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Randomized controlled trial of juzen-taiho-to in children with recurrent acute otitis media☆

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ABSTRACT

Objective: Recurrent acute otitis media (AOM) in young children is rapidly increasing worldwide. Repeated antibiotic use leads to antibiotic-resistant pathogen development. Complementary and alternative medicine approaches have been suggested as a supplemental treatment option to conventional antimicrobial medicine. This randomized, parallel-group, open-label, non-herbal medicine controlled trial assessed the efficacy of a traditional Japanese herbal medicine, juzen-taiho-to (JTT) for AOM prevention in otitis-prone children.

Methods: Children prone to recurrent AOM aged 6–48 months were recruited from 26 otolaryngology clinics in Japan and received conventional AOM treatment based on Japanese guidelines with or without 2 daily oral doses of JTT (0.10–0.25 g/kg/day). The mean number of AOM episodes, coryza episodes, and duration of total antibiotic administration per month were compared during 3-month intervention.

Results: At least one episode of AOM was diagnosed in 71% of JTT-group and 92% of control participants during follow-up. JTT administration reduced the frequency of AOM episodes by 57% compared with children who received conventional treatment alone (0.61 ± 0.54 vs. 1.07 ± 0.72 AOM instances/month; $P = 0.005$) and also significantly decreased number of coryza episodes ($P = 0.015$) and total antibiotic administration ($P = 0.024$).

Conclusions: This is the first report of recurrent AOM prevention by herbal medication. JTT appears to effectively prevent recurrent AOM in children. Subsequent double-blind studies are needed to confirm the beneficial effects of JTT on recurrent AOM and upper respiratory tract infections.

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Abbreviations: AOM, acute otitis media; CAM, complementary and alternative medicine; JTT, juzen-taiho-to; MEE, middle ear effusion; NKT, natural killer cells; URT, upper respiratory tract.

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1. Introduction

Otitis media is very common in children. By 2 years of age, most children (70%) experience at least one episode of acute otitis media (AOM) [1–5]. A subpopulation of children, representing 5–10% of the general population, are otitis-prone, having experienced at least 3 separate episodes of AOM within a 6 months, or more than 4 episodes in 1 year [6–8].

The increase in the number of otitis-prone children and the rapid emergence of drug-resistant bacteria associated with AOM are now generating increasing concern. β-Lactamase-nonproducing ampicillin-resistant strains of *Haemophilus influenzae* and penicillin-resistant *Streptococcus pneumoniae* are particularly common and cause recurrent AOM in Japan [9–11]. In otitis-prone children, the effectiveness of repeated antibiotic therapy for each new infection and prophylactic antibiotic therapy to prevent AOM relapse is quite limited. Furthermore, recurrent use of antibiotics leads to the development of antibiotic-resistant pathogens [12,13] and the imbalance of the normal nasopharyngeal bacterial flora [14]. Surgical insertion of a tympanostomy tube can have a significant role in maintaining a 'disease-free' state [15–17], but clinicians should consider the possible adverse effects of grommet insertion, such as transient or recurrent otorrhea, tympanosclerosis, focal atrophy and persistent perforations which may require repair.

In addition to these conventional treatments for AOM, complementary and alternative medicine (CAM) approaches have been suggested as a supplementary choice for the treatment of recurrent AOM [18–20], because CAM treatments such as herbal medicine and probiotics are commonly used to treat pediatric upper respiratory tract (URT) viral infections in Europe, United States and Asia [21–23]. Viruses play an important role in middle ear viral and following bacterial infection because a URT viral infection usually precedes AOM. *Echinacea*, *Lactobacillus rhamnosus* GG (probiotic), mao-to and kakkon-to (herbal medicine) are considered to reduce the risk of acute URT infections [21,23–25], but no confirmative evidence has shown that these products reduce the incidence of recurrent AOM [24,25].

The unique role played by traditional Japanese herbal medicine, a type of pharmaceutical-grade multi-herbal medicine, is gradually attracting worldwide attention. More than 100 herbal medicines have been used clinically for centuries to treat a wide variety of diseases with very few side effects. Despite, safety and tolerability of most CAM treatments are not precisely defined, all Japanese herbal medicines are standardized and manufactured on a modern industrial scale under strict scientific quality controls. Juzen-taiho-to (JTT) is one of the Japanese herbal medicines that comprises 10 different herbs, and is administered to patients in various weakened conditions, including post-surgery patients and patients with chronic illnesses, where it can alleviate general symptoms such as fatigue, pale complexion, anemia and loss of appetite [26,27]. JTT is used clinically to strengthen the immune functions of patients with various diseases, including cancer, hepatitis. JTT has been suggested to upregulate the host immune system [28–30] and reported to have therapeutic effects against bacterial infection such as perianal abscess [31]. A recent report suggested the beneficial effects of JTT in reducing the episodes of AOM in otitis-prone children [32,33]. JTT has been known for lipopolysaccharides (LPS)-like immunostimulatory activity [34,35]. JTT and LPS induce similar gene expression profiles in monocytes [36,37]. Montenegro et al. suggested the emerging theory of bacterial contribution to the immune-boosting activity of JTT, called "herbal probiotics" [38].

JTT is composed of ten crude drugs, of which the quality is controlled by Japanese Pharmacopia XIII. JTT was prepared as follows. A mixture of Astragali radix (3.0 g), Cinnamomi cortex (3.0 g), Rehmanniae radix (3.0 g), Paeoniae radix (3.0 g), Cnidii rhizome (3.0 g), Atractylodis Lanceae rhizome (3.0 g), Angelicae radix (3.0 g), Ginseng radix (3.0 g), Hoelen (3.0 g), and Glycyrrhizae radix (1.5 g) was added to 285 ml of water and extracted at 100 °C for 1 h. The extracted solution was filtered and the filtrate was spray-dried to obtain the dry extract powder (2.3 g).

The aim of this study was to examine the possible effect of JTT in reducing the incidences of recurrent AOM in young children in a strict diagnostic framework. The primary and secondary endpoints were to investigate whether JTT could reduce the number of infectious episodes of AOM (primary endpoint) as well as URT infection (coryza), the duration of antibiotic administration and the number of children who underwent tympanostomy tube insertion and time (days) until tympanostomy tube insertion during the intervention in otitis-prone children (secondary endpoints). We conducted a randomized, parallel-group, open-label, non-herbal medicine (conventional treatment only) controlled trial between December 2009 and October 2011 to assess the efficacy of JTT for the prevention of AOM in children with recurrent AOM.

2. Methods

2.1. Study settings

The study was conducted according to the principles of the Declaration of Helsinki (as amended in Somerset West, South Africa 1996) and was approved by the Institutional Review Board at each participating university and hospital (Approval No. 2009-032 5587). An independent external group was appointed to monitor the study progress and the safety of the participants.

2.2. Subjects

Children aged 6–48 months who were otitis prone (as documented in their medical records) were recruited from 26 otolaryngology clinics including university hospitals, general hospitals, and private clinics in Japan during December 2009 to October 2011. Children with unwillingness to participate; congenital malformations of the ears, nose, or throat; known allergy to JTT; or receiving immune therapy (e.g., immunoglobulin and steroids) or other Japanese herbal medicine were excluded from the study. Children with tympanostomy tube insertions were also excluded from the study.

2.3. Randomization and intervention

After obtaining informed consent and assent, randomization was performed. Children were randomly assigned to one of 2 groups by permuted block design using an Internet-based central registration system (Captool, Mebix Inc., Tokyo, Japan). One group received JTT and conventional treatment based on the Japanese guidelines for AOM [33], and the control group received conventional treatment only. JTT (Tsumura & Co. Ltd., Tokyo) at 0.10–0.25 g/kg/day was orally administered twice per day for 3 months. No restrictions were imposed on conventional treatments for AOM, including tympanostomy tube insertion or any other disease. After enrollment, children were prospectively followed for 3 months while JTT was administered. The intervention was considered failed if the child received tympanic ventilation tube insertion within 1 month after enrollment (Fig. 1).

2.4. Clinical definition of AOM and treatment

Before starting the study, background information on each child's health, nutrition, day care attendance, passive smoking, and history of respiratory disease was acquired through a questionnaire. AOM was diagnosed by an otolaryngology specialist based on examination of general and tympanic findings according to Japanese clinical practice guidelines for AOM [26]. AOM was diagnosed when one of the following tympanic membrane findings were recognized: hyperemia, protrusion, diminishment of the light reflex, thickening, bullae formation, cloudiness (turbidity), perforation of the tympanic membrane, middle ear effusion (MEE), otorrhea, and edema of middle-ear mucosa. Symptoms indicative of acute middle ear inflammation were otalgia, otorrhea, fever, and crying and/or bad temper.

Recurrent AOM, ''Otitis-prone'', was defined as experiencing at least 3 separate episodes of AOM within a 6-month period or more than 4 episodes in 1 year [6–8]. Children received confirmation follow-up examination by otolaryngologist to ensure recovery of the AOM. A new episode of AOM was diagnosed when the child, after completing treatment with antibiotics and experiencing a period with no clinical signs of AOM, presented new symptoms and otoscopic findings of AOM. Throughout the study, the parents kept a daily diary to report the symptoms of acute URT inflammation, coryza (fever, cough, rhinitis, nasal discharge, sore throat), and middle ear infections; the use of medication including antibiotics; and visits to doctors.

The treatment of AOM was based on Japanese clinical practice guidelines throughout the study period, including recommended antibiotics for AOM (amoxicillin is the first-line antibiotic) in all children [33].

2.5. Outcomes

The primary study outcome was the mean number of AOM episodes per month during the 3-month intervention. As secondary outcomes, we assessed the mean number of coryza episodes, mean duration (days) of total antibiotic administration, and the number of children who underwent tympanostomy tube insertion and time (days) until tympanostomy tube

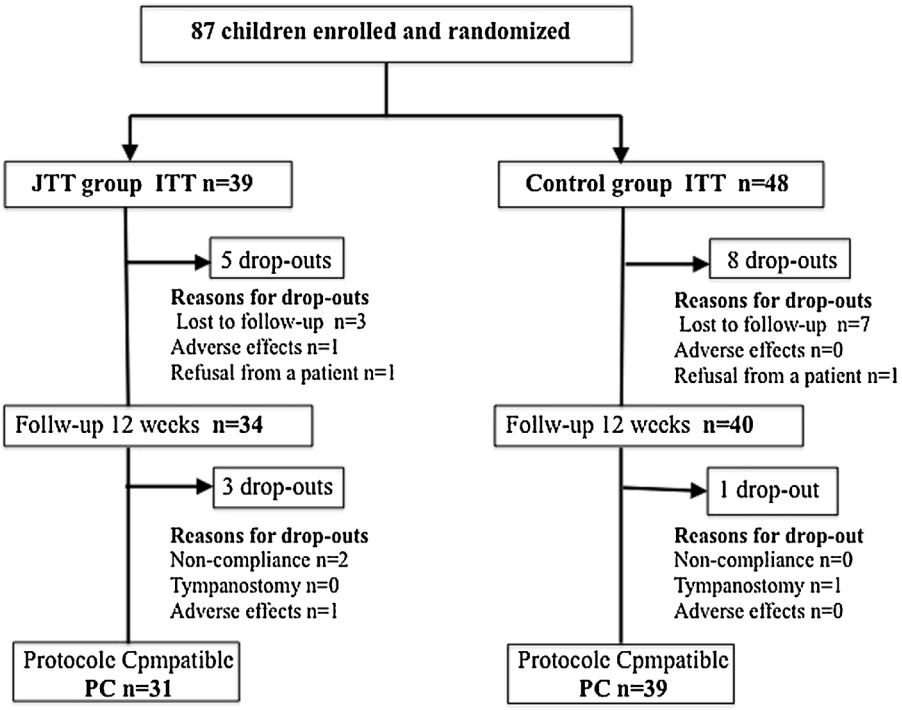

Fig. 1. Flow chart showing the enrollment of subjects. Eighty-seven children who fulfilled the criteria were enrolled in the study. Thirteen children dropped out due to the lost to follow-up ($n = 10$), adverse effects ($n = 1$), and refusal from a patient ($n = 2$) during the 12 week follow-up period. Additionally, a total of 4 children dropped out due to non-compliance ($n = 2$), tympanostomy ($n = 1$), and adverse effects (mild diarrhea) ($n = 1$).

insertion. Each parameter was calculated as the mean number in 30 days (number per month). Because insertion of tympanostomy tubes was effective in preventing recurrent AOM, the value of each parameter before tube insertion was calculated in cases with tube insertion at least 1 month after enrollment.

2.6. Statistical analysis

The mean number of recurrent AOM episodes in Japan was expected to be 4.75 times per month according to previous data (bilateral AOM was counted as 2 times in the study) [32]. Use of JTT would reduce it to 3 times per month with a relative reduction of 37%. Assuming that the standard deviation is 3 times per month, a total of 94 participants were necessary to detect the difference with 80% power. Analysis was performed according to the intention-to-treat principle.

Student's *t*-test or chi-square test was applied for comparisons of baseline characteristics between the 2 groups. Endpoints were compared between the 2 groups by using Wilcoxon's rank-sum test, except for the number of tube insertions, which was tested by using Fisher's exact test, and the duration until tube insertion, which was tested by using log-rank test. $P < 0.05$ was considered significant. Data were analyzed using SAS software version 9.2 (SAS Institute, Tokyo, Japan) by Clinical Study Support, Inc. (Nagoya, Japan). We also analyzed the independent association between AOM episodes (primary study outcome) and several factors using the multivariate logistic regression analysis. Odds ratios (ORs) with 95% confidence intervals (CI) were presented. Statistical analyses were carried out by using Esumi Excel multivariate analysis, version 5.0 (Esumi Corp, Tokyo, Japan), with a significance threshold of 0.05.

3. Results

3.1. Participant flow

Eighty-seven children who fulfilled the criteria were enrolled in the study (47 boys, 40 girls; median age, 17.0 months; mean age, 18.71 months; range 8–41 months) and randomly allocated to one of the treatment groups (Fig. 1). A total of 13 children dropped out owing to the lost to follow-up ($n = 10$), adverse effects ($n = 1$), and refusal from a patient ($n = 2$) during the 12 week follow-up period. One child in JTT treatment group dropped out with an adverse effect of slight skin eruption, but no apparent side effects were observed during the study. Additionally, a total of 4 children dropped out due to non-compliance ($n = 2$), tympanostomy ($n = 1$), and adverse effects (mild diarrhea) ($n = 1$).

The groups demonstrated no differences in pre-treatment characteristics including number of participants in each group, sex, mean age, mean weight, frequency of AOM episodes, type of day care, or passive smoking in the household. Table 1-1 shows pre-treatment characteristics in intention-to-treat (ITT) cases and Table 1-2 shows protocol compatible (PC) cases.

3.2. The effect of JTT treatment on the occurrence of recurrent AOM and coryza

3.2.1. Primary outcome

At least one episode of AOM was diagnosed in 71% of JTT-group and 92% of control participants during follow-up. The mean number of AOM episodes in each month (1M; 0–4 w, 2M; 5–8 w, 3M; 9–12 w) was 0.81, 0.58, and 0.39 in the JTT group and 1.31, 0.72, and 0.93 in the control group. The frequency of AOM gradually decreased during the administration of JTT (Fig. 2a).

Table 1
Baseline characteristics and the number of AOM episodes before the intervention. (1-1) shows pre-treatment characteristics in intention-to-treat (ITT) cases and (1-2) shows protocol compatible (PC) cases.

	JTT group ITT ($n = 39$)	Control group ITT ($n = 48$)	P value*
(1-1)			
Sex (male:female)	17:22	30:18	0.08
Mean age (months)	17.87 ± 6.17	19.40 ± 7.64	0.31
Mean weight (kg)	10.28 ± 1.57	10.41 ± 1.87	0.72
AOM episodes (instances/month)	1.17 ± 0.60	0.98 ± 0.57	0.10
Type of day care			
Day-care center	21	30	0.73
Smoking in the household	11	14	0.99
	JTT group PC ($n = 31$)	Control group PC ($n = 39$)	P value*
(1-2)			
Sex (male:female)	14:17	25:14	0.15
Mean age (months)	17.29 ± 5.28	20.13 ± 8.03	0.29
Mean weight (kg)	10.22 ± 1.38	10.73 ± 1.94	0.21
AOM episodes (instances/month)	1.17 ± 0.60	0.98 ± 0.57	0.10
Type of day care			
Day-care center	18	27	0.27
Smoking in the household	10	14	0.81

The study groups did not significantly differ in pre-treatment characteristics including number of patients in each group, sex, mean age, mean weight, instances of AOM episodes, type of day care, or passive smoking in the household.
* P 0.05 was considered significant.

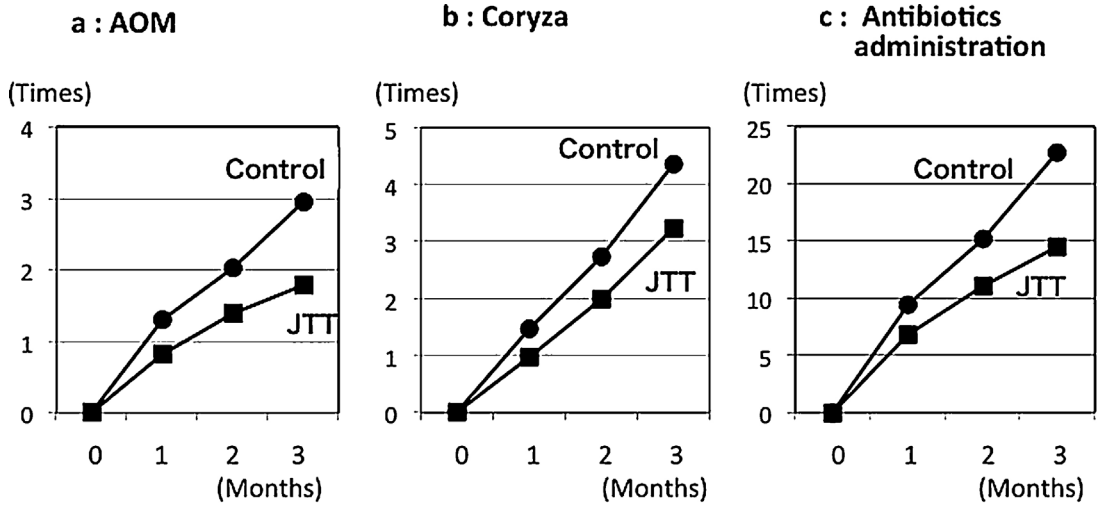

Fig. 2. Mean number of infection episodes of AOM and coryza and duration of antibiotic administration during the intervention. The frequency of AOM and coryza and the duration of antibiotic administration gradually decreased during administration of JTT.

Table 2
Mean number of episodes of the primary and the secondary outcome after the 3-month intervention in the JTT and control groups.

	JTT group PC ($n=31$)	Control group PC ($n=39$)	P value*
AOM episodes (instances/month)	0.61 ± 0.54	1.07 ± 0.72	0.005*
Coryza episodes (instances/month)	1.10 ± 0.62	1.56 ± 0.83	0.015*
Antibiotic treatment (days/month)	4.99 ± 3.21	8.10 ± 5.87	0.024*
Number of tube insertions	2	4	0.68
Duration until tube insertion	81.8 ± 0.27	67.1 ± 0.84	0.46

Oral administration of JTT for 3 months reduced the frequency 1 of AOM episodes by 57% compared with the control group. JTT also reduced both the number of coryza episodes and total days of antibiotic administration after the 3-month administration of JTT.
* P 0.05 was considered significant.

Children in the JTT group had significantly fewer total episodes of AOM than the control group after the 3-month intervention. (Wilcoxon rank-sum test, $P = 0.005$) (Table 2). Mean and standard deviation of the frequency of AOM in the JTT and control groups were 0.61 ± 0.54 and 1.07 ± 0.72 instances/month, respectively (Fig. 2a). Oral administration of JTT for 3 months reduced the frequency of AOM episodes by 57% compared with children who received only conventional treatment.

Table 3
Multivariate logistic regression analysis of AOM episodes and several factors including JTT treatment, sex, age, weight, type of day car e and passive smoking in the household.

	OR	95% CI		P value*
		Lower	Upper	
Treatment (JTT: Control)	6.76	1.17	38.93	0.032*
Sex (male:female)	0.90	0.19	4.40	0.900
Age (months): pre-treatment	0.92	0.79	1.07	0.298
Weight (kg): pre-treatment	0.95	0.53	1.70	0.873
Type of day care				
Day-care center	1.96	0.30	12.76	0.481
Smoking in the household	1.75	0.36	8.42	0.485

Multivariate analysis showed that JTT treatment (OR = 6.76, $P = 0.032$) was the only independent factor of reducing AOM episodes.
* P 0.05 was considered significant.

Multivariate analysis showed that JTT treatment (OR = 6.76, $P = 0.032$) was the only independent factor of reducing AOM episodes (Table 3).

3.2.2. Secondary outcomes

The secondary outcomes were mean number of coryza episodes, mean duration of total antibiotic administration, and the number of children who underwent tympanostomy tube insertion. The frequency of coryza and duration of antibiotic administration tended to gradually decrease during the oral administration of JTT (Fig. 2b and c).

The mean number and standard deviation of coryza episodes and the mean duration of antibiotic administration after the 3-month intervention were 1.10 ± 0.62 instances/month and 4.99 ± 3.21 days/month in the JTT group compared to 1.56 ± 0.83 instances/month and 8.10 ± 5.87 days/month in the control group, respectively. The use of JTT significantly decreased both the number of coryza episodes (Wilcoxon rank-sum test, $P = 0.015$) and the total days of antibiotic administration after the administration of JTT for 3 months (Wilcoxon rank-sum test, $P = 0.024$) (Table 2).

Two patients in the JTT group and 4 patients in the control group received ventilation tube insertion due to recurrent AOM during the follow-up period. The mean duration (days) until tube insertion was 81.8 days in the JTT group and 67.1 days in the control group. No significant difference was observed in the

median number of ventilation tube insertions (Fisher's exact test, $P = 0.68$) or the duration until tube insertion (log-rank test, $P = 0.46$) between the JTT and control groups (Table 2).

4. Discussion

The rapid increase of otitis-prone young children is now emerging worldwide. In such children, the effectiveness of repeated antibiotic therapy for each new infection and prophylactic antibiotic therapy for the prevention of AOM relapse is quite limited. We found that prophylactic 3-months treatment with JTT significantly reduced the risk of recurrent AOM (primary endpoint), coryza, and the mean duration of antibiotics administration in children (secondary endpoints) younger than 4 years old. Our study recommends that it is valuable to treat otitis-prone young children with JTT for 3 months.

Most episodes of AOM are preceded after URT infections, and AOM is the most common diagnosis for which antibiotics are prescribed for children [39]. In our study, the frequency of recurrent AOM decreased in the JTT cohort, and simultaneously the JTT cohort showed significant improvement in coryza and total antibiotic administration. Nasopharyngeal colonization with resistant strains of 3 major AOM pathogens, *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis* is frequent in otitis-prone children and is directly associated with the frequency of AOM. Thus, with conventional antimicrobial treatment for AOM, some patients still suffer from recurrent AOM infection. Antibody responses to the 3 pathogens following AOM are generally reduced in the first 2 years of life and rise rapidly thereafter. Consequently, there is a role in using such additional treatments including herbal medication along with conventional antibiotics in children with recurrent AOM under 2 years old.

Otitis-prone children appear to display a subtle immunologic abnormality that predisposes them to recurrent infections. Otitis-prone children, during the first several years of life, have been reported to demonstrate poor immune system response and the development and immaturity of the acquired immune system, such as lower serum IgG2 levels [40] and low concentration of serum anti-P6 IgG [41]. Immaturity of acquired immune function is a major reason why the majority of otitis-prone patients are under 2 years of age. The pneumococcal conjugate vaccine (PCV 7) is effective in young children, but only 7 serotypes are covered with this conjugate vaccine. Therefore, vaccine strategies are not yet considered successful for AOM and recurrent AOM in children. Although tympanostomy tube insertion is effective for the prevention of recurrent AOM in children [12,13], it is accompanied by the possible adverse effects of tympanostomy tube insertion, such as transient or recurrent otorrhea, tympanosclerosis, focal atrophy and persistent perforations which may require surgical repair.

JTT is one of the traditiona1 Japanese herbal medicines that has been used among Japanese people for long time to treat patients in various weakened conditions. The Japanese Ministry of Health and Welfare has approved 148 Japanese herbal prescription drugs including JTT for reimbursement under the National Health Insurance system. Recently, basic and clinical research has demonstrated the effect of Japanese herbal medicines that justify their wider use [29,42,43]. JTT is known to increase immunity by enhancing immuno-associated mechanisms such as phagocytosis, cytokine production, antibody production, and the mitogenic activity. Moreover, accumulating evidence indicates that JTT upregulates a variety of immune system functions by modulating the production of cytokines, including IL-12 in macrophages and IL-2, 4, 5, and IFN-γ in lymphocytes [28,29,42]. JTT has been known for lipopolysaccharides (LPS)-like immunostimulatory activity [34,35]. JTT promotes LPS-induced IL-12 production and increases natural killer (NKT) cells population [28,29].

JTT positively affects not only acquired immunity but also innate immunity [29]. Recently, Muranaka et al. suggested that JTT affects general immunity indirectly, presumably through interaction with the gut local immune system [44]. The intestinal microflora might be considered to play a certain role in eliciting the beneficial effects of JTT and other herbal medicines. Furthermore, the current study supports the new theory of the bacterial contribution in immune-boosting herbs (so called "herbal probiotics" theory). Montenegro et al. suggested a possibility that *Rahnella* species are enriched in JTT and contribute to its immunostimulatory activity [38].

Although the mechanism of JTT against recurrent AOM has not yet been clarified, further investigations are needed to verify the mechanisms of JTT. In the onset and progression of bacterial and viral infections, increased host immune function may be a viable alternative approach for treatment.

The current results of our study indicate that JTT provides a new strategy for the treatment of otitis-prone children. The limitation of this study was that it was an open label trial. In addition, we could not use a blind assessor in the present study, because there was only one doctor in each participating private clinic. Although the beneficial results of JTT could be due to a Hawthorne (placebo) effect, this situation stresses the importance of continued investigations with placebo-controlled trials. We are preparing subsequent double-blind studies to clarify the effect of JTT on recurrent AOM and URT infections.

5. Conclusion

JTT appears to be an effective treatment for otitis-prone children, and avoiding the overuse of antibiotics will help prevent the emergence of drug-resistant bacteria. This study is the first to report that the incidence of recurrent AOM is reduced by herbal medicine. JTT does not completely prevent the risk of recurrent AOM, but even reducing the incidence can be helpful not only for the child but also for the family. We hope our next study will further identify the mechanisms and confirm the beneficial effects of this herbal medicine.

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The authors have no financial relationships to disclose.

Conflict of interest statement

The authors have no conflict of interest with any other people or organizations.

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