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ORIGINAL ARTICLE

Multicentre, randomised study found that honey had no pharmacological effect on nocturnal coughs and sleep quality at 1–5 years of age

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Abstract

Aim: The World Health Organization has listed honey as a potential treatment for coughs, but there is little evidence to support its use for coughs associated with upper respiratory tract infections (URTIs). This study evaluated how effective honey was for treating nocturnal coughs and sleep difficulties.

Methods: This multicentre, randomised, double-blind, placebo-controlled study focused on patients aged 1–5 years with URTIs and coughs for up to 7 days. They were recruited from 13 general paediatric community clinics in Japan. The participants were given acacia honey or a honey-flavoured syrup placebo in the hour before they were put down to sleep on 2 consecutive nights. Their nocturnal cough and sleep difficulties were assessed on both nights using a 7-point Likert scale.

Results: The data collection for 161 patients took place between 20 November 2021 and 28 February 2022, with 78 randomly allocated to the honey group and 83 to the syrup placebo group. Both groups showed improvements on both the first and second nights, with no significant differences between the two groups.

Conclusion: Both groups showed improvements in their nocturnal coughs and sleep difficulties during the 2-night study, but honey was no more effective than the syrup placebo.

KEYWORDS
coughs, honey, placebo, randomised controlled trial, upper respiratory tract infection

1 | INTRODUCTION

Coughs are a common symptom in paediatric practice, and they can be particularly troubling for children and their parents at night, because they interfere with their sleep. However, there is no established treatment for this condition.[1,2] Coughs are most commonly associated with upper respiratory tract infections (URTIs) and many cultures use honey to treat URTI symptoms, including coughs. In 2001, the World Health Organization (WHO) listed honey as a potential treatment for cough and cold symptoms in its report on

Abbreviations: URTIs, upper respiratory tract infections; WHO, World Health Organization.

treating acute respiratory infections in young children.[3] The report suggested that anti-inflammatory agents could soothe the throat and provide some relief from childhood coughs. However, there has been little evidence published to support the use of honey for symptoms associated with URTIs.[4–6]

The aim of this study was to determine whether honey has antitussive effects. To do this, we compared the effects of a single nighttime dose of honey or a honey-flavoured syrup placebo on nocturnal coughs and sleep difficulties for 2 consecutive nights.

Key Notes

- The World Health Organization has listed honey as a potential treatment for coughs, but there is little evidence to support its use for coughs associated with upper respiratory tract infections (URTIs).
- This multicentre, randomised study focused on patients aged 1–5 years with URTIs and coughs for up to 7 days.
- It found no significant differences in cough symptom scores when honey and a honey-flavoured placebo were used for 2 nights running.

2 | METHODS

2.1 | Study design and patients

Patients were recruited into this multicentre, double-blind, randomised, placebo-controlled study from 13 general paediatric community clinics in Japan. The children were eligible if they were aged 1–5 years and they had URTIs, with an acute cough that had lasted for up to 7 days. Patients were excluded if they had underlying medical conditions, asthma, croup or any other obvious dyspnoea or wheezing when they visited the clinics. They were also excluded if they had taken other medication for their coughs before entering the study, if a physician felt antimicrobials were necessary or if their parents wanted to administer other cough suppressants. Patients with suspected COVID-19 were tested and those that were positive for the virus that causes this were excluded from the study.

The children's parents provided written informed consent after they were provided with full information about the objectives and study protocol. The study protocol was reviewed, and approved, by the Ethics Committee of the Society of Ambulatory and General Paediatrics of Japan (approval number 2021–7). The trial was also registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000047374).

2.2 | Randomisation and masking

Patients were randomly assigned to receive either acacia honey or the honey-flavoured syrup that was used as the placebo control. This was achieved with a 1:1 ratio, using a block randomisation scheme implemented in Microsoft Excel 365 (Microsoft Inc, Washington, USA). One member of the research team (KK) created a random number table, which was kept hidden until the intervention had been completed. The patients, parents, treating physicians and staff were all blinded to the group allocations. The honey group received acacia honey, while the syrup group received a syrup that was created to mimic real honey and had the same colour, viscosity and flavour. This was made from a mixture of fructose, dextrose, sucrose, maltose, honey flavouring and caramel (Table S1). Both the honey and syrup were packed in 10-g doses in small individual glass containers that were labelled with numbers from 1 to 16 and sent to the 13 participating facilities (Figure 1). Half of these contained honey and half contained the placebo syrup. This number was chosen as it ensured that all the facilities had more than enough supplies.

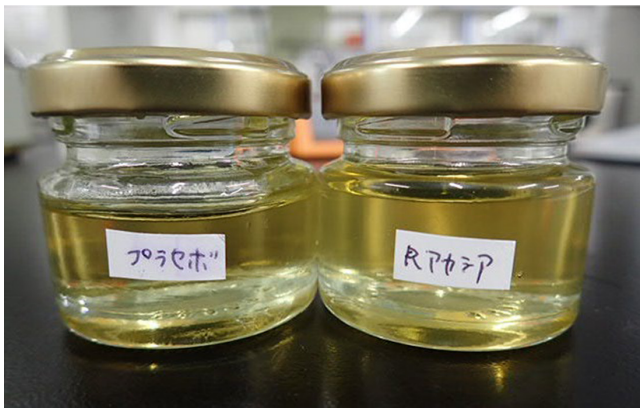

FIGURE 1 Honey and honey-flavour syrup acacia honey on the right, honey-flavour syrup as a placebo on the left

2.3 | Study medications and dosing regimen

After obtaining informed consent, the parents of all participants were asked to complete a questionnaire. This included the children's characteristics and 5 items concerning the frequency, severity, degree and effect of the cough on the child's sleep, and their parents' sleep, the previous night (Figure 2). The survey responses were graded on a 7-point Likert scale. The parents were then given small glass containers of the honey or placebo syrup, 2 plastic 3-ml spoons and a cough evaluation questionnaire. The aim of the questionnaire was to measure any changes in the same 5 items outlined above. The parents were instructed to give the syrup to the children 1 hour before bedtime on 2 consecutive nights. Staff from the participating facilities telephoned the parents the day after each administration to ask whether the children were able to take what they had been given and whether the questionnaire had been completed. During the study period, the parents were instructed to refrain from giving the children first-generation antihistamines, cough suppressants or any other substances that had previously been provided and could affect

FIGURE 2 Cough severity assessment questionnaire. (A) Japanese questionnaire used in this study (B) English version

(A)

①昨晩の咳の頻度
（ 0:全くない 1:とても少ない 2:やや少ない 3:やや多い 4:多い 5:とても多い 6:これまでにないほど多い ）

②昨晩の咳の重症度
（ 0:全くない 1:とても低い 2:やや低い 3:やや高い 4:高い 5:とても高い 6:これまでにないほど高い ）

③昨晩の咳のうるささ
（ 0:全くない 1:とても小さい 2:やや小さい 3:やや大きい 4:大きい 5:とても大きい 6:これまでにないほど大きい ）

④昨晩の咳が子どもの睡眠に与えた影響
（ 0:全くない 1:とても小さい 2:やや小さい 3:やや大きい 4:大きい 5:とても大きい 6:これまでにないほど大きい ）

⑤昨晩の咳が親の睡眠に与えた影響
（ 0:全くない 1:ほとんどない 2:やや小さい 3:やや大きい 4:大きい 5:とても大きい 6:これまでにないほど大きい ）

(B)

1. How frequent was your child's cough last night?
2. How severe was your child's cough last night?
3. How bothersome was last night's cough to your child?
4. How much did last night's cough affect your child's ability to sleep?
5. How much did last night's cough affect your (parent's) ability to sleep?

Scoring:
0: not at all; 1: not much; 2: a little; 3: somewhat; 4: a lot; 5: very much; 6: extremely.

their cough or sleep. However, expectorants, second-generation antihistamines and leukotriene antagonists that did not affect sleep were permitted.

2.4 | Outcome measures

The primary outcome measures were the differences between the 2 groups in the 5 items in the questionnaire on the first and second nights. The secondary outcome measures were changes in the combined scores.

2.5 | Safety assessment

Safety evaluations were conducted on all patients enrolled in the study. The parents were asked if patients were able to take the honey or placebo without problems. The patients were then carefully monitored for gastrointestinal symptoms, such as vomiting and diarrhoea, until the end of the study.

2.6 | Statistical analysis

The required sample size was 73 subjects in each group, with a total of 146 subjects. This was calculated using G*Power software, version 3.1.9.2 (Kiel University, Kiel, Germany), with a two-tailed test, effect size of 0.5, alpha error of 0.05 and power of 0.85. We planned to recruit 160 subjects, allowing for a rate of loss to follow-up of about 10%. The primary outcome was analysed on the basis of intention-to-treat and per-protocol analyses. Between-group comparisons were performed using the chi-square test for categorical variables and the Mann–Whitney U test or t-test for continuous variables. All statistical analyses were performed using StatFlex version 7 (Igakutoukeikenkyujyo, Yamaguchi, Japan).

3 | RESULTS

3.1 | Study population

The study population is outlined in a Consolidated Standards of Reporting Trials diagram in Figure 3. The data collection was carried out from 20 November 2021 to 28 February 2022. A total of 161 patients with URTIs received honey or syrup and were included in the intention-to-treat analysis: 78 in the honey group and 83 in the syrup group. The number of patients enrolled varied from 1 to 16, depending on the facilities, but the study reached the target number. The median age of the patients who completed the study was 2.7 years (range 1.0–5.9 years). The participants' baseline characteristics are summarised in Table 1. There were no significant differences in the baseline clinical characteristics or cough assessments between the 2 groups. In the honey group, 60 patients received expectorants, and 3 received herbal medicines. In the syrup group, 58 patients received expectorants, 1 patient received a leukotriene antagonist for suspected allergic rhinitis, 2 patients received a second-generation antihistamine for eczema, and 3 patients received herbal medicines. A total of 141 patients completed the study and were included in the per-protocol analysis: 68/78 (87.1%) in the honey group and 73/83 (87.0%) in the syrup group.

3.2 | Outcome measures

Both groups showed improvements in all of the 5 questionnaire items and in the combined symptom score on the first and second

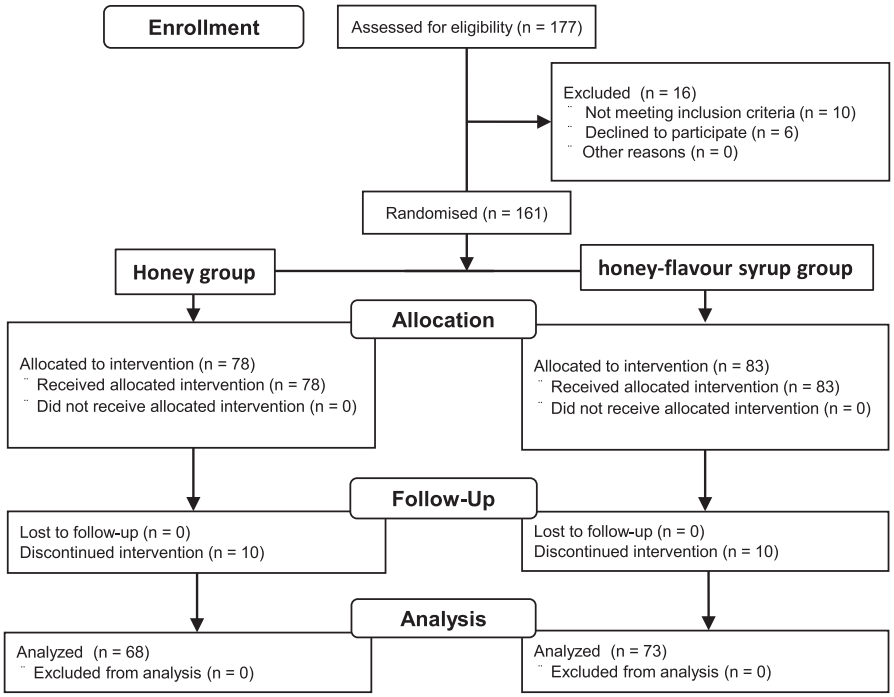

FIGURE 3 Study enrolment, screening and participant inclusion flow chart

TABLE 1 Baseline characteristics

Characteristic	Patients receiving honey ($n = 78$)	Patients receiving honey-flavour syrup ($n = 83$)	p-value
Age, median ± interquartile range, y	2.8 ± 1.7	2.7 ± 2.3	0.24
Sex, no. (%)			
Female	41 (52.6)	32 (38.6)	0.074
Male	37 (47.4)	51 (61.4)	
Day-care attendance	58 (74.4)	62 (74.7)	0.96
Highest body temperature, mean ± SD, °C	37.0 ± 0.65	37.1 ± 0.84	0.39
Duration of illness, mean ± SD, days	2.3 ± 1.5	2.6 ± 1.6	0.29
Cough frequency score, mean ± SD	2.9 ± 1.1	2.7 ± 1.1	0.28
Cough severity score, mean ± SD	2.5 ± 1.0	2.3 ± 1.0	0.28
Bothersome cough score, mean ± SD	2.7 ± 1.1	2.5 ± 1.1	0.27
Effect of cough on child's sleep score, mean ± SD	2.5 ± 1.4	2.2 ± 1.4	0.24
Effect of cough on parent's sleep score, mean ± SD	2.3 ± 1.4	2.0 ± 1.3	0.28
Combined symptom score, mean ± SD	12.7 ± 5.2	11.7 ± 5.1	0.20
Failed to take medication for 1 or 2 days, no. (%)	10 (12.8)	10 (12.0)	0.99

nights in the intention-to-treat analysis. However, there were no significant differences between the honey and syrup groups in either the intention-to-treat analysis (Figure 4) or the per-protocol analysis (Figure 5).

In the intention-to-treat analysis, the combined score of the honey group at baseline was 12.7 ± 5.2 points, which decreased to 7.5 ± 5.0 points for the first night ($p < 0.001$), then decreased further to 5.5 ± 5.2 points for the second night ($p = 0.017$). The syrup group had a baseline score of 11.7 ± 5.1 points, which decreased to 6.8 ± 5.0 points for the first night ($p < 0.001$) and decreased further to 5.0 ± 4.6 points ($p = 0.018$) for the second night. We also compared the scores for the first and second nights to the baseline data. The scores for the first night in the honey and syrup groups decreased by 5.4 ± 6.2 points and 5.0 ± 5.5 points, respectively, from baseline ($p = 0.40$). On the second night, the scores decreased by 7.4 ± 6.1 and 6.8 ± 5.3 points, respectively ($p = 0.54$). There were no differences between the 2 groups, even when testing was limited to severe cases, with a baseline score of 10 or higher. These comprised 59 in the honey group and 53 in the syrup group.

The per-protocol analysis showed that the scores in the honey group and the syrup group decreased by 5.3 ± 6.4 points and by 5.2 ± 5.5 points on the first night, respectively, ($p = 0.52$) and by

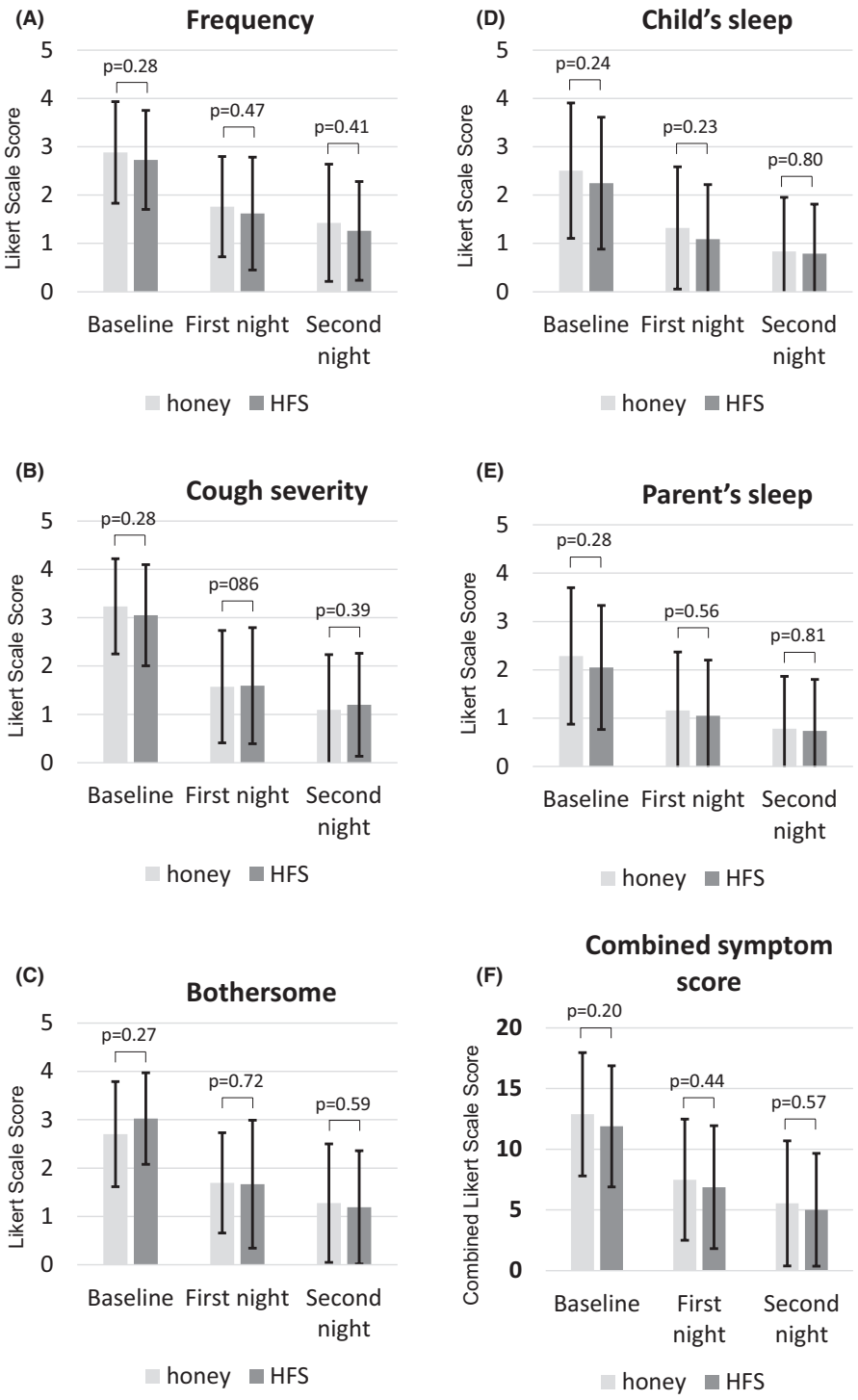

FIGURE 4 Comparison of the effects of honey and honey-flavour syrup on cough frequency in intention-to-treat analysis. (A) Cough frequency. (B) Cough severity. (C) Cough bothersome to the child. (D) Child's sleep. (E) Parent's sleep. (F) Combined symptom score

7.5 ± 6.1 points and 6.8 ± 5.4 points ($p = 0.53$) on the second night. None of these differences were statistically significant.

3.3 | Safety outcomes

Two patients had problems taking the honey and one had a problem taking the syrup. Post-dose vomiting occurred in 4 patients in the honey group and in 1 patient in the syrup group. There was no difference in the rate of adverse events between the 2 groups.

4 | DISCUSSION

Honey has been shown to have well-established antioxidant and antimicrobial effects.[7–9] The WHO has suggested that its topical demulcent effect may contribute to a beneficial effect on coughs.[3] In addition, a Cochrane Report stated that honey may be more effective in alleviating coughs and reducing their impact on a child's sleep at night than no treatment.[4] Moreover, several randomised studies have shown that honey significantly reduced cough symptoms, compared with existing cough suppressants and expectorants.[5,6,10]

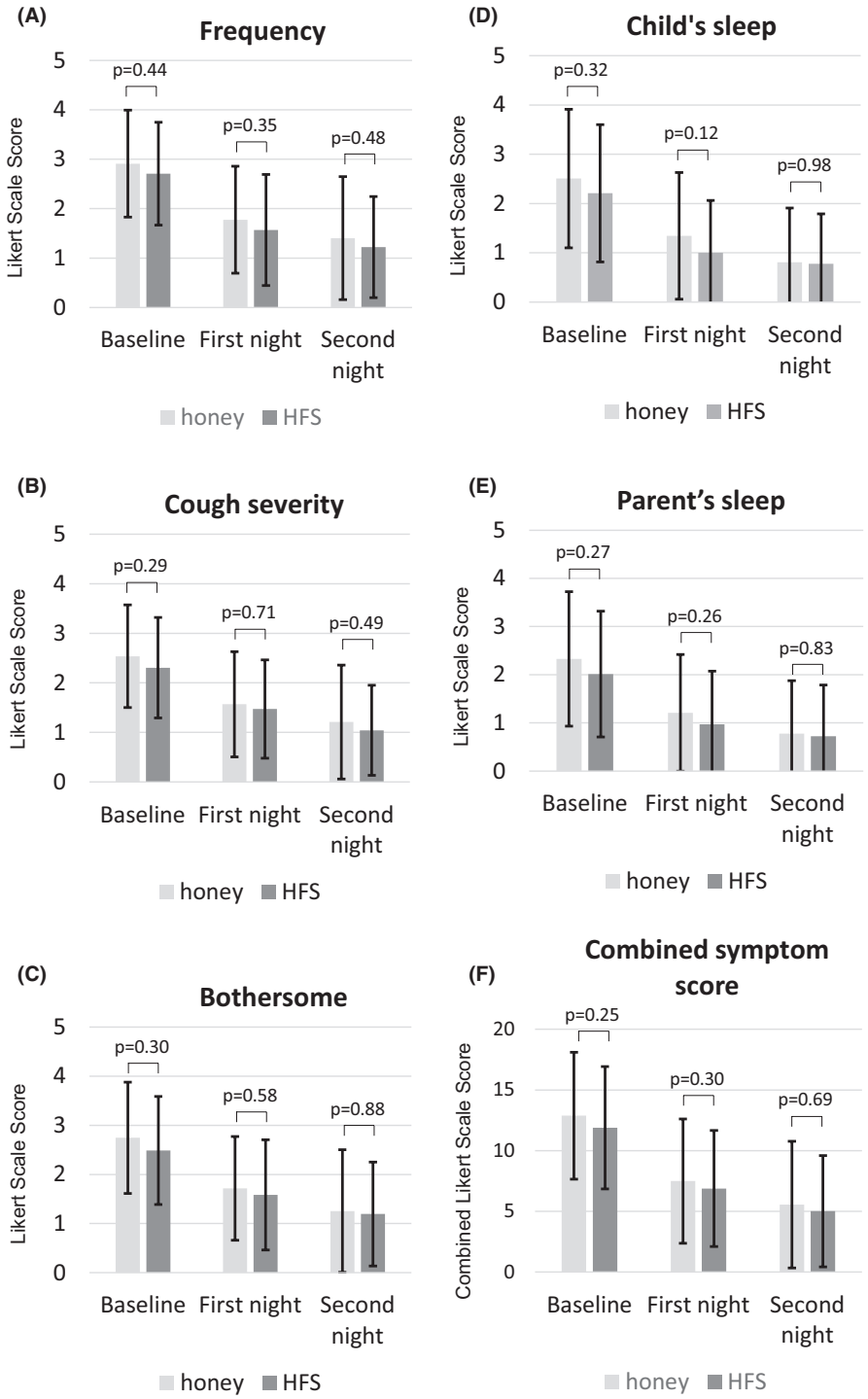

FIGURE 5 Comparison of the effect of honey and honey-flavour syrup on cough frequency in per-protocol analysis. (A) Cough frequency. (B) Cough severity. (C) Cough bothersome to the child. (D) Child's sleep. (E) Parent's sleep. (F) Combined symptom score

However, there is still a lack of strong evidence for using honey for treating coughs.

The present study was a multicentre, double-blind, randomised, placebo-controlled trial to determine whether honey had an antitussive effect.

In contrast to previous studies, it found that honey was not significantly more effective than the syrup that we used as a placebo control. Several factors may be responsible for the differences between our study and previous reports. First, the Likert scale was translated into Japanese, and differences in the wording of the scale from English may have affected the results. Second, the subjects were children who visited primary care paediatricians in Japan. Japan has a universal health insurance system and children have good access to medical facilities, so their parents may seek medical care for their child at an early stage, even for minor symptoms. Third, URTIs may have changed since other studies were conducted. Some honey studies[5,6] were conducted during the transition from the 7-valent to 13-valent pneumococcal conjugate vaccine. The latter now forms part of Japan's routine vaccination programme and the vaccination rate is extremely high. Advances in vaccines and high vaccination

rates may have resulted in changes in the nasopharyngeal flora in Japanese children.[11]

However, our results do not rule out honey as an alternative therapy for coughs. The children in both the honey and placebo syrup groups showed rapid improvements in their cough symptoms within 2 days of visiting the study clinics. Eccles noted that the efficacy of any cough medicine depended on the strong placebo effect of the treatment.[12] Placebo effects can be divided into the perceived placebo effects and the true placebo effects. Perceived placebo effects have been attributed to the taste, viscosity and the colour of the drugs. As the honey-flavour syrup that was used as a placebo control in this study had similar characteristics to honey, it is possible that both the honey and the syrup had equivalent perceived placebo effects. These perceived placebo effects may have been so large that they masked the pharmacological effect of the honey in this study.

Paul et al. reported that honey and dextromethorphan were more effective than no treatment.[5] However, as the children's nocturnal coughs were evaluated by the parents, the major difference between no treatment and honey was that the parents' action of giving their children honey may have created a placebo effect. In addition, the Centers for Disease Control and Prevention recommends honey for sore throats, as it may temporarily moisten the throat and relieve pain.[13] When a child receives temporary relief of their cough symptoms, because their parent has given them honey, it may increase the trust between the child and parent.

Honey is inexpensive, readily available and is often found in households. In contrast, giving children codeine is unsafe[14] and dextromethorphan and diphenhydramine are not recommended child cough suppressants, due to a lack of evidence of efficacy.[15–19] Tipepidine hibenzate, which is often used in Japan, is thought to be ineffective.[20] Honey is relatively safe, as long as it is not given to children under 1 year of age.[21] It is necessary to continue to explore ways in which honey can be used to treat URTI symptoms in children.

5 | LIMITATIONS

This study had several limitations. First, we did not compare the effects of honey to no treatment. Therefore, the observed reduction in cough symptoms in both groups may have been due to the natural course of the disease. Second, quantitatively assessing cough symptoms in children is difficult. This study was limited by the subjective nature of the questionnaire used, as in previous studies. Third, 3 patients in the placebo group received a leukotriene antagonist and a second-generation antihistamine, which are known to reduce allergic reactions and may have had some effect on acute coughs caused by URTIs. Fourth, the dose of honey that was used in this study was less than in previous studies[22] and may not have been sufficient to produce pharmacological effects. In addition, the study was conducted over a 2-day period, but we only evaluated the effects during the night. The parents' evaluation of how much their child was coughing may have varied greatly, depending on whether or not they were asleep themselves.

6 | CONCLUSION

This multicentre, double-blind, randomised, placebo-controlled study demonstrated that honey was no more effective against nocturnal coughs and sleep difficulties in children than a honey-flavoured syrup placebo.

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None.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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REFERENCES

1. Marseglia GL, Manti S, Chiappini E, et al. Acute cough in children and adolescents: a systematic review and a practical algorithm by the Italian Society of Pediatric Allergy and Immunology. Allergol Immunopathol. 2021;49:155-169.
2. Murgia V, Manti S, Licari A, de Filippo M, Ciprandi G, Marseglia GL. Upper respiratory tract infection-associated acute cough and the urge to cough: new insights for clinical practice. Pediatr Allergy Immunol Pulmonol. 2020;33:3-11.
3. Department of Child and Adolescent Health. Cough and Cold Remedies for the Treatment of Acute Respiratory Infections in Young Children. World Health Organization 2001. https://apps.who.int/iris/handle/10665/66856 (Accessed 12 June 2022.)
4. Oduwole O, Udoh EE, Oyo-Ita A, Meremikwu MM, Cochrane Acute Respiratory Infections Group. Honey for acute cough in children. Cochrane Database Syst Rev. 2018;4:CD007094.
5. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM Jr. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007;161:1140-1146.
6. Cohen HA, Rozen J, Kristal H, et al. Effect of honey on nocturnal cough and sleep quality: a double-blind, randomized, placebo-controlled study. Pediatrics. 2012;130:465-471.
7. Allen KL, Molan PC, Reid GM. A survey of the antibacterial activity of some New Zealand honeys. J Pharm Pharmacol. 1991;43:817-822.
8. Gheldof N, Wang XH, Engeseth NJ. Identification and quantification of antioxidant components of honeys from various floral sources. J Agric Food Chem. 2002;50:5870-5877.
9. Bogdanov S, Jurendic T, Sieber R, Gallmann P. Honey for nutrition and health: a review. J Am Coll Nutr. 2008;27:677-689.
10. Cohen HA, Hoshen M, Gur S, Bahir A, Laks Y, Blau H. Efficacy and tolerability of a polysaccharide-resin-honey based cough syrup as compared to carbocysteine syrup for children with colds: a randomized, single-blinded, multicenter study. World J Pediatr. 2017;13:27-33.

11. Chang B, Akeda H, Nakamura Y, et al. Impact of thirteen-valent pneumococcal conjugate vaccine on nasopharyngeal carriage in healthy children under 24 months in Okinawa, Japan. J Infect Chemother. 2020;26:465-470.
12. Eccles R. The powerful placebo effect in cough: relevance to treatment and clinical trials. Lung. 2020;198:13-21.
13. Centers for Disease Control and Prevention. https://www.cdc.gov/antibiotic-use/sore-throat.html?CDC_AA_refVal=https://www.cdc.gov/antibiotic-use/community/for-patients/common-illnesses/sore-throat.html (Accessed 26 April 2022).
14. Livingstone MJ, Groenewald CB, Rabbitts JA, Palermo TM. Codeine use among children in the United States: a nationally representative study from 1996 to 2013. Paediatr Anaesth. 2017;27:19-27.
15. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev. 2012;15(8):CD001831.
16. Paul IM, Yoder KE, Crowell KR, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics. 2004;114:e85-e90.
17. Yoder KE, Shaffer ML, La Tournous SJ, Paul IM. Child assessment of dextromethorphan, diphenhydramine, and placebo for nocturnal cough due to upper respiratory infection. Clin Pediatr (Phila). 2006;45:633-640.
18. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics. 1997;99:918-920.
19. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1):260S-283S.
20. Nishimura T, Kinumaki H, Hosaka T, et al. Effect of tipepidine hibenzate on acute cough with upper respiratory tract infection in children (in Japanese). Gairaishounika 2019;22:124–32. https://nishimura-syounika.com/Asverin.pdf (Accessed 26 April 2022).
21. Centers for Disease Control and Prevention. https://www.cdc.gov/nutrition/chiandtoddlernutrition/foods-and-drinks/foods-and-drinks-to-limit.html (Accessed 26 April 2022).
22. Miceli Sopo S, Greco M, Monaco S, et al. Effect of multiple honey doses on non-specific acute cough in children. An open randomised study and literature review. Allergol Immunopathol (Madr). 2015;43(5):449-455.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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