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Research Article
Infantile colic

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TumsUP Drops: Evaluation of safety and efficacy in infantile colic.

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Objectives: This study aimed to evaluate the safety and efficacy of TumsUP drops in the treatment of infantile colic in infants and toddlers. **Setting and Design:** An active post-marketing surveillance study was conducted in the department of pediatrics of 4 hospitals from August 2020 to February 2021. **Material and Methods:** A total of 200 patients aged two weeks to two years, with symptoms of infantile colic for >3 hours/day, occurring >3 days/week were enrolled. TumsUP (A fixed-dose combination of simethicone 40 mg, dill oil 0.005 mL, and fennel oil 0.0007 mL) oral drops were administered for 7 days. The safety of the study drug and its efficacy in infantile colic symptoms were assessed after the end of the treatment. **Results:** Among 200 patients, 4 (2%) adverse events (AEs) were reported. They were mild, not related to the study drug, and resolved without sequelae. The mean crying time was reduced from 3.35±1.68 hours/day at baseline to 0.37±0.67 hours/day on day 7 (mean reduction: -2.98; 95%CI: -3.24 to -2.72, p<0.001). The mean number of daily episodes of colic reduced from 3.09±1.90 at baseline to 0.47±0.88 on day 7 (mean difference: -2.61; 95%CI: -2.90 to -2.33; p<0.001). A statistically significant (p<0.001) reduction was observed in excessive crying, fussing, sleep disturbances, clenching of fists, bending of arms and legs towards the belly, bloated tummy, redness of the face, flatulence and milk regurgitation on Day 7 as compared to the baseline. Complete remission of infantile colic was reported in 67.84% of patients after 7 days of treatment. **Conclusion:** TumsUP reduced the duration and severity of infantile colic and showed good safety, efficacy and tolerability.

Keywords: Infantile colic, Simethicone, Dill oil, Fennel oil, Fixed-dose combination

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Introduction

Excessive crying among infants is one of the most common complaints for which parents seek pediatric consultation. [1] A leading cause of excessive crying is infantile colic, [2] characterized by episodes of inconsolable crying for more than three hours daily, more than three days per week, for longer than three weeks (Wessel's rule of threes).[1,3] Recently, the Wessel criteria have been further refined in the Rome classification of functional gastrointestinal disorders (Rome IV), with the replacement of the three weeks duration criterion with a 7-day duration criterion.[1] Various causes have been suggested, such as alterations in fecal microflora, intolerance to cow's milk protein or lactose, abnormal gastrointestinal function, increased serotonin secretion, poor feeding technique, and maternal smoking or nicotine replacement therapy.[3] Symptoms of infantile colic include loud piercing cries with hypertonia, facial flushing, withdrawal of legs towards the abdomen, clenching of the fists and flatulence. The crying starts and stops abruptly. [4] There are no established guidelines for the treatment, [4,5] and pharmacological agents are not recommended. [2]

Simethicone is a non-absorbable, de-foaming agent that decreases the surface tension of gut mucus, allowing gas bubbles within the gut to coalesce and promoting easier expulsion of intestinal air. Evidence indicates that herbal preparations like fennel oil and dill oil might reduce crying time.[5] We aimed to evaluate the safety and efficacy of a fixed-dose combination (FDC) of simethicone, dill oil, and fennel oil (TumsUP drops) in the treatment of infantile colic.

Material And Methods

Study Design and Setting

This was an open-label, multicentric, prospective, single-arm, active post-marketing surveillance study to evaluate the safety and efficacy of TumsUP drops in infantile colic patients aged 2 weeks to 2 years. The study was conducted at four centres across India from August 2020 to February 2021. The primary objective was to assess the safety and tolerability of the TumsUP drops, and the secondary objective was to evaluate their efficacy in treating infantile colic.

Ethics: The study was conducted according to the International Council for Harmonization (ICH) E6 (R2) Guideline for Good Clinical Practice (GCP), and Declaration of Helsinki (Brazil 2013), New Drugs and Clinical Trials Rules, 2019 of Central Drugs Standard Control Organization (CDSCO), Ministry of health and family welfare, Government of India, Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research (ICMR) 2017. The study protocol, informed consent documents and other relevant documents were submitted to the respective site institutional ethics committee and were approved by the same. The trial was initiated only after obtaining approval from the respective Institutional Ethics Committees. The clinical trial was registered prospectively with the Clinical Trial Registry of India [CTRI No: CTRI/2020/04/024552].

The parents of the patients were informed about the purpose of the study, the study drug, its effects, the duration of the trial, procedures and the overall plan of the study. Informed consent was obtained from the parents before the enrolment of their children in the study. They were free to withdraw their participation from the study at any time without providing any reason. The investigators could also withdraw any participant from the study if they deemed it appropriate due to safety or ethical reasons or if it was considered detrimental to the well-being of the participant.

Participants: A total of 200 patients aged two weeks to two years, with symptoms of infantile colic for more than 3 hours/day, occurring more than 3 days/week were enrolled. The patients with a history of hyperbilirubinemia, recently diagnosed illness or gastrointestinal disorders, presence of fever, any infection, or congenital anomalies at the time of screening were not considered for the enrolment.

Study Procedure: The history was noted by interviewing the parents. Clinical examination and symptomatic evaluation were carried out and assessed for the eligibility criteria. TumsUP drops containing Simethicone 40 mg, Dill oil 0.005 mL, and Fennel oil 0.0007 mL as fixed-dose combination formulation manufactured by Zuventus Healthcare Limited, Mumbai, India administered for 7 days. Parents were advised by the investigator for the administration of TumsUP drops. The dosage used in this trial was based on the age of the participants as below:

- Infants (Below six months of age): five to 10 drops four times daily, 15 minutes before the feed.
- Infants (six to 12 months of age): 10-20 drops four times daily, 15 minutes before the feed.
- Toddlers (one to two years of age): 20 drops four times daily, 15 minutes before the feed.

All the patients were followed-up at the end of the treatment on Day 7 and symptomatic evaluation and clinical examination were done, along with the occurrence of any adverse event(s).

Outcome Measures: The primary endpoints were the number of patients developing adverse events (AEs) and investigators' and parents' assessment of response to the therapy at the end of the study. The secondary endpoints were a reduction in crying time and severity of infantile colic symptoms from baseline to the end of the treatment period and the number of participants with complete remission at the end of the treatment period.

The assessment of reduction in the severity of symptoms from baseline to the end of the treatment was based on the score of the following symptoms: excessive crying, fussing, sleep disturbance, clenching of fists, bending of arms and legs towards the belly, bloated tummy, redness of the face, flatulence, and milk regurgitation. These signs and symptoms are often seen with infantile colic. [5] The severity score for infantile colic symptoms was defined on a 5-point scale as follows: 5: Much Worse; 4: Somewhat Worse; 3: Slightly improvement; 2: Somewhat Better; 1: Much Better. The investigators and parents were asked to provide their assessment of response to therapy on a scale of one to four, with one indicating poor and four indicating excellent.

Statistical Analysis: The occurrence of infantile colic is varied and reported in up to 40% of infants. [4] Based on the literature, 18-20% of crying duration was reduced with the simethicone treatment compared to the baseline. [6] The statistical calculations were done based on the assumption. A total of 181 subjects were required to detect at least a 25% reduction in crying time at 5% significance with 80% power. Assuming a drop-out rate of 10%, 200 patients were enrolled in the study. Descriptive statistics have been used to summarize the baseline characteristics as mean ± standard deviation (SD) or percentage (%).

The crying duration at the baseline and the end of the treatment was compared using paired t-test. The severity of colic based on the symptom scores at baseline and the end of day 7 was compared using the paired t-test. The statistically analyzed results were presented with a significance level of 0.05 and 95% confidence intervals.

Results

A total of 200 patients were screened and enrolled in this study. Of these, 97 (48.5%) were aged less than six months, 34 (17%) were aged six to 12 months, and 69 (34.5%) were aged one to two years. The majority of the patients [127 (63.50%)] were breastfeeding. All 200 patients had excessive crying problems. Demographic and baseline characteristics are presented in Table 1. All enrolled patients who received at least one dose of the study drug were considered and analyzed for safety. One patient was excluded from the efficacy analysis due to a protocol deviation. The details of the disposition of subjects in the study are given in Figure 1.

Table 1: Demographic and baseline characteristics

Study population	N (%)	200 (100)
Gender		
Male	n (%)	117 (58.50)
Female	n (%)	83 (41.50)
Age		
Age at the time of enrolment (months)	Mean ± SD	8.64 ± 7.74
Gestational age at birth (weeks)	Mean ± SD	37.52 ± 1.54
Weight		
Weight at the time of enrolment (Kgs)	Mean ± SD	6.97 ± 2.96
Weight at birth (Kgs)	Mean ± SD	2.97 ± 0.43
Number of colic episodes	Mean ± SD	3.09 ± 1.90
Number of hours with colic	Mean ± SD	3.85 ± 1.12
Crying Time (hours)	Mean ± SD	3.53 ± 1.65
Feeding Method		
Breast	n (%)	127 (63.50)
Bottle	n (%)	22 (11.00)
Both	n (%)	51 (25.50)

The mean compliance with the study drug was 94.89%. A total of 4 (2%) AEs were reported in this study. The AEs comprised two cases of rhinorrhea and one case each of erythema and rash. The AEs were not related to the study drug, mild in severity and resolved without sequelae. Treatment response to infantile colic was assessed as 'Excellent' by 75.38% of investigators and 68.34% of parents at the end of the study. (Figures 2 and 3)

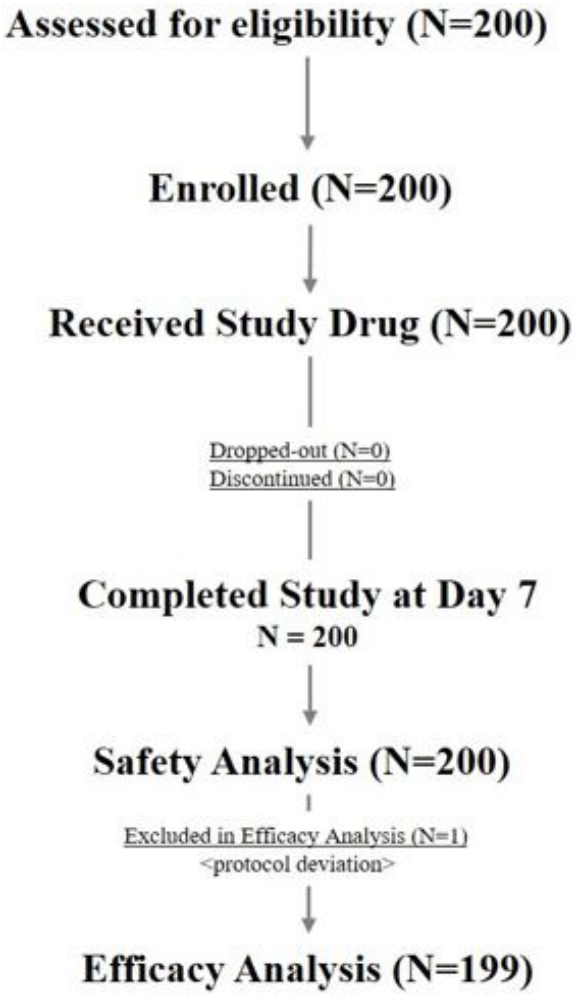

Figure 1: Disposition of subjects

Table 2: Effect of TumsUP drops on infantile colic symptoms

Infantile colic symptoms	Patients with symptoms at baseline (n)	Patients with relief of complete symptom resolution after 7 days of treatment, n (%)
Milk Regurgitation	107	106 (99.07)
Bloated tummy	170	168 (98.82)
Bending of arms and legs towards the belly	145	143 (98.62)
Clenching of fists	141	138 (97.87)
Flatulence	128	125 (97.66)
Fussing	139	135 (97.12)
Sleep disturbance	155	150 (96.77)
Redness of the face	105	101 (96.19)
Excessive Crying	197	188 (95.43)

The mean crying time was reduced from 3.35±1.68 hours/day at baseline to 0.37±0.67 hours/day on day 7 (mean reduction: -2.98 hours/day; 95%CI: -3.24 to -2.72, p<0.001). The mean number of daily episodes of colic reduced from 3.09±1.90 at baseline to 0.47±0.88 on day 7 (mean difference: -2.61; 95%CI: -2.90 to -2.33; p<0.001).

There was a statistically significant (p<0.001) reduction observed in the infantile colic symptoms such as excessive crying, fussing, sleep disturbances, clenching fists, bending of arms and legs towards the belly, bloated tummy, redness of the face, flatulence and milk regurgitation at Day 7 compared to baseline (Figure 4). Complete symptomatic relief was observed in more than 95% of patients after 7 days of treatment with TumsUP drops. (Table 2)

Complete remission of infantile colic was reported in 67.84% of participants after 1 week of treatment. Overall, the mean time of colic per day was 3.85 hours at baseline which was reduced to 0.39 hours on day 7. A significant reduction (mean reduction: -3.46; 95%CI: -3.68 to -3.24; p<0.001) in the meantime of relief from colic was observed at the end of 7 days of treatment with TumsUP drops.

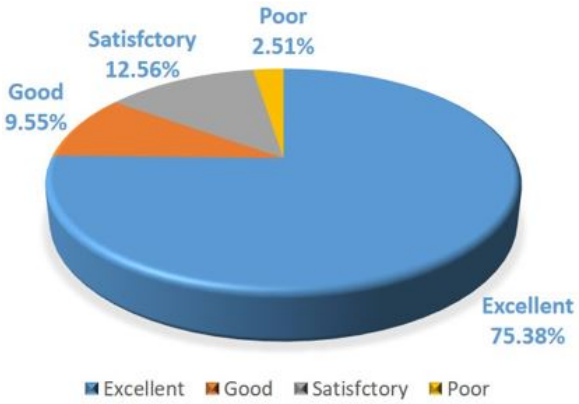

Figure 2: Investigator's response to study treatment

Figure 3: Parent's response to study treatment

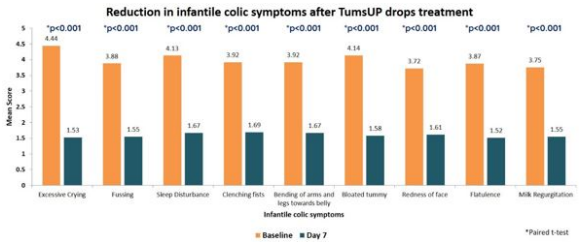

Figure 4: Reduction in infantile colic symptoms

Discussion

Infantile colic affects approximately 10% to 40% of infants worldwide. [3] Although benign and usually self-limiting, the pain causes considerable distress to the infant and children. Persistent infantile colic can lead to parental fatigue, strained parental relationships, and poor parental engagement with their infant. [7] Although many factors have been suspected, the exact cause of infantile colic is poorly understood, and the clinical management is often guided by the physician's experience, as there are no treatment guidelines.[5] On the other hand, there is an excess of information on the internet; much of this advice is conflicting and possibly adds to parental confusion.

Treatment of infantile colic using oral agents can be grouped into the following categories: probiotics, pharmacological treatments (e.g., simethicone, dicyclomine hydrochloride, cimetropium bromide), and complementary therapies (including herbal agents and sucrose). [8] The intestinal microbiota in infants with colic differs from those in healthy controls and supplementation with probiotics can facilitate the colonization of beneficial bacteria. [9,10,11] Several over-the-counter medications are available for relieving the symptoms of infantile colic. The use of conventional medications is either controversial or prohibited in infants less than 6 months of age due to the side effects. [2]

To our best knowledge, this is the first time that a clinical study evaluated the safety and efficacy of FDC of simethicone, fennel oil, and dill oil in infants and toddlers for the treatment of infantile colic. The postulated mechanism in the pathogenesis of colic may be flatulence and spasm of the intestinal smooth muscle. Simethicone decreases the surface tension of gas bubbles in the GI tract and allows their removal from the GI tract. [12] The therapeutic effect of fennel oil and dill oil may be secondary to a spasmolytic action.

The antispasmodic activity of these volatile oils has been tested mainly in animals and it may be due to the blockage of voltage-dependent calcium channels. [13,14]

Simethicone, a defoaming agent, is a pharmacological agent that acts as a detergent to reduce the surface tension of bubbles in the intestinal tract, expels abdominal gas easily and reduces meteorism. It decreases abdominal distension and discomfort due to excessive gas production. [8] It has a favorable safety profile as it is not systemically absorbed. [15] In a randomized trial, 26 infants receiving simethicone had significantly reduced crying episodes in 4 to 7 days of therapy than did the infants receiving a placebo. [16,17] In an open-label trial, symptoms of colic improved in 38 (78%) infants after one day of treatment and in 44 (86%) infants after 7 days of simethicone treatment. [18]

Complementary herbal therapies have an increasingly important role in the management of infantile colic. Herbal supplements such as fennel (Foeniculum vulgare) and dill (Anethum graveolens) are widely used in gastrointestinal complications such as flatulence, indigestion, stomachache, infantile colic and intestinal gas. The volatile oil of fennel (rich in anethole) and dill (rich in carvone) possesses carminative, antioxidant and antispasmodic activity. [19,20]

Foeniculum vulgare has a significant positive effect on the duration of crying time. [21] A systemic review suggested that the preparation containing the fennel is effective in infantile colic with an overall mean reduction in crying time of -72.1 min/day.[22] In a placebo-controlled trial, a herbal extract contacting Foeniculum vulgare showed that colic in breastfed infants improves within 1 week of treatment. Crying time reduction was observed in 85.4% of subjects. [23] Alexandrovich et al assessed the efficacy of fennel on infantile colic in a randomized, double-blinded, placebo-controlled trial. Forty (65%) infants in the fennel group eliminated colic as compared to 23.7% of infants in the control group ($p<0.01$). Cumulative crying time at the end of treatment decreased from 13.5±1.18 to 8.8±1 hours/week to 8.8±1.2 hours/week. [24]

Anethum graveolens is having a soothing effect and is given to babies to treat gripe and relieve hiccups and colic. [20]

The carminative volatile oil in dill helps in digestion and relieves flatulence. It helps the expulsion of gases and also reduces gas formation [25] Dill oil is used in folk medicine as a carminative for the treatment of flatulence, colic and hiccups of infants and children. [26] Attarha et al. compared the effect of fennel extract vs. gripe water containing dill oil in a randomized clinical trial. Both groups revealed a statistically significant decrease in crying time on days 3 and 7. The difference between the two groups was insignificant at all times. [27]

Infantile colic is a behavioural syndrome characterized by excessive paroxysmal crying, that is most likely to occur in the evening. [28] Indeed, for infants and toddlers in this study about two-thirds of the daily total distressed behaviour was observed in the evening. Prolonged crying or fussing, particularly unsoothable crying is a source of anxiety and distress for the parents and a challenge for the healthcare givers. [5,29] TumsUP drops provided a significant reduction in infantile colic symptoms when day 7 of treatment was compared with baseline. The most associated symptom of milk regurgitation, which can cause lung complications, was resolved in all enrolled patients after the completion of 7 days of TumsUP treatment. The results of this study suggest that TumsUP drops are an effective formulation in the management of infantile colic. It showed that the TumsUP administered as oral drops for infantile colic was safe and well tolerated. There was a statistically significant reduction in crying time and number of episodes of colic per day at the end of treatment compared to that at baseline. After 7 days of treatment with TumsUP drops, 95% population showed individual symptomatic relief. Moreover, TumsUP drops achieved complete remission of abdominal colic in 2/3rd the study population. The observed clinical benefits of TumsUP drops might be due to the synergistic actions of its ingredients.

No study has investigated the effect of an FDC of simethicone, fennel oil, and dill oil on infantile colic. Hence, our study would make a valuable contribution to the literature and aid clinical practice in the treatment of infantile colic. The limitation of this study is that there was no comparative arm. Future randomized, controlled, blinded studies on the outcomes of FDC of simethicone, fennel oil, and dill oil in infantile colic with a larger sample size and a comparator arm are warranted to further strengthen the results.

Conclusion

This clinical study observed a significant symptomatic relief from infantile colic symptoms and a reduction in the crying duration and crying episodes in all the patients. There were no related adverse events, either reported or observed, during the study period. Therefore, it may be concluded that TumsUP (FDC of simethicone 40 mg, dill oil 0.005 mL, and fennel oil 0.0007 mL) is clinically safe and effective in the management of infantile colic in infants and toddlers.

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Reference

01. Hjern A, Lindblom K, Reuter A, Silfverdal SA. A systematic review of prevention and treatment of infantile colic. Acta Paediatr. 2020;109(9):1733–1744. *doi: 10.1111/apa.15247 [Crossref][PubMed][Google Scholar]*

02. Sung V. Infantile colic. Aust Prescr. 2018;41(4):105–110. *doi: 10.18773/austprescr.2018.033 [Crossref][PubMed][Google Scholar]*

03. Johnson JD, Cocker K, Chang E. Infantile Colic: Recognition and Treatment. Am Fam Physician. 2015;92(7):577–582. *[Crossref][PubMed][Google Scholar]*

04. Sarasu JM, Narang M, Shah D. Infantile Colic: An Update. Indian Pediatr. 2018;55(11):979–987. *[Crossref][PubMed][Google Scholar]*

05. Zeevenhooven J, Browne PD, L'Hoir MP, de Weerth C, Benninga MA. Infant colic: mechanisms and management. Nat Rev Gastroenterol Hepatol. 2018;15(8), 479–496. *doi: 10.1038/s41575-018-0008-7 [Crossref][PubMed][Google Scholar]*

06. Martinelli M, Ummarino D, Giugliano FP, Sciorio E, Tortora C, Bruzzese D, et al. 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. *Neurogastroenterology & Motility. 2017;29(12):1-8. doi: 10.1111/nmo.13145 [Crossref][PubMed][Google Scholar]*

07. Reijneveld SA, van der Wal MF, Brugman E, Sing RA, Verloove-Vanhorick SP. Infant crying and abuse. Lancet. 2004;364(9442):1340-2. *doi: 10.1016/S0140-6736(04)17191-2 [Crossref] [PubMed][Google Scholar]*

08. Biagioli E, Tarasco V, Lingua C, Moja L, Savino F. Pain-relieving agents for infantile colic. Cochrane Database Syst Rev. 2016;9(9):CD009999. *doi: 10.1002/14651858.CD009999.pub2 [Crossref] [PubMed][Google Scholar]*

09. Ong TG, Gordon M, Banks SS, Thomas MR, Akobeng AK. Probiotics to prevent infantile colic. Cochrane Database Syst Rev. 2019;3(3):CD012473. *doi: 10.1002/14651858.CD012473.pub2 [Crossref] [PubMed][Google Scholar]*

10. Dryl R, Szajewska H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. Arch Med Sci. 2018;14(5):1137–1143. *doi: 10.5114/aoms.2017.66055 [Crossref] [PubMed][Google Scholar]*

11. Indrio F, Di Mauro A, Riezzo G, Civardi E, Intini C, Corvaglia L, et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. JAMA Pediatr. 2014;168(3):228–233. *doi: 10.1001/jamapediatrics.2013.4367 [Crossref] [PubMed][Google Scholar]*

12. Ingold CJ, Akhondi H. Simethicone. [Updated 2022 Jul 4]. In: StatPearls [Internet]. *Treasure Island (FL): StatPearls Publishing; 2022. Available from: [Article][Crossref][PubMed][Google Scholar]*

13. Ignjatović MG, Kitić D, Radenković M, Kostić M, Milutinović M, Ranković GN, et al. The effect of the aqueous and methanol fennel stem extracts (Foeniculum vulgare Miller) on isolated rat ileum contractility. Vojnosanit Pregl. 2018;75(8):809–814. *doi: 10.2298/VSP161001391G [Crossref][PubMed] [Google Scholar]*

14. MK Gharib Naseri, A. Heidari. Antispasmodic Effect of Anethum graveolens Fruit Extract on Rat Ileum. International Journal of Pharmacology. *2007;3(3):260-264. doi: 10.3923/ijp.2007.260.264 [Crossref][PubMed] [Google Scholar]*

15. National Center for Biotechnology Information. PubChem Compound Summary for CID 6433516, Simethicone. https://pubchem. ncbi. *nlm.nih.gov/compound/Simethicone. Accessed Dec. 15, 2022 [Crossref][PubMed][Google Scholar]*

16. Garrison MM, Christakis DA. A systematic review of treatments for infant colic. Pediatrics. 2000;106(1 Pt 2):184-90. *[Crossref][PubMed] [Google Scholar]*

17. Sethi KS, Sethi JK. Simethicone in the management of infant colic. Practitioner. 1988;232(1448):508. *[Crossref][PubMed][Google Scholar]*

18. Becker N, Lombardi P, Sidoti E, Katkin LS. Mylicon drops in the treatment of infant colic. Clin Ther. 1988;10(4):401-5. *[Crossref][PubMed] [Google Scholar]*

19. Saini N, Singh GK, Nagori BP. Spasmolytic Potential of Some Medicinal Plants Belonging to Family Umbelliferae: A Review. Int J Ayurvda Pharm. 2014;5(1):74-83. *doi: 10.7897/2277-4343.05116 [Crossref][PubMed][Google Scholar]*

20. Kaur GJ, Arora DS. Bioactive potential of Anethum graveolens, Foeniculum vulgare and Trachyspermum ammi belonging to the family Umbelliferae-Current status. Journal of Medicinal Plants Research. 2010;4(2):087-94. *doi: 10.5897/JMPR09.018 [Crossref][PubMed][Google Scholar]*

21. Mohammadi G, Ghazanfarpour M, Kargarfard L, Babakhanian M. Effectiveness of herbal medicines containing phytoestrogens to treat infantile colic: a meta-analysis review. Journal of Pediatrics Review. 2019;7(1):1-10. *doi: 10.32598/jpr.7.1.1 [Crossref] [PubMed][Google Scholar]*

22. Larijani B, Esfahani MM, Moghimi M, Shams Ardakani MR, Keshavarz M, Kordafshari G, et al. Prevention and Treatment of Flatulence From a Traditional Persian Medicine Perspective. Iran Red Crescent Med J. 2016;18(4):e23664. *doi: 10.5812/ircmj.23664 [Crossref][PubMed][Google Scholar]*

23. Savino F, Cresi F, Castagno E, Silvestro

L, Oggero R. 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. Phytother Res. 2005;19(4):335-40. *doi: 10.1002/ptr.1668 [Crossref][PubMed][Google Scholar]*

24. Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (Foeniculum Vulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. Altern Ther Health Med. 2003; 9(4):58–61. *[Crossref] [PubMed][Google Scholar]*

25. Harb T, Matsuyama M, David M, Hill RJ. Infant Colic-What works: A Systematic Review of Interventions for Breast-fed Infants. J Pediatr Gastroenterol Nutr. 2016;62(5):668-86. *doi: 10.1097/MPG.0000000000001075 [Crossref] [PubMed][Google Scholar]*

26. Saleh-E-In MM, Sultana N, Rahim MM, Ahsan MA, Bhuiyan MN, Hossain MN, et al. Chemical composition and pharmacological significance of Anethum Sowa L. Root. BMC Complement Altern Med. *2017;17(1):127. doi: 10.1186/s12906-017-1601-y [Crossref][PubMed][Google Scholar]*

27. Attarha M, Rosbahani N, Youssefi P. [Comparison of the effect of fennel essence and gripe water syrup in infantile colic]. Scientific Journal of Kurdistan University of Medical Sciences. 2008;13(1):28-35. *[Crossref][PubMed][Google Scholar]*

28. Lucas A, St James-Roberts I. Crying, fussing and colic behaviour in breast- and bottle-fed infants. Early Hum Dev. 1998;53(1):9-18. *doi: 10.1016/s0378-3782(98)00032-2 [Crossref] [PubMed][Google Scholar]*

29. Zeevenhooven J, Koppen IJ, Benninga MA. The New Rome IV Criteria for Functional Gastrointestinal Disorders in Infants and Toddlers. Pediatr Gastroenterol Hepatol Nutr. 2017;20(1):1-13. *doi: 10.5223/pghn.2017.20.1.1 [Crossref][PubMed] [Google Scholar]*