



RESEARCH ARTICLE

Effect of Ginger Pulu Mandoti Cookies on Breast Milk Production and Breastfeeding Frequency

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ABSTRACT

Pulu Mandoti Ginger Cookies is one of the local wisdom-based supplementary foods substituted. The Research show that ginger can increase breast milk production and breastfeeding frequency. The purpose of analyzing the effect of Pulu Mandoti Ginger Cookies on breast milk production and breastfeeding frequency.

Quasi-experimental with the pretest-posttest control design group. The sampling technique was purposive sampling. The number of samples was 46 nursing mothers who were divided into two groups, namely the intervention group given two pieces (20 grams) / day of Pulu Mandoti Ginger Cookies and the control group given two pieces (20 grams) / day of Pulu Mandoti Cookies, each given for 30 days.

Results of breastfeeding frequency and breast milk production using Paired t-test, Mann-Whitney, and Unpaired t-test, measurement of breast milk production by assessing breast milk volume. Showed an increase in average breast milk production in the intervention group pre-test 128.14 ml/day and post-test increased to 437.53 ml/day \pm 77.18, there was a significant effect on increasing breast milk production with $p = 0.000$ ($p < 0.05$), the control group average pre-test 123.44 ml/day and post-test increased to 357.08 ml/day \pm 95.93, there is a significant effect on increasing breast milk production with $p = 0.000$ ($p < 0.05$). An increase in the frequency of breastfeeding in the Intervention group pre-test 7.26 times \pm 1.18 in the post-test increased to 13.61 times \pm 1.97, there is a significant effect on increasing the frequency of breastfeeding $p = 0.000$ ($p < 0.05$). Control, there was an increase in the frequency of breastfeeding pre-test at 7.09 times \pm 0.10 and at post-test away at 11.26 times \pm 2.05 with $p = 0.000$ ($p < 0.05$), there was an increase in frequency before and after the intervention in each group.

Pulu Mandoti Ginger Cookies affect milk production and breastfeeding frequency.

INTRODUCTION

The life cycle approach focuses on improving human resources from pregnancy to old age, addressing nutritional problems at each stage. Breast milk is crucial for growth and development until 24 months old, but not all mothers realize its importance. Breastfed babies have better nutritional status

compared to formula milk, and their health and intelligence are supported. The mother's diet significantly influences the quality of breast milk, with casein being the main protein (Orisinal O et.al., 2019; Mulya WT et.al., 2021)

The Sustainable Development Goals (SDGs) aim to reduce maternal and infant mortality rates by 2030, ensuring a healthy life and prosperity for all ages. The target is to reduce maternal mortality to below 70 per 100,000 live births, infant mortality to less than 12 per 1,000, and under-five mortality to 25 per 1,000 (Florence I, 2021)

The World Health Organization (WHO) reports that exclusive breastfeeding for infants aged 0-6 months is still 44% of the 2025 target, with 34% still implementing Early Breastfeeding Initiation (IMI) at < 1 hour and 41% using exclusive breastfeeding at < 6 months. In Indonesia, exclusive breastfeeding rates dropped to 12% in 2019, and early breastfeeding initiation rates fell to 48.6% in 2021. Poor coverage in developing countries remains, with only 50.4% exclusively breastfeeding (Indonesia Health Profile., 2022; Sari ID et.al., 2022)

In Indonesia, 71 infants aged 0 to 6 months were exclusively breastfed 100 infants (67.8%). In contrast, the proportion of single owners in rural areas (74.05%) for children aged 0-6 months is better than exclusive breastfeeding. The greater the urban share (69.64%), the weaker the country's economic situation, the greater the exclusive breastfeeding (Health Statistics Profile, 2021)

Director General of Public Health, Ministry of Health of the Republic of Indonesia In 2020, 28,158 children under 5 years in Indonesia died, with 70.0% occurring in newborns aged 0-28 days. However, 19.15% occurred between 29 days and 11 months and 9.9% between 12 and 59 months, indicating a high mortality rate of 32.2% in newborns under 5 years.

Indonesia's nutritional guidelines recommend 330 kcal of additional energy and 20 g of protein for mothers breastfeeding up to 6 months. Exclusive breastfeeding for 0-6 months is only 44% globally. Insufficient milk production is linked to physiological and psychological factors, including maternal malnutrition, weak suckling, enlarged breasts, nipple blisters, low milk production, and decreased milk injection (Indonesian Ministry of Health, 2019; RI Health Profile, 2021; Alindawati R, et.al., 2021)

In South Sulawesi, exclusive breastfeeding coverage in infants increased from 70.52% in 2020 to 76.43% in 2022. In Makassar City, infant mortality rates increased from 33 cases in 2021 to 61 in 2022. The Sudiang Health Centre, which only covered 122 babies, has low coverage, leading to high morbidity and mortality in infants and children (Health Statistics Profile, 2021; Makassar City Health Office, 2022).

Ginger, a rhizome plant with a unique flavor and aroma, is used as a treatment for various ailments. It contains anti-inflammatory substances and antioxidants, which relieve breast pain and aid in milk production. Gingerol oil content, particularly 10-dehydroginger, 10-ginger-dion, and 6-gingerdion, are believed to be key active substances in ginger, enhancing the efficacy of mixed drugs (Ariyanti R, et.al., 2023)

Cookies are round, sweet baked goods made from flour, sugar, and fat, often mixed with other ingredients like raisins, chocolate chips, and nuts. They are popular among both children and adults due to their convenience. This study explores the local wisdom of "Pulu Mandoti" (pulu mandoti rice, added with ginger) in South Sulawesi, a mountainous sticky rice with a distinctive aroma. Similar research was conducted on "Sago" (sago) in Biak, which is added with ginger and can affect milk production and breastfeeding frequency.

Pulu Mandoti Glutinous Rice is a red glutinous rice flour with a fragrant aroma and durability. It contains 73.66% carbohydrates, 6.98% protein, 12.19 µg/g iron, and 116.42 µg/g calcium. In 100g, it contains 47.18 grams of carbohydrates, 10.34 grams of protein, 19.35 grams of fat, 2.76 grams of

coarse fiber, Vitamin C, Vitamin A, glucose, iron, potassium, and calcium (BBLK, 2021; Rezmaniar, et.al., 2024).

Based on the above background, further research needs to be done. This study is unique in that it gives Pulu Mandoti cookies with Ginger to increase breast milk production. The author will research to measure and analyze the fluency of breast milk in breastfeeding mothers by carrying out the theme of Cookies Pulu Mandoti Ginger, which raises Enrekang's local wisdom with the composition of glutinous rice flour and Ginger.

MATERIALS AND METHODS

Experiment Group

This study uses a quasi-experimental design with a pre-test and post-test control group using purposive sampling. This research was conducted in Sudiang Health Center. The sample size consisted of 46 breastfeeding mothers divided into two groups: the intervention group, which was given two pieces (20 grams) per day of Ginger Pulu Mandoti Cookies, and the control group, which was given two pieces (20 grams) per day of Pulu Mandoti Cookies, each given for 30 days.

Tools and materials

The tools used are an electric oven, an electric bowl, a balloon whisk, a sieve, a spatula, a digital scale, and a cake mould. The ingredients are 100 grams of Mandoti pulu rice flour, 60 grams of egg yolk (1 egg), 43 grams of butter, 43 grams of palm sugar, and 60 grams of grated Ginger. the use of ingredients in 1 dough produces 24 pieces

Data Analysis

This study's data analysis was conducted using SPSS software. Various non-parametric and parametric statistical tests, including the Chi-Square, Wilcoxon, Mann-Whitney, Paired T-test, and Unpaired T-test, were used to test the research hypothesis.

RESULTS

Table 1. Characteristics of Respondents in Both

Variables	Intervention				p-value
	Pulu Mandoti Ginger Cookies (intervention)		Pulu Mandoti Cookies (control)		
	N	%	n	%	
Age Group					
< 20 years	1	2.2	1	2.2	
20 - 35 years	21	45.7	21	45.7	1.000 ^a
> 35 years	1	2.2	1	2.2	
Total	23	50	23	50	
Education					
SD	3	6.5	5	10.9	
SMP	4	8.7	4	8.7	0.566 ^a
HIGH SCHOOL	13	28.3	11	23.9	
PT	3	6.5	3	6.5	
Total	23	50	23	50	
Jobs					
IRT	15	32.6	19	41.3	
Honorar	1	2.2	0	0	0.205 ^a
Private	7	15.2	4	8.7	

Total	23	50	23	50	
Compliance					
Total	23	50	23	50	-
Stress					
No Stress	19	41.3	19	41.3	1.000 ^b
Stress	4	8.7	4	8.7	
Total	23	50	23	50	
IMD					
No IMD	4	8.7	3	6.5	1.000 ^b
IMD	19	41.3	20	43.5	
Total	23	50	23	50	

The study found no significant differences in age, education levels, occupation, stress levels, or IMD respondents between the Intervention and Control groups. The Control group had a higher elementary school education level (10.9%), while the Intervention group had a higher high school education level (28.3%). The study also found no significant difference in occupation between the two groups. Respondents with homemakers were more in the Control group (41.3%) than in the Intervention group (32.6%), while those working as honorarium and private employees were more in the Intervention group (15.2%). All respondents with compliant attitudes were present in both groups (100%). There were no significant differences in stress levels between the two groups (41.3%) or in IMD respondents (8.7%).

Table 2. Milk Production Before and After Intervention and control

Breast milk production	Pre	The post	Δ
Group	Mean± SD	Mean± SD	Mean± SD
Intervention	128.14 ml/day± 30.35	437.53 ml/day± 77.18	309.39 ml/day± 46.83
Control	123.44 ml/day± 24.05	357.08 ml/day± 95.93	233.64ml/day± 71.88

Table 2 shows that breast milk production increased significantly in the Intervention group, with an average increase of 309.39±46.83 between pre-test and post-test. In contrast, the Control group showed an average increase of 123.44±24.05 and a post-test increase of 357.08±95.93. The difference in average improvement was greater in the Intervention group, with a value of 309.39±46.83, compared to the Control group's value of 233.64±71.88.

Table 3. Frequency of Breastfeeding of Respondents before and after Intervention and control

Breastfeeding Frequency	Pre	The post	Δ
Group	Mean± SD	Mean± SD	Mean± SD
Intervention	7.26 times± 1.18	13.61 times± 1.97	6.35 times± 0.79
Control	7.09 times± 0.10	11.26 times± 2.05	4.17 times± 1.95

Table 3 reveals a significant increase in breastfeeding frequency among respondents in the intervention group, with an average increase of 7.26± 1.18 at pre-test and 13.61± 1.97 post-test. The difference in average increase between the intervention and control groups was 6.35± 0.79, while the difference in average improvement was more significant in the intervention group, with an average improvement of 6.35± 0.79 compared to the control group's 4.17± 1.95.

Table 4. Nutrient Adequacy Level of Macronutrients, Before and After Intervention and control

Nutrients	Intervention		Control		Δ	p-value
	Mean± SD	RDA (%)	Mean± SD	RDA (%)	Mean± SD	
Energy (kcal)						

Pre	1922.81± 314.38	75.30	1857.21± 234.66	72.43	65.6± 79.72	0.427 ^c
The post	2671.57± 266.66	104.65	2595.92± 250.43	100.65	75.65± 16.23	0.327 ^c
p-value	0.000 ^a		0.000 ^b			
Protein (g)						
Pre	64.78± 11.16	81.04	64.50± 13.32	80.70	0.28± 2.16	0.938 ^c
The post	84.57± 20.46	105.70	75.29± 16.68	94.09	9.28± 3.78	0.099 ^c
p-value	0.001 ^b		0.041 ^b			
Fat (g)						
Pre	57.40± 19.69	85.43	62.02± 17.89	92.30	4.62± 1.8	0.409 ^c
The post	89.93± 31.15	135.22	91.82± 21.42	136.70	1.89± 9.73	0.812 ^c
p-value	0.001 ^b		0.000 ^b			
Carbohydrate (g)						
Pre	285.00± 59.31	70.39	258.42± 49.40	63.78	26.58± 9.91	0.106 ^c
The post	382.34± 69.19	95.22	369.07± 62.57	91.13	13.27± 6.62	0.499 ^c
p-value	0.000 ^b		0.000 ^b			
Vit.A (μg)						
Pre	900.01± 554.11	89.96	568.31± 382.59	56.78	331.7± 171.52	0.026 ^d
The post	1202.30± 646.73	120.13	1190.68± 781.89	119.13	11.62± 135.16	0.956 ^c
p-value	0.073 ^a		0.005 ^b			
Vit.B1 (mg)						
Pre	0.77± 0.16	51.22	0.68± 0.16	45.22	0.09 0±	0.072 ^c
The post	0.85± 0.27	56.61	0.82± 0.15	55.09	0.03± 0.12	0.710 ^c
p-value	0.494 ^a		0.001 ^b			
Vit. C (mg)						
Pre	69.54± 65.27	46.39	35.02± 22.86	23.35	34.52± 42.41	0.055 ^d
The post	154.42± 80.64	102.91	144.31± 85.19	96.17	10.11± 4.55	0.725 ^d
p-value	0.002 ^a		0.000 ^a			
Calcium (mg)						
Pre	712.03± 725.52	59.39	481.63± 260.16	40.13	230.4± 465.36	0.097 ^d
The post	970.89± 780.39	80.91	823.02± 695.01	68.61	147.87± 85.38	0.307 ^d
p-value	0.036 ^a		0.004 ^a			
Iron (mg)						
Pre	19.14± 53.34	106.35	7.79± 2.88	43.30	11.35± 50.46	0.313 ^c

The post	44.66± 123.62	248.13	50.35± 155.36	279.87	5.69± 31.74	0.538 ^d
p-value	0.000 ^a		0.201 ^b			

Table 4 analyzed the effects of pulu mandoti ginger cookies on various nutrients. Results showed differences in energy, protein, fat, carbohydrates, vitamin A, B1, C, and calcium content before and after the intervention of giving the cookies. However, no significant difference was observed in energy, protein, fat, carbohydrates, Vit B1, Vit C, Calcium, and Iron. After the cookies, there were significant differences in these nutrients. The results suggest that pulu mandoti ginger cookies may be a beneficial snack option for those looking to improve their nutritional status. The study also found no significant difference in vitamin A and vitamin B1 before and after the intervention.

Table 5. Effect of Ginger Pulu Mandoti Cookies and Pulu Mandoti Cookies on Pre and Post-Breast Milk Production Between Intervention and control Group

Group	Breast milk production Mean± SD		Mean Difference	p-value
	Pre	The post		
Intervention	128.14 ml/day± 30.35	437.53 ml/day± 77.18	309.39 ml/day± 46.83	0.000 ^a
Control	123.44 ml/day± 24.05	357.08 ml/day± 95.93	233.64 ml/day± 71.88	0.000 ^a
p-value	0.564 ^b	0.003 ^b		

^aPaired_t_test

^bUnpaired_t_test

Table 5 found a significant increase in breast milk production in the intervention group (Pulu Mandoti Ginger Cookies) compared to the control group (Control). The intervention group showed an average increase of 128.14±30.35, followed by a post-intervention increase of 437.53±77.18, resulting in a difference of 309.39±46.83. The control group showed no significant difference in breast milk production before and after the intervention. The difference in average breast milk production between the intervention and control groups was statistically significant ($p=0.000$, $p>0.05$), indicating that the intervention had a positive effect on breast milk production. However, the difference in average breast milk production between the intervention and control groups was statistically significant ($p=0.003$, $p<0.05$).

Table 6. Effect of Ginger and Pulu Mandoti Cookies on Breastfeeding Frequency Pre and Post Between Intervention and control Groups

Group	Frequency Mean± SD		Mean Difference	p-value
	Pre	The post		
Intervention	7.26 times± 1.18	13.61 times± 1.97	6.35 times± 0.79	0.000 ^a
Contro	7.09 times± 0.10	11.26 times± 2.05	4.17 times± 1.95	0.000 ^a
p-value	0.656 ^b	0.000 ^c		

^aMann-Whitney ^bUnpaired_t_test

The study found a significant increase in breastfeeding frequency in the intervention group, with an average increase of 7.26± 1.18 pre and 13.61± 1.97 post. The intervention group showed a difference of 6.35± 0.79 in breastfeeding frequency, while the control group showed no significant difference in breastfeeding frequency. The mean difference in breastfeeding frequency between the intervention

and control groups was $p=0.656$ ($p>0.05$), indicating no difference before the intervention. However, after the intervention, the mean difference was $p=0.000$ ($p<0.05$), indicating a difference in breastfeeding frequency between the intervention and control groups. The results suggest that the intervention may have a positive impact on breastfeeding frequency.

DISCUSSION

Effect of Ginger Pulu Mandoti Cookies and Pulu Mandoti Cookies on Milk Production

The results showed Pulu Mandoti Ginger Cookies intervention led to a significant increase in average milk production, from 128.14 ml to 437.53 ml post-test, with a difference of 309.39 ml. The increase was more significant in the Ginger Cookies group, with a p-value of 0.000.

Ginger consumption can increase breast milk volume, especially during breastfeeding. A study by Maylia Arviyanti (2024) found that 22 postpartum mothers had an average volume of 415.54ml. Ginger's anti-inflammatory and antioxidant properties help overcome pain from breast inflammation, which is common in breastfeeding mothers. Consuming ginger can also facilitate milk production, with the highest volume being 557ml (Maylia Ariyanti, et.al., 2024).

Research by Ariyanti et al. (2023) found that breastfeeding mothers who received ginger extract for seven days after childbirth had higher milk volume (71.2 ml/day) compared to a placebo (61.5 ml/day). However, no differences in serum prolactin were found. In Western Australia, ginger was ranked second (11.8%) in herbs used by breastfeeding mothers to increase milk production (Ririn Ariyanti, et.al., 2023)

The consumption of pulu mandoti cookies can increase breast milk production due to factors like the content of galactogogues. Galactogogs stimulate breast milk production, increase blood flow, and help overcome stagnant milk production. Research shows that 26 types of galactogog plants are commonly used by breastfeeding mothers in Bali, with 82% starting use after childbirth and 95% feeling confident after using herbal galactagogues. This can provide optimal nutrition for the baby and extend breastfeeding periods (Yuniartis P, 2023; Ni Luh Gde, 2021)

Carbohydrates, particularly lactose, provide energy and Calcium absorption for bone growth. Protein aids in bodybuilding, while fat aids in brain development. Vitamins and minerals support growth and health. These nutrients are processed by the mother's body and sent to the mammary glands for high-quality breast milk. Breastfeeding mothers should consume a balanced diet, including iron and calcium, to ensure optimal nutrition for the baby's growth and development (Indrayani D, et.al., 2018)

Nisa Kartika Ningsih's research found that four respondents consumed non-nutritious food and had sufficient breast milk, while 20 respondents had healthy food and adequate breastmilk production. The study found that food consumption is not related to breast milk production, as various nutrients are needed during breastfeeding, including carbohydrates, vitamins, minerals, protein, fat, and sufficient fluid, to improve breast milk production (Ningsih NK, 2020).

Meanwhile, research conducted by Mainunah (2020) shows that the results of testing the relationship between nutritional status and exclusive breastfeeding analyzed using the Chi-Square 3x2 bivariate test obtained a significance value (sig.) $p = 0.002$ ($P = <0.05$), so it is concluded that nutritional status has a significant relationship with exclusive breastfeeding of mothers, where mothers who have good dietary status provide better exclusive breastfeeding than mothers whose nutritional status is worse (Rohman MA, 2020)

A 2018 study found a link between maternal nutritional status and exclusive breastfeeding. Mothers with poor nutritional status had a 3.638 times higher risk of not providing exclusive breastfeeding. This suggests that breastfeeding mothers' nutritional status affects the volume and composition of

breast milk. A balanced diet is crucial for breastfeeding mothers to meet their needs. Research suggests that mothers with good nutrition usually breastfeed their babies for at least 6 months, while those lacking nutrition may not breastfeed for 6 months (Khairunnisa, 2018 ; Hapsari QC, et.al.,2021)

The results showed that both ginger pulu mandoti cookies and pulu mandoti cookies were effective in improving nutritional status, especially in several macronutrients (energy, protein, fat, carbohydrates) and micronutrients (vitamin C, Calcium, Iron). The complex carbohydrate content in these cookies provides sustained energy for the body, while protein contributes to the formation of new cells, including in breast milk production. In addition, pulu mandoti cookies are also rich in various vitamins and minerals, such as vitamin B complex, which plays a role in energy metabolism and red blood cell formation, as well as minerals such as Iron, which is essential for preventing anaemia in breastfeeding mothers (Rezmaniar, et.al., 2024; Busthanul N, et.al.,2021).

Ginger, a spice with a bitter and spicy taste, contains essential compounds like oleoresin, gingerol, and cineole that can boost breast milk production. Its anti-inflammatory properties can relieve breastfeeding discomfort and improve blood circulation. Ginger-infused pulu mandoti cookies showed a higher increase in milk production compared to the control group, indicating its significant contribution to breast milk production (Jauhary H, 2020; Redi Aryanta IW, 2029).

The results of this study have important implications for efforts to increase breast milk production in nursing mothers. Pulu mandoti ginger cookies can be a safe and effective food alternative to increase breast milk production. However, further research with a larger sample size and a more complex research design is needed to confirm the results of this study and identify more specific mechanisms related to increased breast milk production after the consumption of pulu mandoti ginger cookies.

Effect of Ginger Pulu Mandoti Cookies and Pulu Mandoti Cookies on Frequency of Breastfeeding

Frequency is one of the efforts to increase breast milk, ideally the frequency of breastfeeding 8 times per day. Mothers who breastfeed with a good frequency will have the possibility of producing breast milk smoothly. According to the American Academy of Pediatrics/AAP (1997, in the Indonesian Ministry of Health, 2010), it is recommended to breastfeed 8-12 times every day (24 hours), with a duration of 15-20 minutes for each breast (Andri Yulianto, et.al., 2022).

The ability of the breast glands to produce hormones is related to the frequency of this suckling. Milk secretion and production increase with the frequency with which the baby suckles at the mother's breast. The baby will determine his own needs, so it is best to feed him unscheduled (on demand) (Ningsih F, et.al., 2019) . Breastfeeding on demand is the term for this method. This will increase milk production and help prevent breast engorgement. If the baby is crying, the mother should breastfeed him, not for any other reason or because she already feels the need to breastfeed him. A healthy baby will remove one breast within four to seven minutes (Ningsih F, et.al., 2019)

Breastfeeding is crucial for a baby's development, as it stimulates the hypothalamus, anterior hypophysis gland, and posterior hypophysis to produce hormones like prolactin and oxytocin. Correct sucking involves the baby's mouth wide open, vigorous suckling, and painless nipples. The mother's nipples should be rounded, with more areola above the mouth, and the baby's tongue under the nipple. The movement of the child's suction can affect the stimulation of the nipple, which has sensory nerve endings that send impulses to the hypothalamus, anterior hypophysis gland, and posterior hypophysis gland. Regular breastfeeding increases breast milk production, while stopping breastfeeding decreases it. Two reflexes cause milk to come out at the right time: milk formation/production reflex (prolactin reflex) and milk drainage/release reflex (let down reflex). Prolactin stimulates alveolar cells to produce milk, while letdown reflex contracts muscle cells around the alveoli, pushing milk towards the nipple (Ririn Ariyanti, et.al., 2023; Ummah MS, 2019).

Based on the data in Table 4.6 after the paired t-test, it can be seen that the Intervention group increased the frequency of breastfeeding from pre to post-measurements 6 times. In the control group, there was an increase in the frequency of breastfeeding from pre to post-measurements 4 times. The increase in the frequency of breastfeeding in both groups was statistically significant with a p-value <0.05, meaning that there was a difference in the frequency of breastfeeding pre and post-treatment. Giving pulu mandoti ginger cookies increases the frequency of breastfeeding by 2 times compared to giving pulu mandoti cookies.

Many scheduled breastfeeding mothers are unable to learn about breastfeeding frequency due to factors like education and employment. Private sector workers often struggle to dedicate time to breastfeeding. Many mothers do not understand the importance of breastfeeding according to their baby's needs. To prevent breastfeeding problems, health workers should provide information about breastfeeding frequency to mothers, enabling them to breastfeed properly according to their baby's needs (Carroll C, 2019; Salsabila R, et.al., 2023).

It is known that age and education level correlate with the choice of foods a person consumes. People with older age and middle to upper education levels tend to be more selective in choosing what foods they eat (Septiyani D, et.al.,2021) . In this study, it is presumed that samples from both groups accepted both the ginger pulu mandoti cookies and the given pulu mandoti cookies, even under the supervision of enumerators and researchers

CONCLUSIONS

The findings of this study have significant implications for efforts to improve exclusive breastfeeding practices. The use of Pulu Mandoti Ginger cookies as part of a nutritional intervention can be one strategy to address the problem of low breast milk production and support the health of mothers and babies.

CONFLICT OF INTEREST

The authors declare no conflict of interests

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