Efficacy of probiotics in the role of weight gain in infants. A systematic review and meta analysis

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Abstract

Introduction:
Probiotics are being used as an effective intervention in development and growth of underweight infants and children. Its application though is being limited across developing and under developed countries. The present review is aimed to collect recent clinical evidence in terms of anthropometric growth, decrease in frequency of crying among low birth weight infants to promote its use in clinical practice among alternative medicine practitioners.
Method:
A systematic review and meta-analysiswas carried out of all available literature from the past two decades across 5 different search engines. Based on the inclusion and exclusion criteria, of the 79 articles, 6 were selected for the final data extraction.
Results:
Six out of seven studies that showed significant improvement in growth and weight gain in infants with the probiotic supplements. Four out of seven studies showed significant increase in the height and volume of breast milk intake of the infants. Two studies stated increased head circumference. Another study also noted less incidence of crying, stool frequencies.
Conclusion:
Probiotics show promising results in terms of growth, breast milk intake and also crying among low birth weight infants. Further long term studies are needed to see the effect on overall physical and mental development of these infants.

Keywords: Probiotics, infants, weight gain
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Introduction

Low birth weight has been defined by World Health Organization [WHO] as weight at birth of < 2500 grams[1], preterm infants and small for gestational age, constitute about 15% of new born, comprising for about 70% of neonatal deaths. These infants have higher risk of growth retardation, low intelligent quotient [IQ], neurodevelopment impairment such as mental retardation, cerebral palsy, learning disability and morbidity[2, 3].Low birth weight is due to prematurity as a result of high maternal age, smoking, not medically indicated caesarean sections and fertility treatments and multiple births[4, 5].

TheGI hasanincreased intestinal permeability due to an underdeveloped gastrointestinal barrier function. As a result, pathogenic bacteria can translocate from the intestinal lumen and cause systemic infections. Additionally, digestive and absorptive capabilities are diminished due to low concentration of lactase, pancreatic lipase and bile salts. Reducing intestinal permeability is associated with gut maturation that promotes growth and prevents infections[5].

Hence probiotics are used as a potential source to help in gut development. Probiotics are identified as live organisms which have health benefits for the host if taken in adequate amounts in the form of fermented food, dairy products and now recently as infant and toddler formula. The main probiotic organisms used worldwide are genera of Lactobacillus and Bifidobacteriathat are usually found in the gut flora. There are a number of ways in which probiotics improve health.In general, the aim of adding probiotics especially to the infant formula is to promote growth, development and to reduce infections by fostering an intestinal microbiota, similar to breastfed infants. This not only adds to their immunity but also helps in better uptake of the breast milk, metabolism and overall growth through weight gain [5].The objective of this review is to associate the level of evidence published in literature with infant growth across the globe. The success rate of interventions among infants who are given any form of probiotic along with the breast milk and compared with just breast feeding for parameters of weight, head circumference and height is sought through this review.

Methods:

The study was registered with OSF registries for systematic review and meta analysis (https://osf.io/y6h9p). Five electronic bibliographic databases *[Medline, Google Scholar, Scopus, Web of Science, Cochrane Library]* were systematically searched. Literature published between 2000 and January 2021 was searched. All study designs that looked at use of any probiotic supplements for underweight infants were included in the review [Figure 1].

PICOT criteria:

P: Infants on probiotics + breast milk

I: Probiotics

C: Either only breast feed or infant formula

O: Changes in weight, length and any adverse events reported due to probiotics

T: Minimum of 3 months

Search strategy and study selection

Full text articles of potentially eligible studies that met the selection criteria were obtained. MeSH [Medical Subject Headings] terms and text words for 'probiotics', 'infants' and 'weight gain' were used to identify relevant studies. Studies that looked at probiotic use for the infants who did not have any specific disease condition and rather required the management of under-nutrition were included. Inclusion criteria of all databases selected were free full text, randomised control trial, clinical trial of probiotics supplements for weight gain in infants and anthropometric parameters. The criteria for excluded studies were disease specific co-morbidities or birth defects and not containing relevant information on weight assessmentReference lists of all included studies and review articles identified by the search were also checked to identify other relevant studies. Only English language, freely available full text articles were included.No grey literature was assessed. The Peer Review of Electronic Search Strategies (PRESS) checklist was employed to ensure standardization in the electronic search. The

first author assessed the articles and had the same search strategy based on the key words which was cross verified by the remaining authors. All agreed upon the search strategy and the methodology applied. All records were screened individually by each of the authors and no disagreement arose in the final approval. No method was employed to obtain or confirm relevant information from study investigators. Rayyan software was used for the entire literature arrangement and sharing. No sensitivity analyses was performed. All studies were assessed for risk of bias using the JADAD scale.

Data extraction and quality assessment

Studies included were assessed for methodological qualities. The studies fulfilling the qualities of -1. probiotic supplements, 2. Sample setting, 3. Sample size and design, 4. Outcome measures explained clearly were included for the review.

Search key words:

The search strategy for PubMed/Medline is as below:

(("probiotic s"[All Fields] OR "probiotical"[All Fields] OR "probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields]) AND ("weight gain"[MeSH Terms] OR ("weight"[All Fields] AND "gain"[All Fields]) OR "weight gain"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) AND ((y_10[Filter]) AND (ffrft[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))

Outcome measurements

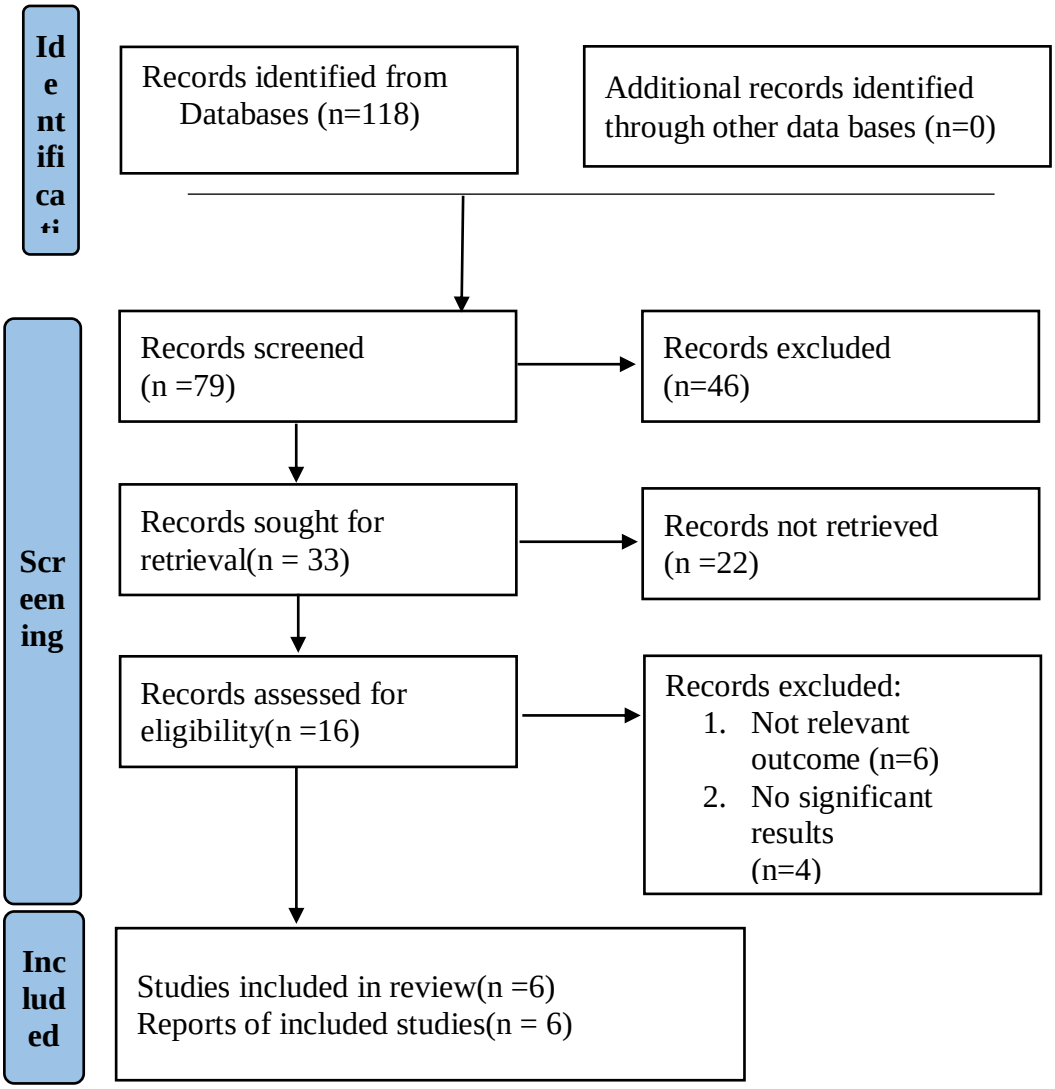
Outcome measures assessed were change in weight, length/height, head circumference, Body Mass Index [BMI], growth measurement units [g/day, z-scores] and any adverse event such as mortality. Primary outcomes included: Short term growth parameters [assessed for entire study duration approximately 4 weeks]: weight gain [grams/week], height[cm/week], head circumference[cm/week]. Secondary outcomes included: Volume of enteral feed and Incidence of crying and stool frequencies. The core outcome to decide the success of the outcome was the weight gain and changes in the head circumference. For continuous measures mean difference was considered for synthesis of the results. The random effect model was used for effect measurement using Revman 5 software for comparing the baseline and post intervention of the probiotic group.Inverse variance was used. There was no method to identify statistical heterogeneity. No other grouping or sub group synthesis or analysis was separately carried out.

Results

Study selection

The PRISMA flowchart of this studies is shown in the figure 1.

Fig 1: PRISMA Flow chart of the literature



One hundred and eighteen papers were identified based on the search, 79 papers were identified for last decade articles and then 31 articles were identified after applying all the filters like clinical trials, randomized control trials, full text. Finally, 6 papers were selected to include in the study. The quality assessment of the selected studies is shown in table 1. Table 2 and 3 describe the primary and secondary outcomes related to the data extraction from the 6 selected articles.

Characteristics and methodological quality of selected studies

Table 1: Quality assessment of the studies included in the systematic review

Author and Year	Place of study	Sample size	Study setting	Aim and Objectives clearly mentioned	Inclusion and exclusion criteria mentioned	Sample size estimation stated clearly	Sampling design stated clearly	Blinding	Criteria Index tool mentioned clearly	Generalizability
Wang et al [6][2021]	China	131	Hospital	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roze´ et al.[7][2012]	France	97	Hospital	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dupont et al[8][2015]	Netherland	119	Hospital	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ostadrahimi et al [9][2013]	Iran	80	Research centre	No	Yes	Yes	Yes	Yes	Yes	No
Agustina et al[10][2013]	Indonesia	494	Hospital	No	Yes	Yes	Yes	Yes	Yes	Yes
Al-Hosni et al[11][2011]	USA	101	Hospital	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Primary outcomes reported in the studies are shown in Table 2.

Table 2: List of primary outcomes included in the systematic review

Author and	Samples	Intervention	Weight	Length	Head	BMI	Z scores	Major findings	Outcome/

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Year			**change**	**and height**	**circumference**				
Wang et al [6][2021]	285	A partially hydrolysed non-ultra filtrated cow's milk protein based Infant Formula [IF] containing a mixture of 0.8 g/100 mL scGOS/lcFOS [9:1 ratio] and B. breve M-16V [3 £ 107 CFU/g].	Increased in both case and control group	Increased in both case and control group	Not mentioned	Not mentioned	The mean weight-for-age z-scores around 0.5 and length-for-age z-score for the IF-fed infants was also around 0.5; whereas for the breastfed infants it was closer to 0.	Equivalence in daily length and weight gain was achieved between the test and control groups	Weight gain, length gain was similar among test and control group.
Roze´ et al.[7][2012]	97	2 strains of probiotics [Lactobacillus rhamnosus LCS742 and Bifidobacterium longum subsp infantis M63, enriched with bovine a-lactalbumin]	Increased P=·053 after 6 months of intervention	Increased	Increased , [Z-score 0·061]	Not specified	Higher in both the probiotic groups	At 1st month, infants exhibited less crying or agitation during the 3 days; preceding the 1-month visit in the experimental group than in	At 1st month, Less crying, Increase in head circumference z score At 6th month, Increase in Weight for

								the control group [P,0·02]. The only difference observed was a trend towards a higher head circumference Z-score in the experimental group [0·96 [SD 0·92] v. 0·56 [SD 0·84], P¼0·05]. At 6th month Weight was not statistically different between the groups, but a trend towards higher weight-for-age [P¼0·053] and head circumference-for-age [P¼0·061] Z-scores was observed in the experimental group	age and head circumference were noted
Dupont et	119	A combination of two	Weight-for-	No	No significant	No	No	The probiotic	No significant

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al[8][2015]		probiotics [Lactobacillus casei CRL431 and Bifidobacterium lactis Bb-12]	length z score Increased (p=0·006)	significant difference	difference	significant difference	significant difference	supplementation had no effect on growth in infants, irrelevant of the nutritional status of the infant at study inclusion	results
Ostadrahimi et al [9][2013]	80	Freeze-dried Lactobacillus casei PXN 37, L. rhamnosus PXN 54, Streptococcus thermophilus PXN 66, Bifidobacterium breve PXN 25, L. acidophilus PXN 35, B. longum PXN 30, L. bulgaricus PXN 39 and fructooligosaccharide 30 min after meal for 30 days	Increased appetite and absorption of nutrients to prevent weight loss.	Changes in height is more with probiotics	No significant difference	No significant difference	No significant difference	The results demonstrated that infants' weight gain and their duration of breast milk intake in the supplemented group were significantly higher than that of the placebo. Infants HAZ and head circumference were not affected by supplementation which might be because of short follow-up period.	No significant change

Agustina et al[10][2013]	494	Infants were randomly assigned to the following groups: a low calcium content of ;50 mg/d [LC group], a regular calcium content of ;440 mg/d, regular calcium plus 5 3 108 CFU/d Lactobacillus casei CRL 431 [casei group], or regular calcium plus 5 3 108 CFU/d Lactobacillus reuteri DSM 17938	Increased (P = 0.03)	Increased height at 6th month (P = 0.04)	Not significant	Not significant	Not significant	The reuteri group experienced significantly greater weight gain [1160 6 650 g; P = 0.03] and WAZ change [0.14 6 0.28 Z; P = 0.03] after 6 months of intervention compared with the RC group	Higher Mean monthly Weight gain and height velocity
Al-Hosni et al[11][2011]	101	Lactobacillus rhamnosus and Bifidobacterium infantis suspended in 0.5 ml of infant's milk. Probiotic supplementation was added to the first enteral feeding and continued once daily with feedings thereafter until discharge	Increased (P value =0.02)	growth velocity (P value = 0.01)	Not significant	Not significant	Not significant	Average daily weight gain and growth velocity were significantly higher in the probiotic infants weighing 501–750 g [P value 0.02, 0.01, respectively].	Significant weight gain and growth velocity along with good enteral feeding

		or until 34 weeks postmenstrual age [PMA]. The control group received non supplemented milk added to their daily feeding							

Secondary outcomes

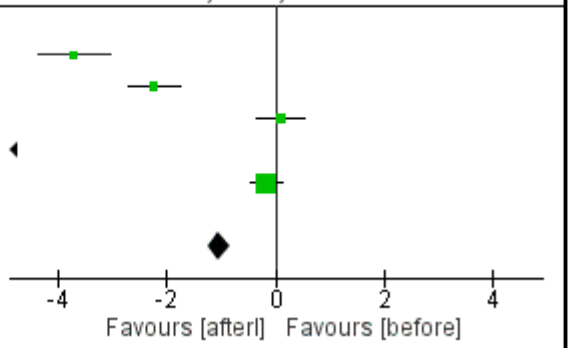
Table 3: List of secondary outcomes included in the systematic review

Author and Year	Incidence of crying	Volume and duration of breast-feeding intake	Recovery rate from any infection	Parent's satisfaction parameter
Wang et al [6][2021]	Not mentioned	Not mentioned	Not mentioned	Slightly decreased stool frequency
Roze´ et al.[7][2012]	Less crying at 1st month, Daily duration of crying or agitation [min] p=0·03	Increased Daily mean ingested volume [ml]	Atopic dermatitis p=0·03,	Number of stools a day reduced p=0·05, Daily duration of sucking thumb reduced [min] p=0·03 After 1st month there was less crying
Dupont et al[8][2015]	Not mentioned	Not mentioned	Not mentioned	Not significant
Ostadrahimi et al [9][2013]	Not mentioned	duration of breast milk intake in the supplemented group were significantly higher than that of the control group	Not mentioned	Not significant
Agustina et al[10][2013]	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Al-Hosni et al[11][2011]	Not mentioned	Enteral feeding rate increased	Not mentioned	Not mentioned

The studies collectively report a positive outcome after probiotic intervention for weight gain (Figure 02).

	Before			After				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Agustina et al; 2013	0	0	0	0	0	0		Not estimable	
Al-Hosni et al; 2012	778	138	50	1,750	340	50	9.9%	-3.72 [-4.37, -3.06]	
Dupont et al; 2015	6	1.2	53	8.6	1.1	53	17.7%	-2.24 [-2.73, -1.75]	
Ostadrahimi et al; 2013	1.21	0.85	37	1.13	0.92	37	20.4%	0.09 [-0.37, 0.55]	
Roze et al; 2012	3,300	390	48	8,015.7	834.7	39	2.9%	-7.43 [-8.64, -6.22]	
Wang et al; 2021	3,198	361	89	3,242	67.9	89	49.0%	-0.17 [-0.46, 0.13]	
Total (95% CI)			**277**			**268**	**100.0%**	**-1.05 [-1.25, -0.84]**	

Heterogeneity: Chi² = 252.26, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 9.95 (P < 0.00001)



Among the studies, there was no uniformity on the mode of intervention and also on the type of probiotic used. Hence this can be a drawback for policy makers in terms of recommendation towards clinical practice. Not all studies reported on incidence of crying, GIT effects or parental satisfaction after probiotic administration. Of the 6 studies, 3 were from Asia and one from France and 2 from USA. Studies from African continent where infant mortality is high, health care is a challenge and preventive measures are essential; were found to be seldom reported. There were no studies from tribal or rural zones where both maternal and child health are reported to be compromised due to nutritional deficiency. None of the studies included attitudes of the parents towards continuation of probiotics post cessation of the trial, since this can be a long term beneficial intervention.

Discussion

This review discovered benefits of probiotic intake in weight, length/height gain and head circumference, in underweight infants, which are the hall marks of a healthy growth in clinical practice. Six out of seven studies that showed significant improvement in growth and weight gain in infants with the probiotic supplements. Four out of seven studies showed significant increase in the height [6][9][10]. Two studies stated about increased head circumference post intervention with probiotics[6][7]. Another study also noted less incidence of crying, stool frequencies [7].Dupont et al [8] has shown that probiotics does not add any benefit to weight gain and in other developments of the infants. This could be due to the short duration of observation in their trial. All the studies doemphasize that probiotic supplements along with breast feeding improved growth and weight in the children for the initial period of 1- 6 months;even though the long term effects are not reported.

The selected research papers are heterogeneous with regards to the underweight infants without associated disease. One reports on the low weight infants[6] and one on the extremely underweight infant[11], and some are based on the variety of supplements. By synchronizing the results on the selected papers, probiotics has conferred many health and nutritional benefits other than the primary and secondary outcome of this review. While some studies have shown there could be a synergistic effect when combining prebiotics and probiotics in weight gain and a modulation of the immune system[6,7,9]. Previous reviews have shown the effectiveness of probiotics in infants with specific disease conditions such as infantile colic, necrotizing enterocolitis and other gastrointestinal disorders, asthma, atopic diseases, and autism spectrum disorders,[13] whereas this is the first to report on the effects of probiotics on infants' growth related to their anthropometric measurements.

Usually, probiotics are added to infant formulas in order to modify the micro-biota ofnon-breastfedanalogous with breast-fed infants who benefit from certain lactic acid bacteria and indigestible oligosaccharides which enhance the proliferation of probiotics[14]. Thisimproves health by affecting the immune system in different ways. They promote cytokine production such as Tissue Necrosis Factor – alpha [TNF-α], Interferon- gamma [IFN-γ], Interleukin-1beta [IL-1β], 6 [IL-6], and 10 [IL-10]. Health benefits conferred by probiotic bacteria are strain specific and not species or genus specific. Some strains increase phagocytic activity of peripheral blood leukocytes [monocytes, polymorphonuclear cells]. Other strains strengthen the mucosal barrier function by promoting the production of mucosal antibodies and reducing the transmucosal transfer of antigens. This reduces the intestinal permeability which in turn promotes growth. Probiotics bacteria also enhance production of low molecular weight antibacterial substances produced by epithelial cells and production of short chain fatty acids, the main energy source for colonocytes [5]. Probiotics alsoencourage the absorption of nutrients like vitamin B12, zinc and calcium and it also reduces the risk of

anaemia[14]. Probiotic help in the weight gain with long-lasting effects[15]. Infant formula fortified with probiotic as a substitute for breast milk, as exclusive breastfeeding in the first six months is a key child survival strategy [14]. So, probiotics can be given as add on effect with breastmilk, it is not a complete food for infants for the growth.

The review highlights the need for more studies beyond 6 months which focuses on similar products in terms of form, concentration and delivery. Costing is also a factor, since growth related factors are a challenge in infants among developing countries. In addition, exploring the use of locally available and culturally acceptable fermented products to serve as a vehicle of probiotics would be essential.Studies from third world countries where medical resources are sparse, the positive effect of probiotics could serve as a solution to the coming generation. We need more studies with regards to its community intervention, home based administration and also in children with compromised immunity like HIV or jaundice. A large scale trials involving cost effective analysis could help ease the nutritional burden for vulnerable future of the society.

Limitations of the present study:

We included studies that were among infants with no comorbidities. The effect on those with birth defects or co morbidities needs to be studied in detail. The present review was focussed only on underweight infants and for short duration. Long term effect studies were not included. Evidence separately for different studies where nutritional interventions are essential need to be tested.

Conclusion

This review found probiotics to be beneficial in terms of weight and height gain in infants. It has strong potential to influence gut microbiota composition and function, as well as no reported risk for any adverse effects. Probiotics seem to be a tool for supporting health, prevention and treatment of many pathologic conditions in the intestine and beyond it. It is suggested that the supplementation promotion of locally available foods with probiotics could be an effective intervention to improve growth in infants. Further research is needed to investigate this benefit comparing well-nourished and under-nourished infants in similar controlled environments. Trials on probiotics should measure anthropometric growth as a primary outcome to strengthen the evidence and explore the acceptability of the use of fermented milk products as a vehicle for probiotics.

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Author statement:

MRM selected the title, developed the proposal, interpreted the data, and prepared the manuscript. SK, SD and SM participated in the title selection, proposal development, and manuscript preparation and assisted the design, commented on the proposal, and approved it.

Conflicting interest:

None

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