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PROBIOTIC FOR PREVENTION AND TREATMENT OF NECROTIZING ENTEROCOLITIS IN PRETERM INFANT

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ABSTRACT

Necrotizing enterocolitis (NEC) is a serious condition that is often experienced by premature babies. NEC can cause inflammation and tissue death in the baby's intestines, potentially leading to life-threatening complications. Therefore, it is necessary to prevent NEC in premature babies, one of which is with probiotics. This study aims to review existing literature regarding the effectiveness of probiotics in the prevention and treatment of NEC in premature infants. This research employs a systematic literature review method. Data collection was conducted by searching for literature in the Google Scholar and PubMed databases. The data analysis was performed using qualitative methods. The research results show that probiotics are therapeutic agents that can be used as an effort to prevent and treat NEC in premature babies. Several studies show that giving probiotics to premature babies can reduce the risk of developing NEC. The most effective probiotic strain is Lactobacillus rhamnosus or combined with Bifidobacterium infantis.

KEYWORDS *Probiotic, Necrotizing Enterocolitis, Preterm, Infant, Pediatric*

INTRODUCTION

Necrotizing enterocolitis (NEC) is a condition characterized by inflammation and death of intestinal tissue, typically arising as a late manifestation of vascular, mucosal, and metabolic disorders in the immature gut. NEC is a common gastrointestinal emergency in newborns and is one of the leading causes of morbidity and mortality in neonatal intensive care units (NICU), with mortality rates ranging from 15% to 30%. No single theory can explain all clinical aspects of NEC pathogenesis. Proposed mechanisms for the development of NEC include immature intestinal motility, digestive processes, circulatory regulation, barrier function, innate immunity, and abnormal bacterial colonization.

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NEC was first mentioned by Mizrahi et al. in 1965, and in 1978, Bell et al. divides it into three degrees based on the severity of the clinical condition. These diagnostic criteria were then modified by Walsh and Kliegman in 1986 (Handoyo, 2018). NEC is a major cause of morbidity and mortality in preterm infants with very low birth weight. The annual healthcare costs for these infants in the United States are estimated to range from $500 million to $1 billion. Common symptoms include gastric retention during enteral feeding, abdominal distension, and blood in the rectum. This severe and debilitating disease results in mucosal inflammation, intestinal epithelial cell death, sepsis, and transmural disease (Johnson-Henry et al., 2016).

Recently, probiotics have been suggested as a preventive measure for NEC. Since abnormal bacterial colonization plays a role in the pathogenesis of NEC, it is hypothesized that probiotics, which are live microbial dietary supplements that enhance gut microbial balance, could help prevent this condition. Various probiotic species have been studied, with the most common belonging to the genera Lactobacillus and Bifidobacterium. Additionally, Saccharomyces boulardii, a type of yeast, is now also considered a probiotic (Lau & Chamberlain, 2015). Probiotic bacteria, as live microbial supplements, colonize the digestive tract and potentially offer benefits to the host. There has been growing interest in the potential health benefits of proactively colonizing the gastrointestinal tract of premature infants (AlFaleh & Anabrees, 2014).

However, the American Academy of Pediatrics takes a more cautious stance, emphasizing the need for further research to address unanswered questions regarding the amount and specificity of probiotics or combinations of probiotics that should be used. Additionally, a recent systematic review analyzing evidence from randomized controlled trials on the use of probiotics in premature infants concluded that there is still not enough evidence to recommend routine use of probiotics. However, currently available data also encourage and justify further research into certain probiotic products (Aceti et al., 2015). This study aims to review existing literature regarding the effectiveness of probiotics in the prevention and treatment of NEC in premature infants.

RESEARCH METHOD

This research utilizes a systematic literature review method. A systematic literature review is a technique used to compile and analyze large volumes of information, serving as a tool to address various questions, including what is effective and what is not, among other types of inquiries (Mohamed Shaffril et al., 2021). This study followed the reporting guidelines for systematic reviews using the PRISMA 2020 diagram. Data collection was conducted by searching for literature in the Google Scholar and PubMed databases with keywords such as "prevention of necrotizing enterocolitis," "treatment of necrotizing enterocolitis," and "probiotics to prevent premature babies," using several specific criteria as follows:

Table 1. Data Criteria

No	Criteria	Inclusion	Exclusion
1	Language	Indonesian and English	Apart from Indonesian and English
2	Publication Period	2014-2024	Before 2014
3	Microorganisms	Probiotics	Apart from probiotics

Based on the established criteria, the research flow and results that will be used in this research are depicted in the following PRISMA diagram:

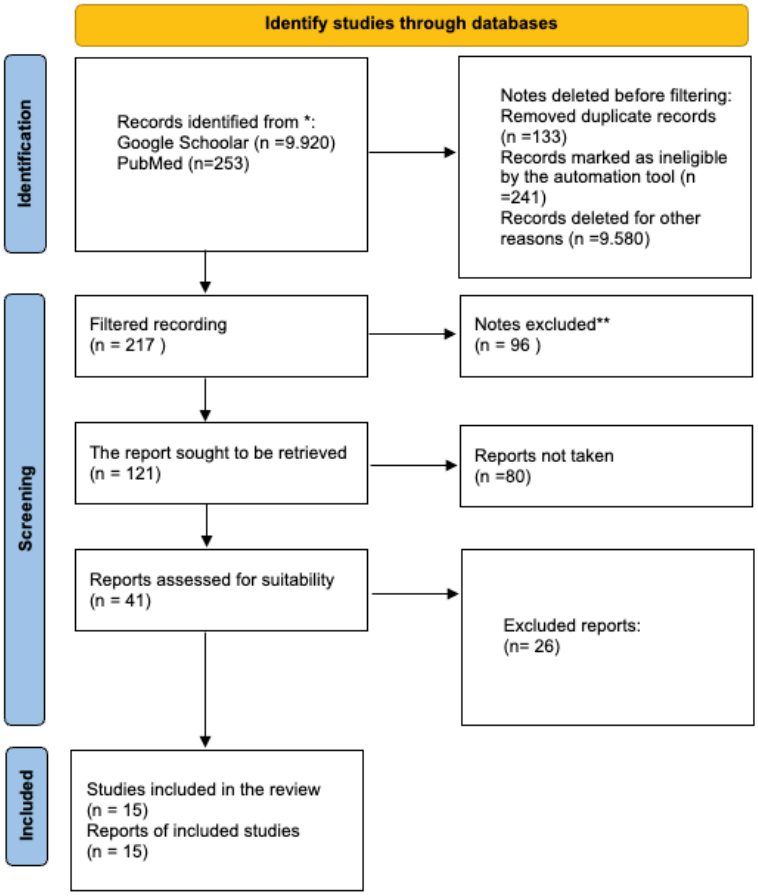

Figure 1. PRISMA 2020 diagram

The data found in the Google Scholar and PubMed databases were 10,173 research results. The data was then filtered by taking the first 10 pages, leaving 217 results. Next, the data was identified for eligibility and 121 eligible results were obtained. Of this number, 41 journals were selected according to the research objectives, then filtered again and finally 15 journals were obtained which were used in this research. The collected data was analyzed using qualitative methods.

RESULT AND DISCUSSION

Table 2. Research Results

No	Author	Research sites	Research result
1	Faleh, K. A., & Anabrees, J. (2014).	Saudi Arabia	This study reported that there were no systemic infections caused by the probiotic organisms used. Probiotic preparations containing Lactobacillus alone or in combination with Bifidobacterium have been shown to be effective. Therefore, enteral probiotic supplementation can prevent severe NEC and reduce mortality in premature infants.
2	Warner, B.B., et al. (2016)	United States of America	Research suggests that a relative increase in Gammaproteobacteria, particularly Gram-negative facultative bacilli, and a decrease in strictly anaerobic bacteria, particularly Negativicutes, are associated with the risk of necrotizing enterocolitis (NEC) in preterm infants. Probiotics have been considered as a potential strategy for the prevention and treatment of NEC with the aim to restore a healthy balance of gut bacterial flora. Although probiotics show potential to reduce the risk of NEC by strengthening gut defenses and inhibiting the growth of pathogenic bacteria, their use should be carefully considered to minimize the risk of product contamination, potential allergic reactions, and interactions with other medical treatments. These precautionary measures are necessary to ensure the safety and effectiveness of probiotics in improving the health of premature infants who are susceptible to NEC.
3	Henry, KCJ, Abrahamsson, TR, Wu, RY, & Sherman, SPM (2016)	Sweden	The use of probiotics or prebiotics along with donor breast milk for the prevention of necrotizing enterocolitis (NEC) in premature infants has shown promising results in studies. Probiotics such as Lactobacillus and Bifidobacterium, when given in a controlled manner and in the right strains, can help restore a healthy balance of gut bacterial flora. This combination not only strengthens the digestive system of premature babies, but also reduces inflammation in the gut, which significantly reduces the risk of NEC. Nonetheless,

			it is important to consider variations in probiotic strains and donor milk composition and closely monitor to minimize the risk of contamination and potential allergic reactions, thereby maximizing the health benefits of this strategy.
4	Handoyo. (2018).	Indonesia	The imbalance of commensal flora in the gastrointestinal tract of preterm infants, which is often characterized by a relative increase in Gammaproteobacteria and a decrease in strict anaerobic bacteria such as Negativicutes, is one of the main reasons for using probiotics to prevent necrotizing enterocolitis (NEC). Probiotics have the potential to restore the balance of healthy gut bacterial flora, reduce the colonization of pathogenic bacteria, and strengthen the gut immune system of preterm infants. This strategy aims to enhance the preterm infant's body's natural defenses against this serious condition, although it needs to be carried out under close supervision to ensure its optimal safety and benefits in a clinical context.
5	Wandro, S., Osborne, S., Enriquez, C., Bixby, C., Arrieta, A., & Whiteson, K. (2018)	United States of America	Although the incidence of necrotizing enterocolitis (NEC), late onset of sepsis, and duration of neonatal intensive care unit (NICU) stay do not significantly influence the large variation in bacterial composition imbalances in the gastrointestinal tract of preterm infants, probiotics remain a potential approach to correcting these bacterial flora imbalances. Probiotics can help correct the balance of gut flora by introducing beneficial strains of bacteria, such as lactobacillus and bifidobacteria, which can strengthen the immune system, lowering gut pH,
6	Baranowski, J.R., & Claud, E.C. (2019).	United States of America	Direct administration of probiotics to premature infants has been shown to be effective in reducing the incidence of necrotizing enterocolitis (NEC), a serious condition that can be life-threatening. Probiotics help in maintaining a healthy balance of gut bacterial flora, improve the body's defenses against infection, and reduce inflammation in the gastrointestinal tract. Nonetheless, the use of probiotics in premature infants is not free from

			potential risks such as product contamination, allergic reactions, or sensitivity to certain types of probiotics. In addition, interactions with other medical treatments also need to be carefully considered. Therefore, it is important to consider the potential benefits as well as the risks involved in using probiotics in premature infants with careful medical supervision to ensure their safety and effectiveness.
7	Morgan, R.L., Preidis, G.A., Kashyap, P.C., & Weizman, A.V. (2020)	Canada	Both single-strain and multistrain probiotic formulations have shown moderate evidence of reducing the incidence of necrotizing enterocolitis (NEC) in low birth weight preterm infants. Research suggests that probiotics can help restore a healthy balance of gut bacterial flora, reduce inflammation, and strengthen the immune system of preterm infants. This evidence highlights that the use of probiotics may be a potential strategy to reduce the risk of NEC, although more research needs to be done to better understand the effects of single strains and multistrains of probiotics on this condition. It is important to carefully select probiotics according to medical recommendations and to closely monitor the response of preterm infants during probiotic use to maximize the benefits.
8	Nolan, L. S., Rimer, J. M., & Good, M. (2020).	United States of America	Preterm infants are at high risk of gut microbiota imbalance and have an immature gut barrier, which increases susceptibility to diseases such as sepsis and necrotizing enterocolitis (NEC). Breast milk is important because it contains various bioactive components that support optimal growth and maturation of the gut and immune system of preterm infants. Breast milk contains antibodies, prebiotics, probiotics, and other growth and anti-inflammatory factors that can help protect preterm infants from infection and restore and maintain a healthy balance of gut microbiota. Exclusive breastfeeding has been shown to reduce the risk of NEC and provide significant long-term health benefits for preterm infants. Therefore, promotion and support of exclusive breastfeeding is essential

			in the care of preterm infants to optimize their health outcomes.
9	Beghetti, I., Panizza, D., Lenzi, J., Gori, D., Martini, S., Corvaglia, L., & Acetim A. (2021)	Italy	Bifidobacterium lactis Bb-12 or B94 has been known to reduce the risk of necrotizing enterocolitis (NEC) in premature infants, although the effect may vary depending on the study and the specific condition studied. Numerous studies support that B. lactis Bb-12/B94, as a single probiotic or in multistrain combinations, can help maintain a healthy balance of gut bacterial flora, strengthen the immune system, and reduce inflammation in the gastrointestinal tract. However, as with other probiotics, their use should be closely monitored to ensure optimal safety and benefit, as well as to understand more about how the interaction of these probiotics affects the risk and development of NEC in preterm infants.
10	Sowden, M., Weissenbruch, M.M., Bulabula, A.N.B., Wyk, L., Twisk, J., & Niekerk. (2022)	south Africa	The use of multistrain probiotics has been shown to be effective in shortening the time taken to achieve full enteral feeding in premature infants, as well as reducing the risk of developing necrotizing enterocolitis (NEC). Multistrain probiotics, with a combination of different types of beneficial bacteria such as Lactobacillus and Bifidobacterium, can help improve digestion and nutrient absorption, as well as strengthen the gut's natural defenses. Thus, the use of multistrain probiotics not only has the potential to speed up the recovery process and restore intestinal function of premature infants, but also reduce the risk of serious complications such as NEC. However, it is important to consider safety and consult with a skilled medical team in deciding the strategy of using these probiotics for premature infants.
11	Barbian, M. E., & Patel, R. M. (2023)	United States of America	The decision to implement probiotic supplementation in preterm infants is complex and influenced by various factors. One of them is the early incidence rate of necrotizing enterocolitis (NEC) in a neonatal care center. If a center has a high incidence rate of NEC, the use of probiotics might be considered as one strategy to reduce the risk of the condition. In addition, it is also

			important to consider other efforts that have been made to reduce the risk of NEC, such as exclusive breastfeeding practices, environmental hygiene, and judicious use of antibiotics. This decision should be made in light of the potential benefits of probiotics in optimizing the gut health of preterm infants, while reducing the potential risks associated with their use. In this context, consultation with an experienced medical team and based on available research evidence is essential to make informed and safe decisions.
12	Mercer, E.M., & Arrieta, M.C. (2023).	Canada	Integrating probiotic supplementation into standard care practices for preterm infants has been shown to be beneficial in preventing acute clinical conditions and improving microbiome changes associated with prematurity. Research suggests that probiotics may help reduce the risk of necrotizing enterocolitis (NEC) by improving the balance of gut bacterial flora, boosting the immune system, and reducing inflammation in the gastrointestinal tract. This integration of probiotics not only accelerates premature babies' recovery and improved gut function, but can also improve their long-term quality of life. However, the decision to adopt probiotics in clinical practice should be carefully considered, taking into account the specific conditions in each neonatal care center and consultation with an experienced medical team to ensure their optimal safety and effectiveness.
13	Sharif, S., Meader, N., Oddie, S. J., Reyes, M. X. R., & McGuire, W. (2020)	English & Spanish	Research on the effectiveness of probiotics in preventing necrotizing enterocolitis (NEC) in premature infants has shown mixed results. Some studies suggest that probiotics may provide significant benefits in reducing the risk of NEC by improving the balance of gut bacterial flora and enhancing the immune function of preterm infants. However, there are also studies that suggest that probiotics may have little or no effect in preventing NEC. This variability could be due to differences in the type of probiotic used, the exact formulation, the dose administered, as well as the characteristics of the preterm infant population studied. Therefore,

			the decision to use probiotics in clinical practice should be based on the latest evidence and consultation with an experienced medical team to evaluate the potential benefits as well as the risks involved.
14	Zhou, J., Yang, M., Wang, F., Liu, S., Hei, M., Jiang, M. (2023)	China	Based on a network meta-analysis (NMA), probiotics and synbiotics show potential as the two preferred dietary supplements for the prevention of sepsis and necrotizing enterocolitis (NEC), as well as reducing mortality in premature infants. Probiotics, with beneficial live bacteria such as Lactobacillus and Bifidobacterium, have been shown to help improve the balance of the gut microbiota, boost the immune system, and reduce inflammation in the gastrointestinal tract. Synbiotics, which combine probiotics with prebiotics (substances that stimulate the growth of good bacteria), may provide additional benefits by promoting the growth and activity of good bacteria in the gut of premature babies.
15	Wang, Y., Florez, I.D., Morgan, R.L., et al. (2023)	Canada	Only multistrain probiotics have been shown to be significantly associated with a reduction in all-cause mortality, including necrotizing enterocolitis (NEC), compared to placebo in several studies. Multistrain probiotics, which combine several types of beneficial bacteria such as Lactobacillus and Bifidobacterium, show potential to reduce the risk of death in premature infants by improving the balance of gut bacterial flora, strengthening the immune system, and reducing inflammation in the gastrointestinal tract.

Necrotizing enterocolitis (NEC) is a serious medical condition that occurs in newborn babies, especially premature or very low birth weight babies. NEC is characterized by inflammation and death of intestinal tissue, which can lead to intestinal perforation and infectious peritonitis. This is one of the most serious complications of intensive neonatal care and requires immediate medical treatment (Meister et al., 2020). Premature babies have a higher risk of necrotizing enterocolitis (NEC) compared with babies born at term. Risk factors that cause this condition include an immature digestive system, lack of blood flow to the intestines, and unbalanced bacterial growth in the intestines. Symptoms of NEC can range from mild digestive problems to severe intestinal inflammation and necrosis, requiring immediate medical

intervention, including surgery if necessary. Therefore, premature infants in particular should be carefully monitored for early detection and appropriate management of the risk of NEC (Kasivajjula & Maheshwari, 2014).

Prevention of necrotizing enterocolitis (NEC) is very important because this condition is one of the most serious complications that can affect premature babies. NEC can cause inflammation, necrosis, and intestinal perforation, which is potentially life-threatening. Premature babies have immature digestive systems and compromised immune systems, so they are more susceptible to NEC. Effective prevention involves several crucial steps, such as exclusive breastfeeding or according to the baby's ability, because breast milk has protective properties against NEC. Additionally, the use of probiotics has shown benefits in reducing the risk of NEC by modulating the composition of gut microbes to maintain a healthy balance (Lin et al., 2014). Practices such as avoidance of overfeeding, selective use of antibiotics, and advanced care in the neonatal intensive care unit (NICU) may also help reduce the risk of NEC. It is important to monitor premature babies closely for early symptoms of NEC and take immediate medical action if necessary. Other steps include strict monitoring of nutrition, prevention of overfeeding, as well as selective use of antibiotics to avoid disrupting the intestinal microbial ecosystem. By carrying out appropriate prevention, it is hoped that the risk and impact of NEC in premature babies can be reduced significantly (Duess et al., 2023).

Probiotics can help maintain a healthy balance of intestinal bacterial flora, improve digestion, and support better nutrient absorption. Additionally, there are indications that probiotics may help reduce the risk of developing allergies in premature babies, although further research is needed to understand the exact mechanisms. The use of probiotics in premature babies should be carried out with supervision and recommendations from skilled medical personnel to ensure maximum benefits and minimal risks (Amara & Shibl, 2015).

The results of the analysis show that administering probiotics directly to premature babies has proven effective in reducing the incidence of necrotizing enterocolitis (NEC), a serious condition that can be life-threatening. NEC often occurs in premature babies because their digestive systems are immature and susceptible to infection. It is believed that probiotics can reduce the risk of NEC by increasing the body's resistance and inhibiting the growth of pathogenic bacteria.

Probiotics are live microorganisms, such as bacteria or yeast, that provide health benefits when consumed in sufficient amounts. These microorganisms are similar to types of bacteria that are naturally found in the digestive tracts of humans and animals. Probiotics work by balancing or increasing the healthy intestinal bacterial flora, which is important for good digestion and a strong immune system. Some general benefits of consuming probiotics include improving digestion, supporting gut health, and may even help reduce the risk of or manage certain medical conditions (Fu et al., 2020).

The administration of probiotics to premature infants, although having significant potential benefits in maintaining the balance of intestinal bacterial flora and

reducing the risk of necrotizing enterocolitis (NEC), cannot be ignored without considering the associated risks. One of the main risks is the potential contamination of probiotic products which could threaten the health of vulnerable premature babies. Additionally, some premature babies may experience allergic reactions or sensitivities to certain types of probiotics, which can lead to complications such as skin rashes or digestive disorders. Other medical treatments the baby is receiving, such as antibiotics, may also potentially interact with probiotics, affecting the effectiveness or safety of those treatments. Therefore, it is important for medical teams to conduct careful evaluations and provide close monitoring when deciding on the use of probiotics in premature babies, to maximize the potential benefits while minimizing the risks involved.

Probiotics have become a major focus in the prevention and treatment of necrotizing enterocolitis (NEC) in premature infants. By introducing beneficial bacteria into the digestive system of premature infants, probiotics aim to modulate gut microbial composition thereby reducing the risk of inflammation and necrosis associated with NEC. Research has shown that probiotics, especially those containing Lactobacillus and Bifidobacterium species, can reduce the incidence of NEC in a significant way. Probiotics work by increasing intestinal defenses, suppressing the colonization of pathogenic bacteria, and improving the integrity of the intestinal barrier in premature babies. However, the use of probiotics in premature babies still requires further research to determine the optimal type, dose and duration, as well as to ensure their safety and effectiveness before they are widely implemented in clinical practice.

CONCLUSION

The results suggest that probiotics may serve as an effective therapeutic agent for the prevention and treatment of NEC in premature infants. Several studies indicate that giving probiotics to premature babies can reduce the risk of developing NEC. The probiotic strain that has been shown to be most effective is Lactobacillus rhamnosus, both used alone and in combination with Bifidobacterium infantis. This study supports the use of probiotics as a potential intervention to address this serious problem in a vulnerable population of premature infants.

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