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

Marquis Von Angelo Syquio G. Joson, MD,[1] Rowena Natividad S. Flores-Genuino, MD, MSc,[2] Belen L. Dofitas, MD, MSc[3] and Leonila F. Dans, MD, MSc[1]

[1]*Department of Pediatrics, Philippine General Hospital, University of the Philippines Manila*
[2]*Department of Anatomy, College of Medicine, University of the Philippines Manila*
[3]*Department of Dermatology, Philippine General Hospital, University of the Philippines Manila*

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 upper respiratory tract infection (URTI) among children and ventilator associated pneumonia (VAP) among critically ill non-COVID-19 patients. Honey soothes the throat by providing symptomatic relief in children with cough. Escin, a dietary supplement from *Aesculus hippocastanum* or horse chestnut extract, had in-vitro activity against SARS virus and Vero E6 cells.
- One retrospective cohort observational study was found describing 55 COVID-19 patients who were receiving a variety of treatment regimens including probiotics. All patients were discharged with no deaths reported.
- 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.

BACKGROUND

Currently, nutritional supplements, animal- and plant-derived, are explored as possible preventive interventions, adjuncts, or treatment to improve health outcomes among COVID-19 patients.

Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits on the host.[1] At present, there are numerous formulations of probiotics authorized in the Philippines (Appendix 1). Efficacy of probiotics is dependent on the specific species, strain and dose for different indications such as promotion of better metabolism, alleviation of intestinal inflammatory disease, prevention of infection, and allergy.[2] Probiotics act on both the innate and acquired immune system and have been shown in non-COVID-19 patients to prevent and decrease the severity of upper respiratory tract infections (URTI), as well as lessen the duration and frequency of acute infectious diarrhea.[3,4,5]

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, p value <0.001, I^2=22%) to at least three episodes (OR 0.56; 95% CI 0.35 to 0.89, p value =0.01, I^2=0%) among non-COVID-19 children but did not prevent URTI among the adult subgroup.[6] Among children with infectious diarrhea, administration of probiotics as an adjunct significantly reduced the mean duration of diarrhea (MD 24.76 hours; 95% CI 15.9 to 33.6 hours, p value <0.0001, I^2=97.1%) and reduced stool frequency on the second day of illness (MD 0.80; 95% CI -1.14 to 0.45, p value <0.0001, I^2=75.4%).[5] Two meta-analyses similarly showed that probiotics significantly prevented VAP among critically ill non-COVID-19 patients (OR 0.70; 95% CI 0.52 to 0.95, p value =0.02, I^2=46% and RR 0.74; 95% CI 0.61 to 0. 90, p value =0.002, I^2=19%).[7,8] 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 were also reported from intake of probiotics.[9] There were also rare reports of immunocompromised patients developing invasive disease from probiotic use.[10]

Honey

Honey was approved by the World Health Organization and the American Academy of Pediatrics (AAP) as a potential treatment to soothe the throat and provide relief for symptomatic cough in children who are older than one year.[11,12] Honey has been reported to have antimicrobial effects through its antioxidant properties and enhancement of cytokine release.[13] However, honey may cause gastrointestinal symptoms, and nervousness or hyperactivity in children.[14] Although generally safe, honey should not be given to children younger than 12 months due to risk of botulism or floppy baby syndrome.[3]

Escin

Escin is a dietary supplement from *Aesculus hippocastanum* or horse chestnut extract investigated to have anti-inflammatory, anti-edematous, venotonic, and endothelial protective properties.[7] In an in-vitro study, escin was one of the active compounds identified to have in-vitro activity against SARS virus and Vero E6 cells.[15,16] Minimal adverse events were reported with intake of escin including gastrointestinal complaints, dizziness, nausea, headache, and pruritus.[17]

OBJECTIVES

For this rapid review, our objective is to gather and summarize evidence on the effectiveness of 3 adjunctive treatment: probiotics, honey, and escin in the management of COVID-19.

METHODS

Research articles were searched in MEDLINE, Cochrane, Clinicaltrials.gov, and Chinese Clinical Trial Registry. Gray literature was searched in MedRxIV, BioRxIV, and ChinaXIV. The search was conducted up to May 15, 2020. The keywords and MeSH terms used were "probiotics", "escin", "honey", and COVID-19 related terms. Combinations of these keywords with Boolean operators were also used (Appendix 2). 84 potential studies were found using the terms stated above. Articles were selected based on the research questions: should probiotics, honey or escin be used in the prevention or treatment of COVID-19?

The study selection criteria included articles in English language that meets the PICO criteria. population: COVID-19 patients of any age, with any comorbidities, any severity; intervention: 1) probiotics, honey, and escin, any dose, any duration; used as prevention or treatment of SARS-COV-2 infection; comparator: placebo, any active control, no intervention; outcomes: any clinical outcome; study design: randomized controlled trials (RCTs), non-randomized studies, observational studies (e.g. cohort, case-control, cross-sectional, case report, case series).

Screening by one reviewer excluded 64 articles. Two independent reviewers assessed the eligibility of twenty-one full-text articles and clinical trials. One observational study and nine clinical trial proposals were included in this rapid review.

The cohort study was appraised using the guide questions from the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort Studies.[18]

DISCUSSION OF INCLUDED STUDIES

We found no completed clinical trials on the efficacy of probiotics, honey or escin among COVID-19 patients.

One retrospective cohort observational study by Jiang et al. described the outcomes of 55 COVID-19 patients who were receiving a variety of treatment regimens, including probiotics, at Wuxi, Jiangsu Province, China.[19] All 55 patients received α-interferon inhalation and lopinavir-ritonavir tablets. Twenty-six (n=26/55) patients received supplementation with probiotic tablets. Other medications given included arbidol, chloroquine, antibiotics, thymosin, intravenous steroids, intravenous immunoglobulins, and low molecular weight heparin. 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 (Appendix 3).

Ongoing Studies

We found five registered clinical trials and one observational study investigating the benefits of probiotics, one registered trial for honey, and two for escin, for patients with COVID-19. (Appendix 4).

RECOMMENDATIONS FROM OTHER GUIDELINES

WHO Interim guidelines, CDC interim guidelines, Infectious Diseases Society of America COVID-19 treatment guidelines, American Thoracic Society did not give any recommendation on the role of probiotics, honey or escin in patients with COVID-19.[20-23]

CONCLUSION

A low-quality observational study that described the use of probiotics among COVID-19 patients showed clinical improvement and no mortality. We found no evidence for the use of honey or escin among patients with COVID-19. Further clinical studies are needed to justify use of these traditional interventions for COVID-19.

Declaration of conflict of interest

No conflict of interest

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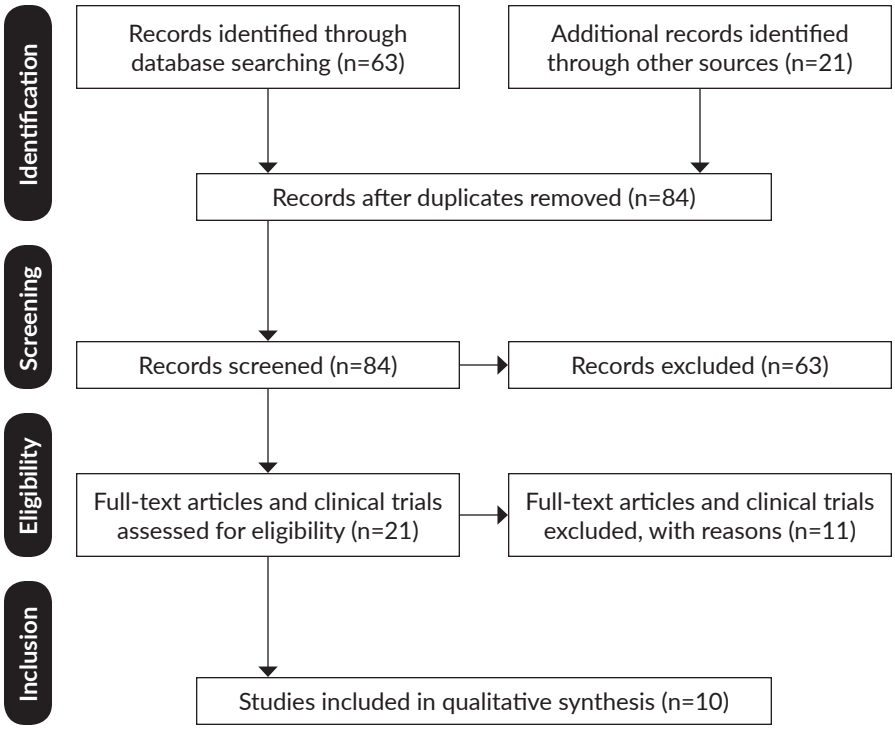
APPENDICES

Appendix 1. Partial List of Probiotics in the Philippine Market

Probiotic	Formulation
BioBita	Per g Lactobacillus sporogenes 25 mg, Clostridium butyricum 5 mg, Bacillus subtilis 3 mg, dried yeast 50 mg, dibasic Ca phosphate 20 mg, ascorbic acid 5 mg, thiamine nitrate 0.3 mg, riboflavin 0.2 mg, nicotinamide 0.1 mg
Bioplus	Probiotics (8 strains culture) 60 mg, Lactobacillus acidophilus 7.5 mg, Bifidobacterium bifidus 7.5 mg, Bifidobacterium longum 7.5 mg, Lactobacillus casei 7.5 mg, Bifidobacterium infantis 7.5 mg, Lactobacillus rhamnosus GG 7.5 mg, Lactobacillus paracasei 7.5 mg, Lactobacillus lactis 7.5 mg, Perilla leaf extr 15 mg, oligosaccharide 11.1 mg, pine bark extr 4.5 mg
Cranbiotix	Cranberry extr (providing proanthocyanidins 72 mg) 240 mg, lyophilized lactobacilli culture (providing not <2 billion CFU consisting L. rhamnosus 3.34 mg, L. acidophilus 10 mg, L. casei 1.336 mg) 36 mg
Erceflora ProbiBears	Lactobacillus acidophilus, Bifidobacterium lactis
Fauna Plus	Probiotics: Lactobacillus acidophilus, Saccharomyces boulardii, Lactobacillus rhamnosus, Lactobacillus plantarum, Lactobacillus reuteri, Lactobacillus casei, Bifidobacterium bifidum
Flora IB	Each cap Probiotics 10 billion cfu: Lactobacillus acidophilus 2 billion cfu, Saccharomyces boulardii 2 billion cfu, Lactobacillus rhamnosus 1.5 billion cfu, Lactobacillus plantarum 1.5 billion cfu, Lactobacillus reuteri 1 billion cfu, Lactobacillus casei 1 billion cfu, Bifidobacterium bifidum 1 billion cfu
Flotera	Lactobacillus reuteri DSM 17938
Floracap	Lactobacillus rhamnosus 1 billion CFU, Lactobacillus reuteri 1 billion CFU
Gastro Flora	Lactobacillus casei 1.6 billion, Lactobacillus rhamnosus 1.6 billion, Lactobacillus acidophilus 0.4 billion, Bifidobacterium longum 0.4 billion
GD Probiotic Food	Lactobacillus gasseri ATCC, Lactococcus thermophilus, Streptococcus lactis, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus arabinosus, Lactobacillus leishmannii, Lactobacillus thermophilus, Leuconostoc mesenteroides, Streptococcus cremoris, Lactobacillus acidophilus, Lactobacillus delbrueckii, Lactobacillus caucasicus, Lactobacillus musicus, Lactobacillus plantarum, Lactobacillus lactis, vit B1, vit B2, vit B3, vit B6, vit B12, folic acid, niacinamide, pantothenic acid, biotin, vit C, β-carotene, inositol, Fe, Ca, K, 19 amino acids, 4 organic acids, minerals
GI Pro Tec	GI Pro Tec 1+ Lactobacillus rhamnosus LGG. GI Pro Tec 7+ Bifidobacterium 30 mg, fructo-oligosaccharide 4,210 mg, silicon dioxide 60 mg, fructose 1,700 mg
Lactodep	Per Lactodep cap Bifidobacterium lactis, Lactobacillus rhamnosus, Lactobacillus bulgaricus, vit B3, vit B5, vit B6, vit B2, vit B1, vit B9, vit B12. Per Lactodep Junior oral drops Lactobacillus rhamnosus SD5217 2 billion CFU, Bifidobacterium lactis SD5219 2 billion CFU, Lactobacillus reuteri DSM26866 1 billion CFU
LactoZinc Probiotics	Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus casei, Bifidobacterium infantis, Bifidobacterium longum, Lactococcus lactis, oligosaccharide, Zn, lactose, maltodextrin, citric acid, sucralose
Lobun Plus	Probiotic mixture & lactic acid bacillus (Strep thermophilus, Lactobacillus acidophilus, Bifidobacterium longum, Lactic acid bacillus) 45 billion cells
Normagut	Saccharomyces boulardii 250 mg (equiv to Saccharomyces cerevisiae 2.5 billion organisms)
PROBx	Bifidobacterium 12
Protexin	Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, Lactobacillus bulgaricus, allicin, fructooligosaccharide (FOS)
Protexin Bio-Kult	Bacillus subtilis 5.4 mg, Bifidobacterium bifidum 1.3 mg, Bifidobacterium breve 1.3 mg, Bifidobacterium infantis 1.3 mg, Bifidobacterium longum 1.3 mg, Lactobacillus acidophilus 1.3 mg, Lactobacillus delbrueckii spp bulgaricus 1.3 mg, Lactobacillus casei 1.3 mg, Lactobacillus lactis 1.3 mg, Lactobacillus plantarum 4.5 mg, Lactobacillus rhamnosus 2.7 mg, Lactobacillus helveticus 1.3 mg, Lactobacillus salivarius 1.3 mg, Streptococcus thermophilus 1.3 mg
Protexin Restore	Per 1 billion CFU/sachet Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus, fructooligosaccharide (FOS)
Protexin Vitality	Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Lactobacillus acidophilus, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus bulgaricus, vit C 40 mg, fructooligosaccharide (FOS)
Provinorm	Lactobacillus acidophilus 2 billion cfu, Lactobacillus rhamnosus 2 billion cfu, Lactobacillus reuteri 2 billion cfu, Lactobacillus plantarum 1 billion cfu, Lactobacillus casei 1 billion cfu, Lactobacillus fermentum 1 billion cfu, Bifidobacterium bifidum 1 billion cfu, fructooligosaccharide 100 mg
Provita Probiotics	Probiotic complex (Bifidobacterium lactis, Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus plantarum, Bifidobacterium breve, Bifidobacterium longum, Lactobacillus paracasei, Lactobacillus rhamnosus, Streptococcus thermophiles, Lactobacillus delbrueckii ssp. Lactis, Lactobacillus helveticus, Lactobacillus reuteri, Bacillus coagulans, Bacillus mesentericus), vit B-complex
ProZinc	Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus casei, Bifidobacterium infantis, Bifidobacterium longum, Lactococcus lactis, oligosaccharide, Zn, lactose, maltodextrin, citric acid, sucralose
Renadyl	Strep thermophilus 15 billion CFU, Lactobacillus acidophilus 15 billion CFU, Bifidobacterium longum 15 billion CFU

Appendix 2A. Literature search

Database	Search strategy / search terms	Date and time of search	Results	
			Yield	Eligible
Medline (COVID 19/MERS)	Search: (((Aescin or Escin) OR (Honey) OR (Probiotics))) AND ((((("Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 OR Human coronavirus 229E OR HCoV-229E OR Human coronavirus NL63 OR HCoV-NL63 OR human coronavirus OC43 OR HCoV-OC43 OR Human coronavirus HKU1 OR HCoV-HKU1 OR Swine Flu OR Camel Flu OR Severe acute respiratory syndrome coronavirus OR "Middle East Respiratory Syndrome Coronavirus" OR MERS#COV OR MERS Coronavirus OR MERS OR SARS))))	May 15, 2020 21:00 GMT+8	46	0
Cochrane Database	Search Name: Probiotics, Honey, Escin - Supplement Rapid Review - MERS, Influenza, COVID Date Run: 15/05/2020 02:55:23 Comment: Date: 5/15/2020 ID Search Hits #1 ("Honey"):ti,ab,kw 912 #2 MeSH descriptor: [Honey] explode all trees 154 #3 ("Probiotic"):ti,ab,kw 4734 #4 MeSH descriptor: [Prebiotics] explode all trees 272 #5 MeSH descriptor: [Probiotics] explode all trees 1942 #6 ("Escin"):ti,ab,kw 69 #7 MeSH descriptor: [Escin] explode all trees 54 #8 #1 OR #2 OR #3 OR #4 #5 OR #6 OR #7 5727 #9 Coronavirus 282 #10 MeSH descriptor: [Coronavirus] explode all trees 13 #11 MERS 60 #12 SARS 295 #13 COVID 291 #14 MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees 107 #15 MeSH descriptor: [SARS Virus] explode all trees 9 #16 H1N1 1309 #17 MeSH descriptor: [Influenza A virus] explode all trees 841 #18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 2263 #19 #8 AND #18 17		17	0
ClinicalTrials.gov	COVID OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 Other term: Probiotics Honey Escin		9	3 (1) (1) (1)
Chinese Clinical Trial Registry	Disease: coronavirus Intervention Probiotic Honey Escin		9	6
MedrXIV/ BioRXIV	COVID Interventions Probiotics Honey Escin		3	1
ChinaXIV	COVID Interventions Probiotics Honey Escin		0	0



Appendix 2B. PRISMA 2009 Flow Diagram.

Appendix 3A. Characteristics of included trials

Author/Title	Journal/ Year	Study design	Country	Disease condition	Population size	Intervention Group(s)	Comparison Group(s)
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	

Primary outcomes	Key Secondary Outcomes	Key Findings	Reported AE	Limitations
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	None	Small sample size

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JBI Critical Appraisal Checklist for Cohort Studies

Reviewer Marquis Go Joson Date

Author Year Record Number

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.

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☒	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☒	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☒	☐	☐
4. Were confounding factors identified?	☐	☒	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☒	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☒	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☒	☐
11. Was appropriate statistical analysis used?	☐	☐	☒	☐

Overall appraisal: Include ☐ Exclude ☒ Seek further info ☐

Comments (Including reason for exclusion)

Very Low Quality of Evidence: no baseline data given to determine whether those given probiotics or none were comparable

Appendix 3B. Critical Appraisal Checklist

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

Appendix 4. Characteristics of clinical trials

Probiotics (6)

No.	Clinical Trial ID/ Title	Status	Start & estimated primary completion date	Study design	Country	Population	Intervention	Comparison Group(s)	Outcomes
1	Evaluation of the Probiotic Lactobacillus Coryniformis K8 on COVID-19 Prevention in Healthcare Workers NCT04366180	Recruiting	2020-04-24 to 2020-06-01	RCT	Spain	Healthcare Personnel Exposed to COVID-19 (n=314)	1 capsule of Lactobacillus K8 per day ($3x10^9$ cfu/day) during 2 months	one placebo capsule per day during 2 months	Incidence of SARS CoV-2 infection in healthcare workers Incidence of hospital admissions caused by SARS-CoV-2 infection Incidence of ICU admissions caused by SARS-CoV-2 infection Incidence of pneumonia caused by SARS-CoV-2 infection Incidence of oxygen support requirement caused by SARS-CoV-2 infection Incidence of gastrointestinal symptoms caused by SARS-CoV-2 infection Days with body's temperature > 37.5 °C Days with cough Days with fatigue Medical treatment
2	Study for the application of novel coronavirus pneumonia (COVID-19) intestinal tract toxicity in diagnosis and its prognostic effect ChiCTR2000032686	Not yet recruiting	2020-05-04 to 2021-12-31	Observational	China (Wuhan)	patients 18-65 years old diagnosed with COVID-19 with diarrhea or positive fecal virus test within 3 months before enrollment	"regular diet" probiotic intervention (n=150)	rifximine intervention none	Changes of microbiota, virology and metabonomics, evaluation of overall symptom relief, frequency of defecation, abdominal distension (with bowel sounds, accompanied by increased gas or frequent belching), evaluation of urgency of defecation, use of remedial drugs, Quality of life (IBS-QOL scale)
3	A randomized, open, controlled trial for diammonium glycyrrhizinate enteric-coated capsules combined with vitamin C tablets in the treatment of common novel coronavirus pneumonia (COVID-19) ChiCTR2000029768	Recruiting	2020-02-12 to 2020-05-12	RCT	China (Wuhan)	Inpatients aged 18-75 y/o; Confirmed with common 2019-nCoV pneumonia	Diammonium Glycyrrhizinate Enteric-coated Capsules combined with vitamin C tablets + Standard antiviral treatment (n=30)	Standard antiviral treatment (n=30)	Primary: Time to clinical recovery Secondary: Time to improvement of virus symptoms Length of hospitalization (healed/discharged) Time to conversion of 2019 nCOV RNA results from RI sample Rate of preventing mild from shifting to moderate or severe Change in lung inflammation absorption Time to temperature recovery;
4	A prospective, multicenter, open-label, randomized, parallel-controlled trial for probiotics to evaluate efficacy and safety in patients infected with 2019 novel coronavirus pneumonia (COVID-19) ChiCTR2000029974	Recruiting	2020-02-09 to 2020-08-31	RCT	China (Shandong) 10 secondary and tertiary hospitals	Diagnosed with mild or moderate novel coronavirus pneumonia (NCP) or those with severe NCP but can take medicines orally or via stomach tube	Live Clostridium Butyricum Capsules and Live Bacillus Coagulans Tablets (n=150)	Regular medication for NCP (n=150)	All-cause mortality Frequency of mechanical ventilation
5	Evaluation of the effect of taking Newgen beta-gluten probiotic composite powder to nutrition intervention of patients with novel coronavirus pneumonia (COVID-19) ChiCTR2000030897	Recruiting	2020-02-11 to 2021-05-1	RCT	China (Zhejiang)	Aged 18 or older, and meet the diagnostic criteria of Diagnosis and Treatment Scheme of Novel Coronavirus Infected Pneumonia published by the National Health Commission	Newgen beta-gluten probiotic composite powder (n=10)	Routine medicines and food (n=10)	Length of hospital stay Length from the day of admission to the day returning to normal body temperature, from admission to two consecutive negative results of respiratory pathogenic nucleic acid test (sampling interval of at least 1 day), and from admission to the chest CT shows significant improvement
6	Evaluation of the effect of taking tricholoma matsutake, cannabis sativa capsule and dendrobium candidum to nutrition intervention of patients with novel coronavirus pneumonia (COVID-19) during convalescence ChiCTR2000030920	Recruiting	2020-02-1 to 2021-05-1	RCT	China (Zhejiang)	Aged ≥18 years old; the person, who is diagnosed as COVID-19 according to the 'Diagnosis and treatment of novel coronavirus pneumonia (trial edition 5)', is treated with de-isolation and meets hospital discharge criteria	Tricholoma matsutake group (n=25) Cannabis sativa capsule group (n=25) Dendrobium candidum group (n=25)	Routine drugs and food (n=25)	Recurrence rate of COVID-19

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

Appendix 4. Characteristics of clinical trials *(continued)*

Honey (1)

No.	Clinical Trial ID/ Title	Status	Start & estimated primary completion date	Study design	Country	Population	Intervention	Comparison Group(s)	Outcomes
1	Efficacy of Natural Honey Treatment in Patients With Novel Coronavirus NCT04323345	Recruiting	2020-04-15 to 2021-01-15	Randomized, Controlled, Single Masked , Investigator Initiated, Multi-center Trial	Egypt	5 - 75 yrs old COVID-19 patient (clinically or PCR confirmed)	Natural Honey supplement 1gm/kg/day divided into 2 to 3 doses for 14 days either orally or through nasogastric tube + standard of care	Standard Care: Supportive measures and lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate or Hydroxychloroquine or oseltamivir with or without azithromycin	Rate of recovery from positive to negative swaps [Time Frame: 14 days] Fever to normal temperature in days [Time Frame: 14 days] Resolution of lung inflammation in CT or X ray [Time Frame: 30 days]

Escin (2)

No.	Clinical Trial ID/ Title	Status	Start & estimated primary completion date	Study design	Country	Population	Intervention	Comparison Group(s)	Outcomes
1	Escin in Patients with Covid-19 Infection NCT04322344	Recruiting	2020-03-23 to 2020-06-30	Non-randomized, double-blind clinical trial	Italy	18 -78 yrs old COVID-19 poor response to standard treatment	Escin tablet 40mg for 12 days Sodium Escinate 20mg IV/day for 12 days (horse chestnut extract) + Standard therapy	Standard therapy (antiviral drugs)	All-cause Mortality rate [Time Frame: up to 30 days]
2	A randomized, parallel controlled trial for the efficacy and safety of Sodium Aescinate Injection in the treatment of patients with pneumonia (COVID-19) ChiCTR2000029742	Recruiting	2020-02-10 to 2020-12-31	Randomized, controlled trial Blinding not stated	China (Wuhan)	Patients Aged 18 to 70 years, diagnosed COVID-19 (mild and severe)	Mild COVID-19: Standard therapy + Sodium Aescinate for Injection (n=30) Severe COVID-19: Standard therapy + Sodium Aescinate for Injection (n=10)	Mild COVID-19: standard therapy (n=30) Severe COVID-19: Standard therapy (n=10) Standard therapy + glucocorticoids (n=10)	CT scan images, Safety, Blood biochemistry, Viral nucleic acid load