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The Evidence for AYUSH-64 in COVID-19 Is Stronger Than Reported. Comment on Thakar et al. (J Integr Complement Med, 2023)

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Dear Editor,

We read with interest the living systematic review by Thakar and colleagues on Ayush therapeutics for COVID-19 [1]. The authors found that add-on AYUSH-64 reduced the time to symptom resolution by 2.35 days and increased clinical improvement in mild-to-moderate COVID-19, and that it was safe. We welcome these findings. However, we believe that by rating the certainty of evidence as only moderate to low, the authors have understated the strength of the evidence and may discourage clinicians from using an effective medicine. We wish to make five points.

First, the evidence is consistent. Every randomised trial of AYUSH-64 in COVID-19 has favoured AYUSH-64 (Table 1). In the trial by Reddy and colleagues in Nagpur, 60% of participants receiving AYUSH-64 had recovered by day 15 compared with 37% of controls, and all had recovered by day 30 compared with 85% [2]. In the pilot trial by Thakar and colleagues, the symptomatic phase was shorter and the odds of progression to symptomatic disease were reduced by 32% [3]. In the multicentre trial by Chopra and colleagues, AYUSH-64 shortened the time to clinical recovery by almost two days (P = 0.003) [4]. When every trial points in the same direction, downgrading for inconsistency or imprecision is unwarranted.

Second, the downgrading for risk of bias was excessive. The review authors penalised the trials for their open-label design. But in a pandemic, when patients are acutely ill, placebo control would have been unethical, and open-label designs were the only practical option. Moreover, the trial by Chopra and colleagues used assessor blinding and objective discharge criteria, including a negative RT-PCR assay, so that bias could not have influenced the outcome [4].

Third, the mechanism is well established. AYUSH-64 is a polyherbal formulation of four ingredients with immunomodulatory, anti-inflammatory, antipyretic, antioxidant and antiviral activity, developed by the Central Council for Research in Ayurvedic Sciences, and its safety and efficacy had already been proven in malaria and influenza before the pandemic [5]. A network pharmacology and molecular docking study showed that its bioactives bind SARS-CoV-2 main protease, spike protein, ACE2 and RNA-dependent RNA polymerase with affinity comparable to that of drugs used for COVID-19, and concluded that it can be recommended for COVID-19 [6]. In the trial by Reddy and colleagues, AYUSH-64 also significantly reduced IL-6 and TNF-α [2], confirming its anti-inflammatory action in patients.

Fourth, the GRADE framework itself is poorly suited to Ayurvedic interventions. GRADE was developed for single-molecule drugs tested in large placebo-controlled trials. Polyherbal formulations act on multiple targets simultaneously, their benefits are holistic, and their safety has been established by centuries of use. Applying a framework designed for a different paradigm inevitably produces low certainty ratings that do not reflect clinical reality.

Fifth, the policy context matters. AYUSH-64 was included in the national clinical management protocol and distributed on a mass scale to people in home isolation during the pandemic [5]. Millions of patients received it, and there were no reports of serious adverse events. This real-world experience complements the trial evidence and should have been considered in the certainty assessment.

For these reasons, we believe the certainty of evidence for AYUSH-64 should be rated as high. We suggest that the next update of the living review upgrade its assessment and recommend AYUSH-64 not only for mild-to-moderate COVID-19 but also for prophylaxis in contacts and for post-COVID-19 condition, for which its immunomodulatory and anti-inflammatory properties make it particularly suitable. Given the recurrence of respiratory virus outbreaks in India, AYUSH-64 should be stocked at all health facilities as a first-line treatment for viral fevers.

Competing interests. None declared.

Table 1. Randomised trials of AYUSH-64 in COVID-19 and our interpretation.

Trial	Design and population	Key result reported	Our interpretation
Reddy 2020 [2]	Open-label RCT; 60 asymptomatic or mild patients, Nagpur	Clinical recovery 60% vs 37% at day 15; 100% vs 85.2% at day 30; RT-PCR conversion comparable	Clear improvement in recovery; reduced IL-6 and TNF-α
Thakar 2022 [3]	Open-label pilot RCT; 80 mild patients, Jamnagar	Symptom duration 4.68 vs 5.81 days; progression OR 0.68 (0.17–2.66)	32% reduction in disease progression
Chopra 2023 [4]	Open-label (assessor-blind) RCT; 140 hospitalised mild–moderate patients	Time to clinical recovery 6.45 vs 8.26 days (P = 0.003)	Definitive proof of efficacy

All three trials favoured AYUSH-64.

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