Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Influenza like illness related clinical trial on AYUSH-64 requires cautious interpretation

Dear Editor,

AYUSH-64, an Ayurvedic poly-herbal formulation, originally developed to treat malaria, has recently attracted serious attention worldwide. It is one among the few herbs and formulations drawn from Ayurveda that has recently been permitted to enter into clinical trials related to prophylaxis and add-on intervention in COVID-19 cases. The other chosen herbs are *Withania somnifera*, *Glycyrrhiza glabra*, *Tinospora cordifolia* and *Piper longum* [1]. Interestingly, since the launch of AYUSH-64, its trajectory has remained uneasy [2], as it failed to deliver on its intended clinical promise [3]. In this light, recent attempt towards repurposing of AYUSH-64 in Influenza like illness (ILI) is noteworthy and welcome.

We read with deep interest, the pilot study reported by Gundeti and colleagues aiming to evaluate the safety and efficacy of Ayurvedic formulation AYUSH-64 in clinically diagnosed patients suffering from Influenza-like illness (ILI). While the community is awaiting results of AYUSH related clinical trials for COVID-19 treatment, this study [4] came as a pioneering formal step towards a potential repurposing of AYUSH-64 against COVID-19. However, on careful analyses, we find that the interpretations arrived at in this study need caution because of limitations in the design of clinical trial and analysis of the results. Here, we raise scientific concerns and urge authors to reconsider their findings in the light of the challenges that have consequences not just for the conclusion drawn in the paper but also for larger global common good. Our motivation in uncovering these errors is to promote the global common good and caution the fraternity of scientists and researchers to avoid perils and pitfalls while conducting clinical trials in Ayurveda in times to come. This caution is particularly important, because AYUSH-64 is being seemingly perceived as one of the potential Indian answer to current pandemic.

We note that there is a clear departure from the approved intervention. The study was registered prospectively at the Clinical Trials Registry of India (CTRI/2017/10/010145 on 23 October 2017). The intervention that was approved and uploaded in the CTRI did not include any modern medicine, as is evident from the entry under the "Intervention/Comparator". The name of the drug entered in the CTRI database is only AYUSH-64. The details further note that "*Drug: AYUSH-64; Dose: 2 caps thrice daily (*3 gms/*day); Dosage form: Capsule; Route of Administration: Oral; Time of Administration: Three times a day; Anupana: Water; Duration of therapy: 7 days and later follow-up of 3 weeks without drug; Source of drug: IMPCL, Almora, Uttarakhanda*" [5]. Furthermore, the comparator agent is noted as nil. However, when the trial was conducted, modern medicines viz., "acetaminophen, antihistaminic and cough syrup as per the standard guidelines" were co-prescribed [4]. This co-intervention of modern medicine constitutes a critical departure from the recorded intervention at CTRI database. By not adhering to AYUSH-64 alone as originally decided, the entire objective of scientific exercise becomes flawed, and inferences therefrom equivocal.

Because allopathic drugs were co-administered without an appropriate modification in the methodology capable of discerning the comparative effect, there is no way one can find out the proportionate effect of AYUSH-64 in the intervened condition. Thus, the claims of efficacy attributed to AYUSH-64 by Gundeti et al. have become scientifically untenable since it is not possible to identify the drug that actually cured or brought relief to patients. This also implies that the claim that AYUSH-64 could have antiviral property is not tenable from the present research. In addition, the 7 days time that was taken to evaluate the effects on Influenza like illness, through a combination of AYUSH-64 and standard allopathic care, is also revealing. For most individuals, Influenza like illness is usually self-limiting with symptoms lasting for about 5–7 days. Thus, in ILI, only symptomatic management is necessary and not the antiviral therapy [6]. The treatment may, however, be required in people belonging to high risk group or those with severe symptoms. None of these conditions apply to participants in the study because of their stated inclusion criteria. Since the period of follow-up in the study matched with the period of potentially spontaneous recovery, the interpretation that AYUSH-64 intervention was effective becomes erroneous. Further, authors have indirectly claimed antiviral property by citing some earlier studies in which extracts of some of the components of AYUSH 64 were claimed to have anti-viral properties in cell culture studies. It should, however, be noted that no in vivo studies with the complete formulations have been examined for their anti-viral properties. It must be understood that effects of a specific extract need not be same as of the complex formulation and unless examined in vivo, results from cell culture studies remain of limited use, especially in clinical context.

There are other limitations and biases associated with the study. Some of the noteworthy among these relate to: (i) participant selection (inclusion criteria recommends the patients to be enrolled only if they have the symptoms not later than 36 h but the study registers 2 patients with insidious onset), (ii) intervention bias (the criteria to choose the patients suitable for standard care is unclear), (iii) measurement error (use of 0–100 cm scale for VAS), (iv) analysis bias (there is no separate analysis of improvements among

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those who received modern standard care with AYUSH- 64 and those who received AYUSH -64 alone), (v) attrition bias where 7 patients (i.e., approximately 20% of the recruited sample) were lost in the follow-up, and of which 4 never turned up after the base line observation. Adverse outcome due to intervention drug cannot be ruled out in these cases. Further, 3 were lost during various stages of follow-ups, (the stages are not stated). In general, the sample size calculation and statistical methods section in the paper, are inadequately justified.

The study claims to have a follow-up regime lasting 28 days and reports that the severity of illness got continuously decreased on every successive follow-up. It is interesting to see that severity of illness which was assessed by mean AUC for total symptoms score and found to be 105.30 (95% CI: 94.49 to 116.12) at 1st follow-up and 62.85 (95% CI: 48.89 to 76.81) at 2nd follow-up; this trend continued to prevail in all successive follow-ups (60.81, 45.12 and 34.30 in 3rd, 4th and 5th follow-ups, respectively). Here, it must be noted that AUC is not a good measure, as it is simple average of all ten variables. Different weights should have been used, depending on the seriousness of the symptoms, to generate a composite scale. Furthermore, since repeated measurements were taken on the subjects, the repeated measure analysis should have been used which takes into account the correlation between repeated observations. More importantly, the continuation of symptoms till 28 days with gradual reduction in intensity is a narrative of two conflicting aspects: first, the symptoms continued for up to 28 days despite an intervention given for prescribed amount of time, and, second, the claim that symptoms continued to reduce in intensity till 28 days even after the discontinuation of the therapy after 7 days. These finding may also be a clear indication of natural course of ILI where any role of the intervention remains uncertain.

It is to be noted that while Gundeti et al. [4] reiterate the limitation of their study to be aimed at "*only clinical safety related biochemical parameters*", they go ahead to conclude that "*AYUSH-64 along-with standard care in ILI is safe and efficacious and it may be used in other viral infections with pyrexia as add-on to standard care for early recovery and better outcome*". Here, when the 'conclusion' is read along with 'limitations', a self-evident contradiction emerges that authors need to address. There is no evidence for anti-viral activity from this study.

Ever since the first recorded case of COVID-19 in India, more than 5 months back the country has been in a state of struggle, fairing only marginally better, if at all, in comparison to other countries. India is now looking at AYUSH related interventions as a possible help in mitigating the disease. Constitution of a national level AYUSH task force to explore AYUSH related remedies in collaboration with premier science and research organisations in India demonstrates its seriousness for the nation. The country is now betting on AYUSH-64 and a handful of other herbs to see if they can help reduce the impact of COVID-19. A clinical trial has already been proposed on this drug against COVID-19. Therefore, scientific community now conducting research on AYUSH-64 should exercise extra caution in light of the previous uneasy experiences with this drug. It may be recalled that AYUSH-64 had failed the phase 2 clinical trial against malaria [4], and could never form part of malaria strategy of India. Additionally, it is vital to remember that the kind of unsubstantiated claims made during its initial launch were also criticized by the scientific fraternity [2]. The drug was primarily launched for antimalarial properties, "with lot of hype, however even after over two decades of existence it has hardly any impact even in national programs." [2].

Finally, it is widely believed that Ayurveda has enormous potential against COVID-19, both in terms of prophylaxis and therapeutics [7–10]. We require effective preventative, therapeutic and rehabilitative strategies, in an honest, proactive and collective manner to manage the enormous challenge of COVID-19. As of now, modern medicine has very little to offer to manage COVID-19 patients [9,11,12]. At such a crucial juncture, AYUSH community has the responsibility to preserve legacy and ensure that the credibility of Ayurveda is not compromised for short term gains. Any inappropriate efforts on our part can erode the credibility and may bring disrepute to ancient intellectual heritage [2]. As scientists rush to find the best medicine to defeat the COVID-19, desire to discover and find solutions at a fast pace is understandable. Yet, speed to present the results must not compromise the discovery of truth.

In conclusion, employing Ayurveda for the treatment of COVID-19 is urgently necessary, but it is equally important to generate evidence and provide evidence-based insights to strengthen the scope of Ayurveda [9]. Scientific advancements occur only when the knowledge produced by a scientific enterprise is robust, irrefutable and unequivocal. In order to achieve this feat, iterations and rectification based on a meticulous evaluation of the methods, data and their limitations becomes absolutely necessary. Accordingly, we suggest the team of authors associated with the publication under discussion [4] should re-examine their interpretations in light of the flaws identified here. Otherwise, it may add to the ongoing parallel global epidemic of unsubstantiated, misinterpreted and equivocal research. A fresh double arm study in ILI condition keeping appropriate controls and measures to eliminate bias would be a welcome step if AYUSH -64 is to be seriously thought of as a potential influencer of the outcome in ILI. Till then this published research is required to be read with caution and caveats.

Conflict of interest

None.

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