

Pediatric Tuina for upper respiratory tract infections of children: A systemic review and meta-analysis

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ABSTRACT

Objective: To evaluate the efficacy of Pediatric Tuina in treating upper respiratory tract infections (URTIs) for children.

Method: We conducted a systematic search of 9 electronic databases from establishment to September 2023. All published randomized controlled trials (RCTs) focused on the efficacy of Pediatric Tuina for children with URTIs compared with medication, no treatment or sham Pediatric Tuina were included for meta-analysis. Review Manager (V.5.3.5) and Stata14.0 were implemented for data analyses. Evidence certainty was evaluated by the GRADEprofiler software.

Result: 12 randomized studies representing 1268 patients met the inclusion criteria. Pediatric Tuina increased the effective rate of URTIs (OR = 3.94, 95% CI: 2.61 to 5.95, P<0.00001), decreased the fever time of URTIs (MD = -0.72, 95% CI: -0.93 to -0.52, P<0.00001). The most commonly used manipulations of the included studies were pushing, kneading, pinching and nipping. The most frequently used acupoints were Tian He Shui, Tian Men, Kan Gong, Tai Yang, Fei Jing. According to the GRADE criteria, effective rate and the fever relieving time were low-quality evidence.

Conclusion: Pediatric Tuina appears to show potential effectiveness in treating Upper Respiratory Tract Infections (URTIs) in children. However, the low certainty of evidence poses a challenge to the reliability of this conclusion. To establish a more solid foundation, multinational and well-conducted randomized clinical trials are essential. These trials would not only support the efficacy of Pediatric Tuina but also guide changes in clinical practice. In the context of relieving symptoms during acute URTI episodes, the common application of pushing and kneading on specific acupoints of Pediatric Tuina on the face and forearm has been observed.

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How to cite this article: Cao L, Deng L, Wang M, Wang D, Zhong Y, Zhang J (2024), Pediatric Tuina for upper respiratory tract infections of children: A systemic review and meta-analysis. Journal of Complementary Medicine Research, Vol. 15, No. 1, 2024 (pp. 146-154)

INTRODUCTION

Upper respiratory tract infections (URTIs), commonly known as the common cold, represent the most widespread ailment globally (Kvaerner et al., 2000). They are characterized by symptoms such as sore throat, rhinitis, rhinorrhea, sneezing, and cough, typically associated with infection in the mucosa of the nose, sinuses, pharynx, and larynx (Eccles, 2005; Heikkinen & Jarvinen, 2003; Van Driel et al., 2018). URTIs are predominantly attributed to viral infections, with Rhinovirus being identified as the most significant causative agent (Gwaltney, 2002). Studies indicate that children experience a higher morbidity rate of URTIs compared to adults, with an average of 6 colds per year in children (Allan & Arroll, 2014). Due to the underdeveloped nature of the respiratory and nervous systems in children, those with URTIs face a heightened risk of fever compared to adults. Furthermore, there is a notable possibility of URTIs recurring as recurrent respiratory tract infections (RRTIs) and progressing to lower respiratory tract infections, hyperpyretic convulsions, and encephal edema (Lim et al., 2018; Putto et al., 1986).

KEYWORDS:

Pediatric Tuina,
upper respiratory
tract infections,
meta-analysis

ARTICLE HISTORY:

Received: Oct 13, 2023
Accepted: Nov 12, 2023
Published: Dec 20, 2023

DOI:

10.5455/jcmr.2024.15.01.20

As a result, URTIs stand out as the primary causes of school absenteeism (Heikkinen & Jarvinen, 2003) and pediatric outpatient visits. This significantly impacts medical and health services (Adams et al., 1999), leading to an extensive economic burden on society^[23]. Given that upper respiratory tract infections (URTIs) are primarily triggered by a multitude of distinct virus types employing varied pathogenetic mechanisms (Gwaltney et al., 2004; Makela et al., 1998), the efficacy and safety of current symptomatic interventions remain uncertain for children (Luks & Anderson, 1996; Van Driel et al., 2018). Consequently, some primary care physicians and parents resort to antibiotics as a perceived effective solution for URTIs (Gonzales et al., 2001; Yu et al., 2014). However, the widespread use of antibiotics in URTIs is a subject of high controversy due to their unsatisfactory impact on viral infections (Andrade et al., 2019; Hersh et al., 2011; Maguire et al., 2018; Mangione-Smith et al., 2015; van de Voort et al., 2018; Yonts et al., 2018). Inappropriate antibiotic prescriptions for children are more likely to contribute to drug resistance and may also elevate the risk of various health issues, including antibiotic-associated diarrhea, diabetes, asthma, obesity, and other related conditions (Kronman et al., 2012; Shao et al., 2017; Stevens et al., 2011; Yonts et al., 2018).

Tuina, or Chinese massage, constitutes a physical therapy rooted in traditional Chinese medicine (TCM). It involves a series of manipulations applied to the body's surface to address various ailments, guided by the principles of TCM (Tao et al., 2016; Yang et al., 2014). Pediatric Tuina is tailored to the specific physiological and pathological characteristics of children, making it a more readily accepted alternative to drugs, especially for younger children who may face challenges in taking medication. As a result, pediatric Traditional Chinese Medicine (TCM) practitioners often incorporate Pediatric Tuina as a complementary treatment for common childhood ailments, including Upper Respiratory Tract Infections (URTIs), anorexia, diarrhea, cerebral palsy, dysplasia, and more (Liang et al., 2020; Luo & Liu, 2012; Peng et al., 2018; Su et al., 2017; Wang et al., 2018; Yang et al., 2017). Pediatric Tuina is extensively utilized in China for the alleviation of symptoms associated with Upper Respiratory Tract Infections (URTIs). Recent studies indicate that Pediatric Tuina may play a role in regulating the function of the immune system (Li et al., 2014; Xia et al., 2018). The utilization of Pediatric Tuina has witnessed a significant surge in the past decade. Despite this, there has been a notable absence of systematic reviews focusing on Pediatric Tuina for children with Upper Respiratory Tract Infections (URTIs). An accurate evaluation of the efficacy of Pediatric Tuina in addressing URTIs holds the potential to advance non-drug treatment options for children and curb the overuse of antibiotics. Hence, there is a pressing need for a systematic review with a meta-analysis to precisely assess the effectiveness of Pediatric Tuina for children with URTIs.

This review aims to fill this gap by consolidating existing evidence on the efficacy of Pediatric Tuina manual therapy in alleviating symptoms of URTIs in children. The approach adheres to the PRISMA reporting guidelines, ensuring methodological rigor. Additionally, we have systematically collected and analyzed the manipulation techniques and regions targeted by Pediatric Tuina in the included studies.

METHOD

Protocol and registration

The protocol for this Systematic review was registered in the

Prospective Register of Systematic Reviews (PROSPERO) : CRD42019126963.

Inclusion and exclusion criterion

Types of patients

- (1). Inclusion criteria: Children (<12 years old) were diagnosed with URTIs.
- (2). Exclusion criteria: Children with severe medical conditions were excluded.

Types of interventions

- (1). Inclusion criteria: Pediatric Tuina should be applied in the experimental group in include study; other kinds of treatment without Pediatric Tuina therapy, no treatment (waiting-list) or sham Pediatric Tuina for comparison.
- (2). Exclusion criteria: The experimental group applied Pediatric Tuina combined with other TCM therapies (such as external used oil or paste with pharmaceutic function or oral herbal medications); pediatric Tuina of the experimental group operated by non-TCM doctors; comparison involved Pediatric Tuina manipulation.

Types of outcomes

The primary outcome was effective rate, and the effective rate is evaluated by alleviation of the symptoms, body temperature or laboratory examination during the acute attack of URTIs. Heal: The body temperature and laboratory examination were normal, the symptoms disappeared; Effective: The body temperature was normal, the symptoms relieved, the laboratory examinations were basically normal; Invalid: The body temperature did not change or rise, symptoms such as running nose, angina, cough did not change or worsen, the laboratory examinations were still abnormal. (State Administration of Traditional Chinese Medicine of China, 1995) Effective rate = (heal cases + effective cases) / total cases × 100%.

The secondary outcomes were time of fever relieving of URTIs and frequency of Pediatric Tuina manipulative methods and acupoints used in the prescription and adverse events during the treatment including swollen, hematoma, and nausea etc.

Types of studies

- (1). Inclusion criteria: Clinical RCT Published in a peer-reviewed journal
- (2). Exclusion criteria: Repeated publications, comments, protocol, conference abstracts, meta-analysis, animal research, case report, review; The data were incomplete; Full-text unavailable literatures.

Search strategy

Studies published on the Pubmed, Embase, Cochrane Library, Web of science, Chinese National Knowledge Infrastructure (CNKI), VIP, Wanfang, China Biomedical Literature Database (CBM), Chinese Clinical Trial Registry System were searched

since the establishment to September 2023, without language restriction.

The computer-based searches combined terms related to (1) the exposures (or interventions,

where appropriate) such as "Tuina", "massage", "manipulation", "massotherapy", "spine pinching", etc. (2) disease or symptoms (eg, "upper respiratory infections", "recurrent respiratory tract infections", "common cold", "acute coryza", "acute laryngopharyngitis", etc. (3) study design(eg, clinical trials, randomized clinical trials). (4) relevant population (eg, "child", "children", "infant", "pediatric").

Data collection and analysis

Selection of studies

All the search results were imported to reference management software to remove duplicate articles. Two independent researchers screened the retrieved literatures by reading the titles abstracts and full text, and then identify the included studies in accordance with the forementioned criteria. Next, the two reviewers independently extracted relevant data from the included studies. including the author, publication year sample sizeauricular acupoints,intervention parameters study design, and outcomes. Disagreements were solved by discussion or consulting a third party arbitrator until a consensus was achieved. The entire process of study selection is performed in the flow diagram(Fig.1) in accordance with the PRISMA Statement guidelines.

Data extraction

Two reviewers independently extracted data on patient characteristics, treatment details, clinical outcomes, adverse events and study quality. If the data provided in the research is unclear, missing or difficult to extract reliably, the corresponding authors were contacted for clarification of the unclear or missing data.

Assessment of risk of bias in included studies

Two reviewers independently assessed the bias risks in each literature studied using the Cochrane Collaboration's Risk of Bias tool.(Higgins et al., 2011) Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias were assessed as low risk, high risk or ambiguous risk in each RCT. Third-party experts were consulted for disagreement.

Data analysis

The data were analyzed with Review Manager 5. 3 software provided by the Cochrane Collaboration and Stata 14.0. Odds ratio (OR) with 95% confidence interval (CI) was adopted for the dichotomous data (eg, effective rate). For continuous data (eg, time of fever relieving), the mean difference (MD) with 95% confidence interval (CI) was adopted. Heterogeneity of the data will be assessed by Q-test and I^2 statistic. Fixed-effect model was applied when heterogeneity is low ($I^2 < 50\%$), while random-effects model for moderate heterogeneity (50-75%). Funnel

plot, Egger's regression symmetry test and trim and fill method were conducted to assess publication bias the number of included studies was more than 10.

RESULTS

Literature Search and Screening

692 articles were searched in nine databases including 517 Chinese articles and 75 English articles, 216 duplicates removed. 378 articles were excluded after the title and abstract screening and 86 articles after the full text screening for not meeting the inclusion criteria as shown in Figure 1. 12 articles were finally included.

Studies Characteristics

All RCTs are conducted in China, involved 1268 patients. The sample size varied from 68 to 198 participants. 12 studies reported effective rate of Pediatric Tuina for acute URTIs, 4(Li, 2019; Su et al., 2017; Zhang, 2016; Liu, 2019) reported fever relieve time. No adverse event was been reported . 6 kinds of Pediatric Tuina manipulative methods were reported in the included studies. More details were shown in Table 1 based on EBM PICO(patient, intervention, control, and outcomes) principle.

Risk of Bias in Included Studies

According to the Cochrane Handbook for Systematic Reviews of In-terventions, we assessed the risk of bias in the included literature. The details of the risk of bias (ROB) assessment are provided in Figures 2. 6(Bian, 2014; Li, 2019; Su et al., 2017; Yang, 2019; Zhao, 2016; Huang et al., 2021) of 12 reported the random sequence generation was assessed to be at low risk. The other 6 RCTs only mentioned random" without provide details of the randomization procedure, was assessed to be at high ROB. None of them stated the calculation of sample size, allocation concealment, blinding of outcome assessment, blinding of participants and personnel were also not reported due to the characteristic of the RCTs involving non-drug interventions, so selection bias, performance bias and detection bias was assessed to be unclear. All of the included studies reported the complete outcome data,and we considered them to be at low ROB of incomplete outcome data and selective reporting. Other bias was unclear.

Outcomes

Effective rate

12 trials involving 1268 children with URTIs reported effective rate. We used the fixed-effects model for statistical analysis due to the low heterogeneity ($P=0.32$, $I^2=13\%$). The pooled analysis showed that effective rate of children in the Pediatric Tuina group were higher than the control groups(OR = 3.94, 95% CI: 2.61 to 5.95, $P < 0.00001$) (Fig. 3). The asymmetrical funnel plot of the 12 trials presented potential publication bias as shown in Fig 4. However, no effect of publication bias was shown on the results with trim and fill method.

The time of fever relieving

4 trials reported the time of fever relieving. The pooled results showed a shorter fever relieving time (MD = -0.72, 95% CI (-0.93, -0.52), $P < 0.00001$) of Pediatric Tuina group compared with the control group with no heterogeneity ($P = 0.73$, $I^2 = 0\%$) (Figure 5).

Frequency of manipulations and acupoints

By collecting and analyzing the treatment protocols, indicating that 6 kinds of manipulation methods were involved of the included studies. As presented in Figure 8, the most commonly used manipulations were pushing, kneading, pinching and nipping. The top 5 acupoints most commonly implemented to relieve URTIs were shown in Table 2. In summary, pushing and kneading on specific acupoints of Pediatric Tuina on the face and forearm were frequently used.

Adverse event

No adverse events were reported in all included studies.

Certainty of evidence by GRADE

The certainty of evidence for key outcomes were all evaluated as low by the GRADE criteria as shown in Table 3. The certainty of evidence was downgraded mainly due to the following reasons: no trial achieved blinding to participants and personnel, no negative result was published.

DISCUSSION

This systematic review and meta-analysis demonstrate that Pediatric Tuina has a positive impact on alleviating upper respiratory tract infections (URTIs). The collected and analyzed manipulation methods indicate that pushing and kneading specific acupoints on the face and forearm through Pediatric Tuina are commonly employed to relieve symptoms during acute attacks of URTIs.

Tuina, a distinctive form of massage, holds its roots in a rich history. The term "massage" itself finds its origin in the Arabic root "mass'h," signifying touch or squeeze. The earliest documented mention of massage dates back to "The Inner Canon of Huangdi," a classical medical literature within Traditional Chinese Medicine (TCM) from 4,000 years ago. The specific term "Tuina" first emerged during the Ming Dynasty in China, marking the inception of this therapeutic practice (Badr et al., 2015). Additionally, it was during this period that the distinctive theoretical framework of Pediatric Tuina took shape. Distinguishing itself from other forms of massage therapy, Pediatric Tuina adheres to the principles of Traditional Chinese Medicine (TCM), specifically drawing guidance from TCM meridian and Zang-Fu theory. As a vital component of Tuina, Pediatric Tuina focuses primarily on preventing and treating common pediatric ailments, while concurrently fostering the overall health and growth of children. However, owing to the distinctive physiological characteristics of children, Pediatric Tuina exhibits unique features, including the utilization of special acupoints and the application of softer and more intricate manipulations. In addition to the fundamental manipulations found in traditional Tuina, such as pressing,

rolling, rubbing, pushing, and kneading, Pediatric Tuina incorporates compound manipulations. For instance, the Kai Tianmen technique involves using two thumbs to push straight from the midpoint of the line between the eyebrows to the front hairline (Gu & Lv, 2017). Our review reveals a positive impact of Pediatric Tuina on treating Upper Respiratory Tract Infections (URTIs) and reducing the duration of fever in children. This aligns with Traditional Chinese Medicine (TCM) theory, which posits that specific manipulations on meridians and acupoints of children can regulate zang-fu conditions and eliminate external pathogens, leading to antipyretic effects. Several studies have indicated that the particular manipulations employed in Pediatric Tuina contribute to fever relief. These manipulations achieve this by enhancing local blood flow, reducing cyclic adenosine monophosphate (cAMP) levels in cerebrospinal fluid during peak fever, and counteracting the effects of pyrogens on the activity of temperature-sensitive neurons in the central nervous system (Dong et al., 2012; Fan et al., 1990). Certainly, further research is imperative to delve into the underlying mechanisms for a more comprehensive understanding. When executed by trained professionals, Pediatric Tuina stands out as a comparatively safe alternative to certain medications. This is the rationale behind our inclusion criteria, limiting studies to those conducted by professional Traditional Chinese Medicine (TCM) doctors or therapists.

Professional TCM doctors implement personalized Pediatric Tuina manipulations tailored to individual children with diverse constitutions, relying on TCM syndrome differentiation—a cornerstone of TCM theories. It's worth noting that in pediatric patients, persistent high fever has the potential to induce febrile convulsions or result in brain damage. This heightened risk is attributed to their relatively higher metabolism, elevated core body temperature, and underdeveloped temperature control abilities (Lim et al., 2018). Our review suggests an intriguing possibility: the combination of Pediatric Tuina with Chinese patent drugs may enhance the effectiveness of fever relief.

Significantly, this review highlights that manipulations administered to children through Pediatric Tuina are characterized by a softer and gentler approach compared to techniques used for adults. The predominant manipulations identified in this review include pushing, kneading, pinching, and nipping. The pushing technique involves applying straight-forward or rotational movements on specific points using the thumb, index, or middle finger pads. Kneading manipulation entails circular movements by fixing the thenar or whorl surface of the middle finger or thumb on a designated part or point. Pinching manipulation is executed by grasping the skin with the pads of the thumb, index, and middle finger, applying opposite forces, and repeatedly pinching and releasing—especially on Ji (spinal). Nipping involves pressing and pricking acupoints with the nail of the thumb or the nails of the thumb and index finger.

In the context of alleviating symptoms during acute upper respiratory tract infections, Pediatric Tuina focuses on specific acupoints on the face and forearms. Notable acupoints include Tian He Shui, Fei Jing or Tian Men, Kan Gong, and Tai Yang (EX-HN 5), Er Hou Gao Gu. The specific manipulations on the face and forearms are believed to aid in expelling exogenous pathogenic factors and preventing unconsciousness, as per Traditional Chinese Medicine (TCM) theory. Despite the valuable insights gained from the included studies, several limitations are noteworthy. Firstly, a majority of the studies lacked sufficient methodological descriptions, with 6 out of the 12 trials referencing randomization methods without providing detailed explanations. Secondly, the challenge of implementing

participant and personnel blinding in non-drug intervention RCTs was acknowledged; however, none of the studies addressed blinding in outcome assessment, raising concerns about potential detection bias. Thirdly, the possibility of publication bias is acknowledged, given that all included studies were published in Chinese, and no primary articles reporting negative results were identified.

It is strongly recommended that future research addresses these limitations through the execution of large, high-quality randomized clinical trials to ensure a robust foundation for meta-analysis. Despite these challenges, this review holds significance as it comprehensively examines the current literature on Pediatric Tuina in relation to URTIs up to the

present date.

CONCLUSION

The review has compiled current literature on Pediatric Tuina in relation to URTIs, revealing a trend of effectiveness through meta-analysis. However, concerns about study quality are noted, highlighting the need for substantial and well-designed randomized clinical trials to facilitate robust meta-analyses. It is strongly recommended that the field awaits future trials for confirmation and firm conclusions.

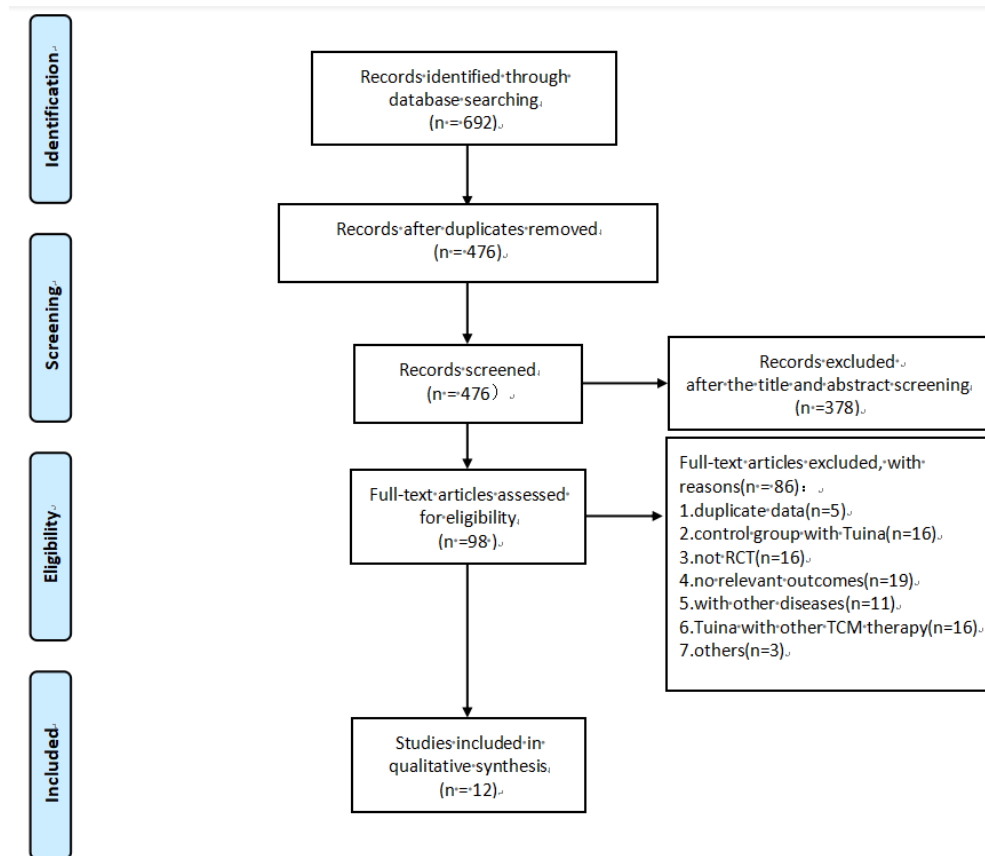


Figure 1: Flow of Literature Screening

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bian 2014	+	?	?	?	+	+	?
Feng 2009	?	?	?	?	+	+	?
Huang 2021	+	?	?	?	+	+	?
Li 2019	?	?	?	?	+	+	?
Liu 2019	?	?	?	?	+	+	?
Ma 2014	?	?	?	?	+	+	?
Su 2017	+	?	?	?	+	+	?
Xie 2016	?	?	?	?	+	+	?
Yang 2019	+	?	?	?	+	+	?
Zhang 2016	?	?	?	?	+	+	?
Zhang 2021	?	?	?	?	+	+	?
Zhao 2016	+	?	?	?	+	+	?

Figure 2: Risk of Bias in Included Studies

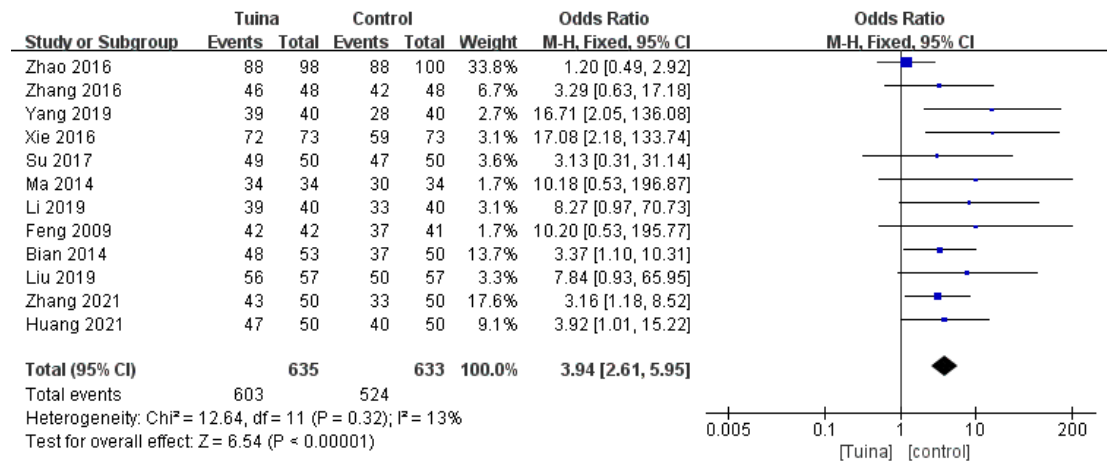


Figure 3: Effective rate of Tuina vs control for Acute URITs

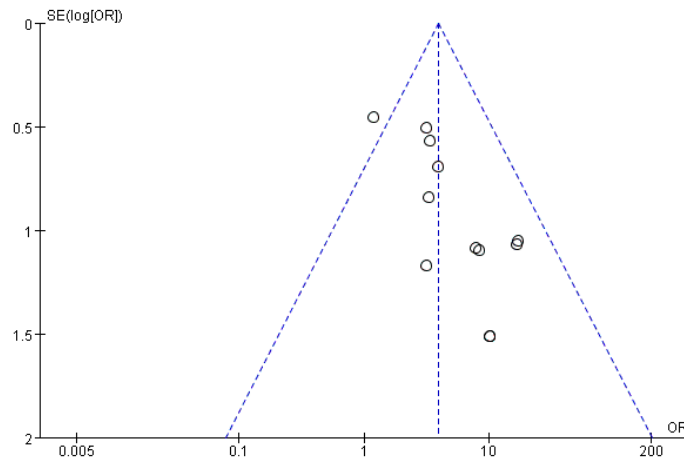


Figure 4: Funnel Plot of Tuina vs Medication For URITs

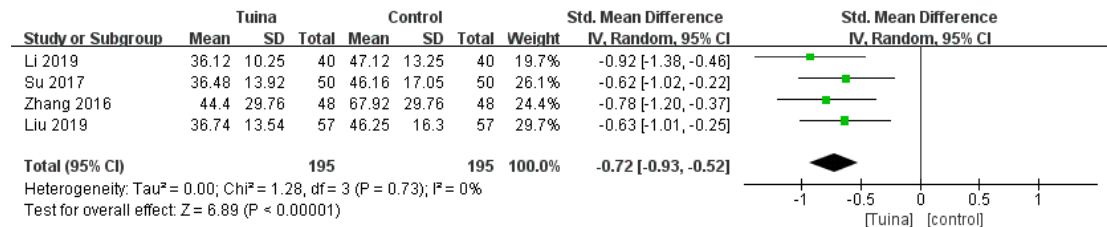
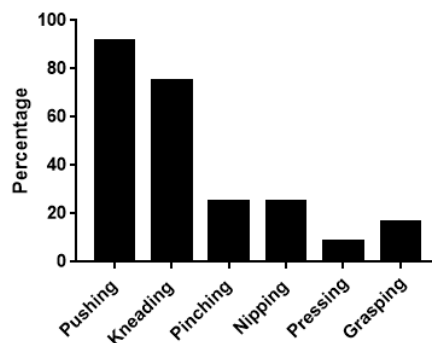


Figure 5: Fever relieving time of Tuina vs control for URITs



Manipulation Methods involved in Tuina treating URITs

Figure 6: Manipulation Involved in Included Studies

Tuina for UTRIs						
Patient or population: patients with UTRIs						
Settings:						
Intervention: Tuina						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Tuina				
effective rate	Study population		OR 3.94 (2.61 to 5.95)	1268 (12 studies)	⊕⊕⊕⊖ low ¹	
	828 per 1000	950 per 1000 (926 to 966)				
fever time	Moderate			390 (4 studies)	⊕⊕⊕⊖ low ¹	SMD -0.72 (-0.93 to -0.52)
	850 per 1000	957 per 1000 (937 to 971)				
The mean fever time in the intervention groups was 0.72 standard deviations lower (0.93 to 0.52 lower)						

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ No explanation was provided

Figure 7: GRADE evaluation form of evidence certainty

Table 1: Study Characteristics of Acute URTIs

Study	Sample(E/C)	Intervention	Types of control	Outcomes	AE
Bian 2014(Bian, 2014)	53/50	PT (pushing, kneading)	Medication (antipyretic-analgesic)	ER	NR
Feng 2009(Feng et al., 2009)	42/41	PT (pressing)	Medication (antipyretic-analgesic)	ER	NR
Li 2019(Li, 2019)	40/40	PT (pushing, kneading, nipping)	Medication(CPD)	①ER②time of fever relieving③symptom score	NR
Ma 2014(Ma, 2014)	34/34	PT (pushing, kneading)	Medication(CPD)	①ER②symptom score	NR
Su 2017(Su et al., 2017)	50/50	PT (pushing, kneading)	Medication(CPD)	①ER ②time of fever relieving ③symptom score	NR
Xie 2016(Xie, 2016)	73/73	PT (pushing, kneading, pinching)	Medication (antipyretic-analgesic)	①ER②fever relieving rate③BRE abnormal rate	NR
Yang 2019(Yang, 2019)	40/40	PT (pushing, kneading, pinching)	Medication(Oseltami vir)	ER	NR
Zhang 2016(Zhang , 2016)	48/48	PT (pushing, pinching, nipping)	Medication(antiviral)	①ER②symptom score	NR
Zhao 2016(Zhao, 2016)	98/100	PT (pushing, kneading, grasping, nipping)	Medication(CPD)	ER	NR
Liu 2019(Liu, 2019)	57/57	PT (pushing, kneading)	Medication(CPD)	①ER ②time of fever relieving ③symptom score	NR
Huang 2021(Huang et al., 2021)	50/50	PT (pushing)	Medication (antipyretic-analgesic)	①ER ②time of fever relieving ③symptom score	NR
Zhang 2021(Zhang et al., 2021)	50/50	PT (pushing, kneading, grasping)	Medication (antipyretic-analgesic)	①ER ②symptom score	NR

Abbreviation AD: adverse events, CPD: Chinese patent drug, E/C: experiment group versus control group, ER: effective rate, NR: not reported, PT: Pediatric Tuina

Table 2: Top 5 Acupoints Most Commonly Implemented for URTIs

Acupoints	Position	Frequency
Tian He Shui	long the midline of forearm from the midpoint of the palmar transverse crease of the wrist to PC3	83.33%
Tian Men	The line from the midpoint between the two eyebrows up to the anterior hairline.	75%
Kan Gong	The transverse line from the medial end to the lateral end of the eyebrow	75%
Tai Yang	EX-HN 5	66.67%
Fei Jing	The unguar whorl surface of the distal part of the ring finger	66.67%

Ethical Approval

As a systematic review and meta-analysis, this study did not involve any new studies of human or animal subjects performed by any of the authors. This research is based on previously published data; ethical approval and patient consent for the study were not required. All analyses were based on previous public studies and published data; thus, no additional ethical approval was necessary.

However, all included studies within this meta-analysis were screened for ethical conduct and only those that reported ethical approval and consent procedures were considered. This screening process ensured that our synthesis included studies that complied with ethical standards in research involving human subjects, adhering to the principles of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Funding details

This work was supported by the Police Physical Fitness Monitoring and Rehabilitation Research Center (Grant No. 202309B01).

Conflict of interest

The authors declare that they have no conflict of interest.

Informed Consent

This article is a systematic review and meta-analysis, and as such, it does not involve the collection of primary data from individual patients. All analyzed data were extracted from previously published studies, where informed consent and ethical approval were obtained and described by the original study investigators. The current study is based on aggregated published data, and no individual patient data were accessed; therefore, informed consent for this synthesis was not required.

Authorship contributions

Conceptualization: Jiayuan Zhang, Liu Cao, Linwen Deng.
 Data curation: Mingming Wang, Dong Wang.
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 Resources: Jiayuan Zhang.
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 Supervision: Jiayuan Zhang, Liu Cao.
 Visualization: Liu Cao, Linwen Deng.

Writing original draft: Jiayuan Zhang, Liu Cao, Linwen Deng.
 Review and editing: Dong Wang, Mingming Wang.

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