Systematic Review 2022:
Effect of probiotics versus herbal remedies on infantile colic

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ABSTRACT:

Infantile colic is one of the most distressing early-life manifestations. Sudden episodes of inconsolable crying without a clear reason or treatment plan might cause parents to try incorrect methods, which can really injure the infant. Many treatment strategies were developed to solve this dilemma; the effectiveness of each is still doubtful. Objective: To compare the effect of probiotics as a recent therapy in the management of infant colic and herbal remedies as one of the most commonly used strategies. By searching national and international databases, 24 randomized clinical trials RCT studies were included (19 examining the effect of probiotics, 5 for herbal remedies). ***Results:*** *The most researched probiotic, Lactobacillus reuteri, exhibits statistically significant improvement and a decrease in the daily average crying time >=50% on days 7, 14, and 21. On day 7, RR (95% CI): 4.3 (2.3-8.7), P value 0.026; on day 14, RR (95% CI): 4.3 (2.3-8.7), P value< .001. A phase III, double-blind, randomized placebo-controlled trial found that the lactobacillus reuteri group cried or fussed for 49 minutes longer than the placebo group, (95% confidence interval 8 to 90 minutes, P=0.02). Fennel emulsion was the most studied in the herbal group with significant improvement to the placebo group (p< 0.01) absolute risk reduction (ARR):41% (95% CI 25 to 57).* ***Conclusions:*** *None of the therapies shows dramatic improvement, and probiotic supplementation's long-term effects are still a concern. More research is needed including local herbal remedies of our community.*

Keywords: *(herbal for infant colic), (probiotic for infant colic).*

INTRODUCTION

Infant colic, which has a 20% global frequency **(Halpern and Coelho, 2016)**, is one of the most upsetting early-life manifestations and one of the most common reasons for parents to seek medical attention for their children **(Vandenplas et al., 2015)**. A KSA poll found that 32% of mothers changed their baby's formula due to infantile colic **(Vandenplas, et al., 2016)**. The prevalence of infant colic in Egypt range between 20% and 37% **(Elhady and Ali, 2013).**

Infant colic is a phenomenon characterized by sudden, uncontrollable outbursts of crying and fussing in infants. The term "colic" describes the ensuing facial flushing, tense abdomen, flatulence, and leg retreat to the belly.

Infant colic was first identified by Thomas Phaire's 1544 **(Vercruyssen, et al., 2020)**, since which many physicians tried to make a clear definition till 1945 when Morris Wessel and colleagues made a significant advancement when they defined infant colic as "crying or fussing more than three hours of the day for more than three days of the week in the first three months of life" **(Wessel et al., 1954)**. Many other criteria and definitions were developed till 2016 when Rome IV criteria defined infant colic as "recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved, with no evidence of infant failure to thrive, fever or illness in infants less than 5 months old" **(Zeevenhooven et al., 2017)**. The precise reason for infantile colic has not been determined despite years of investigation **(Roberts et al., 2004)**.

There are many theories that have been developed that suggest both non-gastrointestinal causes, mostly connected to neurodevelopmental factors, and gastrointestinal causes, which are more common **(Sarasu et al., 2018)** like feeding techniques, excessive intestinal gas, hypersensitivity to cow's milk proteins, transient lactase deficiency, and gut inflammation. Recent research suggests that the altering microbiome may be a factor in infantile colic **(Lin, 2018)**.

All of the known treatments were used, with disappointing results, to address the infant's frequent outbursts of annoyance and weeping, which leave the caregivers feeling terrible and helpless **(Sarasu et al., 2018)**.

Some studies linked infant colic to later childhood sequelae such as sleep problems, allergic dysfunction, and behavioral problems **(Hemmi et al., 2011)**.

Many management strategies were developed over years, but no one of them was effective enough; as:

behavioral modifications and parental counseling, maternal dietary modifications, the use of hydrolyzed infant formulas, antispasmodics, anti-flatulence, lactase supplementation, gripe water, and herbal remedies; all were used with non-satisfactory improvement.

The use of the previous strategies was also associated with the increased economic burden of families and more frustration of caregivers which could lead to the use of alternative erroneous approaches suggested by family, friends, or the internet which may cause real harm for the baby.

Recent rapidly advancing evidence that links altered gut microbiota as a cause of infant colic **(Hill et al, 2014)** and that the gut microbiota of infants with colic differs from that of unaffected infants has given rise to the idea that probiotics can restore this balance and offer a healthier intestinal microbiota landscape **(Daryl et al., 2018)**.

Less weeping has been associated with certain probiotics, including Bifidobacterium and Lactobacillus, which have favorable effects on the gut lumen, epithelial function, mucous barrier, and gastrointestinal motility **(Zeevenhooven et al., 2018)**. The recent use of probiotics for the management of infant colic besides the other commonly used strategies, makes it a challenge to choose the appropriate therapy to manage.

AIM of WORK

Description of the effect of probiotics as a recent therapy in the management of infant colic in comparison with herbal remedies as one of the most commonly used strategies.

OBJECTIVES of THE STUDY

- To evaluate how infantile colic is improved by probiotics and herbal treatments.
- To evaluate the new strategy's impact on parent satisfaction.

MATERIALS AND METHODS

Infantile colic is a common complaint among parents of infants less than six months old, with either medical or traditional methods to relieve this colic.

The present study is comparing the use of herbal remedies as the most common traditional intervention in our community used for infantile colic, and the most recent medical intervention using probiotics.

Study Design

A systematic review without meta-analysis after measuring of homogeneity of the study results, including randomized clinical trials using herbal remedies versus placebo, probiotics versus placebo, and herbal remedies versus probiotics. Only original articles were included with no systematic reviews or meta-analyses.

Search Strategy

Searching the national and international databases among published and grey literature for probiotics and/or herbal remedies for the management of infantile colic. On science direct, PubMed, EKB, Elsevier, Embase, and Google scholar. The keywords of the search were: (infant colic), (infant cry), (herbal or infant colic), and (probiotic or infant colic).

Only randomized clinical trials published between 2003 and 2021 were included.

Criteria for study selection

Inclusion criteria:

- RCTs studies.
- Study population diagnosed as having infantile colic by ROME 3 or 4 criteria.
- Including both breastfed and formula-fed infants.
- Results for parents and/or babies were acknowledged.
- The only language utilized is English.

Exclusion criteria:

- Any comorbidities requiring medical care as pathologic causes of colic like gastroesophageal reflux disease “GERD”

and Cow milk protein allergy.

- Infants receiving any other kind of treatment other than probiotics and/or herbal remedies.
- Other languages except English were excluded.

Sample size

The research sample consisted of 2429 participants from 24 studies included in our systematic review.

Study population

Totally enrolled 2488 participants, 2429 completed the tests, 501 infants enrolled in herbal studies 496 infants completed the herbal studies, and 5 infants didn't complete the herbal study. Probiotic participants; 1987 participants were enrolled; 1937 completed the probiotics studies, and 20 infants don't complete the probiotics studies. 175 pregnant women at the beginning of the last 4 weeks of pregnancy 145 complete, and 30 doesn't. Studies included were 24 studies, 19 probiotics, and 5 herbal studies. Types of studies, 12 were Randomized double blind clinical trials, 2 were prospective single-blind randomized trials, 1 was a prospective randomized study, 1 was a prospective randomized study, 4 were a randomized controlled trial, 1 was a multicenter randomized, open-label, parallel, controlled trial, 1 was A prospective, multicenter, double-masked, placebo-controlled randomized clinical trial, 1 was an open randomized controlled trial, 1 was A double-blind crossover study

Data source

Two independent authors separately searched the articles on science direct, PubMed, EKB, Elsevier, Embase, and Google scholar. Titles and abstracts of the search results were reviewed by two independent authors; duplicated and irrelevant studies were removed. Full-text papers were obtained for studies that met the inclusion/exclusion criteria. This process resulted in 24 articles that were used in our study. The duration of included studies ranges between7 and28 days; with sample size ranging between 19 and 589 infants.

Data Extraction

An extraction sheet was created for data extracted from the included studies, the data

included: the title of the study, name of authors, year and country of publication, sample size of the study, and results of concern. Two independent authors separately reviewed the extraction sheet for duplicates and missing data, any conflict was solved by a group discussion among the research team.

Quality assessment

The quality of the studies was assessed using The Cochrane Collaboration's tool for assessing the risk of bias in randomized control trials **(Higgins et al., 2011).** All trials were generally considered as having a low risk of bias. We excluded the trials with a high risk of bias and unclear bias.

RESULTS

This systematic review included 24 randomized clinical trials, 5 of them used herbal remedies versus placebo & the others use probiotics versus placebo or probiotics versus herbal remedies. Many studies discussed the impact of (lactobacillus reuteuri) in decreasing the number or severity of infantile colic attacks and crying time, most of them found a statistically significant improvement and reduction in the daily average crying time >=50% at day 7 RR (95% CI), *P* value 0.026; at day 14 RR (95% CI): 4.3 (2.3-8.7), *P* value <.001; at day 21 RR (95%CI): 2.6 (1.8-4.0) with *P* value <.001 (table 1).

On the contrary, a phase III, double-blind, randomized placebo-controlled trial by **Valerie Sung, et al., (2014)** found that the lactobacillus reuteuri group cried or fussed 49 minutes more than the placebo group (95% confidence interval 8 to 90 minutes, *P*=0.02) table 2.

Mohammad, et al., (2018) studied the effect of maternal administration of Lactobacillus reuteri in the last 4 weeks of pregnancy and found that the frequency of colic and its higher grades were significantly lower in the intervention group (p = 0.03 for the presence of colic and p = 0.01 for high grades of colic). Delivery mode and infant feeding patterns were not different between the two groups (*P*> 0.05).

Some studies compared the effect of (lactobacillus reuteuri) versus Simethicone in decreasing the number or severity of infantile colic attacks and crying time and found the daily average crying time in the probiotic group was

210 min/day (SD 31) vs 208 min/day (SD 24) in the Simethicone group (p= 0.800). After 7 days, crying time was significantly reduced in the Probiotic group: 140 min/day (SD 51) vs. 172 min/day (SD 43) (p= 0.025). By day 28, the crying time was significantly reduced in L. reuteri infants to only 20 min/day (SD 14) compared to simethicone, 156 min/day (SD 24) (*P*< 0.005) table 3.

Kianifar et al., (2014) studied the effect of synbiotic use on infantile colic and found that the crying time was significantly decreased in the synbiotic group (82.6%) compared with the placebo (35.7%) at day 7 (P < 0.005). On day 30, treatment success was 87% and 46% in the synbiotic and placebo group, respectively (P < 0.01). Symptom resolution was also higher in the synbiotic group (39%) compared with the placebo (7%) at day 7 (P < 0.03) but not at day 30 (56% vs.36%, P = 0.24) table 4.

In these two studies, the impact of (lactobacillus rhamnosus) in association with the elimination of cow's milk from the maternal diet and/or use of extensively hydrolyzed casein formula for formula-fed infants; **Partty et al., (2015)**; found that there was no statistically significant difference in crying time between the treatment and placebo group although the parental report of crying suggested the probiotic intervention effectively. While in Francesco **Savino, et al., (2020),** After supplementation for 28 days with Lactobacillus rhamnosus ATCC 53103, median full-force daily crying was reduced (104 versus 242 min, p < 0.001), and the values of fecal calprotectin decreased significantly (p = 0.026). Furthermore, the probiotic increased the abundance of Lactobacillus (p = 0.048) and total bacteria (p = 0.040); all these effects were not observed in the placebo group (table 5).

In 2021 the use of Bifidobacterium longum CECT7894, by **Chen et al., (2021)** showed significantly shorter crying time (*P* < 0.001) on day 7 [IG vs. PG, median (25−75th percentile): 38 (3.5–40.5) vs. 62 (40–108) min/day], day 14 [IG vs. PG: 20 (0–40) vs. 50 (30–75) min/day], and day 21 [IG vs. PG: 14 (0–33) vs. 40 (28–62) min/day]. Higher responder ratio and fewer crying/fussing episodes on days 7, 14, and 21, and better

stool consistency on day 21 were observed in the IG ($p < 0.01$) as compared to the PG; and the use of Bifidobacterium breve CECT7263, in **Maldonado-Lobón et al., (2021)** showed significantly decreased crying time from the first week of the study ($P<0.05$), whereas the Bb + Lf group and the simethicone group had significantly decreased crying time from the second week ($P<0.05$). The percentage of reduction in the minutes of crying from baseline in the Bb group was significantly higher than that in the Simethicone group every week of the intervention (-40.3 vs -27.6% at 1 week; -59.2 vs -43.2% at 2 weeks; -64.5 vs -53.5% at 3-week and -68.5 vs -59.5% at 4-weeks, $P<0.05$) table 6**.**

In A population of formula-fed healthy infants with colic, the effect of an α-lactalbumin-enriched and probiotic-supplemented formula (Modilac Digest 1) was examined versus the control formula **(Dupont et al., 2010**). There were no differences between groups for the crying duration. With a significant increase in parents' satisfaction related to 'Feeding-related' gastrointestinal side effects improvement ($P<0.001$) table 7.

Few studies discussed the different impacts of herbal use in decreasing the number or severity of infantile colic. **Alexandrovich et al., (2003),** found that the use of fennel emulsion eliminated colic in 65% of infants in the treatment group (40/62) which is significantly better than 23.7% (14/59) in the placebo group ($p< 0.01$) absolute risk reduction (ARR): 41% (95% CI 25 to 57). Another study, by **Savino et al., (2005)** found a reduction in crying time was observed in 35 (85.4%) subjects of the treatment group and in 23 (48.9%) subjects in the Placebo group ($p < 0.005$) within 1 week of treatment with an extract based on Matricariae recutita, Foeniculum vulgare and Melissa officinalis (table 8).

DISCUSSION

Many studies were carried out to study the effect of probiotics and herbal infantile or maternal administration in decreasing the severity or amount of colic.

More than one study discussed the impact of (lactobacillus reuteri) versus placebo in decreasing the number

or severity of infantile colic attacks and crying time, **Francesco Savino et al., (2010)** found that a 50% reduction in the crying time from baseline was significantly higher in the reuteuri group than in the placebo group with *P* values 0.007, 0.01 respectively.

Also, **Kimchau et al., (2015)** found a significantly higher proportion of infants in the L reuteri DSM 17938 group responded to treatment with a 50% crying time reduction compared with infants given a placebo with P 0.035; relative risk, 3.3. While, **Szajewska et al., (2013)** found that treatment success (reduction in the daily average crying time >50%) at day 7 RR (95% CI): - *P* value 0.026; at day 14 RR (95% CI): 4.3 (2.3-8.7*)*, *P* value. *P* <.001; at day 21 RR (95%CI): 2.6 (1.8-4.0), *P* value <.001.

On the contrary, a phase III, double-blind, randomized placebo-controlled trial by Valerie Sung, et al 2014 found that the lactobacillus reuteri group cried or fussed 49 minutes more than the placebo group (95%confidence interval 8 to 90, P=0.02).

One study studied the effect of maternal administration of Lactobacillus reuteri in the last 4 weeks of pregnancy, **Ali et al., (2020)** found that the frequency of colic and its higher grades were significantly lower in mothers in the L. reuteri DSM 26866 group (OR= 2.36; CI 95%, 1.18–4.73) (p = 0.03 for the presence of colic and p = 0.01 for high grades of colic.

Some studies compared the effect of (lactobacillus reuteri) versus Simethicone in decreasing the number or severity of infantile colic attacks and crying time. **Savino and Miniero, (2005)** agreed with **Savino, and Miniero, (2007)** the crying time was significantly reduced in L. reuteri infants compared to simethicone with p< 0.005, while **Kianifar et al., (2014)** studied the effect of synbiotic use in infantile colic and found that the crying time was significantly decreased in the synbiotic group (82.6%) compared with placebo (35.7%) at day 7(*P*<0.005). On day 30, treatment success was 87% and 46% in the symbiotic and placebo group, respectively (*P* < 0.01). Symptom resolution was also higher in the symbiotic group (39%) compared with the placebo (7%) at day 7 (*P* < 0.03) but not at day 30 (56% vs.36%, *P* = 0.24).

Few studies studied the impact of (lactobacillus rhamnosus) in association with the elimination of cow's milk from the maternal diet and/or use of extensively hydrolyzed casein formula for formula-fed infants, **Partty et al., (2015)**; found that there was no statistically significant difference in crying time between the treatment and placebo group although the parental report of crying suggested the probiotic intervention effectiveness, While in **Savino, et al, (2020)** found that crying was reduced at day 28 than at day 0 and the difference is statistically significant $P = 0.001$.

Chen et al., (2021) studied the use of Bifidobacterium longum and found significantly decreased crying time from the first week of the study with a *P* value < 0.001. Also, **Maldonado-Lobón et al., (2021)** found significantly decreased crying time from the first week of the study ($P<0.05$), whereas the combination of *Bifidobacterium breve (Bb)* and *lactobacillus fermentum (Lf)* (Bb+ Lf) group and the simethicone group had significantly decreased crying time from the second week ($P<0.05$). The percentage of reduction in the minutes of crying from baseline in the Bb group was significantly higher than that in the Simethicone group every week of the intervention (-40.3 vs -27.6% at 1 week; -59.2 vs -43.2% at 2 weeks; -64.5 vs -53.5% at 3-week and -68.5 vs -59.5% at 4-weeks, $P<0.05$).

While **Dupont et al., (2010)** studied the effect of an α-lactalbumin-enriched and probiotic-supplemented formula (Modilac Digest 1) versus the control formula and there were no differences between the two groups for the crying duration. With a significant increase in parents' satisfaction related to 'Feeding-related' gastrointestinal side effects improvement with $P<0.001$. However, the long-term sequelae of using probiotic preparation in early life are still under research **(Poindexter, et al., 2021).**

Liu, et al., (2016), in an animal model study, showed that sudden stoppage of probiotic supplementation may cause alteration in gut microbiota, so the dose and duration of probiotic use still need further research.

Few studies discussed the different impacts of herbal use in decreasing the number or severity

of infantile colic, **Alexandrovich et al., (2003)** Found that the use of fennel emulsion eliminated colic in 65% of infants in the treatment group which is significantly better than in placebo group with p< 0.01 absolute risk reduction (ARR) 41%

While **Savino et al., (2005)** and **Altarha et al., (2008)** found a reduction of crying time in the subjects of the treatment group than in the Placebo group with *P* < 0.005 and colic improvement score after 7 days in both the fennel group with *P* value = 0.05) and the gripe water group with *P* value =0.002 than before respectively.

STUDY LIMITATIONS

However, this study is susceptible to some potential shortcomings.

- The effect of probiotic treatments on microbiota was restricted to a few genera, further study of the microbiota is required to provide a more thorough understanding of the effects of probiotic treatments on the microbiota and their connection to infantile colic.
- The majority of the included trials examined probiotics for infants who were exclusively breastfed; further study is needed to determine their effects on formula-fed infants.
- Only one study examined how probiotics affect pregnant mothers and how they may affect infantile colic.
- There has been little research on how herbs affect infantile colic
- Sample sizes for the majority of the included research are modest.

Almost all of the included studies depended on parent reports to estimate the amount of weeping time spent, which is a very subjective method with a high risk of reporting bias. However, parent satisfaction is one of the key goals of the current study.

CONCLUSION

According to the findings in this review, probiotics containing lactobacillus reuteuri showed significant improvement and reduction in the daily crying

time when administrated to Infants younger than 6 months. maternal administration of Lactobacillus reuteri in the last 4 weeks of pregnancy, was found to greatly reduce both the frequency and severity of colic. The crying time was significantly reduced in L. reuteri infants compared to infants treated with simethicone after receiving probiotics containing Lactobacillus reuteri for 28 days. The effectiveness of lactobacillus rhamnosus in treating infantile colic requires further research. The use of herbal remedies is associated with a decrease in the severity of colic.

RECOMMENDATIONS

1- Training on how to use probiotics or herbal remedies by health care professionals and parents.

2- The studies about herbal remedies in managing infantile colic were promising; so more studies are needed in that field.

3- More studies are needed on other types other than those included here about probiotics in managing infantile colic.

4- More studies are needed on the natural safe sources of probiotics in treating infantile colic.

5- Give education programs to the parents to deal with it more efficiently.

6-More research is needed to explore the effects of probiotics on the pregnant mother and their influence on infantile colic.

REFERENCES

Alexandrovich I; Rakovitskaya O; Kolmo E; Sidorova T and Shushunov S (2003):

"The effect of fennel (Foeniculum vulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study." *Alternative therapies in health and medicine*; 9.4: 58.

Ali ASA and Elhady MAA (2013):

Prevalence and risk factors for infantile colic in Egyptian infants. *J Am Sci.;* 9:340–343.

Alves JG; de Brito R de C and Cavalcanti TS (2012):

Effectiveness of Mentha piperita in the Treatment of Infantile Colic: A Crossover Study. *Evid Based Complement Alternat Med*.; 981352.

Attarha M; Rosbahani N and Yosefi P (2008):
"Effect of Fennel Essence and Gripe Water Syrup on Infantile Colic." *Pmj, Archives of Disease in Childhood*; 93: pw387.

Chau K; Lau E; Greenberg S; Jacobson S; Yazdani-Brojeni P; Verma N and Koren G (2015):
"Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating Lactobacillus reuteri DSM 17938." *The Journal of pediatrics;* 166.1: 74-78.

Chen K; Liu C; Li H; Lei Y; Zeng C; Xu S and Savino F (2021):
"Infantile colic treated with Bifidobacterium longum CECT7894 and Pediococcus pentosaceus CECT 8330: a randomized, double-blind, placebo-controlled trial." *Frontiers in Pediatrics*; 9:635176.

Dryl R and Szajewska H (2018):
Probiotics for management of infantile colic: a systematic review of randomized controlled trials. *Arch Med Sci Ams.*; 14(5):1137–1143.

Dupont C; Rivero M; Grillon C; Belaroussi N; Kalindjian A and Marin V (2016):
"α-Lactalbumin-enriched and probiotic-supplemented infant formula in infants with colic: growth and gastrointestinal tolerance." *European journal of clinical nutrition*; 64. 7: 765-767.

Garofoli F; Civardi E; Indrio F; Mazzucchelli I; Angelini M; Tinelli C; and Stronati M (2014):
"The early administration of Lactobacillus reuteri DSM 17938 controls regurgitation episodes in full-term breastfed infants." *International journal of food sciences and nutrition;* 65.5: 646-648.

Halpern R and Coelho R (2016):
Excessive crying in infants. *J Pediatr (Rio J)*; 92(3): S40–5.

Hemmi MH; Wolke D and Schneider S (2011):
Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioral outcomes in childhood: a meta-analysis. *Arch Dis Child*; 96:622-9.

Higgins JP; Altman DG; Gøtzsche PC; Jüni P; Moher D and Oxman AD (2011):
The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. *BMJ.*; 343: d5928.

Hill C; Guarner F; Reid G; Gibson GR; Merenstein DJ; Pot B and Sanders ME; Expert consensus document (2014):
The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*; 11: 506-14.

Indrio F; Di Mauro A; Riezzo G; Civardi E; Intini C; Corvaglia L and Francavilla R (2014):
"Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial." *JAMA pediatrics*; 168.3: 228-233.

Kianifar H; Ahanchian H; Grover Z; Jafari S; Noorbakhsh Z; Khakshour A and Kiani M (2014):
"Synbiotic in the management of infantile colic: a randomized controlled trial." *Journal of pediatrics and child health*. 50.10: 801-805.

Lin P (2018):
The role of the intestinal microbiome in ocular inflammatory disease. *Curr Opin Ophthalmol*.; 29(3):261–266.

Liu Z; Liu W; Ran C; Hu J and Zhou Z (2016):
"Abrupt suspension of probiotics administration may increase host-

pathogen susceptibility by inducing gut dysbiosis." *Scientific reports;* 6.1: 1-12.

Maldonado-Lobón JA; Blanco-Rojo R; Maldonado J; Ali MA; Almazán MV; Suanes-Cabello A and PROBI-COLIC group (2021):

"Efficacy of Bifidobacterium breve CECT 7263 for infantile colic treatment: an open-label, parallel, randomized, controlled trial." *Beneficial Microbes* 12.1, 12.1: 55-67.

Martinelli M; Ummarino D; Giugliano FP; Sciorio E; Tortora C; Bruzzese D and Staiano A (2017):

"Efficacy of a standardized extract of Matricariae chamomilla L., Melissa officinalis L. and tyndallized Lactobacillus acidophilus (HA 122) in infantile colic: An open randomized controlled trial." *Neuro-gastroenterology and Motility.* 29.12: e13145.

Mi GL; Zhao L; Qiao DD; Kang WQ; Tang MQ and Xu JK (2015):

"Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: a prospective single-blind randomized trial." *Antonie Van Leeuwenhoek.* 107.6: 1547-1553.

Pärtty A; Lehtonen L; Kalliomäki M; Salminen S and Isolauri E (2015):

"Probiotic Lactobacillus rhamnosus GG therapy and microbiological programmming in infantile colic: a randomized, controlled trial." *Pediatric research.* 78.4: 470-475.

Poindexter B; Cummings J; Hand I; Adams-Chapman I; Aucott SW; Puopolo KM and Mowitz M (2021):

"Use of probiotics in preterm infants" *pediatrics*; 147.6.

Pourmirzaiee MA; Famouri F; Moazeni W; Hassanzadeh A and Hajihashemi M (2020):

"The efficacy of the prenatal administration of

Lactobacillus reuteri LR92 DSM 26866 on the prevention of infantile colic: a randomized control trial." *European journal of pediatrics*. 179.10: 1619-1626.

Roberts DM; Ostapchuk M and O'Brien JG (2004):

Infantile colic. *American family physician;* 70(4), 735-740

Roos S; Dicksved J; Tarasco V; Locatelli E; Ricceri F; Grandin U and Savino F (2013):

"454 pyrosequencing analysis on fecal samples from a randomized DBPC trial of colicky infants treated with Lactobacillus reuteri DSM 17938." *PloS one*; 8.2: e56710.

Sarasu JM; Narang M and Shah D (2018):

Infantile colic: an update. *Indian pediatrics*;55(11), 979-987

Savino F; Palumeri E; Pelle E; Castagno E; Oggero R and Miniero R (2005):

"328 Lactobacillus Reuteri ATCC 55730 Versus Simethicone in the Treatment of Infantile Colic: A Perspective Randomized Study." *Pediatric Research.* 58.2: 411-411.

Savino F; Palumeri E; Pelle E; Castagno E; Oggero R and Miniero R (2015):

"Preventive effects of oral probiotic on infantile colic: a prospective, randomized, blinded, controlled trial using Lactobacillus reuteri DSM 17938." *Beneficial microbes.* 6.3: 245-251.

Savino F; Galliano I; Garro M; Savino A; Daprà V; Montanari P and Bergallo M (2018):

"Regulatory T cells and Toll-like receptor 2 and 4 mRNA expression in infants with colic treated with Lactobacillus reuteri DSM17938." *Beneficial microbes.* 9.6: 917-925.

Savino F; Cresi F; Castagno E; Silvestro L and Oggero R (2005):

"A randomized double-blind placebo-controlled trial of a standardized extract of Matricariae

recutita, Foeniculum vulgare and Melissa officinalis (ColiMil®) in the treatment of breastfed colicky infants." Phytotherapy Research: *An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*. 19.4: 335-340.

Savino F; Pelle E; Palumeri E; Oggero R and Miniero R (2007):
"Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study." *Pediatrics.* 119.1: e124-e130.

Savino F; Cordisco L; Tarasco V; Palumeri E; Calabrese R; Oggero R and Matteuzzi D (2010):
"Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial." *Pediatrics.* 126.3: e526-e533.

Savino F; Montanari P; Galliano I; Daprà V and Bergallo M (2020):
"Lactobacillus rhamnosus GG (ATCC 53103) for the management of infantile colic: a randomized controlled trial." *Nutrients.* 12.6: 1693.

Sung V; Hiscock H; Tang ML; Mensah FK; Nation ML; Satzke C and Wake M (2014):
"Treating infant colic with the probiotic Lactobacillus reuteri: a double-blind, placebo-controlled randomized trial." *BMJ*, 348.

Szajewska H; Ewa G and Andrea H (2013):
"Lactobacillus reuteri DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial." *The Journal of pediatrics;* 162.2: 257-262.

Vandenplas Y; Abkari A; Bellaiche M; Benninga M; Chouraqui JP; ÇokuÐraþ F and Thapar N (2015):

Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of Age. *J Pediatr Gastroenterol Nutr.;* 61:531-7.

Vandenplas Y; Alturaiki MA; Al-Qabandi W; AlRefaee F; Bassil Z; Eid B and Sokhn M (2016):

Middle East consensus statement on the diagnosis and management of functional gastrointestinal disorders in< 12 months old infants. *Pediatric gastroenterology, hepatology, and nutrition;* 19 (3), 153-161.

Vercruyssen T; Toelen J; Van Aerschot K and Van Wambeke I (2020):

Long-term outcomes of infant colic: a systematic review. *Belgian Journal of pediatrics;* 22(1).41:47

Wessel MA; Cobb JC; Jackson EB; Harris Gs Jr and Detwiler AC (1954):

Paroxysmal fussing in infancy is sometimes called 'colic'. *Pediatrics;* 14: 421-34.

Zeevenhooven J; Koppen IJN and Benninga MA (2017):

The new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers. *Pediatr Gastroenterol Hepatol Nutr*; 20:1-13.

Zeevenhooven J; Browne PD; L'Hoir MP; de Weerth C and Benninga MA (2018):

Infant colic: mechanisms and management. *Nature reviews Gastroenterology & hepatology*; 15(8), 479-496

The search flow chart:

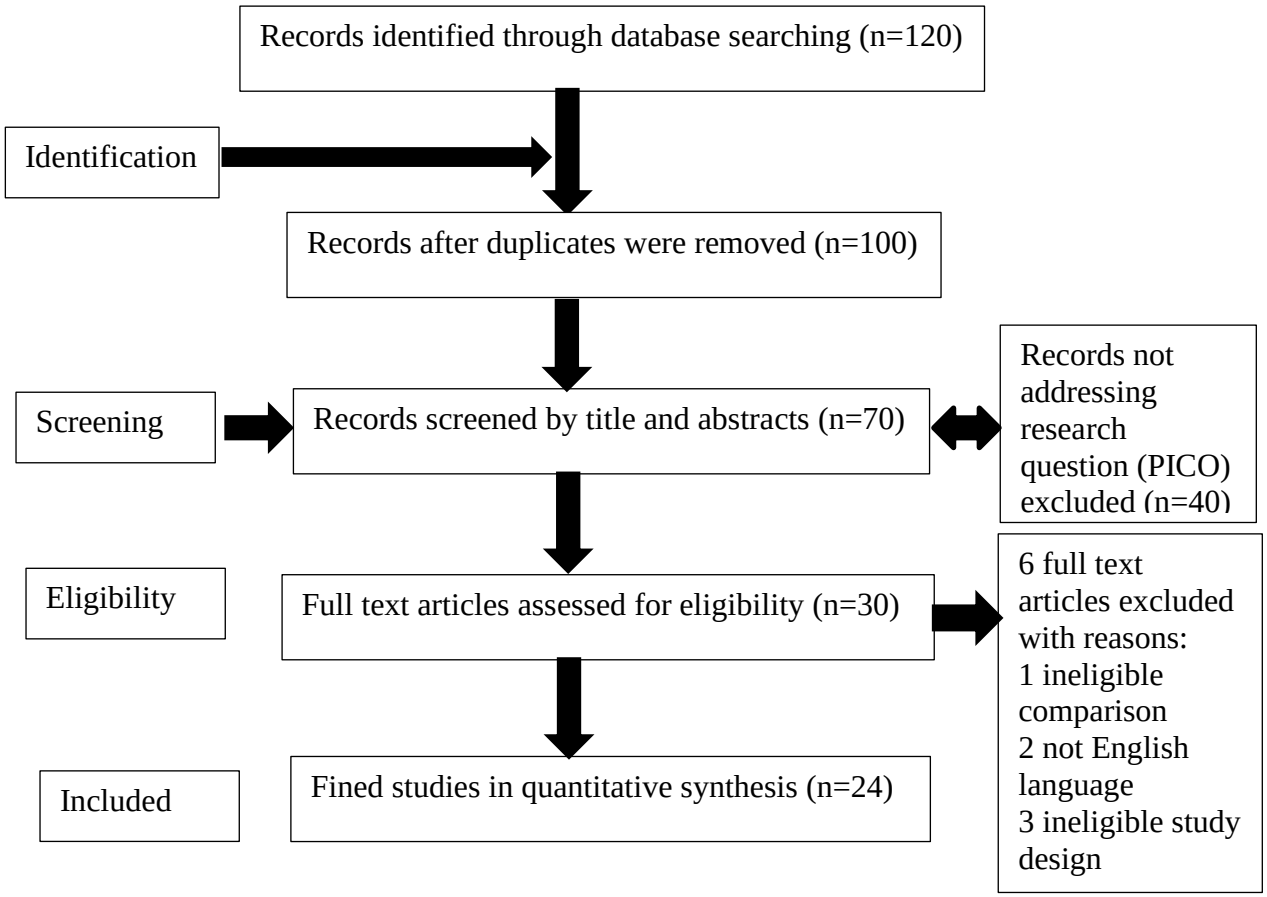

Table (1): Infantile administration of Lactobacillus reuteri versus placebo:

name of the study	authors	year	type	sample size	result
Lactobacillus reuteri DSM 17938 in Infantile Colic	Francesco Savino et al	2010	Randomized, Double-Blind, Placebo-Controlled Trial	46 L reuteri group: 25; placebo group: 21	Responders (50% reduction in crying time from baseline) was significantly higher in the L reuteri group versus the placebo group on days 7 (20 vs 8; P = .006), 14 (24 vs 13; P = .007), and 21 (24 vs 15; P = .036)
Lactobacillus reuteri DSM 17938 for the Management of Infantile Colic in Breastfed Infants	Hania Szajewska et al	2013	Randomized, Double-Blind, Placebo-Controlled Trial	80 probiotic group 40 placebo group 40	Treatment success (reduction in the daily average crying time >=50%) at day 7 RR (95% CI):-, *P* value 0.026; at day 14 RR (95% CI): 4.3 (2.3-8.7), P value <.001; at day 21 RR (95%CI): 2.6 (1.8-4.0), *P* value <.001
454 Pyrosequencing Analysis on Faecal Samples from a Randomized DBPC Trial of Colicky Infants Treated with Lactobacillus reuteri DSM 17938	Stefan Roos, Francesco Savino	2013	RCT	29 15 probiotic group 14 placebo	>50% reduction in crying time; n=21,14 in L reuturi group, 7 in the placebo group with significant difference between groups ($P < 0.01$)
The early administration of Lactobacillus reuteri DSM 17938 controls	Francesca Garofoli, Mauro Stronati	2014	RCT	40 20 intervention group 20 placebo	Parents registered daily: crying minutes, stool frequency and consistency, numbers of regurgitations, Treated infants demonstrated a reduction in daily regurgitations at the end of treatment (p = 0.02),

regurgitation episodes in full-term breastfed infants				group	
Prophylactic Use of a Probiotic in the Prevention of Colic, Regurgitation, and Functional Constipation	Flavia Indrio 1, Ruggiero Francavilla 1	2014	RCT	589 **276** Neonates randomized to receive *Lactobacillus reuteri*, **278** Neonates randomized to receive Placebo	After 1 month of intervention, infants receiving *L reuteri* DSM 17938 displayed a significant decrease in crying time, and a significant increase in evacuation frequency, but no significant difference in regurgitation episodes compared with those given the placebo P value <0.01.
Treating infant colic with the probiotic Lactobacillus reuteri	Valerie Sung, et al	2014	phase III, double-blind, randomized placebo-controlled trial	167 85 probiotics and 82 placebo.	Outcomes at 1 month in treatment and placebo groups: the probiotic group cried or fussed 49 minutes more than the placebo group (95% confidence interval 8 to 90 minutes, *P*=0.02
Probiotics for Infantile Colic: A Randomized, Double-Blind, Placebo-Controlled Trial Investigating Lactobacillus reuteri	Kim Chau et al	2015	A Randomized, Double-Blind, Placebo-Controlled Trial	52, probiotic 24, placebo 28	On day 21, a significantly higher proportion of infants in the L reuteri DSM 17938 group responded to treatment with a $50% crying time reduction compared with infants given a placebo (17 vs 6, *P* = 0. 035; relative risk, 3.3; 95% CI, 1.55- 7.03).

DSM 17938					
Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: a prospective Single-blind randomized trial	Guo-Lin Mi, Jin-Ke Xu	2015	a prospective single-blind randomized trial	39 20 from the treatment group and 19 from the placebo group	A statistically significant reduction in the mean daily crying time (secondary outcome) was observed (32.05 ± 8.30 min/day; P < 0.01) in the treatment group as compared to the placebo group (120.63 ± 20.01 min/day) with a P value of <0.01. The difference in the mean crying time between both groups was statistically significant throughout the treatment period
Regulatory T cells and Toll-like receptor 2 and 4 mRNA expression in infants with colic treated with Lactobacillus reuteri DSM17938	F. Savino, M. Bergallo	2018	RCT	59 infants with colic (n=34) and healthy control infants (n=25). 34 infants with colic of them 18 in the probiotic group and 16 in the placebo group	After *L. reuteri* administration for 28 days in infants with colic, we observed a significant decrease in daily crying time (302.3±19.86 min/day on day 0 vs 76.75±22.15 min/day on day 28, *P*=0.001) The proportion of responders (50% reduction in crying time from baseline) was significantly higher in the *L reuteri* group than in the placebo group on day 28

Table (2): Maternal prenatal administration of Lactobacillus reuteri versus placebo:

name of the study	authors	year	type	sample size	result
The efficacy of the prenatal administration of Lactobacillus reuteri LR92 DSM 26866 on the prevention of infantile colic	Mohammad Ali Pourmirzaiee, et al. Isfahan, Iran)	2020	RCT	145 pregnant women (71 in the placebo and 74 in the probiotics groups)	The frequency of colic and its higher grades were significantly lower in the intervention group ($p = 0.03$ for the presence of colic and $p = 0.01$ for high grades of colic). The frequency of colic presence and its different grades according to mothers' delivery mode and infant feeding patterns were not different between the two groups ($p > 0.05$).

Table (3): Infantile administration of Lactobacillus reuteri versus Simethicone:

name of the study	authors	year	type	sample size	Result
328 Lactobacillus Reuteri ATCC 55730 Versus Simethicone in the Treatment of Infantile Colic: A Perspective Randomized Study	F Savino,R Miniero	2005	A Perspective Randomized Study	46 23 in the probiotic group 23 in the simethicone group	At baseline, the daily average crying time in the P group was 210 min/day (SD 31) vs 208 min/day (SD 24) in the S group (*P*= 0.800). After 7 days, crying time was significantly reduced in the P group: 140 min/day (SD 51) vs 172 min/day (SD 43) (*P*= 0.025). By day 28, the crying time was significantly reduced in L. reuteri infants to only 20 min/day (SD 14) compared to simethicone, 156 min/day (SD 24) (*P*< 0.005). No side effects were observed in either group.
"Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study"	Francesco Savino, Roberto Miniero	2007	prospective randomized study	83 infants completed the trial: 41 in the probiotic group and 42 in the simethicone group.	On day 28, 39 patients (95%) were responders in the probiotic group and 3 patients (7%) were responders in the simethicone group. No adverse effects were reported.
Preventive effects of oral probiotic on infantile colic: a prospective, randomized, blinded, controlled trial using Lactobacillus reuteri DSM 17938	Savino et al (2015) ITALY	2015	RCT	105 51 infants in the study group and 54 infants in the control group	The treatment group showed a lower number of pediatric consultations related to episodes of infant colic than the control group (*P*<0.0001). *L. reuteri* DSM 17938 supplementation at the tested dosage could reduce parental discomfort due to infantile colic. The consumption of this probiotic is associated with a reduction of pediatric consultations for infantile colic, as well as the use of pain-relieving agents and of infant formula.

Table (4): Infantile administration of Synbiotic versus Placebo:

name of the study	authors	year	type	sample size	result
Synbiotic in the management of infantile colic: A randomised controlled trial	Hamidreza Kianifar, et al.	2014	RCT	50 26 were assigned randomly to be treated with synbiotics and 24 with a placebo	The treatment success was significantly higher in the synbiotic group (82.6%) compared with the placebo (35.7%) at day 7 ($P < 0.005$). On day 30, treatment success was 87% and 46% in the symbiotic and placebo groups, respectively ($P < 0.01$). Symptom resolution was also higher in the synbiotic group (39%) compared with placebo (7%) at day 7 ($P < 0.03$) but not at day 30 (56% vs.36%, $P = 0.24$). We encountered no complications related to synbiotic use.

Table (5): Infantile administration of Lactobacillus rhamnosus GG:

name of the study	authors	year	type	sample size	result
Probiotic Lactobacillus rhamnosus GG therapy and microbiological programming in infantile colic	Anna Pärtty, Erika Isolauri	2015	RCT	30 BF & FF Allocated to LGG intervention (n = 15) Allocated to placebo intervention (n = 15)	Daily crying time was comparable between the probiotic (173 min) and the placebo group (174 min; P = 0.99) at the end of the intervention according to the parental diary. However, parents reported a decrease of 68% (95% confidence interval (CI): 58–78) in daily crying in the probiotic and 49% (95% CI: 32–66) in the placebo group (P = 0.05).
Lactobacillus rhamnosus GG (ATCC 53103) for the Management of Infantile Colic	Francesco Savino, Massimiliano Bergallo	2020	A Randomized Controlled Trial	Forty-five colicky breastfed infants	After supplementation for 28 days with Lactobacillus rhamnosus ATCC 53103, median full-force daily crying was reduced (104 versus 242 min, P < 0.001), and the values of fecal calprotectin decreased significantly (P = 0.026). Furthermore, the probiotic increased the abundance of Lactobacillus (P = 0.048) and total bacteria (P = 0.040); all these effects were not observed in the placebo group

Table (6): Infantile administration of Bifidobacterium species:

name of the study	Authors	year	type	sample size	result
Infantile Colic Treated with Bifidobacterium long CECT7894 and Pedi coccus pentosaceus CECT8330	Ke Chen, and Francesco Savino	2021	RCT	A total of 112 exclusively breastfed or mixed-fed infants	infants in the IG had significantly shorter crying time ($p < 0.001$) on day 7 [IG vs. PG, median ($25-75^{th}$ percentile): 38 (3.5–40.5) vs. 62 (40–108) min/day], day 14 [IG vs. PG: 20 (0–40) vs. 50 (30–75) min/day], and day 21 [IG vs. PG: 14 (0–33) vs. 40 (28–62) min/day]. A higher responder ratio and fewer crying/fussing episodes on days 7, 14, and 21, and better stool consistency on day 21 were observed in the IG ($p < 0.01$) as compared to the PG. Conversely, no significant effects on stool frequency or quality of life were observed.
Efficacy of Bifidobacterium breve CECT7263 for infantile colic treatment: an openlabel, parallel, randomised, controlled trial	J A Maldonado-Lobón et al.	2021	RCT	150	the infants in the Bifidobacterium breve group had significantly decreased crying time from the first week of the study ($P<0.05$), whereas the Bb + Lf group and the simethicone group had significantly decreased crying time from the second week ($P<0.05$). The percentage of reduction in the minutes of crying from baseline in the Bb group was significantly higher than that in the Simethicone group every week of the intervention (-40.3 vs -27.6% at 1 week; -59.2 vs -43.2% at 2 weeks; -64.5 vs -53.5% at 3-week and -68.5 vs -59.5% at 4-weeks, $P<0.05$).

Table (7): Administration of α-Lactalbumin-enriched infant formula:

name of the study	authors	year	type	sample size	Result
α-Lactalbumin-enriched and probiotic supplemented infant formula in infants with colic: growth and gastrointestinal tolerance	Dupont et al	2010	RCT	66	the number of infants presenting a reduction in daily crying duration higher than 25% between enrolment and day 15, did not differ between groups (ITT and PP). Nevertheless, irritability and agitation without crying decreased more with the experimental formula (EF)(53.2 min), compared to Control Formula (CF) (21.1 min) (−39.8 vs −13.6%, P=0.036; PP) between enrolment and the day preceding day 15. Also, the crying duration decreased with time in both groups (P=0.003), with a significant increase in parents' satisfaction related to the improvement of GI symptoms (P<0.001).

Table (8): Administration of herbal supplementations:

name of the study	authors	year	type	sample size	result
The effect of fennel (Foeniculum vulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study	Alexandrovich et al.	2003, Russia	A randomized, placebo-controlled study	121 infants (2-12weeks old), 62 in the treatment group, 59in the placebo group	the use of fennel emulsion eliminated colic in 65% of infants in the treatment group (40/62) which is significantly better than 23.7% (14/59) in the placebo group ($p< 0.01$) absolute risk reduction (ARR):41% (95% CI 25 to 57)
A Randomized Double-blind Placebo-controlled Trial of a Standardized Extract of Matricariae recutita, Foeniculum vulgare and Melissa officinalis (ColiMil®) in the	Francesco Savino, et al.	2005	A Randomized Double-blind Placebo-controlled	88 breastfed colicky infants, 41 in the treatment group (chamomile, fennel, and lemon balm), 47 in control	A reduction of crying time was observed in 35 (85.4%) subjects of the treatment group and in 23 (48.9%) subjects in the Placebo group ($p < 0.005$)

Treatment of Breastfed Colicky Infants					
Effect of Fennel Essence and Gripe Water Syrup on Infantile Colic	M Attarha et al	2008, Iran	Randomized clinical trial	81 Fennel group 40, gripe water group 40	After the 7 days of therapy, the colic improvement score was significantly better in both the fennel group (P= 0.05) and the gripe water group (P=0.002) than before, indicating a statistically significant difference.
Effectiveness of Mentha piperita in the Treatment of Infantile Colic: A Crossover Study	Alves et al 2012,	2012, Brazil	a crossover double-blind	30 infants	30 infants aged 8 to 56 days (33 ± 11.1) were studied. The average weight and height were 4.650 g (±415) and 54.2 cm (±3.0), respectively. The maternal age ranged from 14 to 32 years (22.7 ± 5.4) and they had 10.4 years (±2.5) of schooling. All mothers had received prenatal care and 16 (53.3%) had undergone cesarean section. At baseline daily episodes of infantile colic was 3.9 (±1.1) and the mean crying time per day was 192 minutes (±51.6). At the end of the study daily episodes of colic fell to 1.6 (±0.6) and the crying duration decreased to 111 (±28) minutes. All mothers reported a decrease in the frequency and duration of the episodes of infantile colic and there were no differences between responses to Mentha piperita and simethicone. ***P*-value**

					(0.860)
Efficacy of a standardized extract of Matricariae chamomilla L., Melissa officinalis L. and tyndallized Lactobacillus acidophilus (HA122) in infantile colic: An open randomized controlled trial	M. Martinelli, et al	2017	An open randomized controlled trial	176 herbal group(A) 60 probiotic group(B) 59	the RR of experiencing a decrease of 50% from baseline in the daily crying time between infants exclusively or partially breastfeeding and children exclusively formula-fed was equal to 0.94 (95% CI 0.88-1.01; P=.084) in group A, 1.1 (95% CI 0.79-1.53; P=.57) in group B, and 0.853 (95% CI 0.57-1. 27; P=.433) in Group C.

مراجعة منهجية 2022
تأثير مستحضرات البكتيريا النافعة والمستحضرات العشبية على تقلصات الرضع

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1- المعهد القومي للتغذية- القاهره – مصر
2- مستشفى قها التخصصي
3- مستشفى منشية البكري العام
4- مستشفى قويسنا المركزي
5- مستشفى الشرطة بالأسكندرية
6- مستشفى المنشاوي العام

الملخص العربي

تعد مشكلة التقلصات التي تصيب الرضع والتي ليس لها سبب محدد من اكثر المشكلات التي تتسبب في نوبات بكاء طويلة المدى لديهم فلا يتمكن الوالدان من ارضائهم بسهولة؛ مما يؤدي لشعور الأهل بالاحباط مع العلم أن هذه التقلصات تختفي عند بلوغ الطفل خمسة أشهر. وقد أشارت بعض الدراسات الحديثة أن اختلال البكتيريا المفيدة في الجهاز الهضمي للرضيع هو أحد أهم العوامل المؤدية لهذه التقلصات. ولذلك يتم حاليا استخدام البكتيريا المفيدة (البروبيوتك) لخلق توازن بكتيري مناسب يدعم الصحة العامة للجهاز الهضمي للطفل. وقد أثبتت بعض الدراسات فاعلية استخدام بعض الأعشاب الشائعة أو مستحضراتها لتقليل التقلصات؛ ونذكر هنا على سبيل المثال (الشمر والينسون ومستحضرماء غريب العشبي). الغرض من البحث: مقارنة فاعلية مستحضرات البروبيوتك المستحدث استخدامها لعلاج تقلصات الرضع مع فاعلية المنتجات العشبية الشائع استخدامها. بعد البحث خلال قواعد البيانات المحلية والدولية عن تأثير استخدام البكتيريا النافعة واستخدام الأعشاب لعلاج تقلصات الرضع البسيطة؛ تم المقارنة بين 24 دراسة عشوائية بحيث كانت 19 دراسة منهم عن استخدام البكتيريا النافعة (البروبيوتك) بينما كانت 5 دراسات تتحدث عن استخدام الوصفات العشبية. أظهرت النتائج أن مجموعة (اللاكتوباسيلوس روتيري) والتي كانت الأكثر عرضة للدراسة ؛انخفاض واضح في معدل نوبات البكاء اليومي لدى الرضع؛ حيث قلت لأكثر من 50% حين بلوغ الطفل لليوم السابع منذ بداية العلاج؛ وقد كان الشمر هو الأكثر دراسة في المجموعة العشبية والذي أظهر بعض التحسن أيضا. الخلاصة: لم تتمكن أي من العلاجات القائم عليها البحث من الوصول لانهاء تقلصات البطن عند الرضع بشكل نهائي ومازال الأمر بحاجة لمزيد من البحث؛ مع الأخذ بالأعتبار ان الاثار طويلة المدى لمكملات البروبيوتك لا تزال تحت الدراسة.

الكلمات المفتاحية: (عشب لمغص الرضع) ، (بروبيوتيك لمغص الرضع).