Review Article

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Emerging trends from COVID-19 research registered in the Clinical Trials Registry - India

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Since the beginning of the year, the deadly coronavirus pandemic, better known as coronavirus disease 2019 (COVID-19), brought the entire world to an unprecedented halt. In tandem with the global scenario, researchers in India are actively engaged in the conduct of clinical research to counter the pandemic. This review attempts to provide a comprehensive overview of the COVID-19 research in India including design aspects, through the clinical trials registered in the Clinical Trials Registry - India (CTRI) till June 5, 2020. One hundred and twenty two registered trials on COVID-19 were extracted from the CTRI database. These trials were categorized into modern medicine (n=42), traditional medicine (n=67) and miscellaneous (n=13). Of the 42 modern medicine trials, 28 were on repurposed drugs, used singly (n=24) or in combination (n=4). Of these 28 trials, 23 were to evaluate their therapeutic efficacy in different severities of the disease. There were nine registered trials on cell- and plasma-based therapies, two phytopharmaceutical trials and three vaccine trials. The traditional medicine trials category majorly comprised Ayurveda (n=45), followed by homeopathy (n=14) and others (n=8) from Yoga, Siddha and Unani. Among the traditional medicine category, 31 trials were prophylactic and 36 were therapeutic, mostly conducted on asymptomatic or mild-to-moderate COVID-19 patients. This review would showcase the research being conducted on COVID-19 in the country and highlight the research gaps to steer further studies.

Key words Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy - clinical trials - CTRI-India - convalescent plasma therapy - COVID-19 - drug trials - registration - vaccine trials

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported from Wuhan, China, in December 2019. Since then, the disease has spread worldwide and as of June 5, 2020, there were 6,824,499 cases and 408,307 deaths globally[1].

In the absence of any vaccine or definitive therapeutic strategy, medical scientists are working tirelessly to not only save lives but also search for effective treatment modalities against the deadly virus. Drug development is a costly and time-consuming process and is not feasible in the context of the immediate global challenge. Therefore, drug repurposing strategies are being considered to develop safe and effective treatment regimens against the disease. Currently, an array of drugs used for the other

health conditions are being studied for the treatment of COVID-19 in several hundred clinical trials around the globe[2].

Globally, clinical trial registries may be considered the best source to review the ongoing clinical trial scenario as crucial details pertaining to proposed intervention, study type and design, sample size, and outcomes and phase of the trial are publicly available. The Clinical Trials Registry - India (CTRI), one of the primary registries of the World Health Organization's International Clinical Trial Registry Platform (ICTRP), is one such database[3,4].

The CTRI, set up under the aegis of the Indian Council of Medical Research (ICMR), is managed by the ICMR-National Institute of Medical Statistics, New Delhi. The CTRI is a free online registry that prospectively registers clinical trials being conducted in India and also in countries which do not have a primary registry of their own. With the emergence of the pandemic in India, there has been a steady increase in the registration of clinical trials on COVID-19 in the CTRI. Here, we present a comprehensive overview of the COVID-19 trials registered in the CTRI (Tables I-IV). While the results of these trials will decide whether or not any of these proposed therapies are likely to be of use, information about these would help to identify lacunae as well as plan and guide future clinical research.

Trial data extraction

One hundred and twenty three registered COVID-19 trials were extracted from the CTRI database using the term %covid% in the different fields of the CTRI data set. These trials were manually screened and analyzed. One trial was excluded because COVID-19 was in the exclusion criteria in that trial. The remaining 122 trials were tabulated into three categories: modern medicine (including drug trials as well as phytopharmaceuticals, cell- and plasma-based therapies and biological products trials); traditional medicine covering Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy (AYUSH) trials and miscellaneous trials.

COVID-19 trial scenario in India

Multiple therapeutic and preventive trials including those in the traditional systems of medicine are being conducted in India with the common global objective of demonstrating efficacy as well as safety for all in need. Of the 122 clinical trials on COVID-19 registered in the CTRI (as on June 5, 2020), 42 were on the modern system of medicine, 67 on the traditional system of medicine and 13 miscellaneous (Table I). Overall, there were 23 single-armed trials, 68 randomized trials and six cluster randomized trials, while there were 17 non-randomized and eight other (unspecified study design) trials. Most of these trials were either Phase 2 (n=31) or Phase 2/3 (n=13) trials or Phase 3 (n=23) or Phase 3/4 (n=7) trials. Phase was not applicable for 34 trials, and there were only two Phase 1 and five Phase 1/2 trials (Tables II-IV). Of the remaining trials, four trials were marked as Phase 4 trials and two as post-marketing surveillance studies. There was a wide variation in sample size in the registered trials ranging from 6 to 50,000.

Modern medicine

Trials registered in this category (n=42) are subdivided into drug trials (n=28), of which 24 trials are on individual drugs which primarily evaluate their therapeutic efficacy (n=19) as do all of the four combination of drug trials (such as the global Solidarity trial). These trials are being conducted in patients with varying severity of COVID-19 ranging from mild to moderate to severe. The severity of COVID-19 has not been specified in seven of these drug trials (Table I). Others include trials on phytopharmaceuticals (n=2) cell- and plasma-based therapies (n=9) and biological products (n=3). Only one of these is a prophylactic trial on healthy volunteers and all cell- and plasma-based therapy trials are on either moderate/moderate to severe or severe (n=5) COVID-19 patients. While the key features of these registered trials are presented in Table II, these are briefly discussed below.

Drug trials

Antivirals

Solidarity trial: The Solidarity trial is an international clinical trial initiated by the WHO to help find an effective treatment for COVID-19[5]. The trial compares four treatment options remdesivir; lopinavir/ritonavir; lopinavir/ritonavir with interferon beta-1a and chloroquine or hydroxychloroquine (HCQ) against standard of care, to assess their relative effectiveness against COVID-19. The Solidarity trial has been planned as an open-labelled, randomized, parallel-group, multiple-arm trial with a total sample size of 7000 participants, of whom 1500 participants are

Table I. An overview of 122 COVID-19 trials registered in the Clinical Trials Registry - India[#]

Intervention	Number	Type of trial	Participant health condition
Modern medicine (n=42)			
Drug (n=28)			
Individual drugs	24	Therapeutic efficacy=19 Prophylactic efficacy=5	Healthy volunteers at high risk - 4 Healthy volunteers at moderate/high risk - 1 Mild COVID-19 - 5 Mild-to-moderate COVID-19 - 1 Moderate COVID-19 - 1 Moderate-to-severe COVID-19 - 2 Severe COVID-19 - 4 Severity not specified - 6
Combination drugs	4	Therapeutic efficacy=4	Moderate COVID-19 - 1 Mild, moderate, severe COVID-19 - 1 Non-severe and severe COVID-19 - 1 Severity not specified - 1
Phytopharmaceutical (n=2)			
Phytopharmaceutical	2	Therapeutic efficacy=2	Asymptomatic/mild COVID-19 - 1 Moderate COVID-19 - 1
Cell- and plasma-based therapies (n=9)			
Cell- and plasma-based therapies	9	Therapeutic efficacy=9	Moderate COVID-19 - 1 Moderate-to-severe COVID-19 - 1 Severe COVID-19 - 5 Severity not specified - 2
Biological products (n=3)			
Vaccine	3	Therapeutic efficacy=2 Prophylactic efficacy=1	Healthy volunteers at high risk - 1 Moderate-to-severe COVID-19 - 1 Severe COVID-19 - 1
Traditional medicine (n=67)			
Ayurveda (n=45)			
Classical individual agents	11	Therapeutic efficacy=1 Prophylactic efficacy=10	Healthy volunteers at high risk - 1 Healthy volunteers in the community - 9 Asymptomatic/mild symptoms - 1
Classical combination preparations[*]	10	Therapeutic efficacy=4 Prophylactic efficacy=6	Healthy volunteers at high risk - 1 Healthy volunteers in the community - 5 Asymptomatic/mild symptoms - 3 Mild-to-moderate COVID-19 - 1
Patented products	24	Therapeutic efficacy=18 Prophylactic efficacy=6	Healthy volunteers at high risk - 5 Healthy volunteers in the community - 1 Asymptomatic/mild symptoms - 3 Asymptomatic/mild/moderate symptoms - 2 Mild symptoms - 4 Mild-to-moderate COVID-19 - 6 Moderate COVID-19 - 1 Moderate-to-severe COVID-19 - 1 Severe COVID-19 -1
Yoga (n=3)			
Yoga[*]	3	Therapeutic efficacy=2 Stress management=1	Healthy volunteers at high risk - 1 Asymptomatic/mild symptoms - 1 Asymptomatic/uncomplicated illness/mild pneumonia - 1

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Intervention	Number	Type of trial	Participant health condition
		Unani (n=2)	
Unani	2	Prophylactic efficacy=2	Healthy volunteers at risk - 2
		Siddha (n=3)	
Siddha	3	Therapeutic efficacy=2 Prophylactic efficacy=1	Healthy volunteers in community and healthcare workers - 1 Asymptomatic - 1 Asymptomatic/mild/moderate symptoms - 1
		Homeopathy (n=14)	
Homeopathy	14	Therapeutic efficacy=8 Prophylactic efficacy=6	Healthy volunteers in community - 3 Healthy volunteers at high risk - 3 Asymptomatic - 1 Asymptomatic/mild symptoms - 1 Mild - 4 Moderate - 1 Mild/moderate/severe symptoms - 1
		Miscellaneous (n=13)	
Miscellaneous	13	Therapeutic efficacy=2 Prophylactic efficacy=1 Process-of-care changes=9 Diagnostic=1	Healthy volunteers - 4 Severe COVID-19 - 1 Severity not specified - 4 Other (non-COVID-19) - 4

[#]Registered trials as on June 5, 2020; [*]Two Ayurveda classical combination trials included yoga and one yoga trial included Ayurveda interventions. In addition, one Ayurveda trial was in combination with homeopathy and one miscellaneous trial with combination of modern medicine, Ayurveda and homeopathy

to be enrolled from India from 24 sites. The trial is being conducted in India with the support of ICMR.

In addition, a single-centre trial is also underway to assess the safety and efficacy of antiviral combination therapy such as lopinavir–ritonavir combination and HCQ with ribavirin in severe COVID-19-infected patients (CTRI/2020/06/025575).

Favipiravir: A nucleoside precursor, favipiravir, inhibits the influenza virus as well as a number of other RNA viruses[6]. In keeping with global trends, a randomized, open-label, multicentre study to evaluate the efficacy and safety of favipiravir in addition to standard supportive care in patients with mild-to-moderate COVID-19 is currently underway at 12 sites across India (CTRI/2020/05/025114).

Antimalarials

During this pandemic time, chloroquine and HCQ have generated much interest in the global community as potential therapeutic agents against COVID-19[7]. An open-label non-randomized trial showed that HCQ - azithromycin was associated with viral load reduction in COVID-19 patients[8].

Chloroquine: Two open-labelled, randomized controlled trials are being conducted to determine the efficacy of chloroquine in COVID-19 patients who present with severe acute respiratory illness (CTRI/2020/04/024479, CTRI/2020/04/024729).

Hydroxychloroquine (HCQ): In India, the ICMR has proposed a prophylactic dosing schedule of HCQ for healthcare workers[9]. In this regard, a principal investigator (PI)-initiated trial on 500 participants is currently underway wherein the recommended prophylactic dosing regimen is being compared with an alternative dosing pattern for the prevention of new infection and adverse outcomes in those at high risk of infection (CTRI/2020/03/024402). A double-blind, Phase 3 clinical trial, sponsored by the Armed Forces Medical Services, aims to evaluate the efficacy of two different doses of HCQ and also to compare the efficacy of HCQ with or without azithromycin in mild, moderate and severe COVID-19-infected patients. This trial is being conducted at six sites across the country with 300 participants.

In view of the large-scale use of HCQ in India, a study to document the pharmacokinetics of HCQ in the Indian population has also been registered

Table II. Details of modern medicine trials (n=42) on COVID-19 registered in the Clinical Trials Registry - India[#]

Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
				Drug trials (n=28)					
				Antivirals					
1	CTRI/2020/04/024773[*] Solidarity trial	Arm 1: Remdesivir and standard treatment Arm 2: Chloroquine or HCQ and standard treatment Arm 3: Lopinavir with ritonavir Arm 4: Lopinavir with ritonavir plus interferon and standard treatment Arm 5: Standard treatment	Randomized, parallel-group, multiple-arm trial	Open label	Phase 3	1500	All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study	WHO and ICMR, New Delhi DCGI approval: Yes	RJ (2 sites), MP (2 sites), DL, TN (5 sites), MH (7 sites), GJ (4 sites), TS, GJ, AP
2	CTRI/2020/06/025575[*]	Arm 1: HCQ, ribavirin, standard treatment (NS) Arm 2: HCQ, ribavirin, standard treatment (S) Arm 3: Lopinavir, ritonavir, ribavirin, standard treatment (S) Arm 4: Standard treatment (NS) Arm 5: Standard treatment	Randomized, parallel-group, multiple-arm trial	Open label	Phase 3/ Phase 4	175	1. Time to clinical recovery 2. Time to 2019-nCoV RT-PCR negativity in upper respiratory tract specimen	AIIMS, Rishikesh DCGI approval: N/A	UK
3	CTRI/2020/05/025114	Arm 1: Favipiravir Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 3	150	Time until cessation of oral shedding of SARS-CoV-2 virus (time frame: up to 28 days) (time in days from randomization to a negative SARS-CoV-2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab)	Glenmark Pharmaceuticals Ltd, Mumbai DCGI approval: Yes	CG, MH (7 sites), GJ (3 sites), DL
				Antimalarials					
4	CTRI/2020/04/024479	Arm 1: Chloroquine phosphate Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	N/A	32	Number of days of hospitalization	Command Hospital Airforce, Bengaluru DCGI approval: N/A	KA

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
5	CTRI/2020/04/024729	Arm 1: Topical chloroquine and standard treatment Arm 2: Standard treatment	Other	Open label	Phase 2	60	1. The Ct values on days 0, 3, 7, 10 shall be plotted on a graph for all patients. 2. The rate of decline for each patient shall be calculated. The time to cure (COVID-19 RT PCR -ve) shall be determined. 3. The two groups shall be compared for (*i*) rate of decline of Ct values; (*ii*) time to cure; (*iii*) rate of cure or alternate outcome	AIIMS New Delhi DCGI approval: N/A	HR
6	CTRI/2020/03/024402	Arm 1: HCQ Arm 2: HCQ (ICMR regimen)	Randomized, parallel-group, active controlled trial	Open label	Phase 3	500	Infected non-infected	PI initiated, Aster Malabar Institute of Medical Sciences, Kozikhode DCGI approval: N/A	KL
7	CTRI/2020/05/025022	Arm1: HCQ Arm 2: Standard treatment	Other	Open label	Phase 2	166	Progression to moderate-to-severe disease	AIIMS, New Delhi DCGI approval: N/A	DL
8	CTRI/2020/05/025067	Arm 1: HCQ along with standard treatment Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	N/A	6950	Laboratory-confirmed symptomatic COVID-19 cases	George Institute for Global Health India, New Delhi DCGI approval: N/A	TN, KA, DL

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
9	CTRI/2020/04/024904*	Arm 1: HCQ Arm 2: HCQ (high dose) Arm 3: HCQ and Azithromycin	Randomized, parallel group trial	Participant and outcome assessor blinded	Phase 3	300	1. Death 2. Hospitalized on invasive mechanical ventilation or extracorporeal mechanical ventilation 3. Hospitalized on non-invasive ventilation or high-flow nasal cannula oxygen therapy 4. Hospitalized on supplemental oxygen 5. Hospitalized not on supplemental oxygen 6. Not hospitalized with limitation of activity (due to continued symptoms) 7. Not hospitalized without limitation in activity (no symptoms)	Armed Forces Medical Services, New Delhi DCGI approval: N/A	UP (4 sites), DL, GJ
10	CTRI/2020/05/025242	Arm 1: HCQ	Other	N/A	N/A	400	Pharmacokinetics of HCQ	ICMR, New Delhi DCGI approval: N/A	MH
				Immunomodulators					
11	CTRI/2020/04/024948*	Arm 1: Ciclesonide Arm 2: HCQ Arm 3: Ivermectin Arm 4: Standard treatment	Randomized, parallel-group trial	N/A	Phase 2	120	Proportion of patients having virologic cure on day 6 in each of the groups	Lady Hardinge Medical College, New Delhi DCGI approval: N/A	DL
12	CTRI/2020/04/024806	Arm 1: Imatinib Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 2	100	1. Proportion of patients with negative viral titre on day 7 2. Proportion of patients with negative viral titre on day 14	AIIMS New Delhi DCGI approval: N/A	DL

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
13	CTRI/2020/05/024959	Arm 1: Itolizumab, Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 2	30	One-month mortality rate	Biocon Biologics India Limited, Bengaluru DCGI approval: Yes	DL (3 sites), MH (3 sites), KA
14	CTRI/2020/05/025369	Arm 1: Tocilizumab and standard treatment Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 3	180	Proportion showing progressive COVID-19 disease from moderate to severe, or from severe disease to death	Medanta Institute of Education and Research, Gurgaon DCGI approval: Yes	TS, TN, MH (3 sites), HR (4 sites) DL, UP (2 sites)
15	CTRI/2020/04/024846	Arm 1: *Mycobacterium w* and standard treatment Arm 2: Placebo and standard treatment	Randomized, parallel-group, placebo-controlled trial	Participant, investigator and outcome assessor blinded	N/A	40	Improvement in organ dysfunction (or occurrence of new organ dysfunction) based on change in SOFA score and ordinal scale	Cadila Pharmaceuticals Limited, Ahmedabad DCGI approval: Yes	CG, MP, DL, CH
16	CTRI/2020/05/025271	Arm 1: *Mycobacterium w* and standard treatment Arm 2: Placebo and standard treatment	Randomized, parallel-group, placebo-controlled trial	Participant, investigator and outcome assessor blinded	Phase 3	480	Number of patients with increased disease severity	Cadila Pharmaceuticals Limited, Ahmedabad DCGI approval: Yes	DL, MP, CH
17	CTRI/2020/05/025277	Arm 1: *Mycobacterium w* Arm 2: Placebo	Randomized, parallel-group, placebo-controlled trial	Participant, investigator and outcome assessor blinded	Phase 3	4000	Numder of individuals acquiring COVID-19 infection	Cadila Pharmaceuticals Limited, Ahmedabad DCGI approval: Yes	MP, CG, DL, CH

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
18	CTRI/2020/05/025350	Arm 1: *Mycobacterium w*, (heat killed)	Single-arm trial	Open label	Phase 2	50	Clinical improvement, as defined by live discharge from the hospital, a decrease of at least two points from baseline on a modified ordinal scale. Conversion of COVID-19 status to negative	R D Gardi Medical College, Ujjain DCGI approval: N/A	MP
19	CTRI/2020/06/025613	Arm 1: Melatonin Arm 2: Placebo	Randomized, parallel-group, placebo-controlled trial	Participant and investigator blinded	Phase 4	200	SARS-CoV-2 infection rate	PI initiated, AIIMS Rishikesh DCGI approval: N/A	UK
				Anthelmintics					
20	CTRI/2020/04/024858	Arm 1: Ivermectin and standard treatment Arm 2: Standard treatment	Non-randomized, active controlled trial	Open label	N/A	50	Confirm the antivirus effectiveness of ivermectin on coronavirus *i.e.*, COVID-19 then to explore its potential use in the combating to the COVID-19 pandemic	Max Super Speciality Hospital, New Delhi DCGI approval: N/A	DL
21	CTRI/2020/05/025068	Arm 1: Ivermectin Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	Open label		50	Reduction in the viral load in patients with haematological illnesses who are admitted with COVID-19 infection	Christian Medical College, Vellore DCGI approval: N/A	TN
22	CTRI/2020/05/025224	Arm 1: Ivermectin, and standard treatment Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 2	50	Effect of ivermectin on eradication of virus. Test for virus at 1, 3 and 5 days from beginning of trial drug started for the patient in the hospital	RD Gardi Medical College, Ujjain DCGI approval: N/A	MP

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
23	CTRI/2020/05/025333	Arm 1: Ivermectin Arm 2: No intervention	Randomized, parallel-group trial	Open label	Phase 2	2000	1. Resolution of sign and symptoms of COVID-19 2. Negative RT-PCR done 48 h after ivermectin dose 3. Change/reduction in Ct value as reported in RT-PCR for SARS-CoV-2 virus assay	R D Gardi Medical College, Ujjain DCGI approval: N/A	MP
24	CTRI/2020/04/024949	Arm 1: Niclosamide Arm 2: Standard treatment	Randomized, parallel-group trial	N/A	Phase 2	48	Proportion of patients having virologic cure on day 6	Lady Hardinge Medical College, New Delhi DCGI approval: N/A	DL
				Antihypertensive					
25	CTRI/2020/05/025319	Arm 1: Losartan Arm 2: Placebo	Randomized, parallel-group, placebo-controlled trial	Participant and investigator blinded	Phase 3	186	Percentage of patient with treatment failure: (*i*) fall in 1 score in Respiratory SOFA score; (*ii*) new requirement of respiratory assist devices (HFNC, NIV); (*iii*) new requirement of mechanical ventilation; (*iv*) mortality	SGPGI, Lucknow DCGI approval: N/A	UP
				Antioxidant/pro-oxidant					
26	CTRI/2020/05/025336	Arm 1: Resveratrol-copper and standard treatment Arm 2: Sodium-copper-chlorophyllin and standard treatment Arm 3: Standard treatment	Randomized, parallel-group, multiple-arm trial	Open label	Phase 3	300	Proportion of patients who suffer clinical deterioration OR viral persistence at day 10 from the date of randomization (excluding the date of randomization)	Tata Memorial Centre, Mumbai DCGI approval: N/A	MH

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
27	CTRI/2020/05/025337	Arm 1: Resveratrol-copper tablets, and standard treatment Arm 2: Sodium-copper-chlorophyllin and standard treatment Arm 3: Standard treatment	Randomized, parallel-group, multiple-arm trial	Open label	Phase 2	200	Time to clinical improvement, defined as a 2-point improvement on a 7-point ordinal scale	Tata Memorial Centre, Mumbai DCGI approval: N/A	MH
				Antineoplastic					
28	CTRI/2020/06/025664	Arm 1: 2-deoxy-D-glucose and standard treatment Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 2	40	Time to clinical improvement	Dr Reddys Laboratories Limited, Hyderabad and INMAS, DRDO, Delhi DCGI approval: Yes	DL (2 sites), KA, TN, UP (2 sites), MH (4 sites), AP, GJ
				Phytopharmaceuticals (n=2)					
29	CTRI/2020/05/025397	Arm 1: Purified AQCH and standard treatment Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 2	210	Proportion of patients showing clinical improvement. Clinical improvement defined as patient meeting discharge criteria OR a 2-point improvement (from time of enrolment) in disease severity rating on the 7-point ordinal scale	Sun Pharmaceutical Industries Limited, Goregaon, Mumbai DCGI approval: Yes	CG, MH (6 sites), MP, TS, UP, HR, JK, DL, TN
30	CTRI/2020/05/025167	Arm 1: Thymoquinone and standard treatment Arm 2: Standard treatment	Non-randomized active controlled trial	Open label	Phase 2	100	Characterize virologic and clinical response	Intas Pharmaceuticals Ltd, Ahmedabad DCGI approval: N/A	GJ (3 sites)

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
			Cell and plasma based therapies (n=9)						
31	CTRI/2020/04/024775 PLACID trial	Arm 1: Convalescent plasma Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	N/A	Phase 2	452	Composite measure of the avoidance of : (*i*) progression to severe ARDS (P/F ratio 100) or (*ii*) all-cause mortality at 28 days	ICMR, New Delhi DCGI approval: Yes	MH (7 sites), BR, MP (3 sites), TS (2 sites) GJ (6 sites), KA (4 sites), PY, UP (4 sites), DL, TN (5 sites), HR, CH, PB, RJ (2 sites)
32	CTRI/2020/04/024706	Arm 1: Convalescent plasma and standard treatment Arm 2: Random donor plasma and standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 2	40	Proportion of patients remaining free of mechanical ventilation in both groups	Institute of Liver and Biliary Sciences, New Delhi DCGI approval: Yes	DL (2 sites)
33	CTRI/2020/04/024915	Arm 1: Convalescent plasma Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 2	100	The primary outcome was a composite measure of the avoidance of : (*i*) progression to severe ARDS (P/F ratio 100) and (*ii*) all-cause mortality at 28 days	Max Super Speciality Hospital, New Delhi DCGI approval: Yes	DL
34	CTRI/2020/04/024804	Arm 1: Convalescent plasma along with standard treatment Arm 2: Standard treatment	Non-randomized, active controlled trial	N/A	Phase 1/2	24	Safety, efficacy, side effects measured by chest radiograph. Improvement of clinical symptoms including duration of fever, respiratory distress, pneumonia, cough, sneezing, and diarrhoea within three days of the convalescent plasma transfusion	International Stemcell Services Ltd, Bengaluru DCGI approval: Yes	KA (2 sites)

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
35	CTRI/2020/05/025299	Arm 1: Convalescent plasma Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 2	20	Avoidance of progression to severe ARDS	Wockhardt Ltd, Mumbai DCGI approval: Yes	MH
36	CTRI/2020/05/025346	Arm 1: Convalescent plasma and standard treatment Arm 2: Standard treatment	Randomized, parallel-group trial	N/A	N/A	90	Progression to severe ARDS (P/F ratio 100) and all-cause mortality at one month	Government of Tamil Nadu DCGI approval: Yes	TN
37	CTRI/2020/05/025328	Arm 1: Convalescent plasma Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	N/A	Phase 2	100	Composite measure of the (*i*) all-cause mortality at 28 days; (*ii*) improvement of SOFA score post transfusion	Apollo Hospitals Enterprise Limited, New Delhi DCGI approval: Yes	WB, TS, MH, TN, DL
38	CTRI/2020/05/025209	Arm 1: Convalescent plasma Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 2	80	1. All-cause mortality 2. To identify the immune correlates for response to plasma therapy	CSIR, New Delhi DCGI approval: Yes	WB
39	CTRI/2020/05/025432	Arm 1: Cytokine cocktail therapy	Single-arm Trial	Open label	Phase 1	6	Safety of cytokine cocktail therapy	International Stemcell Services Ltd, Bengaluru DCGI approval: Yes	KA

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
Biological products (n=3)									
Vaccines									
40	CTRI/2020/04/024749	Arm 1: Recombinant BCG vaccine - VPM1002 Arm 2: Placebo	Randomized, parallel-group, placebo controlled trial	Participant, investigator, outcome assessor and date-entry operator blinded	Phase 3	5946	1. Number of individuals with laboratory-confirmed COVID-19 infection 2. Number of individuals with laboratory-confirmed COVID-19 infection among other high risk individuals 3. Number of laboratory-confirmed COVID-19 infection with severe, critical or life-threatening disease as assessed by investigator among HCWs 4. Number of laboratory-confirmed COVID-19 infection with severe, critical or life-threatening disease as assessed by investigator among other high-risk individuals	Serum Institute of India Pvt Ltd, Pune DCGI approval: Yes	OR, CG, MH (17 sites), DL (4 sites), GA, KL, AP, UP, WB, CH, HR, RJ, GJ, TN, KA (2 sites)
41	CTRI/2020/04/024833	Arm 1: BCG-Denmark (Green Signal) Arm 2: Placebo	Randomized, parallel-group, placebo controlled trial	Participant, investigator, outcome assessor and date-entry operator blinded	N/A	1826	Proportion of HCW with symptomatic COVID-19 disease	PI initiated, JIPMER, Puducherry DCGI approval: N/A	PY

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
42	CTRI/2020/05/025013	Arm 1: BCG Arm 2: Saline plus standard treatment	Non-randomized, active controlled trial	Participant blinded	Phase 2	60	1. Total duration of hospitalization with COVID-19 symptoms 2. Decrease in viral titre 3. Duration of COVID-19 symptoms	Medical Education and Drugs Department, Mumbai DCGI approval: Yes	MH

[#]Registered trials as on June 5, 2020, [*]Combination therapy trials are mentioned in only one category to avoid duplication. Table data are as per information provided by trialist. The keyword 'Standard treatment' has been used for uniformity and includes the following category as mentioned by the trialist *i.e.*, standard of care, standard care of treatment and supportive management, standard treatment protocol, local-level standard treatment, best supportive care and treatment guidelines as per MoHFW. COVID-19, coronavirus disease 2019; AIIMS, All India Institute of Medical Sciences; ICMR, Indian Council of Medical Research, INMAS, Institute of Nuclear Medicine and Allied Sciences; DRDO, Defence Research and Development Organisation; HCQ, Hydroxychloroquine; R D Gardi Medical College, Ruxmaniben Deepchand Gardi Medical College; SGPGI, Sanjay Gandhi Postgraduate Institute of Medical Sciences; CSIR, Council of Scientific and Industrial Research; WHO, World Health Organization. PI, Principal investigator; N/A, not applicable; AQCH, aqueous extract of *Cocculus hirsutus*; CTRI, Clinical Trials Registry - India; HCQ, healthcare workers; RT-PCR, reverse transcription-polymerase chain reaction; SOFA, sequential organ failure assessment; NS, non-severe; S, severe; Ct, cycle threshold. States and Union Territories (UTs): AP: Andhra Pradesh; AR: Arunachal Pradesh; AS: Assam; BR: Bihar; CG: Chhattisgarh; GA: Goa; GJ: Gujarat; HR: Haryana; HP: Himachal Pradesh; JK: Jammu and Kashmir; JH: Jharkhand; KA: Karnataka; KL: Kerala; MP: Madhya Pradesh; MH: Maharashtra; MN: Manipur; ML: Meghalaya; MZ: Mizoram; N: Nagaland; OR: Odisha; PB: Punjab; RJ: Rajasthan; SK: Sikkim; TN: Tamil Nadu; TR: Tripura; UK: Uttarakhand; UP: Uttar Pradesh; WB: West Bengal; TS: Telangana; AN: Andaman and Nicobar Islands; CH: Chandigarh; DH: Dadra and Nagar Haveli; DD: Daman and Diu; DL: Delhi; LD: Lakshadweep; PY: Puducherry

Table III. Details of AYUSH trials (n=67) on coronavirus disease 2019 registered in the Clinical Trials Registry - India[#]

Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
Ayurveda (n=45)									
Classical (n=21)									
Individual agents (n=11)									
1	CTRI/2020/06/025525	Arm 1: *Guduchi Ghana Vati* Arm 2: Nil	Other	Open label	N/A	20000	Incidence rate of COVID-19 infection	IPGTRA, Jamnagar DCGI approval: N/A	GJ (5 sites)
2	CTRI/2020/05/025488	Arm 1: *Guduchi Ghana Vati* Arm 2: Nil	Randomized, parallel-group trial	Open label	Phase 2/3	12000	Comparative assessment of incidence of COVID-19	NIA, Jaipur DCGI approval: N/A	RJ
3	CTRI/2020/05/025485	Arm 1: *Guduchi Ghana Vati* Arm 2: Standard prophylactic care	Non-randomized, active controlled trial	Open label	Phase 2/3	5000	Comparative assessment of occurrence of COVID-19 infection	NIIMH (CCRAS), Hyderabad DCGI approval: N/A	TS
4	CTRI/2020/05/025385	Arm 1: *Guduchi Ghan Vati* Arm 2: Standard prophylactic care	Non-randomized, multiple-arm trial	N/A	N/A	40000	Comparative assessment of occurrence of COVID-19 infection	CCRAS, New Delhi DCGI approval: N/A	WB, PB, TN, KL (2 sites), MH (2 sites), NL, MP, RJ (2 sites), UP, AS, BR (2 sites), KA, HP, GJ (2 sites), AP
5	CTRI/2020/05/025370	Arm 1: *Guduchi Ghana Vati*	Single-arm trial	Open label	N/A	40	Clinical cure rate: Time to get a negative status of COVID-19	Ayurved University, Jodhpur DCGI approval: N/A	RJ (2 sites)
6	CTRI/2020/05/025213	Arm 1: *Guduchi Ghana Vati*	Single-arm trial	N/A	N/A	1500	Incidence of COVID-19-positive cases as confirmed by RT-PCR	CCRAS, New Delhi DCGI approval: N/A	HP
7	CTRI/2020/05/025088	Arm 1: *Guduchi* Arm 2: Standard prophylactic care	Randomized, parallel-group trial	N/A	Phase 1/2	1200	Comparative assessment of occurrence of COVID-19 infection in healthy volunteers	CCRAS, New Delhi DCGI approval: N/A	AP
8	CTRI/2020/05/025429	Arm 1: *Ashwagandha* + standard prophylactic care Arm 2: Standard prophylactic care	Non-randomized, active controlled trial	Open label	Phase 2/3	5000	Comparative assessment of occurrence of COVID-19 infection	NIIMH (CCRAS), Hyderabad DCGI approval: N/A	TS

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
9	CTRI/2020/05/025332	Arm 1: *Ashwagandha* Arm 2: HCQ	Randomized, parallel-group, active controlled trial	Open label	Phase 2	400	(*i*) Proportion of SARS-CoV-2 infection-free participants on completion of study (*ii*) Proportion of participants contracting COVID-19 during the study period	Ministry of AYUSH; CSIR, New Delhi DCGI approval: N/A	MH
10	CTRI/2020/05/025166	Arm 1: *Ashwagandha*	Randomized, parallel-group trial	Open label	Phase 2/3	1200	Comparative assessment of occurrence of COVID-19 infection	Ministry of AYUSH, New Delhi DCGI approval: N/A	AP
11	CTRI/2020/05/025093	Arm 1: *Yashtimadhu*	Other	N/A	Phase 2/3	1200	Comparative assessment of occurrence of COVID-19 infection	Ministry of AYUSH, New Delhi DCGI approval: N/A	AP
Combination interventions (n=10)									
12	CTRI/2020/05/025171	Arm 1: *Guduchi Ghana Vati* 2.Anu taila 3.Rock salt and turmeric 4. Ayush preventive guidelines Arm 2: Standard prophylactic care	Randomized, parallel-group trial	Open label	Phase 2	50000	Improvement in *bala* of an individual Immuno-stimulation leading to non-development of symptoms of COVID-19 in risk population exposed to infected individuals (*Bala* will be assessed by using specialized proforma including dasvidhapareeksha and other questionnaires which will reveal the physical and mental health of an individual)	AIIA, New Delhi DCGI approval: N/A	DL

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
13	CTRI/2020/05/025069	Arm 1: *Guduchi Ghana Vati (Sanshamani Vati)* or *Sudarshana Ghanavati* or *Ashwagandha*	Single-arm trial	Open label	Phase 3/4	1324	Incidence of COVID-19-positive cases (as confirmed by RT-PCR)	CCRAS, New Delhi DCGI approval: N/A	DL (3 sites)
14	CTRI/2020/05/025482	Arm 1: Curcumin with black pepper Arm 2: Standard treatment	Randomized, parallel-group trial	Investigator blinded	N/A	50	COVID-19 test and acute phase reactants such as D-dimer, CRP, LDH, CBC, ferritin, troponin, cardiac myoglobin, PT INR and appearance of respiratory symptoms	Siddhivinayak Pain Relief Center, Pune DCGI approval: N/A	MH
15	CTRI/2020/06/025637	Arm 1: Piper betel with the combination of *swarnabhasma* (herbomineral combination)	Cluster randomized trial	Participant and investigator blinded	N/A	10	Complete blood picture, serum ferritin, C-reactive protein, LDH, troponin, nucleic acid amplification test and RT-PCR	ABVGMC, Vidisha DCGI approval: N/A	MP
16	CTRI/2020/05/025341*	Arm 1: *Kiratiktadi Kwath; Ashwagandha churna;* Yoga exercises; immunobooster *Ayush Kwath* Arm 2: Standard treatment	Randomized, parallel-group trial	N/A	N/A	30	Efficacy in the management of mild and asymptomatic cases of COVID-19 patients	GS Ayurveda Medical College and Hospital, Ghaziabad DCGI approval: N/A	UP
17	CTRI/2020/04/024731*	Arm 1: *Samshamani Vati*, *Sudarshan Ghana Vati, Khadiradi Vati, Murrchhita Tila Taila* (for Nasya, Arsenic Album 30	Single-arm trial	Open label	Phase 3	50	Episodes and severity of symptoms of respiratory tract infection (cold, sore throat, dry cough, breathlessness)	Parul Institute of Ayurved, Vadodara DCGI approval: N/A	GJ

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
18	CTRI/2020/04/024882	Arm 1: *Kashaya* (decoction) of *Tinospora cordifolia* stem *Piper longum* fruit, and standard treatment Arm 2: Standard treatment	Non-randomized, active controlled trial	N/A	Phase 3	60	1. Percentage of patients progressing to serious/ critical stage of disease 2. Progress of disease as per clinical severity score (COCSS) 3. Number of days of treatment, hospitalization, type of care and site of treatment at hospital, oxygen support requirement, days of ventilation required, period of convalescence and return to normal life activity 4. Number of days taken to test negative for COVID, total days to discharge from hospital 5. Profiling according to *tridosha* 6. Defining the disease according to Ayurveda	Ministry Of AYUSH, New Delhi DCGI approval: N/A	HR
19	CTRI/2020/05/025178	Arm 1: Tab *Samshamani Vati*; Herbal tea; application of *Anu taila; Haridra khanda* Arm 2: Standard prophylactic care	Randomized, parallel-group trial	Open label	Phase 2	140	Improvement in *bala* of an individual *Bala* will be assessed by using specialised proforma including *dashavidhapareeksha* and other questionnaires which will reveal the physical and mental health of an individual	AIIA, New Delhi DCGI approval: N/A	DL

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
20	CTRI/2020/05/025276	Arm 1: *Sanshamani Vati (Tinospora cordifolia*); *Nagaradi kwath* (decoction of *Zingiber officinale, Terminalia chebula* and *Tinospora cordifolia*); *Amalaki Churna* (powder of *Phyllanthus emblica*); Golden Milk (milk with *Curcuma longa*)	Single-arm trial	N/A	Phase 3	50	Time taken and number of patients progressing from asymptomatic to symptomatic condition	Ch Brahm Prakash Ayurved Charak Sansthan, New Delhi DCGI approval: N/A	DL
21	CTRI/2020/05/025398*	Arm 1: *Kiratiktadi Kwath* (Astadashang Kwath) *Sharangdhar Samhita -kwath prakaran; Ashwgandhachurna* with milk; Yoga	Single-arm trial	N/A	N/A	30	1. Efficacy in boosting *Vyadhikshamatwa* and prevention against communicable diseases. 2. Will help in overcoming the anxiety level and stress of HCQs	GS Ayurveda Medical College and Hospital, Hapur DCGI approval: N/A	UP
				Patented products (n=24)					
22	CTRI/2020/06/025557	Arm 1: AYUSH-64 as add on to standard treatment Arm 2: *Yashtimadhu* as add on to standard treatment Arm 3. *Sanshamani Vati* Plus; as add-on standard treatment Arm 4: Standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 2	420	1. Mean time (days) for clinical recovery 2. Proportion of patients showing clinical recovery	Ministry of AYUSH, New Delhi DCGI approval: N/A	MH
				Patented products (n=24)					
23	CTRI/2020/05/025156	Arm 1: AYUSH-64 Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 3/4	60	Clinical cure rate: Time to negative conversion of SARS-CoV-2	CCRAS, New Delhi DCGI approval: N/A	MH
24	CTRI/2020/05/025335	Arm 1: AYUSH-64	Single-arm trial	N/A	Phase 3	40	1. Mean time (days) for clinical recovery as per defined clinical recovery criteria 2. Number of patients showing 'clinical recovery'	CCRAS, New Delhi DCGI approval: N/A	DL

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
25	CTRI/2020/05/025338	Arm 1: AYUSH-64	Single-arm trial	N/A	Phase 2/3	40	1. Mean time (days) for clinical recovery as per defined clinical recovery criteria 2. Number of patients showing 'clinical recovery'	CCRAS, New Delhi DCGI approval: N/A	DL
26	CTRI/2020/05/025214	Arm 1: AYUSH-64 Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 2/3	80	1. Mean time (days) for clinical recovery (day of randomization to the day of clinical recovery) 2. Proportion of patients showing 'clinical recovery'	CCRAS, New Delhi DCGI approval: N/A	CH
27	CTRI/2020/05/025484	Arm 1: Chyawanprash Arm 2: Standard prophylactic care	Non-randomized, active controlled trial	Open label	Phase 2/3	5000	Comparative assessment of occurrence of COVID-19 infection	NIIMH (CCRAS), Hyderabad DCGI approval: N/A	TS
28	CTRI/2020/05/025425	Arm 1: Chyawanprash	Single-arm trial	N/A	Phase 3/4	50	Percentage of participants with SARS CoV-2 positivity as estimated by RT-PCR of nasopharyngeal swab	CCRAS, New Delhi DCGI approval: N/A	DL
29	CTRI/2020/05/024981	Arm 1: Chyawanprash with milk Arm 2: Milk	Randomized, parallel-group trial	Open label	N/A	600	1. Comparative assessment of incidence of COVID-19 2. Comparative assessment of incidence of other non-COVID-19 infections	Dabur India Ltd, Ghaziabad DCGI approval: N/A	GJ (2 sites), MH (2 sites), RJ
30	CTRI/2020/05/025275	Arm 1: Chyawanprash Arm 2: Standard prophylactic care	Randomized, parallel-group trial	N/A	Phase 3	200	Percentage of participants with SARS CoV-2 positivity as estimated by RT-PCR	CCRAS, New Delhi DCGI approval: N/A	DL
31	CTRI/2020/06/025592	Arm 1: Shakti drops; turmeric plus; *Tulsi arka*	Single-arm trial	Open label	Phase 3/4	50	Recovery in the signs and symptoms as fever and respiratory distress	Sri Sri Tattva, Bangalore DCGI approval: N/A	KA

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
32	CTRI/2020/06/025590	Arm 1: Astha-15 capsule and standard treatment Arm 2: Placebo and standard treatment	Randomized, parallel-group, placebo-controlled trial	Participant, investigator and outcome assessor blinded	Phase 3	120	1. Changes in scores of the St. George Respiratory Questionnaire from baseline to EOT visit 2. Changes in scores of the Leicester Cough Questionnaire from baseline to EOT visit	Dalmia Centre for Research and Development, Noida DCGI approval: N/A	AP, RJ, DL, MH
33	CTRI/2020/05/025483	Arm 1: Clevira tablet Arm 2: Standard treatment	Randomized, parallel-group trial	N/A	Phase 3/4	100	1. Time taken for clinical recovery, which is defined as: (*i*) normalization of pyrexia and body pain; (*ii*) respiratory rate <24/minute; (*iii*) SpO_2 rate >94%; (*iv*) relief from cough and maintenance of above for > 72 h 2. Proportion of patients with swabs negative for COVID-19 in RT-PCR at day 5, 10 and 15 3. Reduction of viral load	Apex Laboratories Pvt Ltd, Chennai DCGI approval: N/A	TN
34	CTRI/2020/05/025334	Arm 1: SUVED + Reimmungen	Single-arm trial	N/A	Phase 2	30	Prevention of onset or complications of COVID infection	Health Solutions, Pune DCGI approval: N/A	MH
35	CTRI/2020/05/025343	Arm 1: SUVED + Reimmungen	Single-arm trial	N/A	Phase 2/3	30	Mortality	Health Solutions, Pune DCGI approval: N/A	MH
36	CTRI/2020/05/025340	Arm 1: ShatPlus and standard treatment Arm 2: Standard treatment	Randomized, parallel-group trial	Open label	Phase 1/2	60	1. Number of days for negative PCR confirmatory test from nasopharyngeal swab for SARS-CoV-2 2. Serum levels of CD4, CD8, NK cell panel CD16/CD56, CRP, IgM, IgG	BVG Life Sciences Ltd, Pune DCGI approval: N/A	MH

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
37	CTRI/2020/05/025161	Arm 1: *Aayudh* advance bacteria, viruses Arm 2: Standard treatment	Randomized, parallel-group, active controlled trial	Open label	Phase 2	120	1. Rate of recovery 2. Symptom resolution: fever 3. Symptom resolution: cough 4. Symptom resolution: shortness of breath	Shukla Ashar Impex Pvt Ltd, Rajkot DCGI approval: N/A	GJ
38	CTRI/2020/04/024883	Arm 1: ZingiVir H Arm 2: N/A	Other	Outcome assessor blinded	Phase 4	112	The odds of ratio for improvement on a 7-point ordinal scale on day 15 Each day, the worst score from the previous day will be recorded	Pankajakasthuri Herbal Research Foundation, Thiruvananthapuram DCGI approval: N/A	KA (2 sites), MH
39	CTRI/2020/05/024967	Arm 1: MyVir tablets Arm 2: Standard treatment	Single-arm trial	N/A	Post marketing surveillance	30	Improvement in patients who are assessed daily for symptoms which include cough, fever with or without chills and difficulty in breathing for the period they are in quarantine	Mi Lab LifeSciences Pvt Ltd, Bengaluru, DCGI approval: N/A	KA
40	CTRI/2020/06/025527	Arm 1: Amrta Karuna syrup Arm 2: Standard treatment	Non-randomized, active controlled trial	N/A	Post marketing surveillance	30	1. Improvement in patients who are assessed daily for symptoms which include cough, fever with or without chills and difficulty in breathing	Vopec Pharmaceuticals Pvt Ltd, Chennai DCGI approval: N/A	KA
41	CTRI/2020/05/025326	Arm 1: Tab Pinak	Single-arm trial	N/A	Phase 2	30	Early recovery and reduced mortality	Shree Bharadi Ayurvedic, Maharashtra DCGI approval: N/A	MH

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
42	CTRI/2020/05/025273	Arm 1: Tablet pure Ashwagandha 500 mg; Pure Giloy extract; tablet pure tulsi extract; *Anu Taila*; *Swasari Ras* Arm 2: Placebo therapy	Randomized, parallel-group, placebo-controlled trial	NIL	N/A	120	Virological clearance as measured by RT-PCR of nasopharyngeal swab	Patanjali Research Institute, Haridwar; NIMS, Jaipur DCGI approval: N/A	RJ
43	CTRI/2020/05/025222	Arm 1: AOIM - Z Tablet	Single-arm trial	N/A	Phase 4	275	Prevention of incidence of COVID-19 infection	Shree Dhootapapeshwar Limited, Mumbai DCGI approval: N/A	MH
44	CTRI/2020/05/025434	Arm 1: Zingivir-H	Randomized, parallel-group, placebo-controlled trial	Outcome assessor blinded	Phase 4	135	The odds of ratio for improvement on a 7-point ordinal scale on day 15 and clearance of medically attended lung infection due to RT-PCR confirmed COVID-19 infection	Pankajakasthuri Herbal Research Foundation, Thiruvananthapuram DCGI approval: N/A	KA (2 sites), MH
45	CTRI/2020/06/025556	Arm 1: Virulina Arm 2: Standard treatment	Randomized, parallel-group, placebo-controlled trial	Participant and investigator blinded	N/A	30	1. Time to a negative SARS-CoV-2 RT-PCR result of both oropharyngeal swab and nasopharyngeal swab. 2. Clinical cure based on clinician's assessment of symptoms a. Change in positive COVID-19 status on day 8 and day 15 3. Clinical outcomes a. Proportion of patients on WHO progression scale 0 to 10 on day 8 and day 15	Natural Solutions, Mumbai DCGI approval: N/A	AP

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
				Yoga and Naturopathy (n=3)					
46	CTRI/2020/06/025523	Arm 1: Meditation and breathing exercises and standard treatment Arm 2: Standard treatment	Randomized, parallel-group trial	N/A	N/A	84	Depression, anxiety and stress levels in patients assessed using DASS-21 questionnaire	National Cancer Institute, Jhajjar DCGI approval: N/A	HR
47	CTRI/2020/05/025162	Arm 1: Alternate nostril breathing and guided meditation; (1) *Nadi Shodhan Pranayama*; (2) *Panchakosha* meditation Arm 2: The control group will not receive the intervention.	Randomized, parallel-group trial	N/A	N/A	200	PSQI for sleep quality	JIPMER, Puducherry DCGI approval: N/A	PY
48	CTRI/2020/05/025320*	Arm 1: Yoga and Naturopathy, immune-boosting agents such as ginger Tulsi pepper, Adhimaduram, turmeric, gargling, steam inhalation, Sun bath aromatherapy Arm 2: Standard treatment	Nonrandomized, active controlled trial	N/A	Phase 3/4	658	Time to progress to next stage of severity *i.e.*, from asymptomatic/ uncomplicated/mild pneumonia to moderate/ severe stages	Government Yoga And Naturopathy Medical College, Chennai DCGI approval: N/A	TN (4 sites)
				Unani (n=2)					
49	CTRI/2020/06/025650	Arm 1: *Joshanda* (decoction) of the following: *Behidana (Cydonia oblonga), Unnab (Zizyphus jujube), Sapistan (Cordia myxa)* and *Khameera Marwareed*	Other	Open label	Phase 2	4000	1. Incidence of COVID-19 cases 2. Improvement in immune status using ISQ	Ministry of AYUSH, New Delhi DCGI approval: N/A	KA
50	CTRI/2020/05/025254	Arm 1: *Joshanda* (decoction) and *Khameera Marwareed* Arm 2: *Joshanda* (decoction) and *Tiryaq e Arba* Arm 3: Standard prophylactic care	Non-randomized, multiple-arm trial	N/A	Phase 3	40000	1. Incidence of COVID-19 cases 2. Improvement in immune status using ISQ	CCRUM, New Delhi DCGI approval: N/A	UP, KA, TS, JK, MH, DL

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
				Siddha (n=3)					
51	CTRI/2020/06/025625	Arm 1: *Kabasura Kudineer* and *Bramanandhabairavam* Arm 2: Standard treatment	Other	Open label	Phase 2	86	Proportion of patients confirmed as negative for SARS-CoV-2 in two consecutive throat/nasal swabs (taken 24 h apart) at day 15/day16	Eminentlabs Business Solutions Pvt Ltd, Chennai DCGI approval: N/A	TN
52	CTRI/2020/05/025298	Arm 1: *Kabasura Kudineer Nilavembukudineer*; Arm 2: Standard prophylactic care	Non-randomized, active controlled trial	N/A	N/A	21500	Occurrence of COVID-19 infection	CCRS, Chennai; Ministry of AYUSH, New Delhi DCGI approval: N/A	TN
53	CTRI/2020/05/025215	Arm 1: *Kabasura Kudineer* Arm 2: Vitamin C, zinc supplementation	Randomized, parallel-group trial	Open label	Phase 1/2	50	Reduction in incidence of clinical symptoms of COVID-19, negative conversion of SARS-CoV-2, reduction in viral load of SARS-CoV-2 at the end of treatment and examine the levels immune markers and inflammatory markers	Government Stanley Medical College, Chennai DCGI approval: N/A	TN
				Homeopathy (n=14)					
54	CTRI/2020/06/025530	Arm 1: Aconite 30 + Arsenic album 30 + Allium cepa 30 + Influenzum 30 + Gelsmium 30 + Eupatorium 30 + Echinacia 0 + Thuja 0	Non-randomized, active controlled trial	N/A	N/A	10000	Number of patients with viral fever/COVID-19	Cancer Aid Society, Lucknow DCGI approval: N/A	UP
55	CTRI/2020/05/025491	Arm 1: Arsenic album 30c Arm 2: *Bryonia alba* 30c Arm 3: Camphora 1M Arm 4: Coronavirus-related nosodes (30c potency); Arm 5: Matching placebo pills	Cluster randomized trial	Participant and outcome assessor blinded	Phase 2	1000	Number of patients turning symptomatic	Life Force Foundation Trust, Mumbai DCGI approval: N/A	MH

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
56	CTRI/2020/05/025272	Arm 1: Arsenicum album 30 Arm 2: No. 40 size globules medicated with alcohol 90% v/v is used as placebo	Cluster randomized trial	Participant and investigator blinded	N/A	800	COVID-19 in quarantined persons	Government Homeo Dispensary, Kerala DCGI approval: N/A	KL
57	CTRI/2020/05/025205	Arm 1: Arsenicum album 30c Arm 2: No intervention	Cluster randomized trial	N/A	Phase 2/3	33000	Confirmation of diagnosis for COVID-19 infection based on RT-PCR/end of quarantine period	CCRH, New Delhi DCGI approval: N/A	TN, DL, AP, TS, RJ, WB, KL, MH, UP, GJ
58	CTRI/2020/05/025049	Arm 1: Arsenic album 30c	Cluster randomized trial	Open label	Phase 2/3	100	Clinical recovery (COVID-19 negative) or death	Sai Nidan Homeopathy Clinic, Chhattisgarh DCGI approval: N/A	CG
59	CTRI/2020/05/024986	Arm 1: Arsenic album 30c	Single-arm trial	N/A	N/A	10000	Confirmation of diagnosis for COVID-19 infection/ end of quarantine period as per standard protocol	CCRH, New Delhi DCGI approval: N/A	DL
60	CTRI/2020/05/024969	Arm 1: Arsenic album 30c (variable dose potency and frequency) and standard treatment Arm 2: Placebo and standard treatment	Randomized, parallel-group, placebo-controlled trial	Open label	Phase 2/3	100	Clinical outcome in terms of recovery of patient or requirement of life support (ventilator)/death	Naiminath Homoeopathic Medical College Hospital and Research Centre, Agra DCGI approval: N/A	UP
61	CTRI/2020/04/024926	Arm 1: Arsenic album, *Bryonia alba, Gelsemium,* Antimonium tartaricum, *Crotalus horridus*	Single-arm trial	Participant blinded	Phase 3	100	Clinical recovery (COVID-19 negative) or appearance of symptoms requiring conventional treatment	Naiminath Homoeopathic Medical College Hospital and Research Centre, Agra DCGI approval: N/A	UP

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
62	CTRI/2020/04/024905	Arm 1: Arsenic album, *Bryonia alba, Gelsemium, Antimonium tartaricum, Crotalus horridus* Arm 2: Placebo	Randomized, parallel-group, placebo-controlled trial	Participant blinded	Phase 3	100	Clinical recovery (COVID-19 negative) or death.	Naiminath Homoeopathic Medical College Hospital and Research Centre, Agra DCGI approval: N/A	UP
63	CTRI/2020/04/024857	Arm 1: Arsenic album, Camphora, *Bryonia alba, Helleborus niger, Justicia adhatoda*	Cluster randomized trial	Open label	Phase 1/2	100	Percentage of patient admissions to critical care	Welling Healthcare Private Limited, Mumbai DCGI approval: N/A	MH
64	CTRI/2020/06/025558	Arm 1: *Bryonia alba* 30C Arm 2: Identical placebo	Randomized, parallel-group, placebo-controlled trial	Participant and investigator blinded	Phase 4	300	Prophylactic effect	Aarogya Homoeopathic Medical College and Hospital, Jaipur; Ministry of AYUSH, New Delhi DCGI approval: N/A	RJ
65	CTRI/2020/04/024947	Arm 1: Cadamba 200	Randomized, parallel-group, active controlled trial	N/A	Phase 3	100	Serologically negative blood test for COVID-19	PI initiated, Homeo clinic, Gondia-Maharashtra DCGI approval: N/A	MH
66	CTRI/2020/05/025496	Arm 1: CNV01	Single-arm trial	Open label	Phase 1	10	Safety measure in terms of investigations (PCR) blood parameters	Life Force Foundation Trust, Mumbai DCGI approval: N/A	MH

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Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
67	CTRI/2020/04/024925	Arm 1: Homoeopathic medicine and standard treatment Arm 2: Placebo and standard treatment	Randomized, parallel-group, placebo-controlled trial	Open label	Phase 2	100	Clinical recovery of patient or requirement of life support (ventilator)/death	Bajaj Auto Ltd, Maharashtra DCGI approval: N/A	MH (2 sites)

[#]Registered trials as on June 5, 2020, [*]Trials with combination therapy (involving more than one system of AYUSH) are mentioned in only one category to avoid duplication. AYUSH includes Ayurveda, Yoga, Unani, Siddha, Homeopathy trials. Table data are as per information provided by trialist. The keyword 'Standard treatment' and has been used for uniformity and includes the following category as mentioned by the trialist *i.e.*, standard of care, standard care of treatment and supportive management, standard treatment protocol, local-level standard treatment, best supportive care, treatment guidelines as per MOHFW. The term 'Standard prophylactic care' has been used for uniformity which represents the terminologies used by the trialist for standard preventive measures against COVID-19. AAIA, All India Institute of Ayurveda; ABVGMC, Atal Bihari Vajpayee Government Medical College; AYUSH, Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy; COVID-19, coronavirus disease 2019; CCRAS, Central Council for Research in Ayurvedic Sciences; CCRUM, Central Council for Research in Unani Medicine; CCRS, Central Council for Research in Siddha; CCRH, Central Council for Research in Homoeopathy; CSIR, Council of Scientific and Industrial Research; IPGTRA, Institute for Post Graduate Teaching and Research in Ayurveda; JIPMER, Jawaharlal Institute of Postgraduate Medical Education and Research; NIA, National Institute of Ayurveda; NIIMH (CCRAS), National Institute of Indian Medical Heritage (CCRAS); NIMS, National Institute of Medical Sciences Jaipur; PI, Principal investigator; N/A, not applicable; ISQ, immune status questionnaire; PSQI, Pittsburgh Sleep Quality Index; HCQ, healthcare worker; RT-PCR, reverse transcription polymerase chain reaction; DASS-21, depression, anxiety and stress scale - 21items; DCGI, Drugs Controller General of India; CRP, C-reactive protein; LDH, lactate dehydrogenase; CBC, complete blood count; PT INR, prothrombin time international normalized ratio; NK, natural killer. States and Union Territories (UTs): AP: Andhra Pradesh; AR: Arunachal Pradesh; AS: Assam; BR: Bihar; CG: Chhattisgarh; GA: Goa; GJ: Gujarat; HR: Haryana; HP: Himachal Pradesh; JK: Jammu and Kashmir; JH: Jharkhand; KA: Karnataka; KL: Kerala; MP: Madhya Pradesh; MH: Maharashtra; MN: Manipur; ML: Meghalaya; MZ: Mizoram; N: Nagaland; OR: Odisha; PB: Punjab; RJ: Rajasthan; SK: Sikkim; TN: Tamil Nadu; TR: Tripura; UK: Uttarakhand; UP: Uttar Pradesh; WB: West Bengal; TS: Telangana; AN: Andaman and Nicobar Islands; CH: Chandigarh; DH: Dadra and Nagar Haveli; DD: Daman and Diu; DL: Delhi; LD: Lakshadweep; PY: Puducherry

Table IV. Details of miscellaneous trials (n=13) on coronavirus disease 2019 registered in the Clinical Trials Registry - India[#]

Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
1	CTRI/2020/05/025248	Arm 1: Brief tele-counselling model for coping with psychological concerns associated with COVID-19	Non-randomized, multiple-arm trial	N/A	N/A	128	Anxiety (assessed as a continuous variable on HADS)	PI initiated, MB Hospital RNT Medical College Udaipur DCGI approval: N/A	RJ
2	CTRI/2020/05/025492	Arm 1: Tele-consultation Arm 2: Standard arm with routine follow up visits	Randomized, parallel-group trial	Open label	N/A	2978	Need for emergency room visit or re-hospitalization	JIPMER, Puducherry DCGI approval: N/A	PY
3	CTRI/2020/05/025331	Arm 1: Home-based prehabilitation	Non-randomized, active controlled trial	NIL	N/A	15	Change in emotional functioning by DASS-21, physical functioning by change in performance score (Karnofsky Performance Scale) score and change in respiratory functional parameters	AIIMS, New Delhi DCGI approval: N/A	DL
4	CTRI/2020/05/024962	Arm 1: Povidone-iodine gargles and intranasal application Arm 2: Normal saline	Randomized, parallel-group trial	N/A	N/A	96	Comparing the reduction in the progression, transmission of disease assessed by viral load	Win Medicare Pvt Ltd, Vijaywada DCGI approval: N/A	AP
5	CTRI/2020/05/024983	Arm 1: Topical lignocaine lozenges	Single-arm trial	N/A	N/A	30	Sensitivity of nasal and throat swabs for RT-PCR of COVID-19 after topical lignocaine use	AIIMS, New Delhi DCGI approval: N/A	DL
6	CTRI/2020/04/024776	Arm 1: Chest X-ray artificial intelligence module Arm 2: CT- scan of thorax AI module Arm 3: Voice sampling AI module Arm 4: Normal individuals' chest X-ray, CT-scan thorax and voice sampling	Non-randomized, multiple-arm trial	N/A	N/A	1650	Assess sensitivity and specificity of AI module by performing chest X-ray, CT-thorax and voice sampling	PI initiated RNT Medical College, Udaipur DCGI approval: N/A	RJ (2 sites)

Contd...

Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
7	CTRI/2020/05/025071	Arm 1: Lowest driving pressure-guided PEEP Arm 2: Conventional lung protective ventilation strategy	Randomized, parallel-group trial	Participant blinded	Phase 3	40	Difference in the area under the curve (adjusted to survival time) for Murray's lung injury score in the first 4 days	AIIMS, New Delhi DCGI approval: N/A	DL
8	CTRI/2020/05/025489	Arm 1: CMAC video laryngoscope Arm 2: McGrath MAC video laryngoscope	Randomized, parallel-group trial	Participant and outcome assessor blinded	N/A	60	Time to intubation	AIIMS, New Delhi DCGI approval: N/A	DL
9	CTRI/2020/06/025522	Arm 1: Touren non-channelled video laryngoscope Arm 2: King Vision channelled video laryngoscope	Randomized, cross-over trial	Outcome assessor blinded	N/A	50	Time to intubation	AIIMS, New Delhi DCGI approval: N/A	DL
10	CTRI/2020/06/025589	Arm 1: COVID barrier box with Ambu King vision video laryngoscope Arm 2: COVID barrier box with Macintosh laryngoscope	Randomized, parallel-group, active controlled trial	NIL	N/A	60	Intubation time	AIIMS, Bhubaneswar DCGI approval: N/A	OR
11	CTRI/2020/04/024747	Arm 1: Simulation-based training of ventilatory management of COVID-19 patients	Single-arm trial	Participant and outcome assessor blinded	N/A	26	Prepare a module for non-anaesthesiology trainees to handle ventilators in COVID-19 patients	GSL Medical College, Rajahmundry DCGI approval: N/A	AP
12	CTRI/2020/05/025490*	Arm 1: Chlopromazine + NBE extract concoction + cholecalciferol + *Azadirachta indica* bark extract concoction + *Arsenicum album* + tea + Arm 2: Standard treatment	Randomized parallel-group active controlled trial	Participant and investigator blinded	Phase 2/3	110	Protection from COVID-19 infection	Siddhartha Hospital, Agra DCGI approval: N/A	UP

Contd...

Serial number	CTRI number	Intervention details	Study design	Blinding	Phase	Sample size	Primary outcome	Sponsor and regulatory status	States and UTs
13	CTRI/2020/04/024659	Arm 1: Shreepad Shree Vallabh formulation	Single-arm trial	N/A	Phase 3	30	Improvement in symptoms of ambulatory patients which include cough, fever with or without chills and difficulty in breathing	SSV Phytopharmaceuticals, Mumbai DCGI approval: N/A	MH

[#]Registered trials as on June 5, 2020, [*]Combination trials with modern medicine, Ayurveda and homeopathy. Table data are as per information provided by trialist. AIIMS, All India Institute of Medical Sciences; COVID-19, coronavirus disease 2019; JIPMER, Jawaharlal Institute of Postgraduate Medical Education and Research; MB Hospital RNT Medical College, Maharana Bhupal Hospital, Ravindra Nath Tagore Medical College; PI, principal investigator; AI, artificial intelligence; DCGI, Drugs Controller General of India; N/A, not applicable; HADS, hospital anxiety and depression scale; DASS-21, depression, anxiety and stress scale 21 items; RT-PCR, reverse transcription-polymerase chain reaction. States and Union Territories (UTs): AP: Andhra Pradesh; AR: Arunachal Pradesh; AS: Assam; BR: Bihar; CG: Chhattisgarh; GA: Goa; GJ: Gujarat; HR: Haryana; HP: Himachal Pradesh; JK: Jammu and Kashmir; JH: Jharkhand; KA: Karnataka; KL: Kerala; MP: Madhya Pradesh; MH: Maharashtra; MN: Manipur; ML: Meghalaya; MZ: Mizoram; N: Nagaland; OR: Odisha; PB: Punjab; RJ: Rajasthan; SK: Sikkim; TN: Tamil Nadu; TR: Tripura; UK: Uttarakhand; UP: Uttar Pradesh; WB: West Bengal; TS: Telangana; AN: Andaman and Nicobar Islands; CH: Chandigarh; DH: Dadra and Nagar Haveli; DD: Daman and Diu; DL: Delhi; LD: Lakshadweep; PY: Puducherry

(CTRI/2020/05/025242). In addition, with respect to the growing body of scientific data, regarding risks associated with the use of HCQ, particularly QTc prolongation and cardiac arrhythmias[7], a Phase 2 trial is underway to assess the effect of topical *i.e.,* nasal application of chloroquine in early-stage COVID-19 on viral load and cure rates (CTRI/2020/04/024729).

Immunomodulators

Ciclesonide: A Phase 2 trial being conducted at a government medical college in New Delhi plans to evaluate not only the effects of HCQ but also that of ciclesonide, a glucocorticoid, and ivermectin, an anthelmintic drug, in 120 patients with moderate COVID-19 infection (CTRI/2020/04/024948).

Imatinib: Imatinib, which inhibits BCR - ABL tyrosine kinase, revolutionized the treatment of chronic myelogenous leukaemia[10]. Imatinib has been reported to significantly reduce titres of SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, which depend on ABL kinase activity to fuse and enter into the cells[11,12]. An open-label, randomized, parallel-group Phase 2 trial with imatinib in 100 patients with mild COVID-19 has been registered in the CTRI (CTRI/2020/04/024806).

Itolizumab: This is an anti-CD6 humanized monoclonal IgG1 antibody which acts upstream by inhibiting the co-stimulation of T cells, resulting in decreased release of signature cytokines of Th1 and Th17 cells[13,14]. Sponsored by an Indian pharmaceutical company, this open-label, Phase 2, randomized, parallel-group, active controlled multicenter trial is being conducted on 30 patients with moderate-to-severe COVID-19 to assess mortality rates and possible effects on the dreaded cytokine release syndrome (CTRI/2020/05/024959).

Tocilizumab: Interleukin-6 (IL-6) is believed to play an important role in this syndrome, and an IL-6 receptor blocker, tocilizumab, has generated global interest as a potential agent for patients with severe COVID-19[15]. A multicentric, randomized, Phase 3 trial to evaluate the clinical outcomes and safety of tocilizumab along with standard of care in patients with cytokine release syndrome associated with moderate-to-severe COVID-19 infection has been registered in the CTRI (CTRI/2020/05/025369).

Mycobacterium w: It is a saprophytic cultivable mycobacterium which is a potent immunomodulator. When used as an adjuvant to multidrug therapy, it has been reported to have significant benefits in patients

with tuberculosis, leprosy and HIV-AIDS[16,17]. Three industry-sponsored trials are proposed to be undertaken with this agent in 40 critically ill COVID-19 patients, 480 hospitalized but not critically ill patients as well as 4000 individuals at high risk of contracting the disease. In addition, a Phase 2 observational study with heat killed *Mycobacterium w* as add-on therapy is also underway on 50 hospitalized COVID-19 patients at a private medical college (CTRI/2020/05/025350).

Melatonin: Melatonin is a remarkably safe and established anti-inflammatory and anti-oxidative molecule with significant evidence suggesting its potential for limiting virus-related diseases, which may extend to COVID-19 as well[18]. Melatonin has also been reported to possess significant immunomodulatory effects in cancer[19]. A clinical trial on melatonin is underway to evaluate its role on COVID-19 infection rate along with immune response in high-risk groups after eight weeks of treatment (CTRI/2020/06/025613).

Anthelmintics

Ivermectin: This broad-spectrum antiparasitic agent has been shown to have potent *in vitro* antiviral activity against a variety of viruses. In *in vitro* studies, a single dose has been shown to bring a significant reduction in the replication of SARS-CoV-2[20]. This has generated interest in the possibility of repurposing the drug for the management of COVID-19. A total of four clinical trials (CTRI/2020/04/024858, CTRI/2020/05/025068, CTRI/2020/05/025224, CTRI/2020/05/025333) with ivermectin are underway, three of which aim to establish the therapeutic efficacy of ivermectin in COVID-19 patients. The fourth trial is investigating the prophylactic effect of ivermectin on 2000 healthcare workers or healthy contacts (including children) of COVID-19 patients. The primary outcome for this study is resolution of signs and symptoms of COVID-19 and negative reverse transcription-polymerase chain reaction (RT-PCR) done 48 h after drug administration.

Niclosamide: Used to treat tapeworm infestation, niclosamide inhibits ATP production by uncoupling of oxidative phosphorylation. It has been reported to have *in vitro* antiviral activity[21,22]. A randomized, parallel-group trial which proposes to investigate the virologic cure rates of niclosamide in patients with mild-to-very mild COVID-19 infection has been registered (CTRI/2020/04/024949).

Antihypertensive

Losartan: Angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2 infection and in the process causes internalization and destruction of ACE2[23]. The major complications of COVID-19 are possibly caused by excessive angiotensin II activation due to loss of ACE2 and can be potentially reversed by angiotensin receptor blockers such as losartan[24]. A randomized, parallel-group, placebo-controlled trial of losartan for the prevention of COVID-19 complications has been registered and is being conducted in an academic setting (CTRI/2020/05/025319).

Antioxidant/pro-oxidant agent

Resveratrol-copper and sodium-copper-chlorophyllin: It has been hypothesized that following microbial infection, cell-free chromatin (cfCh) particles are released from dying cells, causing apoptosis and inflammation in the adjoining host cells. This process triggers a vicious cycle leading to sepsis[25]. The novel pro-oxidant combination of resveratrol and copper has been reported to inactivate cfCh and demonstrated improved survival in animal models of sepsis[26].

The commonly used food colorant and dietary supplement, sodium copper chlorophyllin (SCC), has been reported to have significant antimutagenic and antioxidant properties[27]. Two trials with resveratrol-copper and SCC as add-on treatment to standard treatment in asymptomatic/mildly symptomatic patients (Phase 3 trial) as well as hospitalized patients (Phase 2 trial) with COVID-19 have been registered (CTRI/2020/05/025336, CTRI/2020/05/025337).

Antineoplastic

2-deoxy-D-glucose (2-DG): A glucose analogue, 2-deoxy-D-glucose, is believed to have profound effects on a range of diseases such as cancer, viral infection and ageing-related morbidity[28]. Recent *in vitro* studies suggest the potential benefits of using 2-DG to mitigate COVID-19 infection[29,30]. A Phase 2 trial to determine the safety and efficacy of the drug as an adjunctive therapy to standard of care in patients with moderate-to-severe COVID-19 is underway at 12 sites (CTRI/2020/06/025664).

Phytopharmaceutical products

Purified aqueous extract of Cocculus hirsutus (AQCH)

An industry-sponsored trial has been registered with aqueous extract of *Cocculus hirsutus* which is a phytopharmaceutical product derived from the tropical, climbing shrub *C. hirsutus*. This plant has been reported to have significant medicinal properties in a variety of disease conditions including viral

infection[31]. The trial is proposed to be conducted at 14 sites across the country on patients with moderate COVID-19 (CTRI/2020/05/025397).

Thymoquinone

Nigella sativa, commonly known as black cumin, has shown a wide spectrum of biological activities, the most prominent being antioxidant, anti-inflammatory and antimicrobial activities[32]. An open-label, two-arm, parallel study is being conducted to evaluate the efficacy and safety of thymoquinone, a phytopharmaceutical compound extracted from *Nigella sativa* seeds, compared to best supportive care in patients with COVID-19 (CTRI/2020/05/025167).

Cell- and plasma-based therapies

Convalescent plasma therapy (CPT)

For immediate short-term immunity, convalescent plasma therapy (CPT) has generated particular interest as it appears to be safe, to be clinically effective and reduces mortality in times of large-scale epidemics[33-35]. The ICMR has developed a protocol, which is approved by the Drugs Controller General of India, for a multicentre trial (PLACID trial) to test the efficacy of convalescent plasma obtained from recovered COVID-19 patients for administration to moderately ill COVID-19 patients. This is a multicentre, randomized, parallel-group, open-label, active controlled Phase 2 trial to be conducted on 452 patients at 39 sites in India (CTRI/2020/04/024775). In addition, two other trials have been registered which are being conducted by private hospitals on 100 patients each (CTRI/2020/04/024915, CTRI/2020/05/025328). Further, five additional small trials have also been registered investigating the role of CPT in hospitalized severely ill COVID-19 patients (CTRI/2020/04/024706, CTRI/2020/04/024804,CTRI/2020/05/025299,CTRI/2020/05/025346, CTRI/2020/05/025209).

Cytokine cocktail therapy

A Phase 1 trial to evaluate the safety and tolerability of cytokine cocktail therapy in healthy volunteers from healthy donors (derived by T cells) has been registered (CTRI/2020/05/025432). This trial is being conducted at Bengaluru, Karnataka.

Biological products

Vaccines

As per reports, vaccine against COVID-19 is being developed in about 90 institutions worldwide[36]. Bacille Calmette-Guérin (BCG) is believed to stimulate the general immune response with a consequent faster response to infections that could reduce the severity of disease and lead to quicker recovery rates[37]. In India, mass immunization with BCG has been underway since 1948[38]. The global interest in BCG was recently sparked when Miller *et al*[39], reported a negative correlation between BCG immunization status of a country and mortalities due to COVID-19. In the CTRI, currently, there are three BCG vaccine trials registered. One of these is on the BCG-Denmark (Green Signal) vaccine for the prevention of COVID-19 in 1826 healthcare workers, whereas the other is a Phase 3 trial of recombinant BCG VPM1002 vaccine for the reduction in infection incidence and severity of COVID-19 in 5946 high risk individuals. Both these trials are triple-blinded, randomized, parallel-group, placebo-controlled trials (CTRI/2020/04/024833 and CTRI/2020/04/024749, respectively). A single-blind, single-centre Phase 2 trial on 60 patients, is evaluating the therapeutic efficacy of BCG in COVID-I9 (CTRI/2020/05/025013).

Traditional medicine

During this pandemic, the potential of traditional medicine is being actively explored through the conduct of clinical trials to identify prophylactic as well as therapeutic agents. The AYUSH approach to manage the outbreak broadly comprises: preventive and prophylactic, symptom management of COVID-19-like illnesses and add-on interventions to the conventional care[40]. Trials in the AYUSH system of medicine have been registered in the CTRI (n=67) and include Ayurveda (n=45), Yoga and Naturopathy (n=3), Unani (n=2), Siddha (n=3), Homeopathy (n=14) trials (Table III).

Ayurveda

Ayurveda is a comprehensive system of medicine that has been practiced in India for >5000 years[41]. A total of 45 Ayurveda trials (Tables I and III) are currently registered in the CTRI. These are categorized as individual agents (11 trials) or combination preparations (10 trials, of which 3 trials include other systems of AYUSH such as homeopathy and/or yoga) as available under classical interventions. In addition, there are 24 trials registered on patented ayurvedic products. Four major plant products are under investigation, namely *Tinospora cordifolia*, *Withania somnifera*, *Glycyrrhiza glabra* and *Curcuma longa* (only in combination with other agents).

While the classical interventions, individual and combination trials (n=21), are mostly designed to

assess their prophylactic efficacy (n=16) in either healthy human volunteers in the community or those at risk (n=16), the trials with patented products (n=24) are primarily investigating the therapeutic efficacy (n=18) in patients ranging from asymptomatic to moderate to severe COVID-19 patients (Table I).

Classical interventions

Guduchi: *Tinospora cordifolia,* commonly named as *Guduchi*, is used in a variety of conditions in the traditional Ayurvedic literature[42]. *Guduchi* has been reported to possess a range of activities (antipyretic, anti-inflammatory, antioxidant, anti-infective, anti-neoplastic and immuno-modulatory effects) notable in the context of COVID-19[43]. Currently, in the CTRI, there are seven registered trials investigating the role of only *Guduchi*, in healthy high risk individuals in the community to test its role as a preventive agent against COVID-19. Four of these are large trials with sample size ranging from 5000 to 40,000 (the latter has 20 sites across India). In addition, there are three trials exploring the effects of *Guduchi* in combination with other agents. One of these is being conducted on 50,000 police personnel in Delhi (Table III).

Ashwagandha: *Withania somnifera* (Ashwagandha) is well known for its anti-inflammatory, antitumour, anti-stress, antioxidant, immunomodulatory, hemopoietic and rejuvenating properties[44]. In addition, it has been demonstrated to inhibit certain RNA viruses[45]. The role of Ashwagandha in the prevention of COVID-19 is being investigated in three trials registered in the CTRI, one of which is on 5000 high-risk participants (CTRI/2020/05/025429).

Turmeric: The antiviral effects of curcumin, a plant derivative of turmeric, have been demonstrated in *in vitro* studies, which makes it an antiviral drug candidate[46]. Evaluation of the effects of curcumin and adjuvants in COVID-19 patients, in terms of changes in acute-phase reactants and clinical outcome, is being evaluated in a randomized, parallel-group trial on 50 patients (CTRI/2020/05/025482). In addition, polyherbal compounds are being investigated for immunomodulatory and antiviral properties and their potential as therapeutic and prophylactic agents.

Patented products

Currently, there are 24 trials registered on patented products including AYUSH-64 patented by Central Council for Research in Ayurvedic Sciences.

AYUSH 64: A multiplant formulation, AYUSH-64, has been demonstrated to be useful in several research studies carried out over several decades to treat febrile infections including malaria and is considered to possess anti-inflammatory and immunomodulatory effects[47]. One of its components, *Glycyrrhiza glabra* or *Yashtimadhu*, has demonstrated potential as a wound-healing, anti-ulcer and anti-inflammatory agent[48]. In addition, recent studies reveal that *Yashtimadhu* may interfere with viral entry as well as replication, thereby impacting the severity of infection[49]. Further, AYUSH-64 along with standard care has been shown to be effective in influenza-like illnesses with potential for better outcomes[50]. While a community-based clinical study on 1200 healthy but at-risk individuals has been registered in the CTRI to evaluate the preventive role of only *Yashtimadhu*, there are five trials on the proprietary formulation, AYUSH 64 (Table III).

Chyawanprash: This is an ancient Indian polyherbal formulation prepared according to a traditional Ayurvedic recipe. It consists of about 50 different medicinal herbs including *Emblica officinalis* (Indian gooseberry or *Amla*), a rich source of vitamin C, as well as processed minerals and is considered as an essential health supplement[51]. Currently, four trials are registered which are investigating the preventive role of Chyawanprash in high risk healthcare workers/containment zone population as well as the community (Table III).

Yoga and naturopathy

Stress is known to suppress the immune system and is believed to be the harbinger of many diseases including respiratory infections[52,53]. Evidence supports the role of meditation in regulating the stress response and impacting virus-specific immune response[54,55]. Further, *Pranayama* has been shown to have a positive impact on lung function[56]. Currently, three yoga trials are registered, of which two randomized, parallel-group trials focus on the role of *Pranayama* and meditation in the prevention as well as treatment of COVID-19. In addition, in one trial, yoga is being tried in combination with naturopathy and Ayurvedic agents (CTRI/2020/05/025320).

Unani

The Unani system of medicine, originally from Greece, has been influenced by Ayurveda, Siddha and Chinese systems of medicine. Even though an ancient system, Unani medicine also recommends isolation and quarantine during an epidemic. In addition, it also

recommends (*i*) cleanliness, (*ii*) health boosting and immune-modulation, and (*iii*) use of drugs[57]. Two trials investigating the prophylactic role of Unani medicine: one is on 4000 participants and the other on 40,000 participants, have been registered in population at risk of contracting COVID-19 (Table III).

Siddha

The Siddha system, one of the six accepted branches of Indian systems of medicine, is particularly popular in southern India. Although it is similar to Ayurveda in certain aspects, these are two distinct streams of medicine[58]. There are three Siddha trials registered investigating the role of *Kabasura Kudineer*, a Siddha formulation alone and in combination as a preventive agent in the management of asymptomatic COVID-19 patients (Table III).

Homeopathy

Homeopathy focuses on patient characteristics rather than disease *per se*[59]. There has been a call to utilize the benefits of homeopathy as a therapeutic system suitable to cope with this pandemic[60,61]. Several homeopathic agents have been recommended by the Ministry of AYUSH, Government of India, for the prevention of COVID-19. Of the 14 homeopathic trials registered in the CTRI, most (n=11) are of *Arsenicum album 30* or *Bryonia alba* (Table III).

Miscellaneous trials

Thirteen trials have been categorized as miscellaneous trials as these explore a range of interventions such as nutraceuticals, process-of-care changes (n=9) and critical care-related trials and include management of non-COVID-19 patients in the pandemic (Table I). Some of these trials evaluate methods to minimize infection risks, whereas others compare different types of video laryngoscopes for ease of intubation while wearing personal protective equipment (Table IV). Some of the other registered trials in this category include efficacy of nutraceuticals, feasibility of developing a novel artificial intelligence algorithm to screen COVID-19, telemedicine and ventilatory management training to ramp up capacity.

Observational studies

Apart from the clinical trials, the CTRI has registered observational studies on COVID-19 as well. Due to the imposition of lockdown and the imperative need for social distancing, observational studies have been undertaken to assess the impact of COVID-19 on mental health, clinical practice in general and in particular for oncology patients. Findings and observations from these studies would likely help develop better guidelines for the care of the most vulnerable in these pandemic times.

Concluding remarks

Notwithstanding the deadly virulence of the SARS-CoV-2 and the enforcement of widespread physical restrictions, medical researchers in India have risen to the dual challenge of caring for the sick and testing potential therapeutic options. This article culls the data of 122 COVID-19-related trials from the data of over 27,000 trials registered in the CTRI and presents a concise and comprehensive overview of the pharmacological and clinical aspects of the registered trials. This also provides a comprehensive insight into the COVID-19 clinical research underway in the country through CTRI database. This would encourage researchers to critically review CTRI data, identify gaps particularly methodological and design aspects of research and further decide on acceptability of the results. We hope that this information would help researchers to not only understand the clinical research scenario, but also encourage healthy debate, train researchers to avoid obvious errors/oversights, steer clear of repetitive research and indirectly promote the quality of research in the country.

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