Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2022.22075

The Use of Human Milk for Therapeutic Purposes Other Than Nutrition

Mehmet Semih Demirtaş[1], Sıddıka Songül Yalçın[2]

[1]Department of Pediatrics, Aksaray Training and Research Hospital, Aksaray, Turkey
[2]Department of Pediatrics, Division of Social Pediatrics, Hacettepe University, Faculty of Medicine, Ankara, Turkey.

ABSTRACT

Human milk is a popular treatment method applied as a traditional, natural pharmacotherapy that has been going on for many years in many societies. Due to its low cost, widespread and easy use, and lack of undesirable effects, breast milk also has the potential to play a role in evidence-based treatment for tertiary people as well as infant and maternal health. Scientific databases were searched for Literature search from January 1995 to December 2021, including Ovid, PubMed, Google Scholar, Science Direct, ResearchGate, Web of Science Core Collection (Clavirate), and a total of 45 articles from 142 articles written in English were included in the study. According to the results of the current studies reviewed, there is a general conclusion about the positive effects of human milk in the treatment of tertiary persons in addition to the prevention and treatment of common maternal and infantile diseases. Human milk can be used as a different alternative in further studies, especially based on anti-tumoral and cancer studies. In addition, an accessible, safe, and suitable alternative treatment for the treatment of allergic skin and mucous tissue damage in infants and mothers may be suitable for societies with limited access to treatment.

Keywords: Human milk, milk therapy, breastfeeding, breast milk, topical milk treatment, using of colostrum, HAMLET, topical human milk, donor milk

INTRODUCTION

Human milk (HM) is a functional nutrient for newborns and infants, and it not only meets the nutritional needs of the baby with its macro and micronutrient balance, but also supports bioactive substances such as prebiotics, enzymes, and anti-inflammatory agents.[1,2] The majority of studies on the effects of HM are based on short- and long-term effects on infants. Besides protecting infants from infectious diseases and supporting growth and development in short term, it is now appreciated that HM has life-long health effects with protection from metabolic and autoimmune diseases, continuation of cognitive development, and protective effects against cardiovascular diseases and asthma.[3-5]

Before the advent of modern medicine, treatment with HM has been practiced in many societies for many years as part of traditional, natural pharmacotherapy, and ethnomedicine.[6] The preventive and therapeutic role of HM is particularly important for alternative treatments in regions where diagnosis and treatment are inadequate, such as sub-Saharan African countries. In situations where access to treatment is difficult, milk treatment is often a decisive factor for the infant's recovery and survival. Therefore, more evidence-based clinical studies and research on the use of HM, which is easy to use and access, are more common in low- and middle-income countries with stronger traditional structures. Preclinical studies on the content and effects of HM in non-nutritional uses are promising, with more research being done in the near future.[6-8]

Human milk has the potential to be included in the evidence-based treatment of diseases due to its widespread and easy use and the absence of complications (Figure 1). The purpose

Corresponding author:
Mehmet Semih Demirtaş
✉md.semihdemirtas@gmail.com
Received: March 20, 2022
Accepted: March 25, 2022

Cite this article as: Semih Demirtaş M, Yalçın SS. The use of human milk for therapeutic purposes other than nutrition. *Turk Arch Pediatr.* 2022;57(3):255-266.

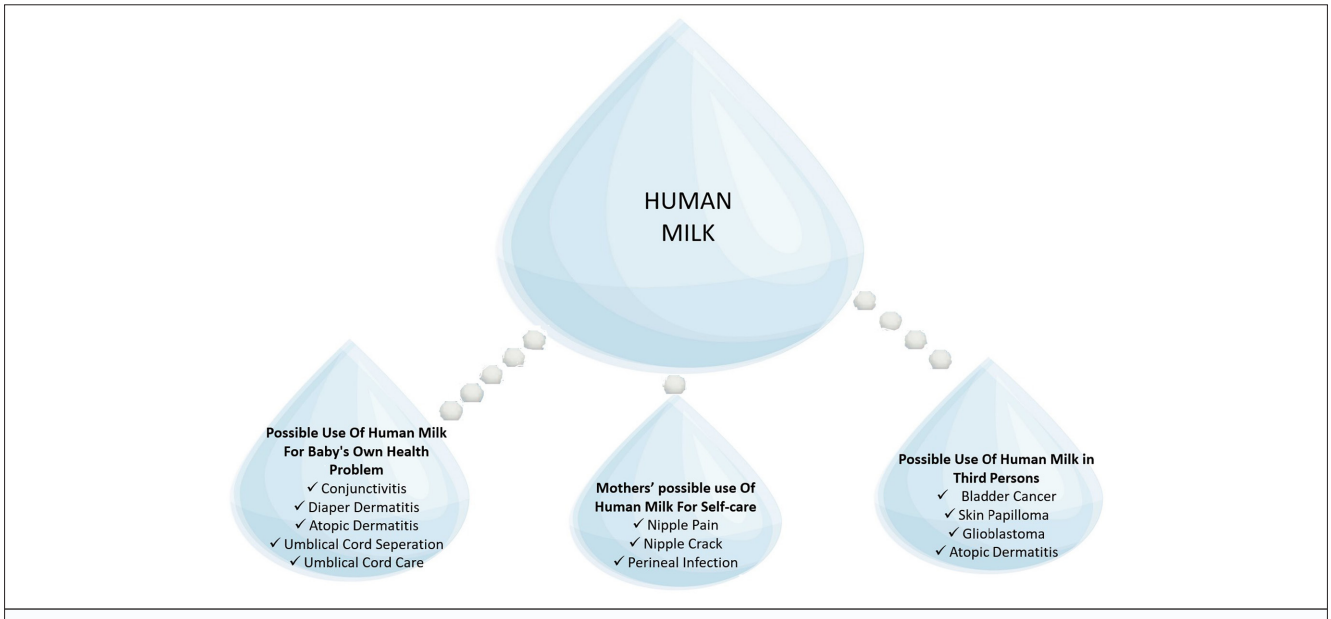

Figure 1. Possible use of human milk.

of this review is to summarize the studies on the therapeutic use of HM other than nutrition.

MATERIALS AND METHODS

The studies obtained as a result of the current literature review consist of intervention studies such as Case-control, case series, and revisions. We applied the Preferred Reporting Items for Screening Meta-Analyses in our study.[9] Various scientific databases were searched for Literature search from January 1995 to December 2021, including Ovid, PubMed, Google Scholar, Science Direct, ReserchGate, and Web of Science Core Collection (Clavirate).

We used the following words as keywords in the literature review: "Human milk," "Breast milk," "Topical Milk treatment," "Using of Clostrum," "Milk therapy," "HAMLET," "Topical Human Milk," and "Donor Milk."

The two co-authors of the study independently searched specified scientific databases and reviewed articles one by one. The specified keywords were examined in a double and triple step with a gradual screening study and a total of 45 articles from 142 articles written in English were included in the study. Human milk use in these studies was related to 21 of the infant's own health problems, 4 studies to the mother's own health problems, 8 studies to third persons use, 8 animal studies, and 4 in vitro/vivo studies.

RESULTS

Possible Use of Human Milk for Baby's Own Health Problem

Eye Problems

Conjunctivitis

The use of HM by mothers and physicians in the treatment of eye diseases has been documented in ancient Egyptian, Roman, and Greek texts.[10] Pishva et al[11] examined the effect of topical breast milk use on conjunctivitis in the first 10 days after birth in a Case-control study conducted on 565 newborns in 1998, the incidence of conjunctivitis was found to be 9.1% and 25.6% in infants receiving HM topically and in the control groups, respectively ($P < .001$). Ghemi et al[12] investigated the use of colostrum in the prophylaxis of neonatal conjunctivitis in their study. The study was carried out with a total of 268 newborns, 89 infants in the topical HM group, 82 infants in the topical erythromycin (0.5%) group, and 97 infants in the control group. Although no difference was found in the HM and erythromycin groups used topically, the frequency of conjunctivitis was found to be higher in the control group than in the other 2 groups (0.5%) ($P = .03$) (Table 1).

Congenital Nasolacrimal Duct Obstruction

In a study by Verd in 2007 evaluating the effect of HM in congenital nasolacrimal duct obstruction, it was revealed that the treatment duration of the group receiving HM topically was shorter than the group receiving antibiotic eye drops (mean: 1.42 months vs. 5.40 months; $P < .001$). In addition, the resolution of epiphora was 15%–50% on the 30th and 60th days in the group receiving local antibiotic eye drops; in the group receiving HM, this rate was 57% and 90%, respectively.[13]

Skin Problems

Studies have been conducted on the application of the effects of HM as a topical treatment in allergic skin diseases such as diaper dermatitis and atopic dermatitis, which are seen with increasing rates in infant and child health in our age.[8]

Diaper Dermatitis

Diaper dermatitis in infants is the most common skin disease, which is a common source of inflammation in newborns, can be seen in 7-50% of infants, and is more common in 7-12 months of age.[14,15] Diaper dermatitis can even predispose to secondary bacterial and fungal infections and skin ulcers, with lipase and protease enzymes disrupting the integrity of the skin after prolonged exposure to urine and feces.[14,16–18] Seifi et al[19]

Table 1. Possible Uses of HM for the Baby's Own Health Problems

System Using HM	Use in Diseases Conditions	Reference Year Place	Study Type, Population, and Groups	Study Design	Results
Eye	**Conjunctivitis**	Pishva[11] 1998/Iran	Case-control, 565 HBM:327, Control: 238	Dropping of HBM before breastfeeding, at least 4 times a day for the first 10 days	The incidence of conjunctivitis in infants receiving HBM topically and in the control groups was 9.1% and 25.6%, respectively ($P < .001$)
		Ghaemi[12] 2014/Iran	Case-control, 268 HBM:89, Control: 65, Antibiotic eye drops:82	Preterm newborns with negative eye swab cultures were randomly divided into three groups. Two drops of colostrum were given to the intervention group. No treatment was applied to the control group, and topical Erythromycin ointment (0.5%) was applied to the 3rd group.	The frequency of conjunctivitis was higher in the control group than those who received topical colostrum and topical erythromycin (0.5%) ($P = .03$).
	Congenital nasolacrimal duct obstruction;	Verd[13] 2007/Spain	Retrospective cohort, 65 HBM:45, Antibiotic eye drops: 20	Mothers administered HBM or antibiotic eye drops.	It revealed that treatment with topical antibiotics lasted longer than the group receiving HBM (mean: 5.40 vs. 1.42 month; $P < .001$).
Skin	**Diaper dermatitis**	Seifi[19] 2017/Iran	Case-control, 30 HM:15, Control: 15	A total of 30 patients with Diaper Dermatitis aged 0-12 months were followed up with scale rash severity. In the case group, AS was dripped 3 times a day.	It revealed that there was a significant difference between the case and control groups in the number of dermatitis rash and lesion score on the 1st and 3rd days ($P = .013$, $P = .005$), showing that this difference was more significant on the 5th day ($P = .004$, $P = .001$).
		Gozen[20] 2014/Turkey	Case-control, 63 HBM:30, ¥Barrier cream: 39	For dermatitis care of newborns in the human HBM group, HBM was applied each diaper change (8 times in a day). In the barrier cream group involved the application of barrier cream containing 40% zinc oxide and cod liver oil.	Although no significant difference was found between the two groups, significantly higher wound healing was found in HBM compared to the barrier cream group ($P = .002$)
		Farahani[21] 2013/Iran	Case-control, 141 HBM:71, ¥Topical 1% hydrocortisone cream 70	141 infants, including children in the first 2 years of age, in which the effects of topical application of breast milk and 1% hydrocortisone were also compared, the study was conducted with two groups that applied 1% hydrocortisone for 7 days and applied HBM to the affected dermatitis area after each breastfeeding.	There was no significant difference after topical application of the drugs tested in both groups and AS alone was as effective and safe as hydrocortisone 1% ointment ($P < .001$).
	Atopic dermatitis	Kasrae[27] 2015/Iran	Case-control, 116 HBM:58, ¥Topical 1% hydrocortisone cream: 58	HBM or hydrocortisone 1% was applied twice a day for 21 days on the atopic dermatitis area. The efficiency of the treatment was defined by the SCORAD index.	The frequency of infants who recovered in the breast milk and 1% hydrocortisone groups was 81.5% and 76%, respectively. Human milk can improve atopic eczema with similar results and is as easy to apply as 1% hydrocortisone ointment ($P < .001$).
		Berents[58] 2015/Norvey*	Case-control, 18 HBM:9, Control:9	The number of HBM droplets depended on the size of the eczema area; the mothers were instructed to cover the whole eczema spot with milk and in both groups were treated with moisturizing cream 3 times a day for 4 weeks.	No effect was found on eczema spots treated with topical application of HBM.

(*Continued*)

Table 1. Possible Uses of HM for the Baby's Own Health Problems (*Continued*)

System Using HM	Use in Diseases Conditions	Reference Year Place	Study Type, Population, and Groups	Study Design	Results
Umbilical cord	**Umbilical cord separation**	Aghamohammadi[32] 2012/Iran	Case-control, 130 HBM:65, ¥DCC:65	While topical HBM application was applied 3 times a day for 10 days in the case group, it was followed without intervention in the dry cord care group (DCC).	The median duration of cord separation was 6 ± 1 days in the HBM topical application group; it was determined as 8 ± 2 days in the DCC group ($P = .001$)
		Golshan[36] 2013/Iran	Case-control, 316 HBM:100, ¥DCC:100, 70% Ethanol: 100	The study was divided into 3 groups: The group that applied HBM and 70% ethanol applied twice a day, while the control group performed DCC.	While the duration of UCS was 6.5 ± 1.93 days in newborns in the HBM group, it was 8.94 ± 2.39 and 7.54 ± 2.37 days in the ethanol and DCC, respectively. Although there was no difference in the frequency of omphalitis between the three groups, the time UCS in the HBM group was significantly shorter than in the ethanol ($P < .001$) and dry care groups ($P < .003$).
		Allam[33] 2015/Egypt-Saudi Arabia	Case-control, 400 HBM:200, ¥DCC:200	While topical HBM application was applied 3 times a day per day until cord separation and 2 days after, it was followed without intervention in the DCC.	It was shown that 80% of the neonates in the topical HBM group had UCS on the third to fourth days and that the HBM group (4 ± 20 days) was significantly lower than the dry UCC (7±10 days) ($P < .001$).
		Vural[37] 2015/Turkey	Case-control, 150 HBM:50, ¥DCC:50, Povidone-iodine: 50	In the HBM and povidone-iodine group, HBM and povidone-iodine were applied directly to the distal end edge of the stump twice a day for 2 days after the UCS.	It was shorter in HBM (7 ± 2 days) and DCC (8 ± 3 days) than in the povidone-iodine group (10 ± 3 days) ($P < .05$).
		Kacho[38] 2006/Iran	Case-control, 312 HBM: 79, DCC: 78, silver sulfadiazine: 77, ethyl alcohol: 78	Topical application was applied to HBM, silver sulfadiazine, and ethyl alcohol groups 3 times a day and continued 2 days after UCS in each group.	The UCS time was found to be in HBM (5 ± 2 days), silver sulfadiazine (10 ± 4 days), ethanol (6 ± 2) days, and DCC (7 ± 2 days) ($P < .001$).
		Abbaszadeh[39] 2016/Iran	Case-control, 162 HBM: 80, chlorhexidine: 82	Topical application was made up to UCS twice a day in HBM and Clorhexidine groups.	It was significantly shorter in the HBM group (7±2 days) than the chlorhexidine group (13±7 days) ($P < .001$).
		Mahrous[6] 2012/Egypt	Case-control, 100 HBM: 50, 70% ethanol: 50	Topical application was applied to HBM, ethanol groups 3 times a day and continued 2 days after UCS in each group.	The UCS time was lower in HBM (4 ± 1 days) than in the ethanol group (8 ± 2 days) ($P < .001$).
		Pujar[35] 2013/India	Case-control, 60 HBM:30, ¥DCC: 30	Topical application was applied to HBM 2 times per 3 days.	The UCS time was lower in HBM 5 days than in the DCC group (9 days) ($P < .005$).
		Dhanawade[34] 2014/India	Case-control, 90 HBM: 45, ¥DCC: 45	Topical application was applied to HBM 2 times per 3 days.	The UCS time was lower in HBM 5 days than in the DCC group (9 days) ($P < .005$).
		Lyngdoh[40] 2018/India	Case-control, 105 HBM:35, Chlorhexidine: 35, ¥DCC: 35	Topical application was applied to HBM and Chlorhexidine groups once a day and continued 2 days after UCS in each group.	It was significantly shorter in the HBM group (7 ± 2 days) than the chlorhexidine (14 ± 3 days) and DCC group (11 ± 3 days) ($P < .001$).

(*Continued*)

Table 1. Possible Uses of HM for the Baby's Own Health Problems (*Continued*)

System Using HM	Use in Diseases Conditions	Reference Year Place	Study Type, Population, and Groups	Study Design	Results
	Umbilical cord infections colonization	Taffazoli[41] 2008/Iran	Case-control, 118 HBM: 61, *DCC: 57	Topical application was applied to HBM 2 times a day and continued 2 days after UCS in HBM group.	They found that *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli and Klebsiella pneumonia* were the most common organisms growing in the umbilical cord and they found that bacterial colonization was significantly lower in the HBM group than in the DCC group (*P* < .001).
		Allam[33] 2015/Egypt Saudi Arabia	Case-control, 400 HBM:200, *DCC:200	While topical HBM application was applied 3 times a day per day until cord separation and 2 days after, it was followed without intervention in the DCC.	*E. coli* and *S. aureus* were found to be 2% less in the HBM group compared to the dry cord care group.
		Lyngdoh[40] 2018/India	Case-control, 105 HBM:35, Chlorhexidine: 35, *DCC:35	Topical application was applied to HBM and Chlorhexidine groups once a day and continued 2 days after UCS in each group.	The growths of *K. pneumoniae, E. coli, S. haemolyticus*, and *Streptococcus* were examined and 72 ± 12. In the culture growths observed at 72 ± 12 hours, less growth was detected in the chlorhexidine group (5.7%) than in the HBM (34.3%) and DCC groups (51.4%) (*P* < .001).

HM, human milk; HBM, human breast milk; HAMLET, human α-lactalbumin made lethal to tumor cells; DCC, dry cord care, UCS, umbilical cord separation; UCST, umbilical cord separation time; BMT, bone marrow transplantation; GBM, glioblastoma; *Use of HM in tertiary person and for baby's own health problem, *: Control Group.

conducted a Case-control study in Iran to evaluate the effect of HM on gland dermatitis with 30 newborns aged 0-12 months and revealed that there was an important difference between the HM and control groups in terms of the number of rashes and lesion scores due to dermatitis on the first and third days (*P* = .013, *P* = .005), and this difference proved to be more significant in the fifth day (*P* = .004, *P* = .001). In a study from Turkey comparing topical HM and moisturizing barrier creams in diaper dermatitis, a significantly higher wound healing was found in the HM group compared to the control group, although there was no significant difference between the HM group and the control groups (*P* = .002).[20] In a study that compared HM and topical application of 1% hydrocortisone in the treatment of diaper dermatitis and included children in the first 2 years, a total of 141 children was conducted with two groups applying 1% hydrocortisone for 7 days and applying topical HM to the dermatitis area after each breastfeeding. Dermatitis status was noted using a scale on days 3 and 7 of the study and there was no significant difference in groups after topical application of the drugs tested, and they stated that the use of HM in the treatment of diaper dermatitis is as effective and safe as hydrocortisone 1% ointment (*P* < .001) (Table 1).[21] It was claimed that bioactive substances such as minerals, fatty acids, and vitamins in HM make baby skin soft and smooth and prevent dryness and brittleness. It is claimed that with this, secondary infections are prevented and the hydrophobic structure of the fatty acids in the HM structure prevents the damage that may occur from feces and urine.[8,17,19,20]

Atopic Dermatitis

Atopic dermatitis, also known as atopic eczema, is an itchy, chronic, inflammatory skin disease with periods of exacerbation and remission that is most common in infants. The lifetime prevalence of the disease, which is seen between 20% and 30% in childhood, is increasing globally.[22-24] Studies with the effects of HM have shown that breastfeeding has a significant effect on reducing allergic diseases, including atopic dermatitis, especially in the first postpartum weeks. A meta-analysis conducted in 2001 reported lower incidence rates of atopic dermatitis when infants with a positive family history of atopy were breastfed exclusively from birth to 3 months of life (OR = 0.58; CI, 0.41-0.92).[25] Similarly, a recent meta-analysis revealed evidence of the protective function of breastfeeding (total and exclusive) on atopic dermatitis in the group with a positive family history.[26] Kasrae et al[27] compared HM and 1% hydrocortisone cream in atopic dermatitis in Iran in 2015 and randomized a total of 104 infants to 21 days of treatment. The frequency of infants who recovered on day 21 in the HM and 1% hydrocortisone groups was 81.5% and 76%, respectively (*P* < .001). The findings showed that HM is as effective as 1% hydrocortisone in the treatment of atopic eczema without any side effects.

Umbilical Cord Care

Sepsis is a condition that can cause morbidity and mortality for newborns and is responsible for 17.6% of neonatal deaths globally.[28] Preventable neonatal deaths due to sepsis can be prevented with appropriate umbilical-cord care (UCC) practices, which can be taken in the early period, especially in poor hygienic environments.[29] The World Health Organization (WHO) advocates the use of dry UCC in high-risk areas with limited

treatment opportunities to not only reduce neonatal death and morbidity and improve infant care but also recommend clinical research on the use of HM and colostrum in UCC.[30,31]

Umblical Cord Separation

Aghamohammadi et al[32] studied the effect of topical HM application on UCS in 130 singleton, term and healthy newborns, and mothers were asked not to let the umbilical cord get in the diaper and not to wash the child until the cord was separated. The median UCS time was found to be 6 ± 1 days in the HM topical application group and 8 ± 2 days in the dry UCC group ($P = .001$). Similarly, Allam et al[33] studied 400 newborns and reported shorter UCS time in the HM group than that in the dry UCC group (4 ± 20 days and 7 ± 10 days, respectively, $P < .001$). In India, Dhanawade et al[34] in their study with 90 newborns in 2014 and Pujar et al.,[35] with 60 newborns: In both studies, the umbilical cord separation time (UCST) was shorter in the group that was applied topically HM (5 days) compared to the dry UCC group (9 days) ($P < .005$).

In the umbilical cord separation (UCS) time study of Golshan et al[36] in which 316 newborns were included, the groups were divided into 3 groups, namely ethanol, HM, or dry (UCC). In the HM group, mothers performed umbilical cord care with HM twice a day. While the duration of UCS time was 6.5 ± 1.93 days in the breast milk group, it was 8.94 ± 2.39 and 7.54 ± 2.37 days in the ethanol and dry UCC group, respectively. Although there was no difference in the frequency of omphalitis among groups, the UCS time in the HM group was significantly shorter than in the topical ethanol ($P < .001$) and dry UCC groups ($P < .003$).

Vural and Kısa[37] in Turkey compared the effect of HM, povidone-iodine, and dry UCC on UCS in 150 healthy newborns. HM (7 ± 2 days) and dry UCC (8 ± 3 days) were shorter than those in the povidone-iodine group (10 ± 3 days) ($P < .05$). Kacho et al[38] compared UCS in 312 newborns with 96% ethyl alcohol and silver sulfadiazine and HM: UCS was found in 5 ± 2 days in the HM group, 10 ± 4 days in the silver sulfadiazine group, 6 ± 2 days in the ethyl alcohol group, and 7 ± 2 days in the control group ($P < .001$). Also, in another study on UCS that included 174 infants in Iran: HM and chlorhexidine groups were compared, and UCS time in the HM group (7±2 days) was reported to be shorter than in the chlorhexidine group (13±7 days) ($P < .001$).[39] Mahrous et al[6] found lower UCS time in the HM group (4±1 days) than in the ethanol group (8±2 days) ($P < .001$). In another study conducted in India in 2018, the UCST was in the HM group (9 ± 2 days), Chlorhexidine group (14 ± 3 days), and dry UCC group (11 ± 3 days) ($P < .001$) (Table 1).[40]

Umbilical Cord Infections/Colonization

In Taffazoli's 2008 study, which included 118 infants in Iran, bacterial colonization of the umbilical cord was examined in 2 groups, namely HM and dry UCC. In the group receiving HM topically, breast milk was dropped to the umbilical cord 3 hours after birth, and this application was continued every 12 hours until 2 days after the UCS. They found that *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia Coli,* and *Klebsiella pneumonia* were the most common organisms growing in the umbilical cord and found that bacterial colonization was significantly lower in the HM group than in the dry UCC group ($P < .001$).[41] In Allam's study with umbilical cord separation, when they were also compared in terms of bacterial colonization, *Escherichia Coli* and *Staphylococcus Aureus* were found to be 2% less in the HM group compared to the dry UCC group.[33] Lyngdoh's UCS study also investigated bacterial growth colonization in the umbilical cord. *K. pneumoniae, E. coli, Staphylococcus haemolyticus*, and *Streptococcus* growths were examined at 72 ± 12 hours and less growth was found in the chlorhexidine group (5.7%) than in the HBM (34.3%) and dry UCC groups (51.4%) ($P < .001$).[40]

Mothers' Possible Use of Human Milk for Self-Care

The perineal problems in normal births and breast-related problems in the postpartum period have led to more studies on the use of HM for the mother's own care in these areas.[42]

Nipple/Nipple Problems

While nipple pain is seen in more than half of the mothers in the first week of postpartum, nipple cracks vary between 15% and 40%. Appropriate treatment and breastfeeding counseling in the early period for cracks and pain in the nipple is a decisive and important factor for the continuity of breastfeeding.[43,44] Mohammadzadeh et al[45] evaluated the effect of HM and lanolin cream on nipple pain and showed a longer recovery time in the group using lanolin cream compared to the HM group ($P = .029$). However, Abou-Dakn et al[46] detected lower pain levels for nipple pain in the group using lanolin cream, showing that these pains subsided with continued treatment in Germany (n=84, $P = .043$). In Turkey, Kirlek et al[42] reported less nipple pain in the group that applied HM topical than an olive oil application. On contrary, olive oil application was found to be reduced the possibility of nipple crack ($P < .05$) (Table 2).

Perineal Infections

The vast majority of women undergo an episiotomy (perineal area incision) during normal delivery, and more than half of them require suturing in the perineal region. The resulting infection of the perineum causes pain and discomfort in the mother, and as a result, mothers may have problems in taking care of themselves and the baby.[47,48] Admasari et al[49] compared HM and povidone-iodine (10%) on perineal ulcer in Indonesia 2017. They showed that the HM Group had a significantly shorter wound healing time than the povidone-iodine group (11 days and 20 days, respectively, $P = .002$) and stated that this result can be explained by bioactive substances such as stem cells, other anti-inflammatory and antioxidant substances in HM.

Possible Uses of Human Milk in Tertiary Persons Except for Mother and Infant

Human milk contains more than just a source of nutrition for an infant; in addition to providing a wide variety of molecules that inhibit infective agents such as antibodies, bactericidins, and bacterial adhesion inhibitors, it also contains bioactive substances against host cells.[2,50,51] After the successful results in the studies on the baby and the mother over the years, studies on the use of HM in tertiary people have begun. These studies are being investigated more intensively, especially in adult cancer studies.[52,53]

Table 2. Areas that HM Can Potentially Use for the Mother's Own Care and Health Problems

System Using HM	Use in Diseases Conditions	Reference Year Place	Study Type, Population, and groups	Study Design	Results
Painful and damaged nipples	**Painfull nipples**	Mohammadzadeh[45] 2005/Iran	Case-control, 225 HBM: 78, Lanolin: 74, Control: 73	While the mothers in the HM group rubbed the painful breast area with HM after each breastfeeding; in the group applying lanolin cream, the mothers were asked to use lanolin locally on the aching area and to clean it before feeding the baby.	It showed a longer recovery time in the lanolin group compared to the HM group ($P = .029$).
	Painfull damaged nipples	Abou-Dakn[46] 2011/Germany	Case-control, 78 HBM: 39, Lanolin: 45	Mothers using HM were instructed to Express and to massage a few drops of HM on the nipples and areola after each feed, which were then allowed to air-dry. nipple trauma and healing rates were rated by the Nipple Trauma Score	Significantly lower pain levels were detected in the lanolin group and these decreased with continued treatment. They noted that lanolin was more effective than HM, including faster healing of nipple trauma ($P = .043$)
	Painfull damaged nipples	Kirlek[42] 2013/Turkey	Case-control, 39 HBM: 13, Olive oil: 13, Control: 13	In the olive oil-administered group, two drops of olive oil dripped onto sterile gauze after each breastfeed and applied to and around the breast-fed nipple; In the HM group, after each feeding, a few drops of breast milk were squeezed and rubbed with the index finger around the breast-fed nipple and its surroundings.	While pain was reported less in the group that applied HM topical for nipple pain, olive oil application decreased the possibility of nipple cracking ($P < .05$).
Perineal infection	**Perineal infection**	Admasari[49] 2017/Indonesia	Case-control, 30 HBM: 15, Control: 15	In both groups, HM and povidone-iodine (10%) were applied to the wound area twice a day for 7 days with a cotton swab. The REEDA Scale was used for perineal infections.	They showed that the HM Group (11 days) had a significantly shorter wound healing time than the povidone-iodine (10%) (20 days) group ($P = .002$).

HM, human milk; HBM, human breast milk.

Bladder Cancer

In Mossberg's study with 9 newly diagnosed bladder cancers: Human α-lactalbumin made lethal to tumor cells (HAMLET) injections were administered locally into the bladder for 5 consecutive days prior to bladder surgery. It was determined that a large number of tumor cells were excreted in the urine 2 hours after the injection. Most of these cells showed some evidence of apoptosis. It was also determined that there was a decrease in tumor size during cystoscopy.[54]

Skin Papilloma

In a Swedish study investigating the therapeutic efficacy of HAMLET in 45 patients with skin papillomas: Patients with severe, treatment-resistant papillomas on the hands and feet were given HAMLET in the case group and saline solution in the control group daily for 3 weeks. The lesion volume of the papillomas was reduced by more than 75% after topical application of 3 weeks of HAMLET therapy ($P < .001$). In addition, complete resolution of all lesions of papillomas occurred in approximately 83% of HAMLET-treated patients after 2 years, and resolution time was shorter in the group assigned to receive HAMLET in the first phase of treatment than in the group that received placebo at baseline (2.4 vs. 9.9 months; $P < .01$) (Table 3).[55]

Intestinal inflammation

Khandelwal et al[56] included 33 patients aged 0-5 years in Cincinnati and showed that intestinal inflammation including IL-8 and IL-10 levels decreased in bone marrow transplant patients who were given HM compared to others ($P = .04$ and $P = .02$, respectively).

Atopic Dermatitis

While the majority of studies with atopic dermatitis were conducted with breastfed infants' own milk,[57] Berents et al[58] also studied the HM of different infants in Norway. They stated that

Table 3. Possible Uses of HM in Tertiary Persons Other Than Mother and Baby

System Using HM	Use in Diseases Conditions	Reference Year Place	Study type, Population and Groups	Study Design	Results
Cancer and antitumoral	**Bladder cancer**	Mossberg[54] 2007/Sweden	Case Series, 9	Nine male patients awaiting transurethral surgery for newly diagnosed or recurrent superficial bladder cancer were invited to participate in the study and received 5 daily intravesical instillations of HAMLET (25 mg/ml) during the week before scheduled surgery	A large number of tumor cells were found to be excreted in the urine 2 hours after injection, and most of the excreted cells showed evidence of apoptosis and most were quantified. Reduction in tumor size was detected during cystoscopy.
	Skin papilloma	Gustafsson[55] 2004/Sweden	Case-control, 45 HAMLET (α-Lactalbumin–oleic acid):20, Control: 20	α-Lactalbumin–oleic acid or saline placebo was applied daily for three weeks and the change in the volume of each lesion was recorded. After this first phase of the study, 34 patients participated in the second phase, an open-label trial of a three-week course of α-lactalbumin–oleic acid.	Topical application of HAMLET reduced lesion volume by more than 75% ($P < .001$). In addition, a significant reduction in lesion volume was observed in all HAMLET-treated patients, and complete resolution of all lesions occurred in approximately 83% of HAMLET-treated patients after two years (2.4 vs. 9.9 months; $P < .01$).
Others	**Intestinal inflamation**	Khandelwal[56] 2019/USA	Case-control, 46 HBM:32 (donor milk n = 23, breastfeeding infants n = 9), Control: 12	Enroll and randomize patients 2:1 to receive either donor HM preparation formulated especially from the study (Prolacta Bioscience, Duarte, CA) or standard feeding with formula. Some of these 42 children being enrolled in the study were receiving mothers' own milk at the time of the study and were enrolled on the human milk arm without any randomization Controls received standard cow's milk-based nutritional supplementation through enteral tubes,	They showed that IL-8 and IL-10 were decreased and intestinal inflammation decreased ($P = .04$, $P = .02$, respectively) in patients with HM given BMT.
	Atopic dermatitis	Berents[58] 2015/Norvey*	Case-control, 18 HBM: 9, Control: 9	The number of HBM droplets depended on the size of the eczema area; the mothers were instructed to cover the whole eczema spot with milk and in both groups were treated with moisturizing cream 3 times a day for 4 weeks.	No effect was found on eczema spots treated with topical application of HBM.
	Neurocognitive development	O'Connor[64] 2016/Canada	Case-control, 363 HBM (Donor):181, Control:182	Infants were fed either donor milk or formula for 90 days	NEC development was found to be significantly lower in the group using donor HM compared to the group using formula product (1.7%, 6.6%, respectively, $P = .002$).

HM, human milk; HBM, human breast milk; HAMLET, human α-lactalbumin made lethal to tumor cells; BMT, bone marrow transplantation; NEC: necrotizian entereocolit. *Use of HM in tertiary person and for baby's own health problem, ˣcontrol group.

they could not show a significant effect in the study compared to the HM and control (moisturizing cream) group. However, as a limitation, the study was conducted with only 6 children, aged 18.5 months, having atopic dermatitis (Table 3).

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is observed in approximately 1-10% of infants hospitalized in neonatal intensive care units, and more than 80% of cases are preterm newborns.[59] In some

studies, in which the use of donor HM was used in neonatal intensive care units when the mother's own milk could not be used, the relationship with NEC was examined.[60-63] In the study of O'Connor et al[64] with 363 babies with extremely low birth weight, among the secondary results it was found that NEC developed at a lower rate in the donor HM group compared to the formula milk group (1.7% and 6.6%, respectively, $P = .002$).

In Vivo/Vitro and Animal Studies Using Human Milk

As of today, the importance of HM is well understood not only in scientific fields but also in all layers of society. As known, breastfed babies are less likely to get infectious diseases and their immune systems are stronger, breastfeeding mothers are less likely to get breast cancer.[2,8,50] Given the micro/macronutrient balance and bioactive substances in HM and the immunomodulatory effect of HM, the idea of using HM for therapeutic purposes was created in different diseases and areas. With this awareness, studies of the effects of HM on human diseases in laboratory experiments and on animal models have begun. The Svanborg group's 1995 study on the effect of bacterial adherence of breast milk on a human lung cancer cell line: The discovery that HM kills malignant cells has created a new revolution in the field of medicine. It was revealed that this result was due to the selective, cytotoxic activity of α-lactalbumin, a strong Ca (2+) inducer and apoptosis-inducing agent (HAMLET).[52] HAMLET is formed during low pH precipitation of the casein fraction, which allows the α-lactalbumin structure to partially open and binds with the fatty acid. HAMLET induces rapid carcinoma cell detachment in vitro and in cancer patients after topical application of the lyophilized complex.[65] Ho et al[53] conducted a HAMLET study in 2017 and demonstrated the therapeutic efficacy of HAMLET on glioblastoma, bladder, and intestinal cancer in animal studies. Moreover, HAMLET had also been shown to target skin papillomas and bladder cancers.

Eye Problems

In the HM study in animal experiments, Diego et al[66] investigated the effect of HM in a mouse dry eye model. They observed that mice were able to maintain corneal epithelial thickness after topical application of HM and noted that the epithelial damage score decreased after 4 days of HM treatment ($P < .001$). This experiment was the first Case-control study to compare HM with topical cyclosporine, showing that HM can maintain corneal epithelial thickness in a mouse model of dry eye. Asena et al[67] showed that topical use of HM drops resulted in faster and better healing of central corneal epithelial defects than either the treatment with serum drops or artificial tears or the control group in BALB/c mice ($P < .001$) (Table 4).

Bladder Cancer

Mossberg et al[68] compared infusions of HAMLET for 8 days with phosphate-buffered saline PBS in mice with MB49 implanted murine bladder cancer cells. The therapeutic effect of HAMLET infusions on tumor development in the bladder cancer model was demonstrated ($P = .02$). Besides, HAMLET-treated mice had more lacked detectable tumors than mice in the control group (33% vs. 0%, $P < .02$) and a significant reduction of tumors (mean score 1.9 vs. 2.5, $P < .02$).

Glioblastoma

The therapeutic efficacy of HAMLET against human glioblastomas was also investigated. In a mice model (n = 20), 7 days after transplantation of human glioblastoma cells via injection, HAMLET was applied to the tumor area by intracerebral convection-enhanced application for 24 hours. At 8 weeks, local infusions of HAMLET delayed tumor development and prolonged survival. HAMLET induced tumor apoptosis in vivo and no toxic side effects were observed in adjacent intact brain tissue or untransformed human astrocytes (Table 4).[69]

Intestinal Cancer

In a human colon cancer model examining the effects of HAMLET on intestinal cancer: $Apc^{Min/+}$ mice were given 10 mg of HAMLET solution periorally twice daily for 10 days. Perioral administration of HAMLET resulted in up to 58% reduction in polyp count in this model ($P < .0001$). In addition, it was shown that HAMLET specifically accumulated in tumor tissue and the expression of important oncoproteins such as B-catenin, Ki67, COX2, and VEGF were decreased ($P = .003$, $P = .001$, $P = .028$, $P = .005$, respectively). It has also been shown to inhibit gene expression in the Wnt signaling pathway in whole-genome transcriptomic analysis ($P < 0.0001$).[70]

Umbilical Cord Infections

Ramsey et al[71] evaluated the antimicrobial capacity of colostrum against *Chlamydia trachomatis* in 1998. They collected colostrum from 13 postpartum women and tested colostrum in an in vitro analysis of chlamydial growth inhibition using HeLa 229 cells as the host cell line. Interestingly, growth of *Chlamydia trachomatis* was significantly inhibited in a dose-response manner and the inhibition of chlamydial growth occurred at ≤15 min when incubated with chlamydia prior to addition to HeLa 229 monolayers. They interpreted the chlamydial growth inhibition activity of colostrum as freeze-proof, more concentrated than breast milk, and cannot bind to interferon or antibody activity. They concluded that topically applied colostrum can be effective in the prophylaxis of *Ophthalmia neonatorum* from chlamydia in the absence of appropriate treatment modalities. In a study conducted in Niger where the in vitro activity of term HM on *O. neonatorum* organisms was evaluated: sensitivity level to colostrum and mature HM was reported to be 57% and 28% in *E. coli,* and 50% and 0% and *S. aureus*, respectively.[72]

CONCLUSION

This review provides information on the non-nutritional uses of HM in infants, mothers, and tertiary persons. According to the results of the current studies reviewed, there is general agreement on the positive effects of HM in the treatment of tertiary persons, especially in the prevention and treatment of common maternal and infantile diseases. To date, side effects and complications have not been demonstrated in HM administration treatments. HM can be used as a different alternative in these studies, especially based on anti-tumoral and cancer studies. In addition, an accessible, safe, and suitable alternative treatment for the treatment of allergic skin and mucous tissue damage in mothers and infants may be suitable for societies with limited access to treatment. In order to evaluate the benefits of HM, randomized, double-blind, multicenter

Table 4. Uses of HM in In Vivo/Vitro and Animal Studies

System Using HM	Use in Diseases Conditions	Reference Year Place	Study Type, Population, and Groups	Study Design	Results
Eye	**Dry eye syndrome**	Diego[66] 2016/USA	Animal in vivo study, 91	An 8-week old female BALB/c mice with dry eye syndrome were treated with HBM, nopal, nopal extract derivatives, or cyclosporine four times daily for 7 days. Punctate staining and preservation of corneal epithelial thickness were used as indices of therapeutic efficacy.	They observed that human milk can preserve corneal epithelial thickness in a mouse model of dry eye. Epithelial damage reflected in point scores decreased after four days of treatment with milk ($P < .001$). Reduction in corneal epithelial thickness was largely prevented by administration of whole milk (33.2 ± 2.5 μm) or fat-reduced milk (36.1±1.58 μm), outcomes that were similar to treatment with cyclosporine (38.52 ± 2.47 μm), a standard in current dry eye therapy.
	Corneal epithelial wound healing	Asena[67] 2016/Turkey	Animal in vivo study, 24 HBM: 6, Topical artificial tears: 6, topical autologous drops: 6, control: 6	Topical eye drops were applied for 3 days 4 times in a day at the same time to all groups and HM was obtained from a lactating mother, under her consent who had a 6-month-old term infant.	It showed that topical use of breast milk resulted in faster and better healing of central corneal epithelial defects than either the treatment with serum drops or artificial tears or the control group ($P < .001$).
Cancer	**Bladder cancer**	Mossberg[68] 2010/Sweden	Animal in vivo study, 6	Bladder tumors were established by intravesical injection of MB49 cells into poly L-lysine treated bladders of C57BL/6 mice. Treatment groups received repeat intravesical HAMLET instillations and controls received α-lactalbumin or phosphate buffer for 8 days.	The therapeutic effect of HAMLET was confirmed with a more pronounced difference in tumor development ($P = .02$). HAMLET-treated mice had more detectable tumors (±) than controls (33% vs. 0%, $P < .02$) and tumors were significantly reduced compared to controls (mean score 1.9 vs. 2.5, $P = .02$).
	Glioblastoma	Fischer[69] 2004/Norway	Animal in vivo study, 20	Human GBM tumors were generated by transplantation of GBM biopsy spheroids in rats (Han:rnu/rnu Rowett, n = 20). After 7 days, HAMLET was applied to the tumor area by intracerebral convection-enhanced application for 24 hours; and α-lactalbumin, a native, folded variant of the same protein, was used as control	8 weeks later, local infusions of HAMLET delayed tumor development and prolonged survival. HAMLET induced tumor apoptosis in vivo and no toxic side effects were observed in adjacent intact brain tissue or untransformed human astrocytes.
	Intestinal cancer	Puthia[70] 2014/Sweden	Animal in vivo study, 30 Hamlet: 15, Sham-treated: 15	For the HAMLET therapeutic protocol, 8–10-week-old male mice were orally gavaged with 10 mg of HAMLET in 400 μL phosphate= buffered saline (PBS), twice daily for 10 days.	Peroral administration of HAMLET resulted in up to 58% reduction in tumor size and polyp count in this model ($P <$ .0001). In addition, it was shown that HAMLET specifically accumulated in tumor tissue and the expression of important oncoproteins such as B-catenin, Ki67, COX2 and VEGF were decreased ($P = .003$, $P = .001$, $P = .028$, $P = .005$, respectively).
Umbilical cord	**Umbilical cord infections/ colonization**	Ramsey[71] 1998/USA	In vitro Study, 13	It was tested in an in vitro analysis of Chlamydial growth inhibition using colostrum collected from 13 postpartum women and HeLa 229 cells as the host cell line.	In all samples, it significantly inhibited chlamydial growth in a dose-responsive manner. They also demonstrated that inhibition of Chlamydial growth occurred at ≤15 minutes when incubated with chlamydia prior to addition to HeLa 229 monolayers of chlamydial growth inhibition activity of colostrum and freeze-proof, more concentrated than breast milk, and cannot bind to interferon or antibody activity.
		Ibhanesebhor[72] 1996/Nigeria	In vitro Study, 22	Colostrum (defined as milk obtained <7 days after delivery) and mature milk (defined as milk 2 weeks or more postpartum), 8 were obtained from breastfeeding mothers not receiving any form of medication.	Susceptibility level to colostrum and mature AS *Escherichia coli* and *Staphylococcus aureus* were reported to be 57% and 28% and 50% and 0%, respectively.

HM, human milk; HBM, human breast milk; HAMLET. human α-lactalbumin made lethal to tumor cells, GBM, glioblastoma, [x]Control group.

controlled studies should be conducted in appropriate ethical conditions, and the number of studies in this area is very few to date.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.S.D, S.S.Y.; Design – M.S.D, S.S.Y.; Supervision – S.S.Y.; Resources – M.S.D.; Materials – M.S.D, S.S.Y.; Data Collection and/or Processing – M.S.D.; Analysis and/or Interpretation – M.S.D., S.S.Y.; Literature Search – M.S.D.; Writing Manuscript – M.S.D., S.S.Y.; Critical Review – S.S.Y.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Kramer MS. "Breast is best": the evidence. *Early Hum Dev*. 2010;86(11):729-732. [CrossRef]
2. Yalçın SS, Demirtaş MS, Yalçın S. Breastfeeding while pregnant: a country-wide population study. *Breastfeed Med*. 2021;16(10):827-834. [CrossRef]
3. Binns C, Lee M, Low WY. The long-term public health benefits of breastfeeding. *Asia Pac J Public Health*. 2016;28(1):7-14. [CrossRef]
4. Cope MB, Allison DB. Critical review of the World Health Organization's (WHO) 2007 report on 'evidence of the long-term effects of breastfeeding: systematic reviews and meta-analysis' with respect to obesity. *Obes Rev*. 2008;9(6):594-605. [CrossRef]
5. Ip S, Chung M, Raman G, et al. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess (Full Rep)*. (Full Rep). 2007;153(153):1-186.
6. Mahrous ES, Darwish MM, Dabash SA, Ibrahim M, Abdelwahab SF. Topical application of human milk reduces umbilical cord separation time and bacterial colonization compared to ethanol in newborns. *Transl Biomed*. 2012;3(1):1-10.
7. Arroyo R, Martín V, Maldonado A, Jiménez E, Fernández L, Rodríguez JM. Treatment of infectious mastitis during lactation: antibiotics versus oral administration of Lactobacilli isolated from breast milk. *Clin Infect Dis*. 2010;50(12):1551-1558. [CrossRef]
8. Witkowska-Zimny M, Kamińska-El-Hassan E, Wróbel E. Milk therapy: unexpected uses for human breast milk. *Nutrients*. 2019;11(5). [CrossRef]
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100. [CrossRef]
10. Baynham JT, Moorman MA, Donnellan C, Cevallos V, Keenan JD. Antibacterial effect of human milk for common causes of paediatric conjunctivitis. *Br J Ophthalmol*. 2013;97(3):377-379. [CrossRef]
11. Pishva N, Mehryar M, Mahmoudi H, Farzan R. Application of topical breast milk for prevention of neonatal conjunctivitis. *Irn J Sci*. 1998;23:55.
12. Ghaemi S, Navaei P, Rahimirad S, Behjati M, Kelishadi R. Evaluation of preventive effects of colostrum against neonatal conjunctivitis: a randomized clinical trial. *J Educ Health Promot*. 2014;3:63. [CrossRef]
13. Verd S. Switch from antibiotic eye drops to instillation of mother's milk drops as a treatment of infant epiphora. *J Trop Pediatr*. 2007;53(1):68-69. [CrossRef]
14. Blume-Peytavi U, Hauser M, Lünnemann L, Stamatas GN, Kottner J, Garcia Bartels N. Prevention of diaper dermatitis in infants--a literature review. *Pediatr Dermatol*. 2014;31(4):413-429. [CrossRef]
15. Gupta AK, Skinner AR. Management of diaper dermatitis. *Int J Dermatol*. 2004;43(11):830-834. [CrossRef]
16. Afshari Z, Jabraeili M, Asaddollahi M, Ghojazadeh M, Javadzadeh Y. Comparison of the effects of chamomile and calendula ointments on diaper rash. *Evid Based Care*. 2015;5(2):49-56.
17. Helms LE, Burrows HL. Diaper dermatitis. *Pediatr Rev*. 2021;42(1):48-50. [CrossRef]
18. Rowe J, McCall E, Kent B. Clinical effectiveness of barrier preparations in the prevention and treatment of nappy dermatitis in infants and preschool children of nappy age. *Int J Evid-Based Healthc*. 2008;6(1):3-23. [CrossRef]
19. Seifi B, Jalali S, Heidari M. Assessment effect of breast milk on diaper dermatitis. *Dermatol Reports*. 2017;9(1):7044. [CrossRef]
20. Gozen D, Caglar S, Bayraktar S, Atici F. Diaper dermatitis care of newborns human breast milk or barrier cream. *J Clin Nurs*. 2014;23(3-4):515-523. [CrossRef]
21. Farahani LA, Ghobadzadeh M, Yousefi P. Comparison of the effect of human milk and topical hydrocortisone 1% on diaper dermatitis. *Pediatr Dermatol*. 2013;30(6):725-729. [CrossRef]
22. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. *PLoS One*. 2012;7(7):e39803. [CrossRef]
23. Ertam Sağduyu İ, Su Küçük Ö, Alper FS, et al. Türkiye Atopik Dermatit Tanı ve Tedavi Kılavuzu-2018. *TÜRKDERM-Deri Hastalıkları ve Frengi Arşivi*. 2018;52(1):6-23.
24. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109-1122. [CrossRef]
25. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol*. 2001;45(4):520-527. [CrossRef]
26. Lin B, Dai R, Lu L, Fan X, Yu Y. Breastfeeding and atopic dermatitis risk: a systematic review and meta-analysis of prospective cohort studies. *Dermatology*. 2020;236(4):345-360. [CrossRef]
27. Kasrae H, Amiri Farahani L, Yousefi P. Efficacy of topical application of human breast milk on atopic eczema healing among infants: a randomized clinical trial. *Int J Dermatol*. 2015;54(8):966-971. [CrossRef]
28. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet*. 2015;385(9966):430-440. [CrossRef]
29. Coffey PS, Brown SC. Umbilical cord-care practices in low- and middle-income countries: a systematic review. *BMC Preg Childbirth*. 2017;17(1):68. [CrossRef]
30. Stewart D, Benitz W, Umbilical cord care in the newborn infant. *Pediatrics*. 2016;138(3) [CrossRef]
31. Organization WH. *Care of the Umbilical Cord: A Review of the Evidence*; Geneva: WHO; 2001.
32. Aghamohammadi A, Zafari M, Moslemi L. Comparing the effect of topical application of human milk and dry cord care on umbilical cord separation time in healthy newborn infants. *Iran J Pediatr*. 2012;22(2):158-162.
33. Allam NA, Megrin W, Talat AM. The effect of topical application of mother milk on separation of umbilical cord for newborn babies. *Am J Nurs Sci*. 2015;4(5):288-296. [CrossRef]
34. Dhanawade AR. A study to assess the effectiveness of breast milk application on umbilical cord stump among newborns of mother's undergone caesarean section in tertiary care maternity hospitals of Sangli, miraj, kupwad corporation area. *Innov Pharm Pharmacother*. 2014;2(3):386-394.

35. Pujar M, Deepa M, Francis F. Breast milk application-an emerging trend to reduce timing of cord separation (tcs) among newborns. *IOSR JNHS*. 2013;1(4):39-42.
36. Golshan M, Hossein N. Impact of ethanol, dry care and human milk on the time for umbilical cord separation. *J Pak Med Assoc*. 2013;63(9):1117-1119.
37. Vural G, Kisa S. Umbilical cord care: a pilot study comparing topical human milk, povidone-iodine, and dry care. *J Obstet Gynecol Neonatal Nurs*. 2006;35(1):123-128. [CrossRef]
38. Ahmadpour-Kacho M, Zahedpasha Y, Hajian K, Javadi G, Talebian H. The effect of topical application of human milk, ethyl alcohol 96%, and silver sulfadiazine on umbilical cord separation time in newborn infants. *Arch Iran Med*. 2006;9(1):33-38.
39. Abbaszadeh F, Hajizadeh Z, Jahangiri M. Comparing the impact of topical application of human milk and chlorhexidine on cord separation time in newborns. *Pak J Med Sci*. 2016;32(1):239-243. [CrossRef]
40. Lyngdoh D, Kaur S, Kumar P, Gautam V, Ghai S. Effect of topical application of human breast milk versus 4% chlorhexidine versus dry cord care on bacterial colonization and clinical outcomes of umbilical cord in preterm newborns. *J Clin Neonatol*. 2018;7(1):25. [CrossRef]
41. Tafazoli M, Amiri FL, Mohammadzadeh A, Esmaeili HE, Ghazvini K. Dose topical application of breast milk affect on bacterial colonization in umbilical cord? *Koomesh*. 2008;10(1):29-36.
42. Kirlek F, Akdolun-Balkaya N. Erken Postpartum Dönemde Meme Başı Ağrısı ve Çatlaklarının Önlenmesinde Anne Sütü ve Zeytinyağının Etkisi. *Hemşirelikte Araştırma Geliştirme Derg*. 2013;15(2):17-34.
43. Fraser DM, Cullen L. Postnatal management and breastfeeding. *Obstet Gynaecol Reprod Med*. 2009;19(1):7-12. [CrossRef]
44. Loke AY, Chan LK. Maternal breastfeeding self-efficacy and the breastfeeding behaviors of newborns in the practice of exclusive breastfeeding. *J Obstet Gynecol Neonatal Nurs*. 2013;42(6):672-684. [CrossRef]
45. Mohammadzadeh A, Farhat A, Esmaeily H. The effect of breast milk and lanolin on sore nipples. *Saudi Med J*. 2005;26(8):1231-1234.
46. Abou-Dakn M, Fluhr JW, Gensch M, Wöckel A. Positive effect of HPA lanolin versus expressed breastmilk on painful and damaged nipples during lactation. *Skin Pharmacol Physiol*. 2011;24(1):27-35. [CrossRef]
47. Masterson BJ. Selection of incisions for gynecologic procedures. *Surg Clin North Am*. 1991;71(5):1041-1052. [CrossRef]
48. McCandlish R, Bowler U, van Asten H, et al. A randomised controlled trial of care of the perineum during second stage of normal labour. *Br J Obstet Gynaecol*. 1998;105(12):1262-1272. [CrossRef]
49. Admasari Y, Santoso B, Suherni T, Mashoedi ID, Mardiyono M. Breast milk as an alternative for postpartum perineal care. *Belitung Nurs J*. 2017;3(3):238-245. [CrossRef]
50. Nuzzi G, Trambusti I, DI Cicco ME, Peroni DG. Breast milk: more than just nutrition! *Minerva Pediatr (Torino)*. 2021;73(2):111-114. [CrossRef]
51. Thai JD, Gregory KE. Bioactive factors in human breast milk attenuate intestinal inflammation during early life. *Nutrients*. 2020;12(2). [CrossRef]
52. Håkansson A, Zhivotovsky B, Orrenius S, Sabharwal H, Svanborg C. Apoptosis induced by a human milk protein. *Proc Natl Acad Sci U S A*. 1995;92(17):8064-8068. [CrossRef]
53. Ho JCS, Nadeem A, Svanborg C. HAMLET - A protein-lipid complex with broad tumoricidal activity. *Biochem Biophys Res Commun*. 2017;482(3):454-458. [CrossRef]
54. Mossberg AK, Wullt B, Gustafsson L, Månsson W, Ljunggren E, Svanborg C. Bladder cancers respond to intravesical instillation of HAMLET (human alpha-lactalbumin made lethal to tumor cells). *Int J Cancer*. 2007;121(6):1352-1359. [CrossRef]
55. Gustafsson L, Leijonhufvud I, Aronsson A, Mossberg AK, Svanborg C. Treatment of skin papillomas with topical alpha-lactalbumin-oleic acid. *N Engl J Med*. 2004;350(26):2663-2672. [CrossRef]
56. Khandelwal P, Andersen H, Romick-Rosendale L, et al. A pilot study of human milk to reduce intestinal inflammation After bone marrow transplant. *Breastfeed Med*. 2019;14(3):193-202. [CrossRef]
57. Güngör D, Nadaud P, LaPergola CC, et al. Infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a systematic review. *Am J Clin Nutr*. 2019;109(Suppl_7):772S-799S. [CrossRef]
58. Berents TL, Rønnevig J, Søyland E, Gaustad P, Nylander G, Løland BF. Topical treatment with fresh human milk versus emollient on atopic eczema spots in young children: a small, randomized, split body, controlled, blinded pilot study. *BMC Dermatol*. 2015;15:7. [CrossRef]
59. Juul Ladegaard PB, Rasmussen L, Zachariassen G. [Necrotising enterocolitis]. *Ugeskr Laeger*. 2018;180(21)
60. Brown JVE, Walsh V, McGuire W. Formula versus maternal breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2019;8:CD002972. [CrossRef]
61. Cañizo Vázquez D, Salas García S, Izquierdo Renau M, Iglesias-Platas I. Availability of donor milk for very preterm infants decreased the risk of necrotizing enterocolitis without adversely impacting growth or rates of breastfeeding. *Nutrients*. 2019;11(8). [CrossRef]
62. Chowning R, Radmacher P, Lewis S, Serke L, Pettit N, Adamkin DH. A retrospective analysis of the effect of human milk on prevention of necrotizing enterocolitis and postnatal growth. *J Perinatol*. 2016;36(3):221-224. [CrossRef]
63. Kantorowska A, Wei JC, Cohen RS, Lawrence RA, Gould JB, Lee HC. Impact of donor milk availability on breast milk use and necrotizing enterocolitis rates. *Pediatrics*. 2016;137(3):e20153123. [CrossRef]
64. O'Connor DL, Gibbins S, Kiss A, et al. Effect of supplemental donor human milk compared With preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial. *JAMA*. 2016;316(18):1897-1905. [CrossRef]
65. Trulsson M, Yu H, Gisselsson L, et al. HAMLET binding to alpha-actinin facilitates tumor cell detachment. *PLoS One*. 2011;6(3):e17179. [CrossRef]
66. Diego JL, Bidikov L, Pedler MG, et al. Effect of human milk as a treatment for dry eye syndrome in a mouse model. *Mol Vis*. 2016;22:1095-1102.
67. Asena L, Suveren EH, Karabay G, Dursun Altinors D. Human breast milk drops promote corneal epithelial wound healing. *Curr Eye Res*. 2017;42(4):506-512. [CrossRef]
68. Mossberg AK, Hou Y, Svensson M, Holmqvist B, Svanborg C. HAMLET treatment delays bladder cancer development. *J Urol*. 2010;183(4):1590-1597. [CrossRef]
69. Fischer W, Gustafsson L, Mossberg AK, et al. Human alpha-lactalbumin made lethal to tumor cells (HAMLET) kills human glioblastoma cells in brain xenografts by an apoptosis-like mechanism and prolongs survival. *Cancer Res*. 2004;64(6):2105-2112. [CrossRef]
70. Puthia M, Storm P, Nadeem A, Hsiung S, Svanborg C. Prevention and treatment of colon cancer by peroral administration of HAMLET (human alpha-lactalbumin made lethal to tumour cells). *Gut*. 2014;63(1):131-142. [CrossRef]
71. Ramsey KH, Poulsen CE, Motiu PP. The in vitro antimicrobial capacity of human colostrum against Chlamydia trachomatis. *J Reprod Immunol*. 1998;38(2):155-167. [CrossRef]
72. Ibhanesebhor SE, Otobo ES. In vitro activity of human milk against the causative organisms of ophthalmia neonatorum in Benin City, Nigeria. *J Trop Pediatr*. 1996;42(6):327-329. [CrossRef]