ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

REVIEW ARTICLE

Clinical effectiveness of traditional Chinese medicine in modulating gut microbiota for pediatric *Mycoplasma pneumoniae* pneumonia: A systematic review and meta-analysis

Supplementary Files

Table S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for the current study. Obtained from the PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Section and Topic	Item #	Checklist item	Location where item is reported
		Title	
Title	1	Identify the report as a systematic review.	Page 1. Title section
		Abstract	
Abstract Structured summary	2	See the PRISMA 2020 for Abstracts checklist. Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; and treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions; and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Page 1. Abstract section
		Introduction	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1. Introduction section
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	Page 1. Introduction section
		Methods	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2, 2.1 Eligibility criteria section of 2. Materials and methods.
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 2, 2.2 Search strategy section of 2. Materials and methods.
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Page 2, 2.2 Search strategy section of 2. Materials and methods.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2, 2.3 Research selection section of 2. Materials and methods.

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Table S1. (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
		Methods	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 2, 2.3 Research selection section of 2. Materials and methods.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, and analyses), and if not, the methods used to decide which results to collect.	Page 2, 2.3 Research selection section of 2. Materials and methods.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics and funding sources). Describe any assumptions made about any missing or unclear information.	Page 2, 2.3 Research selection section of 2. Materials and methods.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3, 2.4 Risk of bias in individual studies section of 2. Materials and methods.
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio and mean difference) used in the synthesis or presentation of results.	Page 3, 2.5 Statistical analysis section of 2. Materials and methods.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 3, 2.5 Statistical analysis section of 2. Materials and methods.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 3, 2.5 Statistical analysis section of 2. Materials and methods.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3, 2.5 Statistical analysis section of 2. Materials and methods.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	Page 3, 2.5 Statistical analysis section of 2. Materials and methods.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis and meta-regression).	Page 3, 2.5 Statistical analysis section of 2. Materials and methods.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 3, 2.5 Statistical analysis section of 2. Materials and methods.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3, 2.4 Risk of bias in individual studies section of 2. Materials and methods.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3, 2.4 Risk of bias in individual studies section of 2. Materials and methods.
		Results	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 3, 3.1 Database search section of 3. Results.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 3, 3.1 Database search section of 3. Results.
Study characteristics	17	Cite each included study and present its characteristics.	Page 3, 3.2 Study characteristics section of 3. Results.

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Table S1. (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
		Results	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 3, 3.3 Results of Literature Quality Evaluation section of 3. Results.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Page 3, 3.4 Meta-analysis section of 3. Results.
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Page 3, 3.4 Meta-analysis section of 3. Results.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 3, 3.4 Meta-analysis section of 3. Results.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 3, 3.4 Meta-analysis section of 3. Results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7, 3.6 Sensitivity analysis and publication bias assessment section of 3. Results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7, 3.6 Sensitivity analysis and publication bias assessment section of 3. Results.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 7, 3.6 Sensitivity analysis and publication bias assessment section of 3. Results.
		Discussion	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 8, 4 Discussion section
	23b	Discuss any limitations of the evidence included in the review.	Page 13, 4.3 Limitations and Shortcomings section of 4. Discussion.
	23c	Discuss any limitations of the review processes used.	Page 13, 4.3 Limitations and Shortcomings section of 4. Discussion.
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14, 5 Conclusion section
		Other Information	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 1, Systematic Review Registration section.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 1, Systematic Review Registration section.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 1, Systematic Review Registration section.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 14, Funding section.
Competing interests	26	Declare any competing interests of review authors.	Page 14, Conflict of interest statement section.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; and any other materials used in the review.	Page 14, Data availability statement section.

Note: Reference of PRISMA checklist: BMJ 2021;372:n71. doi: 10.1136/bmj.n71; From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. For more information, visit: http://www.prisma-statement.org/.

Table S2. Search strategy for the respective database

Database name	Search strategies
CNKI	TKA=(“中药”) AND TKA=(“肠道菌群”+“肠道微生物”+“胃肠道微生物”) AND TKA=(“肺炎支原体肺炎”+“支原体肺炎”) AND TKA=(“儿童'+'婴幼儿”) AND FT=“随机”
Wanfang	主题:(“中药") and 主题:(“肠道菌群” or “肠道微生物" or “胃肠道微生物") and 主题:(“肺炎支原体肺炎" or “支原体肺炎") and 主题:(“儿童" or “婴幼儿") and 全部:(随机)
VIP	(M=(中药) or K=(中药)) and (M=(肠道菌群 or 肠道微生物 or 胃肠道微生物) or K=(肠道菌群 or 肠道微生物 or 胃肠道微生物)) and (M=(肺炎支原体肺炎 or 支原体肺炎) or K=(肺炎支原体 or 支原体肺炎)) and (M=(儿童 or 婴幼儿) or K=(儿童 or 婴幼儿)) and U=随机
SinoMed	1 “中药”[不加权:扩展] 2 “胃肠道微生物组”[不加权:扩展] 3 “肺炎，支原体”[不加权:扩展] 4 “儿童”[不加权:扩展] 5 “中药”[常用字段:智能] 6 “胃肠道微生物组”[常用字段:智能] OR “胃肠道微生物”[常用字段:智能] OR “肠道微生物”[常用字段:智能] OR “肠道菌群”[常用字段:智能] 7 “肺炎支原体肺炎”[常用字段:智能] OR “支原体肺炎”[常用字段:智能] 8 “儿童”[常用字段:智能] OR “婴幼儿”[常用字段:智能] 9 (#1) OR (#5) 10 (#2) OR (#6) 11 (#3) OR (#7) 12 (#4) OR (#8) 13 (#9) AND (#10) AND (#11) AND (#12) 14 “随机”[全部字段:智能] 15 (#13) AND (#14)
Pubmed	#1”Pneumonia, Mycoplasma”[Mesh] #2 ((((Mycoplasma Pneumonia[Title/Abstract]) OR (Mycoplasma Pneumonias[Title/Abstract])) OR (Pneumonias, Mycoplasma[Title/Abstract])) OR (*Mycoplasma pneumoniae* Infection[Title/Abstract])) OR (*Mycoplasma pneumoniae* Infections[Title/Abstract]) #3 (#1) OR (#2) #4 “Gastrointestinal Microbiome”[Mesh] #5(((((((((((((((((((((((((((((((((((Gastrointestinal Microbiomes[Title/Abstract]) OR (Microbiome, Gastrointestinal[Title/Abstract])) OR (Gut Microbiome[Title/Abstract])) OR (Gut Microbiomes[Title/Abstract])) OR (Microbiome, Gut[Title/Abstract])) OR (Gut Microflora[Title/Abstract])) OR (Microflora, Gut[Title/Abstract])) OR (Gut Microbiota[Title/Abstract])) OR (Gut Microbiotas[Title/Abstract])) OR (Microbiota, Gut[Title/Abstract])) OR (Gastrointestinal Flora[Title/Abstract])) OR (Flora, Gastrointestinal[Title/Abstract])) OR (Gut Flora[Title/Abstract])) OR (Flora, Gut[Title/Abstract])) OR (Gastrointestinal Microbiota[Title/Abstract])) OR (Gastrointestinal Microbiotas[Title/Abstract])) OR (Microbiota, Gastrointestinal[Title/Abstract])) OR (Gastrointestinal Microbial Community[Title/Abstract])) OR (Gastrointestinal Microbial Communities[Title/Abstract])) OR (Microbial Community, Gastrointestinal[Title/Abstract])) OR (Gastrointestinal Microflora[Title/Abstract])) OR (Microflora, Gastrointestinal[Title/Abstract])) OR (Gastric Microbiome[Title/Abstract])) OR (Gastric Microbiomes[Title/Abstract])) OR (Microbiome, Gastric[Title/Abstract])) OR (Intestinal Microbiome[Title/Abstract])) OR (Intestinal Microbiomes[Title/Abstract])) OR (Microbiome, Intestinal[Title/Abstract])) OR (Intestinal Microbiota[Title/Abstract])) OR (Intestinal Microbiotas[Title/Abstract])) OR (Microbiota, Intestinal[Title/Abstract])) OR (Intestinal Microflora[Title/Abstract])) OR (Microflora, Intestinal[Title/Abstract])) OR (Intestinal Flora[Title/Abstract])) OR (Flora, Intestinal[Title/Abstract])) OR (Enteric Bacteria[Title/Abstract])) OR (Bacteria, Enteric[Title/Abstract])) #6 (#4) OR (#5) #7(((Traditional Medicine, Chinese[Title/Abstract]) OR (Chinese Traditional Medicine[Title/Abstract])) OR (Traditional Chinese Medicine[Title/Abstract])) OR (Chinese Medicine, Traditional[Title/Abstract]) #8 “medicine, Chinese traditional”[Mesh] #9 (#7) OR (#8) #10 (“Child”[Mesh]) OR “Infant”[Mesh] #11((Infants[Title/Abstract]) OR (Minors[Title/Abstract])) OR (Only Child[Title/Abstract]) #12 (#10) OR (#11) #13 (((#3) AND (#6)) AND (#9)) AND (#12)

(*Cont'd...*)

Table S2. (*Continued*)

Database name	Search strategies
Cochrane Library	#1 TS=(Mycoplasma Pneumonia OR Mycoplasma Pneumonias OR *Mycoplasma pneumoniae* Infection OR *Mycoplasma pneumoniae* Infections OR "Pneumonia, Mycoplasma") #2 TS=(Gut Microbiome OR Gastrointestinal Flora OR Gut Flora OR Intestinal Flora OR "Gastrointestinal Microbiome") #3 TS=(Chinese Traditional Medicine OR Traditional Chinese Medicine OR Chinese Medicine, Traditional OR "medicine, Chinese traditional") #4 TS=(Children OR Infants OR Minors OR "Child") #5 #1 AND #2 AND #3 AND #4
Embase	#1 "Pneumonia, Mycoplasma"/exp #2 "Mycoplasma Pneumonia":ab, ti OR "*Mycoplasma pneumoniae* Infections":ab, ti #3 #1 OR #2 #4 "Gastrointestinal Microbiome"/exp #5 "Gut Microbiome":ab, ti OR "Gastrointestinal Flora":ab, ti OR "Gut Flora":ab, ti OR "Intestinal Flora":ab, ti #6 #4 OR #5 #7 "medicine, Chinese traditional"/exp #8 "Chinese Traditional Medicine":ab, ti OR "Traditional Chinese Medicine":ab, ti OR "Chinese Medicine, Traditional":ab, ti #9 #7 OR #8 #10 "Child"/exp #11 "Children":ab, ti OR "Infants":ab, ti OR "Minors":ab, ti #12 #10 OR #11 #13 #3 AND #6 AND # 9 AND # 12

Abbreviations: CNKI: China National Knowledge Infrastructure; Embase Database: Excerpta Medica Database; SinoMed: The Chinese Biomedical Literature Database; VIP: The Chinese Scientific Journals Full-Text Database.

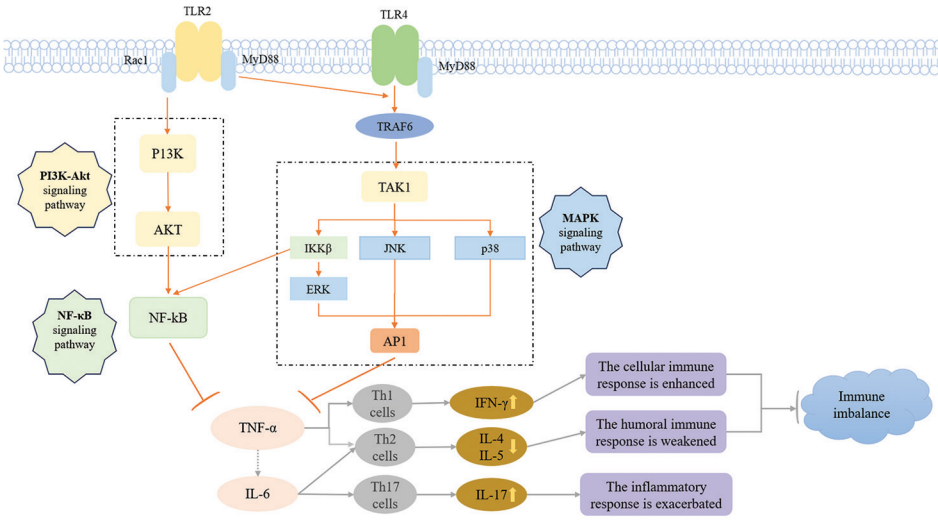

Figure S1. Mycoplasma pneumonia-associated mechanisms. When *Mycoplasma pneumoniae* infection occurs, its lipid-associated membrane proteins (MP-LPPs) are recognized by Toll-like receptor (TLR) 2 and TLR4 on the host cell surface. TLR2 activation triggers the phosphoinositide 3-kinase (PI3K)-Protein Kinase B (Akt) signaling pathway through Ras-related C3 botulinum toxin substrate 1 (Rac1), leading to AKT activation. AKT regulates various cellular processes, including cell survival, proliferation, and metabolism. TLR2 and TLR4 initiate signaling through the adaptor protein myeloid differentiation primary response 88 (MyD88). Following TLR4 recognition, the signal is transmitted to TGF-β-activated kinase 1 (TAK1) through TNF receptor-associated factor 6 (TRAF6), which subsequently activates downstream molecules, including inhibitor of nuclear factor kappa-b kinase subunit β (IKKβ), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p38). These events culminate in the activation of the activator protein 1 (AP1) transcription factor, leading to the release of inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α and interleukin (IL) 6) and the initiation of inflammatory responses. TNF-α enhances T helper (Th) 1 cell function and promotes interferon (IFN) γ production, thereby enhancing the cellular immune response. Conversely, TNF-α and IL-6 inhibit Th2 cell function and reduce the production of IL-4 and IL-5, thereby weakening the humoral immune response. Simultaneously, TNF-α induces IL-6 expression, promotes Th17 cell differentiation, increases IL-17 production, and exacerbates the inflammatory response
Abbreviation: MAPK: Mitogen-activated protein kinas.