



Should Probiotics, honey, and escin be used in the prevention or treatment of COVID-19?

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This rapid review systematically summarizes the available evidence of probiotics, honey, and escin in the prevention and treatment of COVID-19.

KEY FINDINGS

There is very limited low-quality evidence documenting efficacy of probiotics and no evidence for the use of honey and escin for COVID19. Further clinical studies are needed to justify use of these traditional interventions for COVID-19.

- Probiotics may prevent URTI among children and ventilator associated pneumonia among critically ill non-COVID-19 patients (3,4,5). Honey has the potential to soothe the throat and provide relief for symptomatic cough in children who are older than one year (11,12).
- Escin, a dietary supplement from *Aesculus hippocastanum* or horse chestnut extract, had in-vitro activity against SARS virus and Vero E6 cells (15,16).
- Based on one meta-analysis, probiotics may significantly prevent at least one episode of URTI (OR 0.43; 95% CI 0.29 to 0.63, I²=22%) to at least three episodes (OR 0.56 [0.35,0.89], I²=0%) among non-COVID-19 children but did not prevent URTI among the adult subgroup (6). Two metanalyses similarly showed that probiotics significantly prevent VAP among critically ill non-COVID-19 patients [OR 0.70 [0.52, 0.95] I²=46%] and RR 0.74, [0.61, 0.90], I²=19%) (7,8). But both studies found no significant decrease in overall mortality and no effect on the risk of diarrhea among critically ill non-COVID-19 patients. Minor gastrointestinal effects such as abdominal cramping, nausea, soft stools, flatulence, and taste disturbance are reported from intake of probiotics (9). There are also rare reports of immunocompromised patients developing invasive disease from probiotic use (10).
- One low-quality retrospective cohort observational study by Jiang et al described the outcomes of 55 COVID-19 patients who were receiving a variety of treatment regimens at Wuxi, Jiangsu Province, China (19). Twenty-six (n=26/55) patients received supplementation with probiotic tablets. They reported that all 55 patients were discharged, and no deaths occurred. This study was deemed to be of low quality because of several biases. The study design was descriptive and non-comparative with unequal representation among the two groups precluding conclusions on treatment efficacy. No strategies were mentioned that dealt with the confounding biases from the variety of treatment regimen given to both groups. The baseline characteristics among groups were statistically different leading to significant biases.
- We found no completed clinical trials nor systematic reviews studying the efficacy of probiotics, honey or escin among COVID-19 patients.
- The most common adverse effects of probiotics, honey and escin are minor gastrointestinal complaints.
- We found five registered clinical trials and one observational study investigating the benefits of probiotics, one registered trial for honey, and two for escin.
- WHO Interim guidelines, CDC interim guidelines, Infectious Diseases Society of America COVID-19 treatment guidelines, and the American Thoracic Society did not give any recommendation on the use of probiotics, honey or escin in patients with COVID-19.

REFERENCES

1. Sanders M. Probiotics: Definition, Sources, Selection, and Uses. *Clinical Infectious Diseases*. 2008 Feb; 46(s2): S58-S61.
2. Rijkers GT, Bengmark S, Enck P, Haller D, Herz U, Kalliomaki M, et al. Guidance for Substantiating the Evidence for Beneficial Effects of Probiotics: Current Status and Recommendations for Future Research. *The Journal of Nutrition*. 2010 Mar 1; 140(3): 671S-676S.
3. Allan GM, Arroll B. Prevention and treatment of the common cold: Making sense of the evidence. *CMAJ*. 2014 Feb 18; 186(3): 190-199.
4. Kanauchi O, Andoh A, AbuBakar S, Yamamoto N. Probiotics and Paraprobiotics in Viral Infection: Clinical Application and Effects on the Innate and Acquired Immune Systems. *Current Pharmaceutical Design*. 2018 Jan 18; 24.
5. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *Cochrane Database of Systematic Reviews*. 2010 Nov 10;(11).
6. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database of Systematic Reviews*. 2015 Feb 3;(2).
7. Bo L, Li J, Tao T, Bai Y, Ye X, Hotchkiss RS, et al. Probiotics for preventing ventilator-associated pneumonia. *Cochrane Database of Systematic Reviews*. 2014 Oct 25;(10).
8. Manzanares W, Lemieux M, Langlois PL, Wischmeyer PE. Probiotic and synbiotic therapy in critical illness: A systematic review and meta-analysis. *Critical Care*. 2016 Aug 19; 20(1).
9. Doron S, Snyderman DR. Risk and safety of probiotics. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2015 May 15; 60 Suppl 2(Suppl 2): S129-S134.
10. Snyderman D. The Safety of Probiotics. *Clinical Infectious Diseases*. 2008 Feb; 46(s2): S104-S111.
11. World Health Organization. Cough and cold remedies for the treatment of acute respiratory infections in young children. 2001.
12. Coughs and Colds: Medicines or Home Remedies? *American Academy of Pediatrics*. 2018 Nov 21.
13. Israili ZH. Antimicrobial properties of honey. *American Journal of Therapeutics*. 2014; 21(4): 304-323.
14. Oduwole O, Udoh EE, Oyo-Ita A, Meremikwu MM. Honey for acute cough in children. *The Cochrane database of systematic reviews*. 2018 Apr 10; 4(4): CD007094-CD007094.
15. Gallelli L. Escin: A review of its anti-edematous, antiinflammatory, and venotonic properties. *Drug design, development and therapy*. 2019 Sep; 13: 3425-3437.
16. Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YSE, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proceedings of the National Academy of Sciences of the United States of America*. 2004 Jul 6; 101(27): 10012-10017.
17. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *The Cochrane database of systematic reviews*. 2012 Nov 14; 11(11): CD003230-CD003230.
18. Aromataris , Munn Z. *Joanna Briggs Institute Reviewer's Manual*. 2017; The Joanna Briggs Institute.
19. Jiang X, Tao J, Wu H, Wang Y, Zhao W, Zhou M, et al. Clinical features and management of severe COVID-19: A retrospective study in Wuxi, Jiangsu Province, China. *medRxiv*. 2020 Apr 14;: 2020.04.10.20060335.
20. WHO Interim Guidelines Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. [Online].; March 13,2020. [cited 2020 May 13. Available from: [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
21. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VCC, et al. *Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19*. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2020 Apr 27;: ciaa478.

22. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health.. [Online]. [cited 2020 May 13. Available from: <https://www.covid19treatmentguidelines.nih.gov/>.
23. Wilson KC,CSH,BCaRJ. COVID-19: Interim Guidance on Management Pending Empirical Evidence. From an American Thoracic Society-led International Task Force. [Online].; April 3, 2020 [cited 2020 April 13. Available from: <https://www.thoracic.org/covid/covid-19-guidance.pdf>.

Appendix 1. Characteristics of included trials

Author/ Title	Journal/Year	Study design	Country	Disease condition	Population size	Intervention Group(s)	Comparison Group(s)	Primary outcomes	Key Secondary Outcomes	Key Findings	Reported AE	Limitations
Jiang, Xiufeng Et al. Clinical features and management of severe COVID-19: A retrospective study in Wuxi, Jiangsu Province, China	medRxiv 2020	Retrospective Observational Single-center	China (Jiangsu)	COVID-19	55 COVID-19 patients who received variety of treatment regimen including probiotics (26/55)	none		No mortality was reported among the 26 patients or 47.3% who received probiotics tablets.	The median duration of hospitalization among all patients was 16.0 days (IQR 5.0-10.0; patients with severe disease had longer hospitalization compared with those with non-severe disease (23.0 days vs 16.0 days, p=0.003; HR=0.37 [95% CI 0.21-0.65], p=0.0012). Patients with severe disease also stayed significantly longer in hospital after negative PCR test (14.0 days vs 6.0 days, p=0.002; HR=0.38 [95% CI 0.21-0.66], p=0.0010)	No mortality was reported in this study		Small sample size Baseline characteristics of groups were not stated