Title

AYUSH interventions for COVID-19 - a living systematic review and meta-analysis

[First report]

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Abstract

Background

In India, alternative and complementary therapies (AYUSH medicines) are utilized in COVID-19 management extensively. This study was planned to assess the prophylactic and therapeutic effectiveness of AYUSH interventions on COVID-19 through a living systematic review and meta-analysis approach.

Methods

Different databases like Pubmed; the Cochrane central register of controlled trials; WHO COVID-19 database; the central trial registry - India; Digital Helpline for Ayurveda Research Articles and AYUSH research portal, and pre-print repositories were searched with appropriate search strategies from 1st December 2019 to 1st April 2021. Randomized clinical trials, Non-Randomized Studies of Interventions conducted on the AYUSH system of medicine aimed at either prevention or treatment were included. Clinical improvement, WHO ordinal scale, viral clearance, incidences of COVID-19 infection, and mortality will be considered as primary outcomes. Secondary outcomes will be the use of O_2 therapy or mechanical ventilator, admission to high dependency unit or emergency unit, duration of hospitalization, the time to symptom resolution, and adverse events. Data will be synthesized, and the risk of bias will be assessed with RevMan 5.4 tool. The risk of bias of included studies was evaluated by RoB-2 and ROBINS-I tools, and the certainty of the evidence ranked through the GRADE approach.

Results

Of 2,977 studies retrieved, only 12 studies were included in the systematic review. In a moderately certain trial on standalone AYUSH versus Standard care, viral clearance was hastened in the standalone AYUSH group. Add-on AYUSH had shortened time to symptom resolution by about two days compared to standard care with moderate certainty. However, Add-on AYUSH intervention may hasten clinical improvements but has little to no effects on viral clearance. AYUSH prophylaxis may reduce the risk of COVID-19 with low certainty.

Conclusion

Rational use of integrated or standalone AYUSH interventions in mild to moderate COVID-19 patients may provide therapeutic benefits. The effect of AYUSH prophylaxis in the reduction of incidence of COVID-19 in high-risk populations is uncertain. The effect estimates may be

changed with additional evidence in upcoming updates.

Protocol registration: The study has been registered in PROSPERO (CRD42021244831)

Keywords: Ayurvedic Medicine, AYUSH, Complementary therapies, COVID-19, Systematic review and meta-analysis

1. Introduction

As of 21st January 2022, Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) has infected over 328 million people, with a mortality toll approaching 5.6 million.[1] As novel variants of SARS-CoV-2 continue to arise, public health professionals are concerned about their transmissibility, re-infection rates, illness severity, and treatment effectiveness.[2] Researchers throughout the globe are working persistently to understand better, cure, and eradicate COVID-19, resulting plethora of COVID-19 studies available, many of which are ongoing. As no promising treatment is available, people are opting for alternative treatment either for prevention or cure.[3] Countries such as China and India are testing the efficacy of their traditional medicines on COVID-19, either as an adjunct or standalone in management of COVID-19.[4,5,6] In India, Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) are five alternative and complementary therapies that have long been popular in society and are frequently utilized in COVID-19 management.[7]

Since the pandemic, the ministry of AYUSH (the Indian system of medicine's regulatory authority) released guidance based on an advisory panel of AYUSH experts and preliminary evidence.[8] Traditional herbs and measures having anti-viral, anti-bacterial, and anti-microbial properties, which have been around for decades for various respiratory ailments, were advocated.[9] Plenty of the recommended formulations, such as Ayush 64, Chyawanprash, Guduchi Ghanavati, Arsenica Album, Kabasura Kudineer, and Nilavembu Kudineer, have undergone scientific studies to determine their prospective preventive or therapeutic impact.[10]

Some AYUSH intervention trials have previously been accomplished and published or are in the process of being published.[11] Clinicians, patients, guideline bodies, and governmental agencies face issues when appraising the evidence of published trials. The findings of such research must be meticulously appraised and summarized through evidence syntheses to ascertain the strength of the evidence.

This study was intended to assess the Traditional System of Indian medicine's (AYUSH system) effectiveness in reducing the incidence, duration, and severity of COVID-19 through a living systematic review and meta-analysis. We intend to monitor continuous evidence and update the review bimonthly if new evidence permits until three updates.

2. Methods

2.1. Criteria for inclusion and exclusion

2.1.1. Study types

All Randomized Clinical Trials (RCTs) and Non-randomized studies of Interventions (NRSI) published in the English language, irrespective of their publication status, were included. Reviews, case reports, case series, opinions were excluded.

2.1.2. Participant types

Participants with risk of COVID-19 exposure or suspected, probable, or confirmed COVID-19 independently of the disease severity, gender, age, or ethnicity were included. The pregnant and lactating female populations were excluded.

2.1.3. Intervention types

Intervention or exposure from the AYUSH system of medicine, either standalone or add-on, aimed at prophylaxis or treatment, irrespective of their dose, dosage form, duration of treatment, number of medications used, were included. Isolated molecules from plant products, phytoconstituents, and nutraceuticals were excluded.

2.1.4. Outcomes measures

For studies intended for therapeutic purposes, primary outcome measures were clinical improvement (closest to 14 days), the ordinal scale for disease severity (closest to 7 days), mortality (up to 60 days), and viral clearance (closest to 07 days). Secondary outcomes were the use of O2 therapy, use of a ventilator (closest to 30 days), admission to high dependency

unit or emergency unit (closest to 30 days), duration of hospitalization, the time to symptom resolution, and adverse events.

For Prophylaxis studies, primary outcome measures were incidences of COVID-19 infections and mortality; and secondary outcomes were symptomatic SARS-CoV2 infection, disease severity, and adverse events.

Clinical improvement has been defined as 'achieving health status of an absence of symptoms attributed to COVID-19 and/or Saturation of Peripheral Oxygen (SpO2) > 93%'. If individual studies reported data for the same or similar outcomes at different times, we included one outcome that provided the most complete information for analysis. Surrogate outcomes were excluded.

2.2. Literature searches

We have searched the following databases, e.g., Pubmed; the Cochrane central register of controlled trials (CENTRAL); WHO COVID-19 database; the central trial registry - India (CTRI); Digital Helpline for Ayurveda Research Articles (DHARA) and AYUSH research portal, and other pre-print repositories viz. Medxiv, SSRN, OSF. These databases were searched from 1st December 2019 to 1st April 2021. Hand searches had been conducted on the reference lists of eligible primary studies.

Search terms were as follows: "COVID - 2019 OR "SARS-CoV-2" OR "NCP" (Novel Coronavirus Pneumonia) OR "Corona Virus Disease-19" OR "COVID-19" AND "Indian Traditional Medicine" OR "AYUSH" OR "Ayurveda" OR "Yoga Naturopathy" OR "Unani" OR "Siddha" OR "Homeopathy." A combination of medical subject headings [MeSH] terms and other text words were used. The summary of search items is summarized in a supplemental file.

2.3. Data collection and extraction

Bibliographic references were managed through the Endnote X9 tool. A pair of reviewers, subsequent to practice and calibration exercises, independently screened all titles and abstracts followed by full texts of trials that were identified as potentially eligible. A third reviewer arbitrated the discord between these reviewers if raised and not solved by discussion.

Reviewers independently extracted data in standardized data extraction form incorporating relevant items. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (state, age, sex, smoking habits, comorbidities, risk level, setting and type of care, and severity of covid-19 symptoms for studies of treatment), intervention/exposure characteristics (name of Medicine, dose, duration), and outcomes of interest (means or medians and measures of variability for

continuous outcomes; the number of participants analyzed and the number of the event for dichotomous outcomes). We updated the status of the publication of pre-print articles once they were published in peer-reviewed journals. These data were entered in Review Manager 5.4 software and cross-checked for accuracy. Authors of the articles were contacted via email and telephonically when any information required for data analysis was missing or ambiguous, and weekly follow-up was done for one month.

2.4. Quality/risk of bias assessment of included studies

The risk of bias was assessed for each study by two reviewers independently. Revised Cochrane tool for assessing the risk of bias RoB-2 was used for RCTs, and Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) was used for Non-Randomized Studies of Interventions (NRSIs) to rate studies at outcome level. Domains for RoB-2 tool[12] were: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in the measurement of the outcome and for in ROBINS-I[13] were: bias due to confounding; bias in the selection of participants; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in the measurement of the outcome; bias in the selection of the reported result. Across these domains, we have rated the risk of bias of studies at i) low risk of bias, ii) some concerns, and iii) high risk of bias. Overall, the risk of bias was rated as low risk when the low risk of bias was across all the domains. When at least one domain bears some concerns, then the overall risk of bias ranked with some concerns, and studies were judged as high risk when at least one domain falls in high risk or multiple domains fall in some concern category. Any discrepancies were solved by discussion between the reviewers; when not possible, a third reviewer acted as an arbiter.

2.5. Data analysis

To interpret the results, relative effects for outcomes were calculated by Risk Ratio (RR) or Odds Ratio (Peto's OR) in dichotomous data, and for the continuous outcome, mean difference with standard deviation [with 95% Confidence Interval (CI)] was measured. If the unit of any measures was not found uniform across the included study, we converted it into a standardized value for analysis.

Given the complexity of the investigated interventions, we attempted to categorize the included study into two broad categories, therapeutic and prophylaxis. Each is further classified into standalone AYUSH intervention and add-on AYUSH intervention. RCTs and NRSIs were analyzed separately. We assumed any missing data at random and analyzed only the available data (i.e., ignoring the missing data). We meta-analyzed the outcomes data

where two or more studies were available and displayed in forest plots. As clinical heterogeneity was anticipated random effect model was selected for meta-analysis. I^2 test statistics tested heterogeneity between the studies. All analyses were run in Review Manager 5.4 (RevMan 5.4) software.

We considered certain variables such as age, disease severity, drug dose, the diagnostic status of the patients, and type of interventions for the sub-group analysis. Sensitivity analysis was planned considering fixed and random effect models and the risk of bias. We planned a funnel plot method for meta-analysis to assess reporting bias, including at least ten trials of varying sizes.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the evidence level of the results.[14] Two reviewers, after training and calibration exercises, classified the certainty of each outcome and comparison as high, medium, low, and very low. These classifications were done on the considerations of risk of bias, inconsistency, indirectness, publication bias, and imprecision.[15]

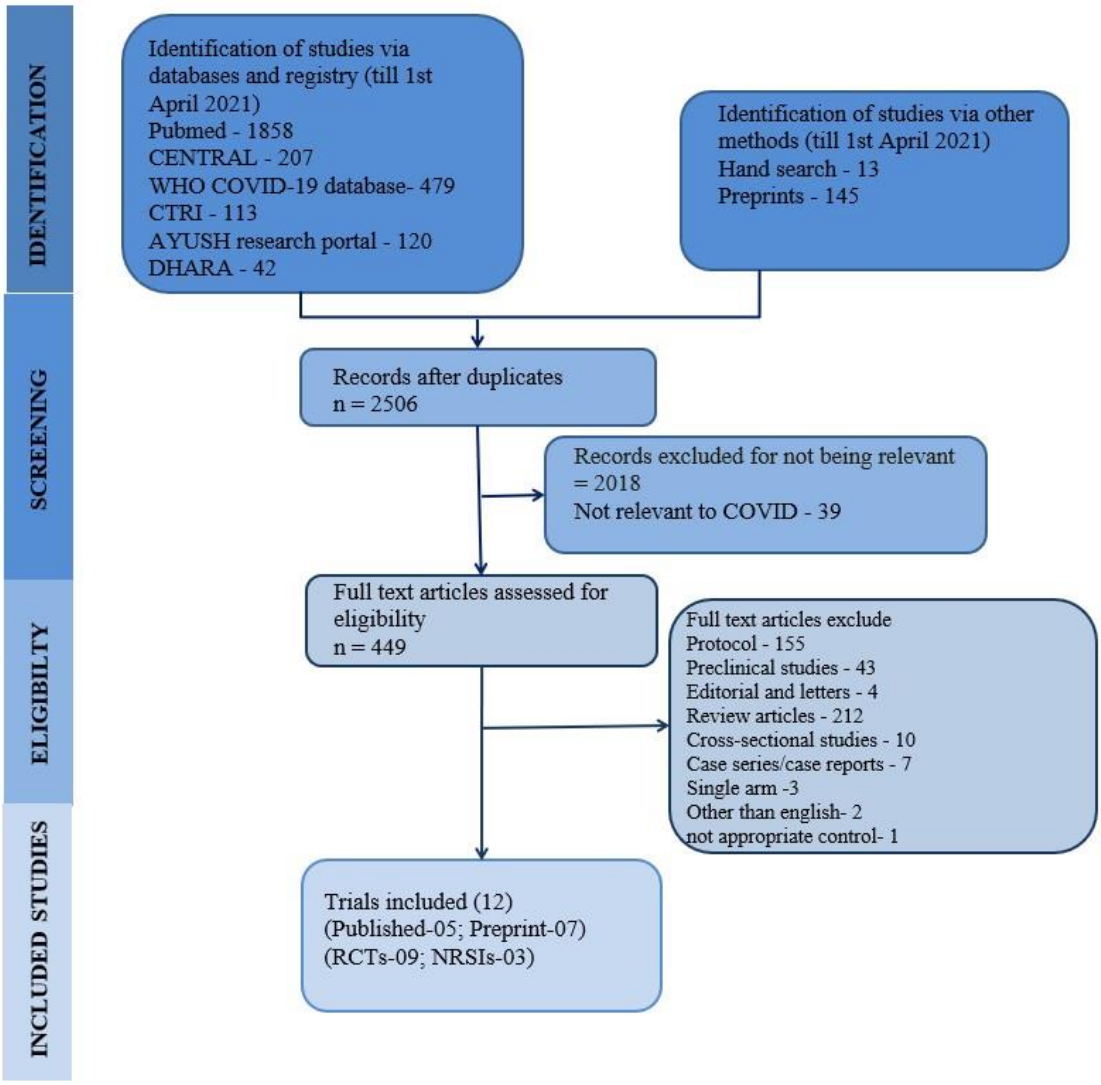
After reviewing relevant published literature and consulting with an expert team, we eliminated a few outcomes from the protocol, such as biomarker analysis in the therapeutic domain. We perceived immune status and quality of life in the prophylaxis domain, as they were not relevant to the study's objectives. As preliminary studies were available for each AYUSH intervention, meta-analysis was performed on AYUSH interventions as a whole. However, in subsequent updates, the effect of individual drugs of AYUSH systems will be appraised if more trials become available.

3. Results

3.1. Study characteristics

A total of 2,977 studies were retrieved from different databases, including hand searches. After removing duplicates with Endnote X9 and manually, a total of 2506 titles and abstracts were screened, and 2057 records were excluded for non-relevant. Out of the remaining 449 studies, 436 articles were excluded, not meeting pre-specified inclusion criteria. One report was excluded during the data extraction process, which used AYUSH interventions as a comparator,[16] finally 12 manuscripts were included.[17-28] Detail description of the study selection and elimination process has been depicted in figure 1. All the articles were in the English language only.

Figure 1: PRISMA flow chart



Among included studies of the therapeutic domain, 2 RCTs examined the benefit of AYUSH-64,[17,18] 2 studies (1 RCT, 1 NRSI) of Guduchi Ghanavati,[19,20] each one RCT on different multiple Combinations of Ayurveda medicines (coded as AYUSH regimen-I, II, III, IV, V, VI, and VII).[21-26] AYUSH Regimen III and IV were examined in a single RCT.[23] In the prophylactic domain, 1 RCT reported the benefit of Chyawanprash[27] and 1 NRSI of Guduchi Ghanavati.[28]All therapeutic trials included mild to moderate disease illness only. No study reported on severe or critical illness. One prophylaxis study was conducted on individuals at

very high risk of exposure (health care professional)[27,] and one community trial was conducted on moderate to very high-risk populations.[28] Out of 12, 10 trials were conducted in-patients hospital setting.

All prospective studies were registered, whereas all observational studies were not (table 1). Four articles were peer-reviewed published manuscripts, [21,22,24,26] one was pre-proof,23 and seven were pre-print. [17-20,25,27,28] Among all, 6 studies were add-on AYUSH interventions studies [17,18,21,24-26]and 6 were standalone interventions. [19,20,22,23,27,28] One study reported with placebo control[22] whereas eleven reported standard of care as a comparator.

Detailed baseline demographic and other variables were presented in the supplementary file. Certainty of evidence for each outcome of individual AYUSH intervention included in the study was also depicted in the supplementary file. Table 1 presents the summary characteristic of included study.

Table 1. Summary of included studies.

Authors Year Reference	**Study design**	**Disease Stages**	**Sample Size (n) Gender (M/F) Age (Mean Years) in Intervention/ Control**	**Intervention (Regimen)**	**Control (Regimen)**	**duration (Days)**	**Study Outcomes**
Therapeutic RCT							
R. Govind Reddy [17] 2020 CTRI/2020/05/025156	RCT	Mild	30/30 I - 18/12; C-18/12 I- 43.68, C-35.22	2 tablets of AYUSH-64 (500 mg each) administered thrice daily + standard care	Standard care (Paracetamol+ Vitamin C+Zinc+ Hydroxychloroquine+ Doxycycline+ Azithromycin + Amoxycillin with Potassium Clavulanate+ Favipiravir as per the clinical condition of the patient)	30 days	(1) Clinical improvement [closest to 14 days] (2) Adverse events (3) Viral clearance [closest to 07 days]
A. Thakar [18] 2020 CTRI/2020/06/025855	RCT	Mild	40/40 I -26/14; C - 27/13 I- 40, C-35.31	2 tablets of AYUSH-64 (500 mg each) thrice daily orally + standard care	Standard care (vitamin-C (200 mg)+B complex+ folic acid+Azithromycin and / or Augmentin (625 mg)+ HCQ (200 mg)+	14 days	(1) Use of O2 therapy [closest to 30days] (2) Symptomatic SARS-CoV2 infection (3) Ordinal scale for disease severity (4) Time to symptom

					Cetrizine (10 mg)+ pantoprazole (40mg)+ Paracetamol (500 mg) SOS as per stage and condition of patients)		resolution (total duration of symptoms)
Umesh Shukla [19] 2020 CTRI/2020/07/026840	RCT	Asymptomatic + mild symptomatic	15/15 I -12/03; C -11/04 I- 30.27, C-30.27	Guduchi Ghanavati two tablets (250 mg each) twice daily	HCQ has given in the maintenance dose of 800 mg for the first day followed by 400 mg per day for the next five days	10 days	(1) Adverse events (2) Viral clearance [closest to 07 days]
Ganpat Devpura [22] 2020 CTRI/2020/05/025273	RCT	Asymptomatic+mild symptomatic	45/50 I -77.78/22.22; C-84/16 I- 33.4, C-35.4	AYUSH regimen-II (1 g of Giloy Ghanavati +2 g of Swasari Ras +0.5 g each of Ashwagandha and Tulsi Ghanavati BD. + Anu Taila 4 drops nasal drop morning)	Placebo	07 days	(1) Viral clearance [closest to 07 days]
Adil Rais [23] 2020 CTRI/2020/06/025800	RCT	Asymptomatic+mild symptomatic	I_1,I_2/C-40,40/39 I_1-27/13; I_2-30/10 C-30/10 I-NR, C-NR	I_1 - AYUSH regimen-IV (Vyaghradi Kashaya 50 ml BD with 250 mg of Pippali powder empty stomach morning and evening+Sanshamani Vati 2 tablets 500 mg BD) I_2 - AYUSH regimen-III (Shunthi Churna 2 grams with warm water BD after meals +Rasona Kalka 1 gram with warm water OD)	Tab Vitamin C + Tab Paracetamol	10 days	(1) Viral clearance [closest to 07 days]
Pankaj Wanjarkhedkar [24] 2020 CTRI/2020/07/026602	RCT	mild/moderate symptomatic	62/39 I -NR; C-NR I- 44.03, C-41.59	AYUSH regimen-V (Two tablets Dasamoolkaduthrayadi Kashaya + Guluchyadi Kwatham BD + Standard of care	Standard of care (Paracetamol + Pentaprazole +Domeperidone) 1 OD+HCQ 400 mg Day 1, 200 mg for 5 days +Dexamethasone as per schedule+Azithromycin 500 mg OD/Ceftriaxone IV /Doxycycline IV +Clexane Subcute / Heparin (Unfractionate	07 days	(1) Clinical improvement [closest to 14 days] (2) Duration of hospitalization

					d) Subcute + Remdesivir IV + Tocilizumab IV + Colchicine (as per schedule)		
Anusha Rao [25] 2020 CTRI/2020/07/026371	RCT	Mild	15/15 I -11/04; C -12/03 I- 27.2, C-28.20	Standard care+ AYUSH regimen-VI (Kabasura Kudineer (2 tablets taken thrice a day + Shakti drops (6 drops with 100 ml of water thrice a day + Turmeric plus tablets (2 tablets thrice a day)	Standard care (paracetamol, antitussives, vitamin C, Zinc, antibiotics and ivermectin)	21 days	(1)Clinical improvement [closest to 14 days] (2) Adverse events (3) Viral clearance [closest to 14 days]
S.M. Chitra [26] 2020 CTRI/2020/06/025856	RCT	Asymptomatic+mild/ moderate symptomatic	100/100 I -71/29; C-69/31 I- 42.98, C-45.68	AYUSH Regimen-VII (Kabasura Kudineer 60 ml BD, Vasantha Kusumakaram Mathirai (130 mg) 1 tablet BD, Thippili Rasayanam 2 gms BD, Adathodai Manapagu 15 ml BD with 30 ml lukewarm water)+ standard treatment	Standard treatment (Hydroxychloroquine+Ivermectin+Azithromycin+Paracetamol+Omez+ Vitamin C+Zinc)	14 days	(1) Adverse events (2) Viral clearance [closest to 14 days] (3) Time to symptom resolution
Therapeutic NRSI							
Abhimanyu Kumar [20] 2020 NA	NRSI (Retrospective study)	Asymptomatic	40/51 E -33/07; NE-39/12 E- 47.3, NE-46.7	Guduchi Ghan Vati 500 mg BD	Standard care	14 days	(1) Adverse events (2) Symptomatic SARS-CoV2 infection (3) Viral clearance [closest to 07 days] (4) Duration of hospitalization
Anup Thakar 2020 [21] NA	NRSI (Retrospective cohort study)	Asymptomatic	541/221 E -410/131; NE-154/67 E- 35.33, NE-33.86	AYUSH regimen-I (Dashamula and Pathyadi Kwatha 20 ml each + Trikatu Churna 2g+ Sanshamani Vati 500 mg+AYUSH -64 500 mg +Yastimadhu Ghanavati 500 mg, 5-6 times OD)+Vitamin-C 500 mg+Azithromycin 500 mg OD for the first five days paracetamol (500mg) s.o.s. in pyrexia	Vitamin-C 500 mg+Azithromycin 500 mg OD for the first five days paracetamol (500mg) s.o.s. in pyrexia		(1) Mortality [up to 60 days] (2) Adverse events (3) Symptomatic SARS-CoV2 infection (4) Time to symptom resolution
Prophylaxis RCT							
Arun Gupta, [27] 2020 CTRI/2020/05/025275	RCT (prophylaxis)	Healthy healthcare workers	99/100 I -58/41; C -47/53 I- 32.122, C-33.357	Chyawanprash 12 g twice for 30 days	No prophylaxis	30 days 150 days (extended)	(1) Admission to high dependency unit or emergency unit [closest to 30days]

							(2) Adverse events (3) Incidences of COVID-19 infections (4) Symptomatic SARS-CoV2 infection
Prophylaxis NRSI							
Anup Thakar [28] 2020 CTRI/2020/06/025525	NRSI (Non randomized clinical trial Prophylaxis)	High-risk population	15992/4953 I -11393/4599; C -3164/1789 I- 38.7, C-37.2	Two tablets (250 mg each) of Guduchi Ghanavati twice a day	No prophylaxis	28 days	(1) Adverse events (2) Incidences of COVID-19 infections

3.2. Quality/risk of bias of included studies

The risk of bias assessments for each study is presented in figure 2 and 3. Among 9 RCTs, 6 studies had a high risk of bias associated with measurements of the outcomes or selection of the reported results,[17,22-26] remaining studies had some concerns (Figure 2).[18,19,27] Out of 3 NRSIs, 1 study had a high risk of bias associated with the selection of participants and measurements of the outcomes[20] whereas other studies had some concerns (Figure 3).[21,28] No study had a low risk of bias in this systematic review. We also reported outcome wise risk of bias of the included studies and presented them in the supplementary file.

Figure 2: Risk of bias assessment (RoB-2) for RCTs.

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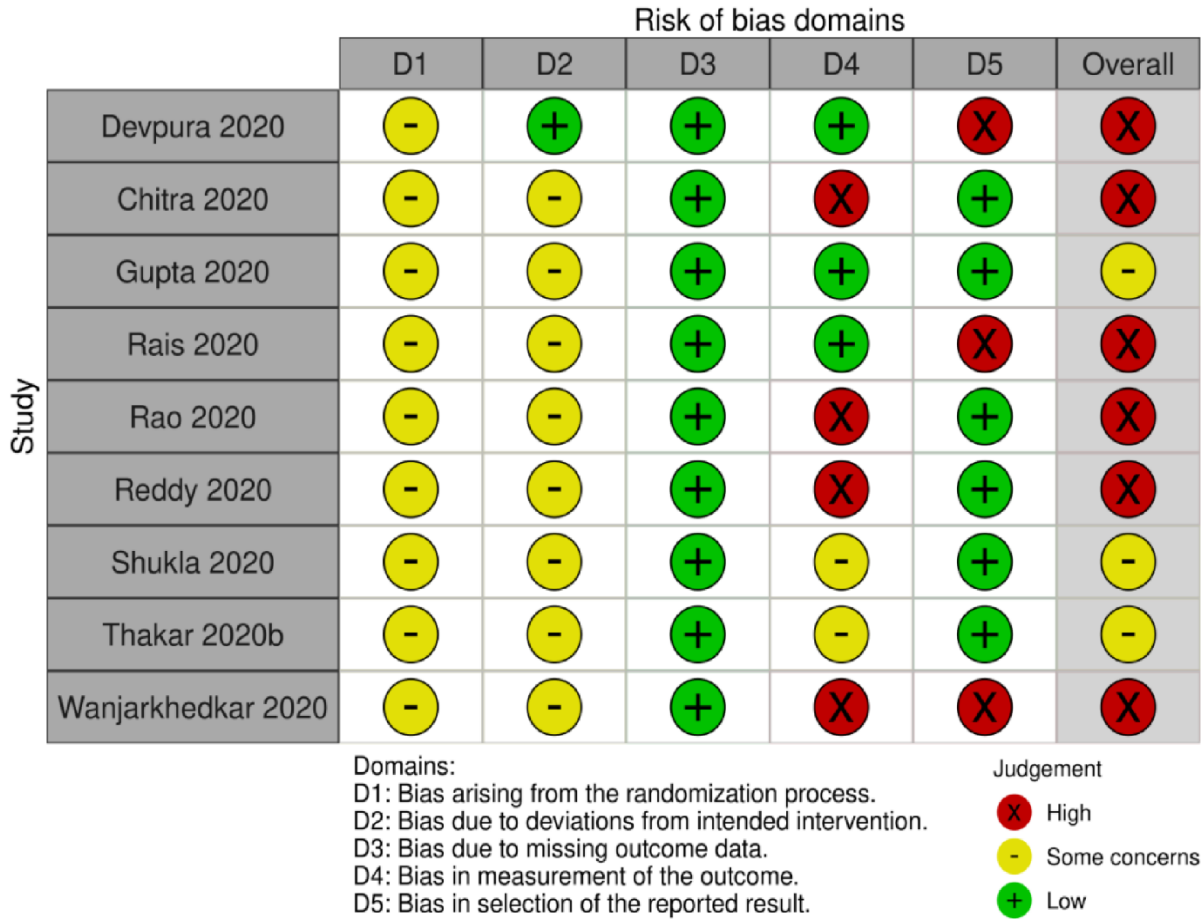

Figure 3: Risk of bias assessment (ROBINS I) for NRSIs.

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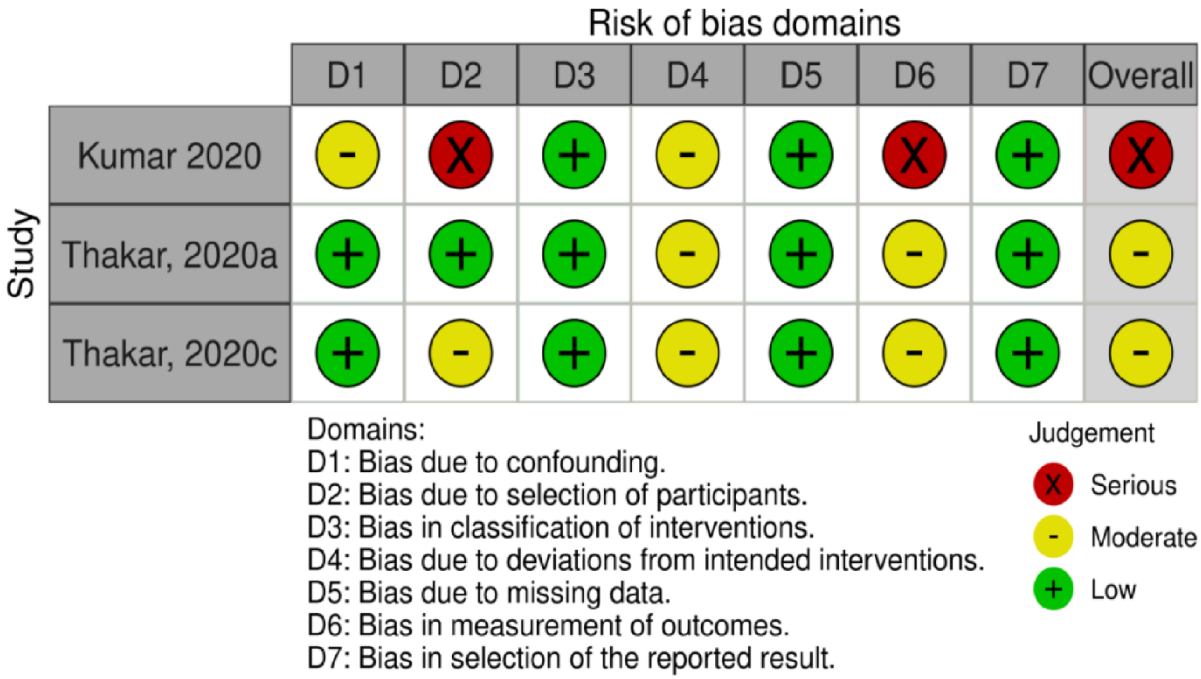


3.3. Intervention effects

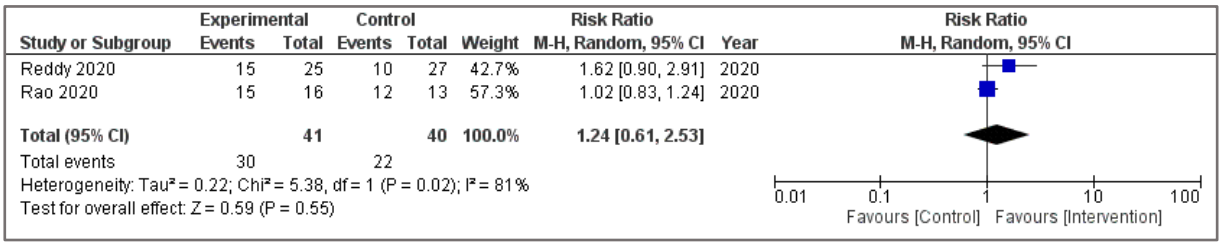
3.3.1. <u>Therapeutic</u>

3.3.1. 1. Clinical improvement

Add-on AYUSH interventions vs. Standard care

Two RCTs (n=81) reported clinical improvement as outcome[17,25] (Figure 4). The proportion of clinically improved patients of COVID-19 was marginally higher in add-on AYUSH interventions compared to Standard care; however, the finding was statistically not significant [RR 1.24 (95% CI: 0.61 to 2.53); risk difference 132 more per 1,000 (from 215 fewer to 841 more)]. Substantial heterogeneity (I^2=81%) was observed owing to diverse interventions. The high risk of bias, significant heterogeneity, and imprecision associated with both studies leads to very low evidence certainty.

Figure 4.: Forest chart of clinical improvement.

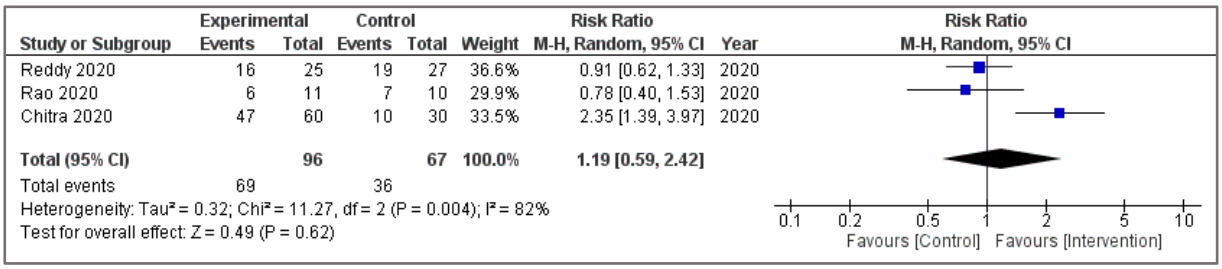


3.3.1.2. Viral clearance

[A.] Add-on AYUSH interventions vs. Standard care

Three RCTs (n=163) of add-on AYUSH interventions [17,25,26] reported viral clearance measured with polymerase chain reaction cut-off points. No apparent difference was observed between groups in the proportion of patients with add-on AYUSH interventions or standard care [RR 1.19 (95% CI: 0.59 to 2.42); risk difference 99 more per 1,000 (from 214 fewer to 741 more)]. The individual trials' results do not consistently lead to considerable heterogeneity (I^2=82%) related to varied interventions. Certainty of evidence was very low, associated with serious imprecision and substantial heterogeneity. (Figure 5)

Figure 5.: Forest chart of viral clearance (Add-on AYUSH intervention).

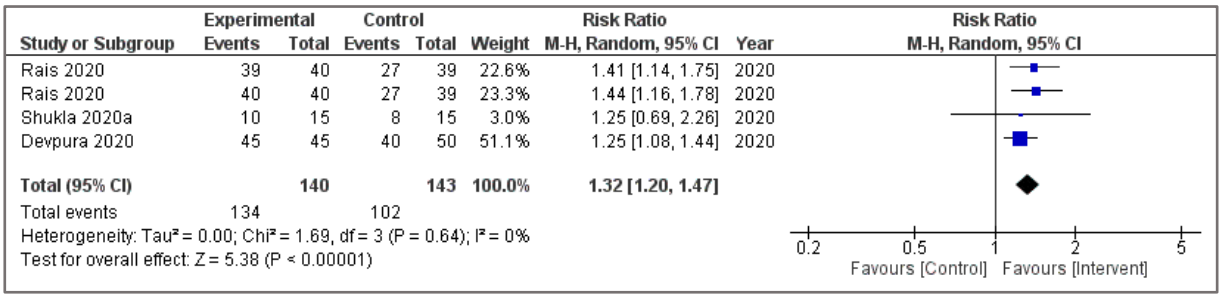


[B.] Standalone AYUSH interventions vs. Standard care

Three RCTs [19,22,23] (283) on AYUSH interventions reported viral clearance. With moderate certainty, a higher proportion of negative RT-PCR patients was reported in the standalone AYUSH interventions group compared to patients who received Standard care [RR 1.32 (95%

CI: 1.20 to 1.47); risk difference 228 more per 1,000 (from 143 more to 335 more)]. As the findings were consistent, no heterogeneity (I^2=0%) was observed. High risk of bias downgraded certainty one step to moderate. (Figure 6) Further, results from one NRSI showed standalone AYUSH might increase viral clearance in COVID-19 patients [RR 6.22 (95% CI: 3.28 to 11.77), which also supports meta-analyzed data of RCTs. (Table 4)

Figure 6.: Forest chart of viral clearance (Standalone AYUSH intervention).



3.3.1.3. The time to symptom resolution

Add-on AYUSH interventions vs. Standard care

Two RCTs (n=274) reported time to symptom resolution [18,26] wherein patients who received add-on AYUSH regimen had 1.88 days shorter symptom duration than patients who received standard care [Mean difference -1.88 days; 95% CI (-2.22 to -1.54); Mean in standard care 5.5 days]. No heterogeneity (I^2=0%) and moderate certainty were observed. (Figure 7) One NRSI with low certainty showed add-on AYUSH intervention may reduce total symptom duration compared to standard care (Risk difference -1.68 days; 95% CI -2.14 to -1.22, Mean in standard care 5.34 days).

Figure 7.: Forest chart of the time to symptom resolution.

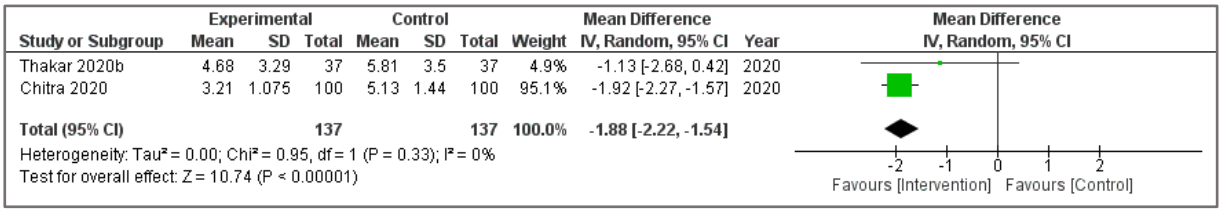


Table 2: Summary of findings for certainty of evidence [Add-on AYUSH interventions].

Add-on AYUSH intervention compared to Standard Care for COVID 19 (mild/moderate)

Patient or population: COVID 19 (mild/moderate patients)
Setting: Inpatients
Intervention: Add-on AYUSH intervention
Comparison: Standard Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	**Risk with Add-on AYUSH intervention**				
viral clearance follow up: mean 07 days	522 per 1,000	**621 per 1,000** (308 to 1,000)	**RR 1.19** (0.59 to 2.42)	165 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	The evidence is very uncertain about the effect of add-on AYUSH intervention on viral clearance.
Time to symptom resolution	The mean time to symptom resolution was **5.5** days	MD **1.88 days lower** (2.22 lower to 1.54 lower)	-	274 (2 RCTs)	⨁⨁⨁◯ MODERATE [a,c]	Add-on AYUSH intervention likely results in a reduction in time to symptom resolution.
Clinical improvement	550 per 1,000	**682 per 1,000** (336 to 1,000)	**RR 1.24** (0.61 to 2.53)	81 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	Add-on AYUSH intervention may have little effect on clinical improvement, but the evidence is very uncertain.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations
a. Downgraded because of the issue with randomization process and/or measurement of outcomes.
b. Substantial heterogeneity among study results.
c. Downgraded because CI is wider.

Table 3: Summary of findings for certainty of evidence [Standalone AYUSH interventions].

Stand alone AYUSH intervention compared to Standard Care for COVID 19 (mild/moderate)

Patient or population: COVID 19 (mild/moderate patients)
Setting: Inpatients
Intervention: Stand alone AYUSH intervention
Comparison: Standard Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	**Risk with Stand alone AYUSH intervention**				
Viral clearance	713 per 1,000	**942 per 1,000** (856 to 1,000)	**RR 1.32** (1.20 to 1.47)	283 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	Standalone AYUSH intervention likely hastens viral clearance.

Stand alone AYUSH intervention compared to Standard Care for COVID 19 (mild/moderate)

Patient or population: COVID 19 (mild/moderate patients)
Setting: Inpatients
Intervention: Stand alone AYUSH intervention
Comparison: Standard Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care	Risk with Stand alone AYUSH intervention				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations
a. Downgraded due to high risk of bias

3.3.1.4. Adverse events

[A.] Add-on AYUSH interventions vs. Standard care

Three RCTs [17,25,26] and one NRSI[21] reported adverse events. Among them, one study[25] reported the trivial event on this outcome (only three events in intervention and one event in standard care group). No adverse event was reported in any of the remaining studies. Therefore, the effects of such interventions on adverse events remain uncertain.

[B.] Standalone AYUSH interventions vs. Standard care

One RCT[26] and one NRSI[27] reported adverse events. In either of the trials, no adverse events were observed.

3.3.1.5. Other outcomes

Some outcomes such as ordinal scale for disease severity, duration of hospitalization, and use of O_2 therapy were reported by individual RCT or NRSI and could not be meta-analyzed; hence, a summary of their effect measures is presented in table 4. No death occurred in any of the trials that reported mortality; therefore, the effect of these interventions on mortality remains uncertain. [17,18,20,21]

3.3.2. Prophylaxis

3.3.2.1. Incidence of COVID-19 infections

[A.] Standalone AYUSH interventions vs. no prophylaxis

One RCT[27] reported that standalone AYUSH intervention might reduce the risk of incidence of COVID-19 infection; however, the finding was statistically non-significant, [RR 0.48 (95% CI: 0.09 to 2.58); 22 fewer per 1,000 (from 38 fewer to 67 more)]. One NRSI [22] showed standalone AYUSH intervention might have trivial to no effect on the incidence of COVID-19 infection [RR 0.79 (95% CI: 0.44 to 1.41); 1 fewer per 1,000 (from 2 fewer to 1 more)]. The certainty of the evidence was low due to the high risk of bias and imprecision for both studies.

Table 4: Measure of effects of outcomes reported in individual studies.

S. N.	Outcome	Included studies	Sample size I/C	Intervention (Event/total or $\bar{X}$±SD)	Control (Event/total or $\bar{X}$±SD)	Measures	Effect estimate [95% CI]
[A.] RCT studies							
1.	Ordinal scale for disease severity	Thakar et al. [18]	37/37	-0.43±1.16	-0.29±1.07	MD	-0.14 [-0.65,0.38]
2.	Use of O_2 therapy	Thakar et al.[18]	37/37	2/37	1/37	RR	2.00 [0.19, 21.11]
3.	Duration of hospitalization	Wanjarkhedkar et al.[24]	60/39	6.7±2.4	12.8±2.1	MD	-0.70 [2.06 ,0.66]
4.	Symptomatic SARS-CoV2 infection	Gupta et al.[27]	98/95	0/98	4/95	Peto OR	0.13 [0.02, 0.92]
5.	Incidence of COVID-19 infections	Gupta et al.[27]	98/95	2/98	4/95	RR	0.48 [0.09, 2.58]

[B.] NRSI studies							
1.	Viral clearance	Kumar et al.[20]	40/51	39/40	8/51	RR	6.22 [3.28,11.77]
2.	Duration of hospitalization	Kumar et al.[20]	40/51	6.4±2.4	12.8±2.1	MD	-6.40 [-7.34,-5.46]
3.	The time to symptom resolution	Thakar et al.[21]	541/221	3.66±1.55	5.34±3.35	MD	-1.68 [-2.14,-1.22]
4.	Incidence of COVID-19 infections	Thakar et al.[28]	15729/4845	41/15729	16/4845	RR	0.79 [0.44, 1.41]

$\bar{X}$±SD - Mean±Standard deviation; CI- Confidence Interval; MD - Mean Difference; RR - Risk ratio; Peto OR - Peto Odd's Ratio

3.4. Subgroup and Sensitivity analysis

Due to the lack of sub-group-specific raw data, no subgroup analysis could be performed. We looked at the sensitivity of meta-analyzed findings using two different techniques: first, altering the statistical model employed (fixed effect vs. random effect) and second, substituting the effect of measures (RR by OR by RD or MD by SMD). In sensitivity analysis, consistent results were observed when we changed the model from random effect to fixed effect for all four outcomes. The significance of the results was maintained stable when effect measures (RR/MD) were replaced with others. Sensitivity analysis suggested findings were robust and did not alter overall results. (Table 5)

Table 5: Sensitivity analysis of data by changing statistical model or effect measures.

S.N	**Outcomes**	**STATISTICAL MODEL**			**EFFECT MEASURE**		
		-	Fixed effect	Random effects	OR [95% CI]	RD [95% CI]	SMD [95% CI]
1.	Clinical improvement [Add-on]	RR [95% CI]	1.27 [0.94, 1.71]	1.24 [0.61, 2.53]	2.32 [0.82, 6.58]	0.11 [-0.14, 0.36]	-
2.	Effect on Viral clearance [Add-on]	RR [95% CI]	1.38 [1.03, 1.85]	1.19 [0.59, 2.42]	1.54 [0.27, 8.90]	0.10 [-0.31, 0.50]	-

3.	Effect on Viral clearance [Standalone]	RR [95% CI]	1.34 [1.20, 1.50]	1.32 [1.20, 1.47]	9.73 [1.86, 50.96]	0.25 [0.17, 0.32]	-
4.	Time to symptom resolution [Add-on]	MD [95% CI]	-1.88 [-2.22, -1.54]	-1.88 [-2.22, -1.54]	-	-	-0.93 [-2.08, 0.22]

CI- Confidence Interval; MD - Mean Difference; SMD - Standardized Mean Difference; RR - Risk ratio; RD - Risk Difference; OR - Odd's Ratio

4. Discussion

4.1. Summary of evidence

This living systematic review and meta-analysis give an inclusive outline about the evidence of AYUSH interventions on COVID-19 till 2nd April 2021. It included six trials on standalone AYUSH therapies,[19,20,22,23,27,28] other six on add-on AYUSH interventions.[17,18,21,24-26]Among conglomerate of AYUSH system; we find research manuscripts only on Ayurveda and Siddha discipline. No studies reported other systems such as Yoga and naturopathy, Unani and Homeopathy medicines. In Ayurveda, interventions used were AYUSH-64,[17,18] Guduchi Ghanavati,[19,20,28] Chyawanprash [27] and five different regimens [21-24] and Siddha, one regimen containing Kabasura Kudineer mainly.[26] One regimen had Ayurveda and Siddha drugs, both.[25] The shreds of evidence for all interventions of therapeutic purpose were come from mild to moderate patients only; this may be the reason for the no mortality reported or very few events reported on the use of oxygen therapy/ventilator in studies. Little evidence about adverse effects for most interventions has been provided so far by studies on COVID-19 patients.

The overall quality of the evidence was moderate to low mostly due to the high risk of bias and/or imprecision. The risk of bias of included studies was some concerns to high, primarily because of unmasking, lack of allocation concealment, inappropriate reporting of results, and inclusion of NRSI; however, NRSIs were synthesized separately.

Meta-analysis suggested that add-on AYUSH intervention may hasten the symptomatic recovery, whereas standalone AYUSH intervention may accelerate the rate of viral clearance. However, evidence suggests integrated use has limited effects on viral clearance and clinical improvements. Standalone AYUSH interventions may reduce the incidence of COVID-19 when administered as prophylaxis.

4.2. Agreements and disagreements with other reviews

This study is a first of its kind of research that assess the impact of interventions used in the conglomerate of the AYUSH system of medicines on COVID-19 patients. However**,** one narrative review [29] has been conducted to determine the effects of traditional Indian medicinal plants against acute respiratory infection (COVID-19, SARS, Influenza, and Respiratory syncytial virus infection). This review did not conduct a meta-analysis on clinical data that could not be compared.

4.3. Limitations of the review

Significant limitations of this study are the inclusion of NRSIs and pre-print articles which may decrease the quality of evidence. However, we assessed the risk of bias assessment of NRSIs on the ROBINS I tool to rank the certainty of evidence accordingly. Considering urgency for the information and many studies published first in pre-print repositories, pre-prints were also included. We cannot ignore the possibility of publication bias as positive result studies are more likely to be published and published sooner than negative result studies; however, the inclusion of pre-print may reduce the publication bias. There was a language restriction as only studies published in the English language were included in this study. Most of the studies included have a small sample size and a high risk of bias because of unmasking. In many studies, trivial events were reported that may lead to sparse data bias; however, we anticipate resolving the issue as the living review progresses. However, the effect of individual drugs on AYUSH systems of medicines could not be appraised because of the limited trials on each drug. It is envisaged that drug-specific effects would be considered in subsequent updates if more trials become available.

5. Conclusion

Evidence of the first version of living systematic review and meta-analysis concludes that integrated or standalone AYUSH drugs are likely to provide therapeutic benefits through escalating the viral clearance and clinical recovery in mild to moderate COVID-19 patients in comparison to standard care. AYUSH prophylaxis and standard preventive measures may reduce the risk of COVID-19 infection in the at-risk populations compared to standard care only. Summary of this systematic review may facilitate the physicians to make evidence-based decisions in their clinical practice and assist policymakers in modifying recommendations on AYUSH medicines for their logical and prudent usage either as an integrated or standalone strategy in the management of COVID-19. This review is intended to update bi-monthly; therefore, with additional pieces of evidence, we may look forward to new

effect estimates in upcoming updates.

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Author contributions

Conceptualization: MG, KS. Methodology: MG, KS. Validation: MG, KS, RK. Formal analysis: KP. Investigation: KP, MG, RK. Resources: AT. Writing – Original Draft: MG, KP, RK. Writing – Review & Editing: AT, KS. Visualization: KS, RK. Supervision: AT, KS. Project administration: AT, KS. Funding acquisition: AT.

Conflict of interests

No, there are no competing interests for any author.

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Ethical statement

This manuscript did not involve human subjects or laboratory animals, so no ethical approval was required for this manuscript.

Data availability

Data associated with this paper has been provided as a supplementary file. Any additional data related to this paper will be provided upon request.

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