucous membranes and is effective at preventing the entry of microorganisms into the tissue and as an anti-inflammatory. IgA concentration contributes to the development and growth of children as much as 80% to 90% of the total immunoglobulin in breast milk and the baby will receive about 0.3 grams/kg/day of protein. This shows that breast milk can be absorbed by the baby's intestine and will be transferred to the bloodstream by about 10%, where basically the action is local (Palmeira & Carneiro-Sampaio, 2016).

IgA and IgM are related molecules, if IgA is decreased, IgM acts as the first line of defense that helps ward off foreign antigens from entering the body. However, IgA molecules will remain active in the digestive tract of newborns and have an impact on the binding of commensal microorganisms (pathogens, toxins, viruses or other microorganisms) such as lipopolysaccharides, which can prevent adherence and penetration into the epithelium without triggering an inflammatory reaction that can harm the baby (Palmeira & Carneiro-Sampaio, 2016). Likewise in babies who get breast milk from their mothers with Covid-19, where the molecules in breast milk work their best not to transmit the virus into the baby's body through vertical transmission through the breastfeeding process.

Based on immunochemical tests that show IgA from breast milk can live in the baby's stool. This shows that IgA is not destroyed by the digestive organs and protects the entire intestinal tract, so that it is able to bind to antigens of enteropathogenic origin. Thus, locally produced IgA antibodies will promote the inhibition of excessive colonization of microorganisms from mucous membranes, as well as antigen penetration (Palmeira & Carneiro-Sampaio, 2016). Research studies on antigens derived from the coronavirus (Covid-19) revealed that when a PCR test was carried out by taking a specimen from the reactive feces of children, it showed that there was a coronavirus in the stool through this test. This is due to the occurrence of virus replicas that can host the digestive system and come out together with feces (Tang et al., n.d.). So, in covid-19 reactive children who are getting breast milk, it should still be given to reduce the spread of the virus in the body because living cells from breast milk (IgA, IgM) are able to help the virus travel so it doesn't spread around it.

Immunoglobulin M is a component that has a second high level after IgA which has a concentration of about 2.5 mg / mL. IgM plays an important role in protecting the mucosal surface of the baby. Then, the next component is immunoglobulin G, where IgG plays a role in activating phagocytosis by transferring antigens to lamina propria to activate B-cells which can affect the adaptive response of the baby and have a concentration of about 0.1 mg / mL (10% of serum). IgG is the lowest concentration in breast milk. The level of immunoglobulin IgG concentration indicates that the formation of the infant's immune system is due to the development of the infant's adaptive immunity to produce an increase in the amount of IgG (Palmeira & Carneiro-Sampaio, 2016).

CONCLUSION

The period of the Covid-19 pandemic is a condition that is of concern to the wider community, especially for breastfeeding mothers. In connection with breastfeeding during this pandemic, health workers have a role to give education for mothers, their husband, and all of family member to provide nutrition to their babies through the breastfeeding process. The content of breast milk is very good for the baby's growth and can ward off viruses or other microorganisms that need to be delivered so that the baby does not lose his right to exclusively breastfeed for up to six months or can continue for two years. Living cells in breast milk such as IgA, IgM and IgG with their respective roles can increase the body's immunity in infants and avoid infection or other diseases. Then, the vertical transmission between mother and baby is not through plasma cells but through direct contact caused by small particles of fluid through the mouth, eyes and nose.

SUGGESTION

Following up on this discussion, it is necessary to develop a study on the typical response that arises from IgA, IgM, IgG and is able to protect infants from Covid-19. Then, a study of the correlation of vertical transmission between mother and her baby during pregnancy to breastfeeding, where the study findings are presented. In this systematic review, the mechanism is not specific. So, it is hoped that the large amount of literature that appears can add insight to readers and as recommendations for new knowledge.

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