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

Journal of Herbal Medicine 29 (2021) 100472

Contents lists available at ScienceDirect

Journal of Herbal Medicine

journal homepage: www.elsevier.com/locate/hermed

Research paper

Comparative retrospective open-label study of ayurvedic medicines and their combination with allopathic drugs on asymptomatic and mildly-symptomatic COVID-19 patients

Acharya Balkrishna [a,b], Aarti Ben Bhatt [c], Pratima Singh [a], Swati Haldar [a], Anurag Varshney [a,b,d,*]

[a] Drug Discovery and Development Division, Patanjali Research Institute, Roorkee-Haridwar Road, Haridwar 249405, Uttarakhand, India
[b] Department of Allied and Applied Sciences, University of Patanjali, NH-58, Haridwar 249405, Uttarakhand, India
[c] Patanjali Chikitsalaya, UL-17A, Harekrishna Complex, Paldi, Ahmedabad 380007, Gujarat, India
[d] Special Centre for Systems Medicine, Jawaharlal Nehru University, New Delhi-110067, India

ARTICLE INFO

Keywords:
COVID-19
Divya Swasari Ras
Giloy Ghanvati
Tulsi Ghanvati
Anu Taila
Ashwagandha
Ayurveda

ABSTRACT

Introduction: Treatment for COVID-19 was ambiguous in the beginning of the pandemic. At that time, the conventional medical system was grappling to cope with the rapidly spreading pandemic. The potential of Ayurveda, one of the branches of traditional Indian medicine (TIM), with a 5000 year old history, employing medicines derived from plants and other natural sources, against COVID-19 has been explored through a comparative retrospective open-label study.

Methods: Reported here are the remedial effects of Ayurvedic medicines alone or in combination with Allopathic treatment on 59 asymptomatic or mildly symptomatic COVID-19 patients, across multiple COVID-19 care centers in Ahmedabad, India. The patients were confirmed for COVID-19 infection through RT-qPCR of nasopharyngeal swabs. With informed consents from the patients, the sourced data was divided into 'Allopathic and Ayurvedic' [AlloAyur] (n = 41) and 'Ayurvedic only' [Ayur] (n = 18) groups, based on the type of treatment the patients decided to receive, that is Ayurvedic medicines with Allopathic treatment or Ayurvedic medicines alone, respectively. Ayurvedic medicines included oral doses and nasal drops; the dosage and regime were decided based on the recommendations from Ayurvedic texts. The Allopathic medicines included Azithromycin, Vitamin-C and anti-histamines. Acetaminophen was also administered when necessary, by the attending physician. The patients were observed for symptomatic improvement.

Results: Primary outcome of this study was the symptomatic relief from COVID-19. Data collected over a period of two months, showed that more patients exhibited symptomatic relief in Ayur goup (83.33 %) than in the AlloAyur group (48.78 %) within the first 13 days of treatment. No visible adverse effects were observed. This indicated faster and safe symptomatic resolution among those treated with Ayurvedic medicines alone.

Conclusion: Patients receiving only Ayurvedic medicines on average were symptomatically relieved faster than those receiving Allopathic and Ayurvedic medicines together.

1. Introduction

COVID-19, the disease with influenza-like symptoms in mild to moderate cases and acute respiratory distress syndrome (ARDS)-like symptoms in severe cases, was first reported in December 2019 and soon spread across the world as a pandemic (Lu et al., 2020; Zhu et al., 2020). The new coronavirus, SARS-CoV-2, was identified to be the causative agent of this disease (Zheng, 2020). The human cost alone of COVID-19 is distressing, let alone the socio-economic and psychological burdens that has compounded the crisis. In the absence of any specific drug, management of COVID-19 relies on supportive care and non-specific treatments. WHO has recognized the long standing history of Traditional Medicine (TM) and understands it as an inherited legacy of repertoire of knowledge, skills and practices indigenous to a culture.

* Corresponding author at: Drug Discovery and Development Division, Patanjali Research Institute, Roorkee-Haridwar Road, Haridwar 249405, Uttarakhand, India.
E-mail address: anurag@prft.co.in (A. Varshney).

https://doi.org/10.1016/j.hermed.2021.100472
Received 20 September 2020; Received in revised form 2 April 2021; Accepted 18 May 2021
Available online 21 May 2021

Table 1
Constituents of the Ayurvedic medicines used in this study.

Ayurvedic Medicine	Scientific name of the constituent	Traditional name (in Hindi)
Divya Swasari Ras (DSR)[1]	*Glycyrrhiza glabra* L.	Mulethi
	Syzygium aromaticum (L.) Merr. & L.M.Perry	Lavang
	Cinnamomum zeylanicum Blume	Dalchini
	Pistacia integerrima J.L. Stewart ex Brandis	Kakdasinghi
	Cressa cretica (L.)	Rudanti
	Zingiber officinale Rosco	Sounth
	Piper nigrum (L.)	Marich
	Piper longum (L.)	Chhoti pipal
	Anacyclus pyrethrum (L.) Lag.	Akarkara
	Herbally processed calcined mica ash	Abhraka bhasma
	Herbally processed calcined shell of Pearl oyster ash	Mukta-shukti bhasma
	Herbally processed calcium rich gypsum ash	Godanti bhasma
	Herbally processed calcined cowry shell ash of *Cypraea moneta* (L.)	Kapardak bhasma
Giloy Ghanvati (GG)[2]	*Tinospora cordifolia* (Willd.) Miers	Guduchi
Ashwagandha Capsule (AC)[3]	*Withania somnifera* (L.) Dunal	Ashwagandha
Tulsi Ghanvati (TG)[4]	*Ocimum sanctum* (L.)	Tulsi
Anu Taila (AT)[5]	*Leptadenia reticulate* (Retz.) Wight & Arn.	Jivanti
	Phyla nodiflora	Jala
	Cedrus deodara	Devdaru
	Cyperus scariosus	Nagarmotha
	Cinnamomum zeylanicum Blume	Dalchini
	Vetiveria zizanioides	Sevya (Useera)
	Hemidesmus indicus	Anantmool (Sareeva)
	Santalum album	Swet Chandan
	Berberis aristata	Daruhaldi
	Glycyrrhiza glabra L.	Mulethi
	Cyperus scariosus	Plawa
	Aquilaria agallocha	Agaru
	Asparagus racemosus	Satavari
	Boerhavia diffusa	Punarnava
	Aegle marmelos	Bel
	Nymphaea stellata Willd	Utpala
	Solanum indicum	Brahati
	Solanum virginianum	Kantkari
	Pluchea lanceolata	Surbhi (Rasna)
	Desmodium gangeticum	Salparni
	Uraria picta	Prashanprani
	Embelia ribes	Vidang
	Cinnamomum tamala	Tejpatra
	Amomum aromaticum Roxb.	Truti (Suksmaila)
	Vitex negundo	Renuka
	Mallotus philippensis	Kamala Kinjala
	Goat milk	Ajadugdha
	Sesame oil	Till taila

[1]Detailed ingredient composition of DSR and respective plant parts has been described in Balkrishna et al., 2020b; [2]Chemical characterization of GG (containing stem extracts) and [3]AC (containing root extracts) have been described earlier (Balkrishna et al., 2021b, 2021d); [4]TG contains whole plant extracts; [5]AT prepared according to the classical ayurvedic formulation (Pharmacopoeia Commission for Indian Medicine & Homeopathy, 2016; Vaidyanath, 2017).

TMs might or might not be explicable; nevertheless, used in the maintenance and improvement of health. China has reported several studies claiming the efficacy of Traditional Chinese Medicine (TCM) against COVID-19. In fact, three formulations, Lianhua Qingwen Capsule, Jinhua Qinggan Granule, and Xuebijing Injection have been made commercially available (Koe, 2020). However, these TCMs are not free from skepticism as scientists outside China feel that these treatments might not be acceptable, particularly, in the absence of rigorous clinical data (Cyranoski, 2020). Therefore attempts, at making TCM evidence based are being made through reviewing and meta-analyses of entries from various databases (Li et al., 2020), case reports (Ren et al., 2020) and clinical trials (Lim, 2020; Xu and Zhang, 2020; Yang et al., 2020). However, such assiduous efforts towards exploring the potentials of Ayurveda, the 5000-year-old system of Traditional Indian Medicine (TIM) against COVID-19 is grossly lacking. Based on pilot study and short-term clinical trials, The National Centre for Complementary and Integrative Health has reported the effectiveness of TIM against diseases like, osteoarthritis, rheumatoid arthritis, type 2 diabetes, ulcerative colitis and breast cancer ("Ayurvedic medicine: In depth," 2019). Interestingly, *Charak Samhita*, one of the canonical texts of Ayurveda recognizes epidemic as *janapadodhwamsa vikara*, which literally translates into a disease that can destroy human habitations through massive death rate. Ayurvedic medicines were used to treat patients during 2006 outbreak of Chikungunya epidemic in India (Girija and Sivan, 2020). From Ayurvedic point of view, COVID-19 is also an epidemic. However, except for a single case study report (Girija and Sivan, 2020) and a few recent trial reports (Devpura et al., 2021; Wanjarkhedkar et al., 2020) on Ayurvedic treatment ameliorating COVID-19 infection, there is no contemporary scientific evidence suggesting the potential role of Ayurveda in preventing, containing and treating COVID-19. Ayurveda uses medicines derived from natural sources (Rastogi et al., 2020). There are government advisories on using Ayurvedic treatments as immunity boosters and pragmatic planning for Ayurvedic intervention against COVID-19 (Ministry of AYUSH, 2020; Rastogi et al., 2020). Nevertheless, there is a lack of evidence, generated through planned clinical studies on remedial effect of TIM against COVID-19.

Using the principles of Ayurveda, the authors have developed a prescription to treat COVID-19, which includes commercially available

medicines, Divya Swasari Ras (DSR), Giloy Ghanvati (GG), Ashwagandha capsule (AC), Tulsi Ghanvati (TG) and Anu Taila (AT). Constituents of these medicines are listed in Table 1.

DSR is a poly herbo-mineral formulation; its constituents are mentioned in classical ancient Ayurveda, for the treatment of disorders related to respiratory tract such as, cough, bronchitis, asthma, rhinitis and excessive mucous formation which have been validated through preclinical studies (Balkrishna et al., 2020b). DSR has been used in clinical settings at several Ayurvedic hospitals across India, on several thousand patients as registered in Patanjali Electronic Medical Records (PEMR).

GG is composed of natural compounds extracted from *Tinospora cordifolia* (traditionally, known as 'Giloy' or 'Guduchi' in India). Computational studies have shown that tinocordiside, one of the major phytocompounds, of *T. cordifolia* docks into the ACE2-RBD complex, and therefore, has the potential to disrupt this critical interaction (Balkrishna et al., 2020a). Besides, *T. cordifolia* is an excellent immunostimulant and effective against various microbial infections (Sinha et al., 2004). Other major phytocomponents, reported in *T. cordifolia*, tinosporine, diterpenoid furano lactone, tinosporaside, cordifolide, cordifol, syringin, clerodane furano diterpene, tinosporidine, columbin, heptacosanol, b-sitosterol and tinosporide, cordifolioside A and syringin, possess immunomodulatory activity. In fact, tinosporin, diterpenoid has been claimed specially for the treatment of viruses including all subgroups of retroviruses (HIV-1, HIV-2), HTLV and Herpes simplex Virus (HSV) (Ghosh and Saha, 2012).

ACs are composed of natural compounds from *Withania somnifera* (traditionally, known as Ashwagandha in India). Like tinocordiside, withanone, one of the major phytochemicals present in *W. somnifera* could also bind at the interface of SARS-CoV-2 spike (S) protein receptor binding domain (RBD) and host ACE2 receptor complex, as suggested by docking and molecular dynamic simulation studies. This disrupted the ACE2-RBD interaction, critical for the entry of virus into host cell (Balkrishna et al., 2021c). Other computational studies have reported that withanone can also target SARS-CoV-2 main protease (M^{pro}) and host transmembrane TMPRSS2 (Kumar et al., 2020a, 2020b). *Ocimum sanctum* (Tulsi) provides a vast array of health benefits, anti-viral effects, being one of them (Cohen, 2014; Mahajan et al., 2013; Pattanayak et al., 2010). *O. sanctum* is very rich in phytochemicals. It has been discovered that scutellarein, a natural flavone found in *O. sanctum*, docks into the active site of RNA dependent RNA Polymerase (RDRP) enzyme of SARS-CoV-2 coronavirus, which is indispensable for viral multiplication (unpublished data).

Nasal congestion, anosmia, runny nose, sneezing, fever and whole-body fatigue are symptoms associated with COVID-19 infection. In Ayurvedic practice, Anu Taila is used for Nasya processes (nasal drops) to reduce inflammation in nasal passage and respiratory tract. The poly-herbal components of Anu Taila, *Aegle marmelos* (Nicolis et al., 2009; Pynam and Dharmesh, 2018; Rajaram et al., 2018), *Asparagus racemosus* (Gautam et al., 2009; Kanwar and Bhutani, 2010; Tiwari et al., 2017), *Aquilaria agallocha* (Yadav et al., 2013b), *Cedrus deodara* (Gupta et al., 2011), *Cinnamomum verum* (Hagenlocher et al., 2013), *Coleus vettiveroides* (Ma et al., 2019), *Cyperus esculentus* (Krichene et al., 2016), *Cyperus rotundus* (Kamala et al., 2018), *Desmodium gangeticum* (Yadav et al., 2013a), *Elettaria cardamomum* (Majdalawieh and Carr, 2010), *Embelia ribes* (Shirole et al., 2015), *Glycyrrhiza glabra* (Lee et al., 2019), *Nelumbo mucifera* (Zhao et al., 2010), *Ocimum sanctum* (Choudhury et al., 2014), and *Pogostemon cablin* (Yang et al., 2018) have anti-inflammatory potential and can ameliorate pro-inflammatory cytokines such as IL-1β, TNF-α, IFN-γ, IP-10, MCP-1, IL-4, and IL-8.

Despite, all this information, clinical research data on the effects of Ayurvedic medicines on COVID-19 are almost non-existent. Therefore, a comparative retrospective open-label study on the COVID-19 positive patients in different COVID-19 care centers across Ahmedabad, Gujarat, India was conducted to evaluate the potential remedial effects of the Ayurvedic medicines on this disease.

2. Materials and methods

2.1. Study population and study design

With informed consent, the medical data of 59 patients who chose to be given either Allopathic treatment in combination with Ayurvedic medicines ('AlloAyur' group) (n = 41) or Ayurvedic medicines alone ('Ayur' group) (n = 18) between May 2020 and June 2020 was mined. These patients, after being confirmed as COVID-19 positive through RT-qPCR of nasal swab samples, were admitted at various COVID-19 care centers in Ahmedabad, Gujarat, India. Data was sourced from medical record departments (MRDs) of these care centers. Clinically, these cases were asymptomatic to mildly symptomatic in nature. None of these patients had any international travel history. Primary outcome of this study was symptomatic resolution of COVID-19 infection.

2.1.1. Inclusion criteria

Patients between 10–80 years of age from either gender, who were either asymptomatic or demonstrated one of the clinical symptoms, namely, fever, cough, headache, fatigue, sore throat, nasal congestion and dyspnea (mild). All patients were verified to be positive for COVID-19 through RT-qPCR for nasopharyngeal swab tests. Ability to give informed consent was the other important inclusion criteria.

2.2. Exclusion criteria

Patients with severe COVID-19 and ARDS symptoms and any co-morbid condition, such as, end stage renal disease (ESRD), decompensated heart failure and decompensated liver failure, responsible for life expectancy less than a year were excluded from the study.

2.3. Study completion criteria

The study completion criteria included regaining normal body temperature, relief from cough, headache, fatigue, sore throat, nasal congestion and/or dyspnea. Alleviation of COVID-19 symptoms were monitored for at least 72 h to ensure no relapses before discharge of the patients were approved from the care center and concomitantly, from the study.

2.4. Treatment

The Allopathic medicines administered were based on the symptoms exhibited by the patients. Under the treatment regime of Allopathic medicines, Azithromycin along with Vitamin-C and anti-histamine were given. Acetaminophen was also administered, when necessary, by the attending physician. Ayurvedic medicines administered were based on the principles mentioned in the texts on Traditional Indian Medicine (TIM). Total daily doses of 2 g each of DSR and GG and 1 g each of AC and TG, respectively, were administered orally with lukewarm water. DSR was given 30 min before meals. The rest were given 30 min after meal. 4 drops of AT were applied to each nostril 1 h before breakfast. A daily dosage regime for these Ayurvedic medicines is provided in Table 2. DSR, GG, TG, AC and AT are commercially available Ayurvedic medicines. DSR (Batch #A SWV002) and AT (Batch # B ANT070) were sourced from Divya Pharmacy, Haridwar, India and were manufactured as per license number UK-274/2013. AC (Batch # AF20/98), GG (Batch # AAHZ20/012) and TG (Batch # AAH20/052) were sourced from Patanjali Ayurved Ltd., Haridwar, India and were manufactured as per license number: Uttara/Ayu-117/2007.

2.5. Patient evaluation

At baseline, the clinical symptoms of the patients such as, body temperature, cough, fatigue, headache, sore throat, nasal congestion and dyspnea were monitored. Subsequently, these parameters were

Table 2
Recommended Daily Ayurvedic Treatment Regime for COVID-19 Patients.

Ayurvedic Medicine*	Daily Dose #		Time of Administration (Daily)	
	Morning	Evening	Morning	Evening
Divya Swasari Ras (500 mg)	2 tablets	2 tablets	30 min BEFORE breakfast	30 minutes BEFORE dinner
Giloy Ghanvati (500 mg)	2 tablets	2 tablets	30 min AFTER breakfast	30 minutes AFTER dinner
Ashwagandha Capsule (500 mg)	1 capsule	1 capsule		
Tulsi Ghanvati (500 mg)	1 tablet	1 tablet		
Anu Taila	4 drops in each nostril	---	60 min BEFORE breakfast	---

* Detailed composition of these Ayurvedic medicines have been provided in Table 1.
\# Half doses for the patients below 15 years.

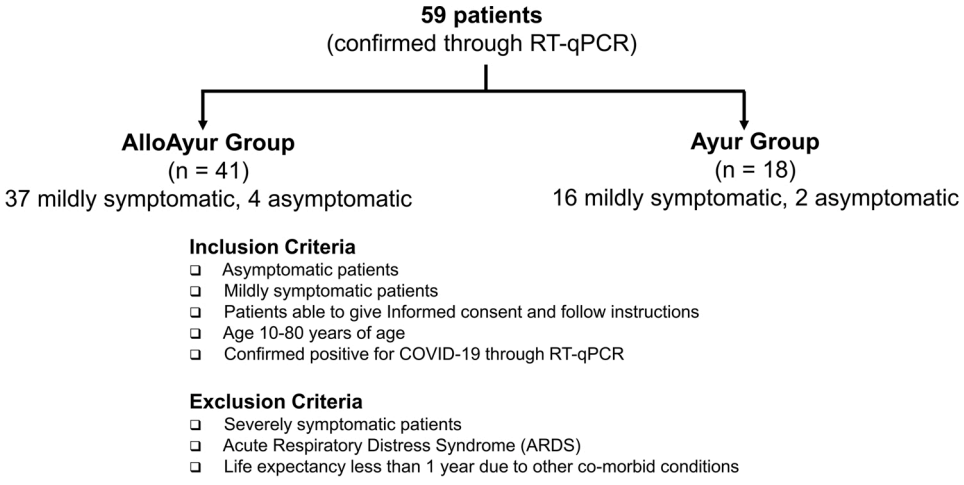

Fig. 1. Design of the study.
Schematic showing the study groups, sample sizes, inclusion and exclusion criteria. A larger sample size of intervention group was the result of going by patients' decisions to the type of treatment to be administered; most opted for Ayurvedic medicine along with Allopathic medicine (AlloAyur group).

regularly tracked along with any other visible symptoms or any side-effects of the treatment.

2.6. Data representation

Overall and group-wise age distributions are represented as percent COVID-19 cases in different age ranges. Gender distribution within each age group is shown as percent male/female of the total patients within that particular group and is shown as proportional bar graphs. Gender distribution within study groups is represented as pie chart. Percent recovery within and after 13 days in the AlloAyur and Ayur groups are represented as proportional bar graphs. The trend in recovery in both groups was compared through Kaplan Meier curve using GraphPad Prism 7.0 (San Diego, CA, USA).

3. Results

3.1. Freedom to choose treatment options affected the sample sizes of study groups

Although the authors intended to include asymptomatic to mildly symptomatic patients, the patient pool that was observed presented mostly mildly symptomatic cases. 53 out of 59 patients (89.8 %) were mildly symptomatic. The intervention was to cover a wide age range and thus, included patients between 10–80 years, accordingly, the dosages varied. For patients below 15 years, half of the dose mentioned in Table 1 was administered. Since, patient consent was the key modulator in grouping, we eventually had 41 patients in the AlloAyur group and 18 in the Ayur group. Sizes of the groups was practically an outcome of the decisions the patients took. The study plan, inclusion and exclusion criteria and number of asymptomatic and mildly symptomatic cases in each group are mentioned in Fig. 1. No patients with severe symptoms,

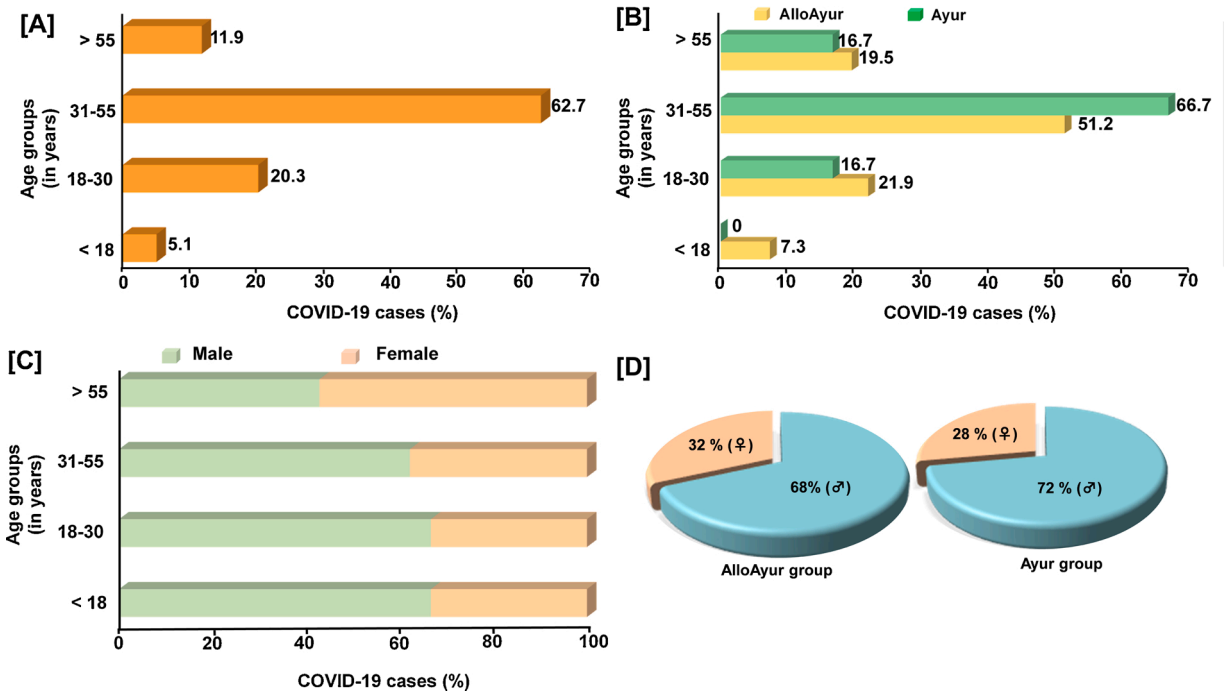

Fig. 2. Age and gender distribution.
[A, B] Frequency distribution of all the enrolled COVID-19 cases (A) and separately within AlloAyur and Ayur groups (B) across different age groups. [C] Gender distribution across different age groups. [D] Gender distribution in the AlloAyur and Ayur groups.

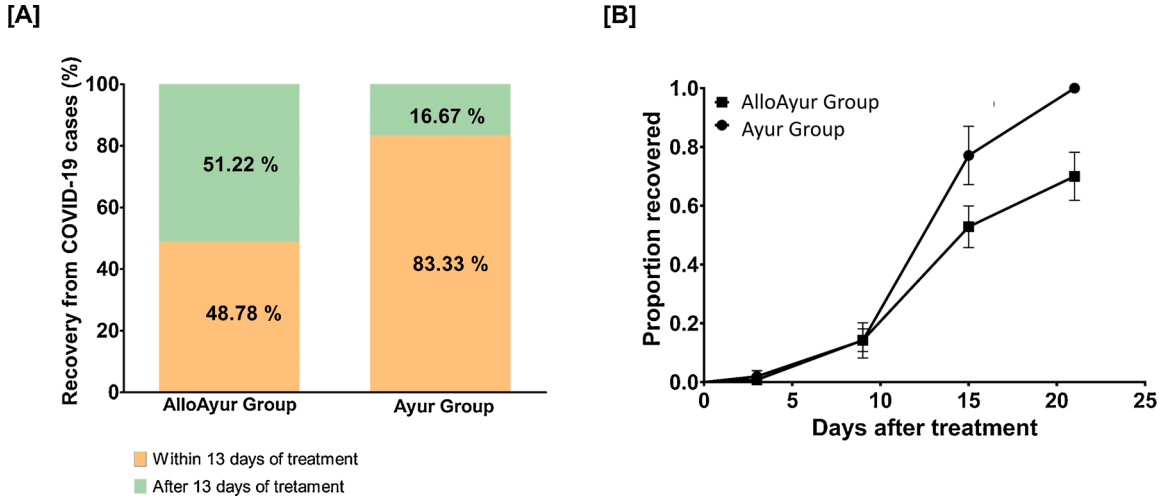

Fig. 3. Effect of Ayurvedic medicines on the time of recovery of COVID-19 patients.
[A] Recovery efficiencies in the AlloAyur and Ayur groups within and after 13 days of treatment. [B] Kaplan Meier Curve showing proportion of recovery.

who required respiratory aids were included. Such patients would be beyond their judgement for informed consent or taking any decision. Patients with acute respiratory distress syndrome (ARDS) were also excluded because of the reasons mentioned earlier for those with severe symptoms. In order to keep the readouts of our observations clean and as much noise-free as possible, patients with co-morbidities responsible for life expectancies less than a year were also excluded.

3.2. Age and gender distribution among the observed patients

The authors analyzed the age distribution of the COVID-19 cases that were followed in this study and found that most of them (62.71 %) were in the age bracket of 31–55 years, followed by 20.34 % and 11.86 % in the age groups of 18–30 and > 55 years, respectively. Only 5% cases were observed among patients < 18 years of age (Fig. 2A). Similar age distribution was observed separately for both the study groups (Fig. 2B). No mortality was reported. It was found that male patients under the authors observation were more prone to COVID-19 infection in all the age groups except beyond 55 years where the trend switched with 57.14 % patients to be female and 42.86 % patients to be male. 66.67 % of total patients below 18 years and between 18-30 years of age, were male and 33.33 % were females. Similarly, 62.16 % of total patients between 31–55 years were male while 37.84 % were females (Fig. 2C). In order to rule out the possibility of skewed gender distribution affecting the primary observation on remedial effects of Ayurvedic medicines on COVID-19 infection, the male-female percentages in the AlloAyur and Ayur groups were analyzed. The gender distribution within these groups were similar; AlloAyur group had 68 % male and 32 % female and Ayur group

had 72 % male and 28 % female (Fig. 2D).

3.3. Patients receiving Ayurvedic medicines alone exhibited faster recovery

The most encouraging observation is the trend of expedited symptomatic relief in the Ayur group where the patients were on Ayurvedic medicines only. 15 out of 18 patients in this group were relieved from COVID-19 symptoms within the first 13 days of treatment exhibiting 83.33 % recovery. In comparison, out of 41 patients in the AlloAyur group, 20 experienced symptomatic relief making a 48.78 % recovery within the first 13 days (Fig. 3A). A Kaplan Meier curve was plotted to quantitatively visualize the pattern of recovery efficiencies within the AlloAyur and Ayur groups. Up to 9 days of treatment, similar proportion of recovery was seen in both the groups. However, the recovery proportion was visibly more in the Ayur group, than the AlloAyur group, by day 15 of the treatment. This proportion became 1 by day 21, indicating 100 % recovery by this time in the Ayur group. Unlike the Ayur group, the recovery proportion in the AlloAyur group by day 21 was 0.7, demonstrating visible lagging behind. However, the calculated Mantel-Cox log rank p value was 0.0854, suggesting that the difference between the two curves was not statistically significant. This was likely to be the effect of non-uniformity of the group sizes and overall small sample size. Therefore, a statistically significant remedial effect on COVID-19 infection in the Ayur group, in comparison to the AlloAyur group, could not be deduced. A bigger sample size with uniformity in patient distribution is required to establish the statistical significance and give verity to this observation. In addition, the other important observation was the absence of any adverse side-effects associated with these Ayurvedic medicines in this study.

4. Discussion

The main aim of this study was to evaluate the potential of Ayurvedic medicines against COVID-19 infection. The premise for this study has been recognition of epidemic in Ayurveda, mention of treatments for ailments with symptoms resembling those of mild to moderate cases of COVID-19 and reports on anti-viral, immune-modulatory and anti-inflammatory effects of the Ayurvedic medicines being studied or their individual constituents (Balkrishna et al., 2021b, 2020b, 2020a; Choudhury et al., 2014; Gautam et al., 2009; Gupta et al., 2011; Hagenlocher et al., 2013; Kamala et al., 2018; Kanwar and Bhutani, 2010; Lee et al., 2019; Mahajan et al., 2013; Majdalawieh and Carr, 2010; Nicolis et al., 2009; Pattanayak et al., 2010; Pynam and Dharmesh, 2018; Rajaram et al., 2018; Sinha et al., 2004; Tiwari et al., 2017; Yadav et al., 2013a).

Ayurveda is a well-documented form of medicine with historical roots. The formulations and dosage of the medicines used in this study were based on the information from different ancient texts of Ayurveda. Formulation and dosage of DSR was adopted from *Bhav Prakash Nighantu*, *Ayurved Sar Sangraha*, Ayurvedic Formulary of India and Ayurvedic Pharmacopoeia of India (Namjoshi, 2003; Pharmacopoeia Commission for Indian Medicine and Homeopathy, 2016). Similarly, information on AC, GG and TG was obtained from *Bhav Prakash Nighantu*, on page numbers 393, 269 and 509, respectively (Lucas, 2017). Composition and dosage recommendations for AT were guided from *Ayurved Sar Sangrah* (page number 679) (Vaidyanath, 2017) and Ayurvedic Pharmacopoeia of India (Pharmacopoeia Commission for Indian Medicine and Homeopathy, 2016). The constituting natural compounds present in these medicines have well-established safety profiles from their routine applications in treating patients according to Ayurvedic practices as also evident from absence of adverse effects in the context of the current study. This was a comparative open-label retrospective study to check the hypothesis that medicines used in Ayurvedic treatments can ameliorate asymptomatic to mildly symptomatic cases of COVID-19. Thus, instead of a pre-meditated design, this study was shaped entirely by the patients' discretion after they were made aware of the objective of the study. This reflected as the apparent non-uniformity of group sizes. The authors ensured through the exclusion criteria that no critical case was included. Nevertheless, this study has offered observations encouraging enough to consider the potentials of Ayurvedic medicines against the novel coronavirus and pursue similar studies on a bigger scale.

This study was supervised by suitably qualified physicians. The risks and burdens of the Ayurvedic interventions used in this study were judged prior to the treatments being tested. This complied with one of the provisions of the World Medical Association (WMA, declaration of Helsinki) that allows unproven interventions to be studied (Carlson et al., 2004). Moreover, the medicines used in this study have their firm roots in Ayurveda, the ancient Indian science of medicine, with the safety of usage well documented therein. The formulations and recommended applications of the Ayurvedic medicines used here are already mentioned in Ayurveda, implicating that they have already been in use without toxicity issues, as also evident from absolute lack of visible side-effects in the patients. Three patients had Diabetes mellitus, one was hypertensive and two had both Diabetes mellitus and hypertension yet responded positively towards the treatment without any adverse effects.

The authors observed that the patients who decided to take only Ayurvedic medicines were relieved of their symptoms faster as compared to those who chose to supplement their Allopathic treatments with Ayurvedic medicines. This was evident from the higher percentage of patients on Ayurvedic medicines only recovering by the thirteenth day of treatment as compared to those who received both Allopathic and Ayurvedic medicines. All the patients on Ayurvedic medicines were completely relieved of their symptoms by 21 days of treatment while, the recovery proportion was 0.7 among those who decided to take the combinatorial treatment of Allopathic and Ayurvedic medicines. Due to the small sample size, this observation with a log rank p value of 0.0854 was not quite statistically significant, nevertheless, without missing to establish an expedited time of symptomatic relief from COVID-19 with only Ayurvedic treatment.

COVID-19 causes viraemia after entering the body and the main clinical manifestations are fever, pharyngalgia, fatigue, diarrhea and other non-specific symptoms. The phytochemicals present in the Ayurvedic medicines mentioned here work at different steps of viraemia, such as, to prevent viral entry (Balkrishna et al., 2021b, 2020a), to inhibit viral replication (unpublished data), and to reduce inflammation of the respiratory tract and strengthen immunity (Balkrishna et al., 2020b). Observations from a randomized placebo controlled pilot clinical study, that evaluated the effectivity of these medicines on a slightly larger asymptomatic to mildly symptomatic patient pool, upholds our findings from this study (Devpura et al., 2021). For better patient compliance, AC, GG and TG were combined and formulated into a tablet, called 'Coronil' and subsequently, its pharmacological effects against SARS-CoV-2 spike protein have been confirmed through *in-vitro* ((Balkrishna et al., 2021a) and *in-vivo* (Balkrishna et al., 2020c) studies.

The observation that only Ayurvedic medicines were capable of comparatively faster symptomatic resolution of COVID-19 relative to Allopathic-Ayurvedic combinatorial treatment actually testifies the newly emerging concept of herb-drug interactions (HDI) (Borse et al., 2019). Allopathy and Ayurvedic medicines have different pharmacokinetic and pharmacodynamic properties. Allopathy medicines work as single target agents, while Ayurvedic formulations, being composed of mainly, phytochemicals, are capable of multi-targeting. With an increase in the acceptance of integrative treatment approach, combining conventional and complementary principles, better understanding of HDIs has become necessary, because, this combination does not always lead to synergism (Borse et al., 2019). In this case, the combinatorial treatment is likely to have experienced antagonistic effect as evident from visibly less effective symptomatic resolution of COVID-19 in the AlloAyur group.

Non-uniform sizes of the study groups was a prominent drawback of this study. However, the two groups were comparable in terms of everything else at the baseline, except for their sizes. In fact, the gender distribution within the two groups (68 % male, 32 % female in AlloAyur group versus 72 % male, 28 % female in Ayur group) clearly reflects that they are comparable in terms of the disease prevalence with respect to gender. COVID-19 positive cases included in this study were asymptomatic or mildly symptomatic, therefore, the efficacy of Ayurvedic medicines on the severe patients and patients with co-morbidities require further evaluation as the observations from this trial cannot be generalized to them. Moreover, the study was non-blind and was based on patient preference rather than random allocation of study groups. These drawbacks might lead to lack of balance on unmeasured characteristics. Nevertheless, the observations from this study do serve as forerunner for a randomized study with bigger sample size in future, which could address these limitations efficiently.

5. Conclusions

In conclusion, this study demonstrated that in comparison of Allopathic to Ayurvedic combinatorial intervention, Ayurvedic medicine alone can reduce the time to symptomatic recovery in asymptomatic and mildly symptomatic COVID-19 patients. This study also implicates the potential of Ayurvedic medicine against COVID-19 infection.

Funding

This research received no external funding. Ayurvedic medicines were sourced by Patanjali Research Institute and the expenditure was covered by internal funding of the institute. The Allopathic medicines administered to the participating patients were provided by the COVID-19 care centers where the patients were assigned.

Ethical approval

This study was approved by the Institutional Ethical Committee (IEC) of Amena Khatun Hospital, Ahmedabad, Gujarat, India (Ref. No. AKHEC/2020/0719/01). IEC of Amena Khatun Hospital is registered with Ministry of Health and Family Welfare, Government of India (Registration No. ECR/1090/Inst/GJ/2018).

Consent to participate and publish

Written informed consent of the participants or their parents/guardian (in case of minor patients) was obtained for participation in the study and publication of the data.

CRediT authorship contribution statement

Acharya Balkrishna: Conceptualization, Resources, Project administration, Funding acquisition. **Aarti Ben Bhatt:** Methodology, Validation, Investigation, Visualization. **Pratima Singh:** Software, Validation, Formal analysis, Visualization. **Swati Haldar:** Software, Validation, Formal analysis, Data curation, Writing - original draft. **Anurag Varshney:** Conceptualization, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The test articles, DSR and AT were sourced from Divya Pharmacy, Haridwar, Uttarakhand, India and test article AC, GG and TG were sourced from Patanjali Ayurved Ltd., Haridwar, Uttarakhand, India. Acharya Balkrishna is an honorary trustee in Divya Yog Mandir Trust and holds an honorary managerial position in Patanjali Ayurved Ltd., Haridwar, India. Besides, providing the test article, Divya Pharmacy or Patanjali Ayurved Ltd. was not involved in any aspect of this study. All other authors have no conflicts of interest to declare.

Acknowledgments

First and foremost, we are thankful to the patients who gave their consent to use their information in this survey. We express our sincere gratitude to Dr. Alok Verma and Dr. Dilip Patel for their whole-hearted support throughout this study. We are grateful to Drs. Nishchal Pandya, Nidhi Rishi, Kunal Shah and Sonika Raj for their support as attending physicians for this study. We extend our thankfulness to Mr. Vijay Vyas and Ms. Aanal Vyas for patient co-ordination and data collection; and to Dr. Rajesh Mishra for classical Ayurved literature supports. We are also thankful to Dr. Ashutosh Shukla, Ms. Priyanka Kandpal, Mr. Gagan Kumar and Mr. Lalit Mohan for their swift administrative supports.

References

Ayurvedic medicine: In depth [WWW Document], 2019. Natl. Cent. Complement. Integr. U.S. Dep. Heal. Hum. Serv. Natl. Institutes Heal. URL https://nccih.nih.gov/health/ayurveda/introduction.htm (accessed 7.2.20).

Balkrishna, A., Pokhrel, S., Varshney, A., 2020a. Tinocordiside from Tinospora cordifolia (Giloy) may curb SARS-CoV-2 contagion by disrupting the electrostatic interactions between host ACE2 and viral S-Protein receptor binding domain. Comb. Chem. High Throughput Screen. 23 https://doi.org/10.2174/1386207323666201110152615.

Balkrishna, A., Solleti, S.K., Singh, H., Tomer, M., Sharma, N., Varshney, A., 2020b. Calcio-herbal formulation, Divya-Swasari-Ras, alleviates chronic inflammation and suppresses airway remodelling in mouse model of allergic asthma by modulating pro-inflammatory cytokine response. Biomed. Pharmacother. 126, 110063 https://doi.org/10.1016/j.biopha.2020.110063.

Balkrishna, A., Solleti, S.K., Verma, S., Varshney, A., 2020c. Application of humanized zebrafish model in the suppression of SARS-CoV-2 spike protein induced pathology by tri-herbal medicine coronil via cytokine modulation. Molecules 25, 5091. https://doi.org/10.3390/molecules25215091.

Balkrishna, A., Haldar, S., Singh, H., Roy, P., Varshney, A., 2021a. Coronil, a tri-herbal formulation, attenuates spike- protein mediated SARS-CoV-2 viral entry into human alveolar epithelial cells and pro-inflammatory cytokines production by inhibiting spike protein-ACE-2 interaction. J. Inflamm. Res. 14, 869–884.

Balkrishna, A., Khandrika, L., Varshney, A., 2021b. Giloy Ghanvati (Tinospora cordifolia (Willd.) hook. F. And thomson) reversed SARS-CoV-2 viral spike-protein induced disease phenotype in the xenotransplant model of humanized zebrafish. Front. Pharmacol. 12, 1–14. https://doi.org/10.3389/fphar.2021.635510.

Balkrishna, A., Pokhrel, S., Singh, H., Joshi, M., Mulay, V.P., Haldar, S., Varshney, A., 2021c. Withanone from Withania somnifera attenuates SARS-CoV-2 RBD and host ACE2 interactions to rescue spike protein induced pathologies in humanized zebrafish model. Drug Des. Dev. Ther. 15, 1111–1133.

Balkrishna, A., Solleti, S.K., Singh, H., Sharma, N., Varshney, A., 2021d. Withanolides from Withania somnifera ameliorate neutrophil infiltration in endotoxin-induced peritonitis by regulating oxidative stress and inflammatory cytokines. Planta Med. 1–14. https://doi.org/10.1055/a-1438-2816.

Borse, S.P., Singh, D.P., Nivsarkar, M., 2019. Understanding the relevance of herb–drug interaction studies with special focus on interplays: a prerequisite for integrative medicine. Porto Biomed. J. 4, e15. https://doi.org/10.1016/j.pbj.0000000000000015.

Carlson, R.V., Boyd, K.M., Webb, D.J., 2004. The revision of the Declaration of Helsinki: past, present and future. Br. J. Clin. Pharmacol. 57, 695–713. https://doi.org/10.1111/j.1365-2125.2004.02103.x.

Choudhury, S.S., Bashyam, L., Manthapuram, N., Bitla, P., Kollipara, P., Tetali, S.D., 2014. Ocimum sanctum leaf extracts attenuate human monocytic (THP-1) cell activation. J. Ethnopharmacol. 154, 148–155. https://doi.org/10.1016/j.jep.2014.03.049.

Cohen, M.M., 2014. Tulsi - Ocimum sanctum: a herb for all reasons. J. Ayurveda Integr. Med. https://doi.org/10.4103/0975-9476.146554.

Cyranoski, D., 2020. China is promoting coronavirus treatments based on unproven traditional medicines. Nature. https://doi.org/10.1038/d41586-020-01284-x.

Devpura, G., Tomar, B.S., Nathiya, D., Sharma, A., Bhandari, D., Haldar, S., Balkrishna, A., Varshney, A., 2021. Randomized placebo-controlled pilot clinical trial on the efficacy of ayurvedic treatment regime on COVID-19 positive patients. Phytomedicine 84, 153494. https://doi.org/10.1016/j.phymed.2021.153494.

Gautam, M., Saha, S., Bani, S., Kaul, A., Mishra, S., Patil, D., Satti, N.K., Suri, K.A., Gairola, S., Suresh, K., Jadhav, S., Qazi, G.N., Patwardhan, B., 2009. Immunomodulatory activity of Asparagus racemosus on systemic Th1/Th2 immunity: implications for immunoadjuvant potential. J. Ethnopharmacol. 121, 241–247. https://doi.org/10.1016/j.jep.2008.10.028.

Ghosh, S., Saha, S., 2012. Tinospora cordifolia: one plant, many roles. Anc. Sci. Life 31, 151. https://doi.org/10.4103/0257-7941.107344.

Girija, P.L.T., Sivan, N., 2020. Ayurvedic treatment of COVID-19/SARS-CoV-2: a case report. J. Ayurveda Integr. Med. https://doi.org/10.1016/j.jaim.2020.06.001.

Gupta, S., Walia, A., Malan, R., 2011. Phytochemistry and pharmacology of Cedrus deodera: an overview. Int. J. Pharm. Sci. Res. 2, 2010–2020. https://doi.org/10.13040/IJPSR.0975-8232.2(8).2010-20.

Hagenlocher, Y., Bergheim, I., Zacheja, S., Schäffer, M., Bischoff, S.C., Lorentz, A., 2013. Cinnamon extract inhibits degranulation and de novo synthesis of inflammatory mediators in mast cells. Allergy Eur. J. Allergy Clin. Immunol. 68, 490–497. https://doi.org/10.1111/all.12122.

Kamala, A., Middha, S.K., Karigar, C.S., 2018. Plants in traditional medicine with special reference to Cyperus rotundus L.: a review. 3 Biotech 8, 1–11. https://doi.org/10.1007/s13205-018-1328-6.

Kanwar, A.S., Bhutani, K.K., 2010. Effects of Chlorophytum arundinaceum, Asparagus adscendens and Asparagus racemosus on pro-inflammatory cytokine and corticosterone levels produced by stress. Phyther. Res. 24, 1562–1566. https://doi.org/10.1002/ptr.3218.

Koe, T., 2020. It' S Official : China Adds Three TCM Formula to COVID-19 Standard Therapy [WWW Document]. URL https://www.nutraingredients-asia.com/Article/2020/04/24/It-s-official-China-adds-three-TCM-formula-to-COVID-19-standard-therapy (accessed 1.4.21).

Krichene, D., Artieda, D.A., Zarrouk, M., Astiasaran, I., 2016. International journal of pharmacy. Int. J. Pharm. 3, 211–216.

Kumar, V., Dhanjal, J.K., Bhargava, P., Kaul, A., Wang, J., Zhang, H., Kaul, S.C., Wadhwa, R., Sundar, D., 2020a. Withanone and withaferin-A are predicted to interact with transmembrane protease serine 2 (TMPRSS2) and block entry of SARS-CoV-2 into cells. J. Biomol. Struct. Dyn. https://doi.org/10.1080/07391102.2020.1775704.

Kumar, V., Dhanjal, J.K., Kaul, S.C., Wadhwa, R., Sundar, D., 2020b. Withanone and caffeic acid phenethyl ester are predicted to interact with main protease (Mpro) of SARS-CoV-2 and inhibit its activity. J. Biomol. Struct. Dyn. https://doi.org/10.1080/07391102.2020.1772108.

Lee, S.A., Lee, S.H., Kim, J.Y., Lee, W.S., 2019. Effects of glycyrrhizin on lipopolysaccharide-induced acute lung injury in a mouse model. J. Thorac. Dis. 11, 1287–1302. https://doi.org/10.21037/jtd.2019.04.14.

Li, Y., Liu, X., Guo, L., Li, J., Zhong, D., Zhang, Y., Clarke, M., Jin, R., 2020. Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: protocol for a systematic review and meta-Analysis. Syst. Rev. 9, 1–6. https://doi.org/10.1186/s13643-020-01343-4.

Lim, G.Y., 2020. TCM And COVID-19 : China Conducting Trials to Test Efficacy and Safety of Traditional Herbal Interventions [WWW Document]. URL https://www.nutraingredients-asia.com/Article/2020/04/06/TCM-and-COVID-19-China-conducting-trials-to-test-efficacy-and-safety-of-traditional-herbal-interventions (accessed 1.4.21).

Lu, H., Stratton, C.W., Tang, Y.W., 2020. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J. Med. Virol. 92, 401–402. https://doi.org/10.1002/jmv.25678.

Lucas, D.S., 2017. Bhav Prakash Nighantu (Indian Materia Medica of Shri Bhavamishra). Chaukhambha Visvabharati.

Ma, C., Zou, L., Xia, Y., Tu, Y., Xue, D., Yang, Y., Liu, D., Liu, Y., Wu, H., Dan, H., You, P., 2019. Extracts of Coleus forskohlii relieves cough and asthma symptoms via modulating inflammation and the extracellular matrix. J. Cell. Biochem. 120, 9648–9655. https://doi.org/10.1002/jcb.28243.

Mahajan, N., Rawal, S., Verma, M., Poddar, M., Alok, S., 2013. A phytopharmacological overview on Ocimum species with special emphasis on Ocimum sanctum. Biomed. Prev. Nutr. 3, 185–192. https://doi.org/10.1016/j.bionut.2012.08.002.

Majdalawieh, A.F., Carr, R.I., 2010. In vitro investigation of the potential immunomodulatory and anti-cancer activities of black pepper (Piper nigrum) and cardamom (Elettaria cardamomum). J. Med. Food 13, 371–381. https://doi.org/10.1089/jmf.2009.1131.

Ministry of AYUSH, G. of I, 2020. Ayurveda's Immunity Boosting Measures for Self Care During COVID 19 Crisis. Ministry of AYUSH, Government of India.

Namjoshi, A.N., 2003. The Ayurvedic Formulary of India, The Ayurvedic Formulary of India. Govt. of India, Ministry of Health & Family Welfare, Dept. of Indian Systems of Medicine and Homoepathy.

Nicolis, E., Lampronti, I., Dechecchi, M.C., Borgatti, M., Tamanini, A., Bezzerri, V., Bianchi, N., Mazzon, M., Mancini, I., Giri, M.G., Rizzotti, P., Gambari, R., Cabrini, G., 2009. Modulation of expression of IL-8 gene in bronchial epithelial cells by 5-methoxypsoralen. Int. Immunopharmacol. 9, 1411–1422. https://doi.org/10.1016/j.intimp.2009.08.013.

Pattanayak, P., Behera, P., Das, D., Panda, S., 2010. Ocimum sanctum Linn. A reservoir plant for therapeutic applications: an overview. Pharmacogn. Rev. 4, 95–105. https://doi.org/10.4103/0973-7847.65323.

Pharmacopoeia Commission for Indian Medicine & Homeopathy, 2016. The Ayurvedic Pharmacopoeia of India, first. ed. Ministry of AYUSH, Government of India.

Pynam, H., Dharmesh, S.M., 2018. Antioxidant and anti-inflammatory properties of marmelosin from Bael (Aegle marmelos L.); Inhibition of TNF-α mediated inflammatory/tumor markers. Biomed. Pharmacother. 106, 98–108. https://doi.org/10.1016/j.biopha.2018.06.053.

Rajaram, A., Vanaja, G.R., Vyakaranam, P., Rachamallu, A., Reddy, G.V., Anilkumar, K., Arunasree, K.M., Dhyani, A., Prasad, N.K., Sharma, S., Chandra Joshi, M., Kimothi, G.P., Brindavanam, N.B., Reddanna, P., 2018. Anti-inflammatory profile of Aegle marmelos (L) Correa (bilva) with special reference to young roots grown in different parts of India. J. Ayurveda Integr. Med. 9, 90–98. https://doi.org/10.1016/j.jaim.2017.03.006.

Rastogi, S., Pandey, D.N., Singh, R.H., 2020. COVID-19 pandemic: a pragmatic plan for ayurveda intervention. J. Ayurveda Integr. Med. 2–5. https://doi.org/10.1016/j.jaim.2020.04.002.

Ren, Jling, Zhang, A.H., Wang, X.J., 2020. Traditional Chinese medicine for COVID-19 treatment. Pharmacol. Res. 155, 104743 https://doi.org/10.1016/j.phrs.2020.104743.

Shirole, R.L., Shirole, N.L., Saraf, M.N., 2015. Embelia ribes ameliorates lipopolysaccharide-induced acute respiratory distress syndrome. J. Ethnopharmacol. 168, 356–363. https://doi.org/10.1016/j.jep.2015.03.009.

Sinha, K., Mishra, N., Singh, J., Khanuja, S., 2004. Tinospora cordifolia (Guduchi), a reservoir plant for therapeutic applications: a Review. Indian J. Tradit. Knowl. 03, 257–270.

Tiwari, N., Gupta, V.K., Pandey, P., Patel, D.K., Banerjee, S., Darokar, M.P., Pal, A., 2017. Adjuvant effect of Asparagus racemosus Willd. Derived saponins in antibody production, allergic response and pro-inflammatory cytokine modulation. Biomed. Pharmacother. 86, 555–561. https://doi.org/10.1016/j.biopha.2016.11.087.

Vaidyanath, 2017. Ayurved Sar Sangrah. Shri Vaidyanath Ayurved Bhawan Ltd.

Wanjarkhedkar, P., Sarade, G., Purandare, B., Kelkar, D., 2020. A prospective clinical study of an Ayurveda regimen in COVID 19 patients. J. Ayurveda Integr. Med. 1–5. https://doi.org/10.1016/j.jaim.2020.10.008. Available.

Xu, J., Zhang, Y., 2020. Traditional chinese medicine treatment of COVID-19. Complement. Ther. Clin. Pract. 39, 101165 https://doi.org/10.1016/j.ctcp.2020.101165.

Yadav, A.K., Agrawal, J., Pal, A., Gupta, M.M., 2013a. Novel anti-inflammatory phytoconstituents from Desmodium gangeticum. Nat. Prod. Res. 27, 1639–1645. https://doi.org/10.1080/14786419.2012.761620.

Yadav, D., Mudgal, V., Agrawal, J., Maurya, A., Bawankule, D., Chanotiya, C., Khan, F., Thul, S., 2013b. Molecular docking and ADME studies of natural compounds of agarwood oil for topical anti-inflammatory activity. Curr. Comput. Aided-Drug Des. 9, 360–370. https://doi.org/10.2174/1573409911309030012.

Yang, H.M., Zhuo, J.Y., Sun, C.Y., Nie, J., Yuan, J., Liu, Y.L., Lin, R.F., Lai, X.P., Su, Z.R., Li, Y.C., 2018. Pogostone attenuates TNF-α-induced injury in A549 cells via inhibiting NF-κB and activating Nrf2 pathways. Int. Immunopharmacol. 62, 15–22. https://doi.org/10.1016/j.intimp.2018.06.029.

Yang, Y., Islam, M.S., Wang, J., Li, Y., Chen, X., 2020. Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. Int. J. Biol. Sci. 16, 1708–1717. https://doi.org/10.7150/ijbs.45538.

Zhao, L., Wang, X., Chang, Q., Xu, J., Huang, Y., Guo, Q., Zhang, S., Wang, W., Chen, X., Wang, J., 2010. Neferine, a bisbenzylisoquinline alkaloid attenuates bleomycin-induced pulmonary fibrosis. Eur. J. Pharmacol. 627, 304–312. https://doi.org/10.1016/j.ejphar.2009.11.007.

Zheng, J., 2020. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int. J. Biol. Sci. 16, 1678–1685. https://doi.org/10.7150/ijbs.45053.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G.F., Tan, W., 2020. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733. https://doi.org/10.1056/NEJMoa2001017.