

A retrospective analysis of the effect of the intervention of *Arogya Kashayam* in COVID-19 positive cases in Madhya Pradesh

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Abstract

Introduction: Coronavirus disease (COVID-19) is a newly identified strain of corona virus that causes illness ranging from the clinical features similar to the common cold to a fatal condition due to severe respiratory failure. According to the WHO, there have been more than 26.3 million confirmed COVID-19 cases in more than 190 countries to date. In light of the outbreak, various treatment modalities have been considered, including traditional medicine, which has been widely used in the pandemic of severe acute respiratory syndrome (SARS) and H₁N₁ influenza. Ayurveda contributes a measurable ratio in the world's traditional practices. As per the guideline of directorate of AYUSH, Government of Madhya Pradesh, cases of COVID-19 were intervened with *Arogya Kashayam* (AK-20), a decoction prepared from the herbs at 88 COVID Care Centers (CCC) across the state. **Aim:** To evaluate retrospectively, the effect of the intervention of AK-20 in COVID-19 positive cases as stand alone or in combination with hydroxychloroquine (HCQ) administered at CCC in Madhya Pradesh. **Materials and Methods:** It is a retrospective study with 4432 COVID-19 reverse transcription-polymerase chain reaction (RT-PCR) tested positive cases including 2750 males and 1682 females between 5 and 80 years of age. All the cases were intervened with AK-20 as stand alone or in combination with HCQ. Moreover, these patients were also given Zinc and Vitamin C simultaneously. The intervention of AK-20 was made through the district level government AYUSH machinery, and the related data were collected in specially designed case report form. The data were analyzed retrospectively, and outcomes included the RT-PCR testing or asymptomatic discharge from the CCC as per the prevailing ICMR guidelines. **Results:** The present study reveals that out of 4432 COVID-19 RT-PCR-positive cases, 2817 (63.56%) received HCQ with AK-20 and 1615 cases (36.43%) received AK-20 as a stand alone treatment. Among the cases that received HCQ and AK-20, 2681 cases (94.17%) recovered completely in an average of 6.8 days and among those who were on standalone AK-20, 1502 cases (93.00%) recovered completely in the same average days. The Chi-square test showed that both the groups were equally effective ($P < 0.01$; $F = 0.3764$). **Conclusion:** The retrospective analysis showed that the treatment practices of AK-20 standalone or in combination with HCQ applied in COVID-19 positive cases at CCC in Madhya Pradesh were effective against SARS coronavirus 2 disease. A significant number of cases was tested negative or asymptotically discharged from both the groups of interventions. Moreover, AK-20 alone has shown statistically equal results to that when used in combination with HCQ therapy.

Keywords: Antiviral drugs, *Arogya Kashayam*, immunomodulation, severe acute respiratory syndrome, corona virus

Introduction

Novel coronavirus disease (COVID-19) is acute and severe infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) virus.^[1] The interventional committee on taxonomy of viruses has confirmed SARS CoV-2 as the name of the virus owing to the virus genetic similarity to the SARS CoV, taking into account that there may be differences in disease spectrum and mode of transmission.^[2] Since its outbreak, nearly 26.3 million people

have been affected in more than 190 countries worldwide.^[3] The exponential spread of this disease accentuates the urgent

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need for effective therapy. Various new drugs are being tested for control and prevention of deadly viruses, but there is no established treatment protocol fixed as anti-viral therapy against SARS Cov-2.

In India, it accounts for nearly 40 Lakh confirmed cases with a growth rate of 3.8% and with 2.41% of case fatality rate.^[4] According to the studies, the most common symptoms include fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), dyspnea (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%) and chills (11.4%).^[5] In the absence of effective antiviral therapy against SARS CoV-2, the clinical approach is focused on systematic management and on immune enhancer activities of the presently available drugs.

How to contend this deadly virus and its transmission is the question present till now. In this scenario, there exists a window of opportunities in terms of traditional plant-based medicines. Traditional medicine of China has an excellent track record in successfully treating SARS CoV-1 in 2002.^[6] A variety of plant-based metabolite derivatives are used to treat many diseases. One of the important examples is cinchona-derived quinine. In the present situation, widely used hydroxychloroquine (HCQ) is also a structural analog of quinine. The report of the WHO-China Joint mission on COVID-19 during February 16, 2020 to February 24, 2020 has reported the widespread use of Traditional Chinese Medicine as part of the clinical guideline as per the protocol on the prevention and control of COVID-19 edition-6 for the management of COVID-19. The epidemic period of China has therefore witnessed a significant reduction in the rate of mild to severe cases by 27.4% and the clinical cure rate in laboratory diagnosed cases was 90%.^[7] Ayurveda is an important part of the world's complementary and alternative medicine. Ayurveda offers a wide variety of applications of traditional medicines for the well-being of humans. According to the WHO, more than 80% of the population relies on traditional remedies for their primary ailments as per the WHO global report on traditional and complementary medicine 2019. Various Ayurvedic herbs have been proved scientifically for noncommunicable disease as well as acute infection conditions. In recent years, several infectious diseases were well managed with Ayurveda. Ayurveda not only offers to overcome the symptoms of the disease, but it also balances the *Tridosha*, which is the fundamental functional unit of the body.

A study opines that glycyrrhizin, a saponin isolated from *Glycyrrhiza glabra* Linn. is reported to be effective in SARS-CoV by inhibiting viral replication.^[8,9] Molecular docking simulation and binding interaction analysis with SARS CoV-2 spike glycoprotein suggested that glycyrrhizic acid disturbed angiotensin-converting enzyme 2 (ACE-2) receptor at entry-level and glyasperin A inhibited the replication process of the virus.^[10] Similarly, various plant-based metabolites are reported to have anti-viral properties.^[11] This emphasizes the need for studying plant-based formulation to

evade the viral load in host tissue. Considering the need for scientific validation and generating evidence of *Ayurvedic* drugs in the prevention and management of COVID-19, the Government of Madhya Pradesh, Department of AYUSH had taken initiative to conduct multi-centric research in 30 districts over 88 centers throughout Madhya Pradesh. A committee was constituted by the government vide letter no./S.St./Comm. AYUSH/2020/1713, Bhopal dated April 22, 2020; which recommended an herbal formulation named *Arogya Kashayam-20* (AK-20), a combination of seven herbs, namely *Guduchi* (*Tinospora cordifolia* (Wild.) Hook. f. and Thoms.), *Yashthimadhu* (*Glycyrrhiza glabra* Linn.), *Bhumyamalaki* (*Phyllanthus niruri* Linn.), *Haritaki* (*Terminalia chebula* Retz.), *Shunthi* (*Zingiber officinale* Roscoe), *Maricha* (*Piper nigrum* Linn.) and *Pippali* (*Piper longum* Linn.) to be used in COVID-19 positive cases in COVID care centers (CCC) to evaluate its therapeutic effects in the management of COVID-19.

About the drug

The decoction of the AK-20 was distributed among the cases of COVID-19 in COVID care centers of various districts of Madhya Pradesh for 10 days. Every 20 g of *Kashayam* powder contained the following drugs in the ratio, as shown in Table 1.

Standardization

The sample of drugs under the study was evaluated for quality evaluation and standardization at Government Drug Testing Laboratory, Gwalior (Madhya Pradesh). The foreign matter, powder microscopy, loss on drying, water-soluble extractive and alcohol soluble extractives including thin-layer chromatography (TLC) was done to check the quality of the powder sample. Since the form of drug taken is *Kwatha* (decoction), certain parameters were also evaluated after the preparation of standard *Kwatha*, for example, pH value, total solids, specific gravity at 25°C, refractive index, and TLC of the extractives. The results of analysis of sample *AK-20 Churna* (sample Id-DTL/20/129A) showed that the particle size of the sample was 30-6-mesh with greenish gray color and slight aromatic odor. In microscopic examination, starch grains, cork cells, crystal fibers, stone cells and crystals of calcium oxalate were found. The loss on drying was 10.40% at 105°C with water soluble extractives 16.66% and on 8.43% alcohol soluble extracted. The TLC of sample showed three

Table 1: Ingredients of *Arogya Kashayam powder-20*

Name of drug	Part used	Ratio (g)
<i>Guduchi</i> (<i>Tinospora cordifolia</i> [Wild.] Hook. f. and Thoms.)	Stem	4
<i>Shunthi</i> (<i>Zingiber officinale</i> Roscoe)	Rhizome	4
<i>Bhumiamalaki</i> (<i>Phyllanthus niruri</i> Linn.)	Whole plant	3
<i>Yashthimadhu</i> (<i>Glycyrrhiza glabra</i> Linn.)	Root	2
<i>Haritaki</i> (<i>Terminalia chebula</i> Retz.)	Fruit	2
<i>Pippali</i> (<i>Piper longum</i> Linn.)	Fruit	2
<i>Maricha</i> (<i>Piper nigrum</i> Linn.)	Fruit	3

major spots at 254 nm and four at 366 nm, respectively. Similarly, the *Kwatha* (sample Id-DTL/20/129B) had dark brown color with pleasant odor. The pH was 5.5 with specific gravity 1.0388%. TLC of sample showed two major spots at both the wavelength.

Method of preparation

To the coarse powder of AK-20 (altogether 20 g) 400 ml of water was added and boiled to reduce it up to 200 ml. This 200 ml decoction was given in two equal doses morning and evening before meal to the cases of COVID-19 fulfilling inclusion criteria.

Targeted population

The present study analyzed positive asymptomatic and mild symptomatic cases of COVID-19 isolated in CCC and dedicated COVID hospital notified by the Government of Madhya Pradesh.

Materials and Methods

Study design

This is a retrospective analysis of multi-centric intervention. The detailed data were collected from 88 centers of 30 districts through the Government AYUSH machinery involved in the distribution of decoction and collection of data in a specially prepared case report form. Based on the inclusion criteria, all eligible cases were included and analyzed. The details in format included personal information, contact history, hospital stay, types of intervention, reverse transcription–polymerase chain reaction (RT-PCR) testing details, and the discharge summary.

Sample

The present analysis included all COVID-19 RT-PCR test positive cases ($n = 4432$) who were intervened with AK-20 in 88 COVID care centers. The study period started from April 23, 2020 to July 15, 2020. Cases remained admitted in CCC as on July 15, 2020 were excluded from this retrospective analysis.

Inclusion criteria

- COVID-19, real-time RT-PCR test positive cases
- The present analysis included asymptomatic and mildly symptomatic cases of COVID-19 aged between 05 and 80 years without any discrimination of gender, caste, and religion
- Participants who signed informed consent and followed the instructions.

Exclusion criteria

- Severe cases of COVID-19 (SaO₂ <90%) were excluded from the study
- Participants with acute respiratory distress syndrome were excluded
- Patients of life expectancy <1 year due to other co-morbid conditions were also excluded.

Ethical approval

Before the commencement of intervention of AK-20 throughout Madhya Pradesh, Ethical approval was obtained

from the Institutional Ethics Committee of Pt. Khushilal Sharma Government Ayurveda College and Institute, Bhopal vide letter no. K1sgaci/IEC/2020/005 Bhopal dated April 22, 2020. Written informed consent was obtained from patients before starting the intervention.

Screening

The data were also examined by the committee constituted under the Ministry of AYUSH, Government of India, and the comments/observations were communicated vide letter no. s. st./comm. AYUSH/2020/2162 dated May 18, 2020 and D.O. letter no. st./Ayush Sec./20/34 dated June 18, 2020.

Results

A retrospective analysis of 4432 COVID-19 positive cases in 88 centers of 30 districts of Madhya Pradesh was undertaken. The analysis included 2750 male cases and 1682 female cases registered for intervention with AK-20. In the present analysis, all the cases were divided gender-wise and then into four age groups, namely ≥ 5 to ≤ 14 years, >14 to ≤ 40 years, >40 to ≤ 60 years, and more than 60 years of age. Furthermore, each age group was categorized into four subcategories based on the days of the intervention of AK-20 and HCQ, namely 1–3 days, 4–7 days, 8–10 days, and more than 10 days if any. On analysis, it was revealed that all the cases were intervened with either AK-20 alone or in combination with HCQ. Hence, the results were evaluated based on these two types of interventions. Some of these cases were also given Vitamin-C (Ascorbic acid) and Zinc as a supplement irrespective of the intervention group.

From the study, it was evident that the maximum number of COVID-positive cases was considered for intervention in the district Morena (702), Gwalior (486), Ujjain (467), and Indore (395) [Figure 1]. Out of these, 62.04% of patients were male and 37.96% were female which also supports the existing trend of the higher number of male cases probably due to elevated ACE levels in their alveolar cells than those of women. According to a study, the binding of SARS-CoV-2 on ACE causes an elevated expression of ACE2, which can lead to damage to alveolar cells [Figure 2].^[12,13] As depicted in Figure 3, the maximum number of cases in the present series were from the age group of >14 – ≤ 40 years (58.79%) followed by >40 – ≤ 60 years of age (28.11%) and ≥ 5 – ≤ 14 years of age group 6.61% and 6.47% cases from >60 years of age group.

Among ≥ 5 – ≤ 14 years of age group, out of 293 cases, 27 (9.2%) cases were treated for 1–3 days, 62 (21.16%)

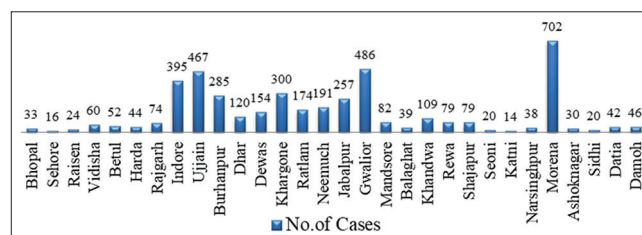


Figure 1: District wise cases

cases for 4–7 days, 156 (53.24%) cases for 08–10 days, and 48 (16.38%) cases were treated for >10 days. Among these, 276 (94.19%) cases were administered with AK-20 alone and 17 (5.80%) cases were given HCQ along with AK-20. Among the cases who were on standalone (AK-20 treatment), 96% cases remained asymptomatic or were found negative and got discharged from isolation centers as per the ICMR guidelines. While in the other group, all the 17 cases (100%) recovered and were discharged in due course of time. It is important to note that in this age group of participants, only 34.05% of the cases in the AK-20 group and 17.60% cases in the HCQ + AK-20 group were tested for RTPCR after the treatment. The rest were discharged asymptotically from the hospital after completion of the isolation period. However, 2.89% of the cases from the AK-20 alone group were referred to the higher centers due to unsatisfactory improvement as per guidelines [Figure 4].

In >14–≤40 years of age group, out of 2606 cases, 190 (7.29%) cases were treated for 1–3 days, 574 (22.02%) cases for 4–7 days, 1325 (50.84%) cases for 8–10 days, and 517 (19.83%) cases for >10 days. Among these, 861 (33.03%) cases were administered with AK-20 alone and 1745 (66.96%) cases were treated with AK-20 with HCQ. In this age group, 93.60% of the cases were found to be improved as per prevailing ICMR guidelines by AK-20 alone while 96.26% of cases were found to be improved with HCQ along with AK-20 treatment. However, 05.94% of the patients in the AK-20 alone group and 2.81% cases in the HCQ + AK-20 group were referred to the higher centers due to unsatisfactory improvement [Figure 5].

In the >40–≤60 years of age group, out of 1246 cases, 106 (8.50%) cases were treated for 1–3 days, 253 (20.30%) cases for 4–7 days, 676 (54.25%) cases for 8–10 days, and 211 (16.94%) cases for >10 days. Among these, 378 (30.34%) cases were administered with AK-20 as standalone and

868 (69.66%) cases were intervened with AK-20 and HCQ together. The analysis shows that in this age group, 91% of cases were found to be clinically improved or tested RTPCR negative after the treatment with AK-20 alone, and in another group (HCQ + AK-20), 92% cases were discharged from the hospital after recovery as per the guidelines. However, 8.73% of cases in the *Arogya Kashayam* group and 6.45% cases in AK20+HCQ group were referred to higher centers [Figure 6].

In the >60 years of age group, 287 patients were under the treatment. Out of these, 38 (13.24%) cases were treated for 1–3 days, 69 (24.04%) cases for 4–7 days, 143 (49.82%) cases for 8–10 days, and 37 (12.89%) cases for >10 days. Among these, 100 (34.84%) cases were given with AK-20 and 187 (65.16%) cases were given AK-20 and HCQ together. In this age group, 87% of cases from the AK-20 group improved and were discharged as per the ICMR guidelines while 80.21% cases who were receiving HCQ and AK-20 treatment regimen found to be improved and were discharged as per guidelines. However, 13% of the patients in the AK-20 alone group and 16.57% cases in the HCQ + AK-20 group required referral to the higher centers due to unsatisfactory improvement [Figure 7].

In this series, out of 4432 cases, the number of female cases was 1682 (37.96%), whereas the male cases were 2750 (62.04%). The outcome of intervention reveals that out of 595 female cases registered during the study period with AK-20 standalone treatment, 560 (94.17%) cases recovered completely and were discharged from the center. However, 34 patients (5.71%) required referral to higher centers. Whereas those registered with AK-20+HCQ group, i.e., 1087 (64.62%) were reported to be recovered completely in due course of time. However, 41 (3.77%) cases only required referral as per the prevailing guidelines [Figure 8].

The analysis of the data revealed that among the total 2750 male COVID-19 positive cases, 1020 (37.09%) were registered with AK-20 as standalone treatment. Out of that 942 (92.35%)

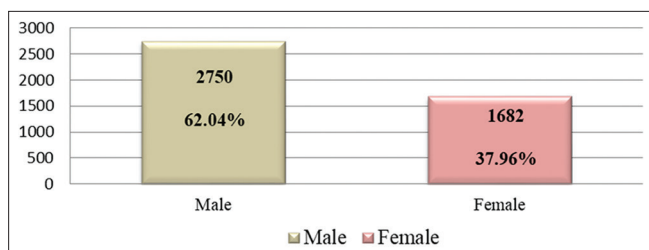


Figure 2: Gender wise cases

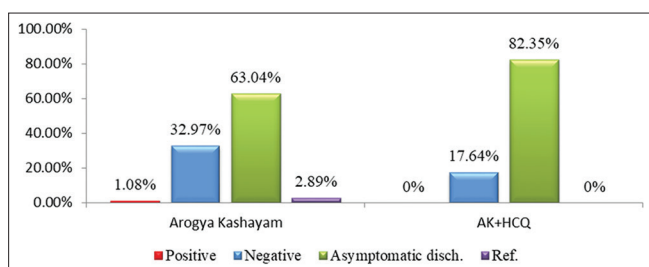


Figure 4: ≥5–≤14 age treatment wise (M+F)

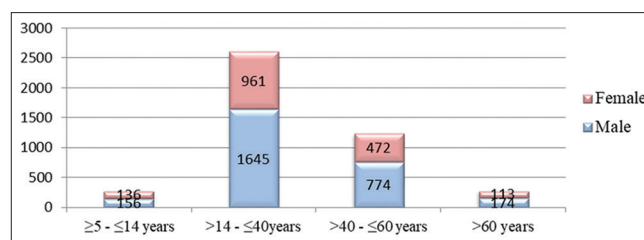


Figure 3: Age wise distribution

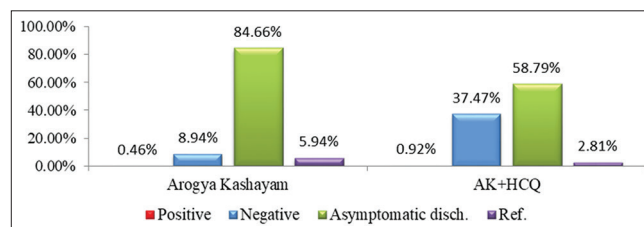


Figure 5: >14–≤40 age treatment wise (M+F)

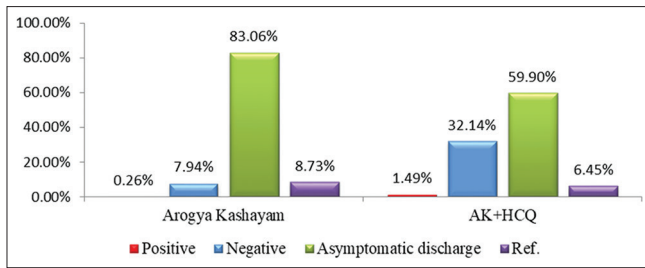


Figure 6: >40–≤60 age treatment wise (M+F)

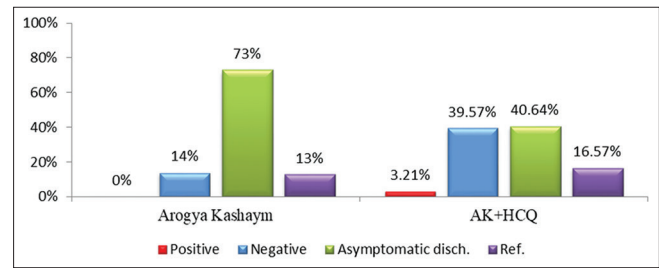


Figure 7: Greater than 60 age treatment wise (M+F)

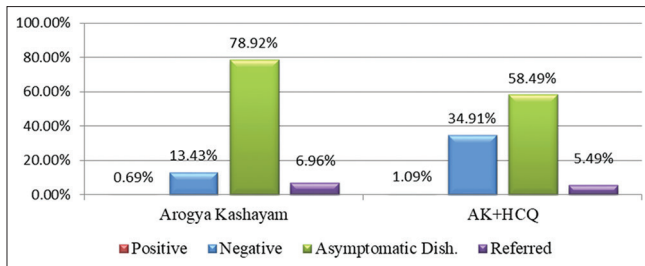


Figure 8: Result in male cases

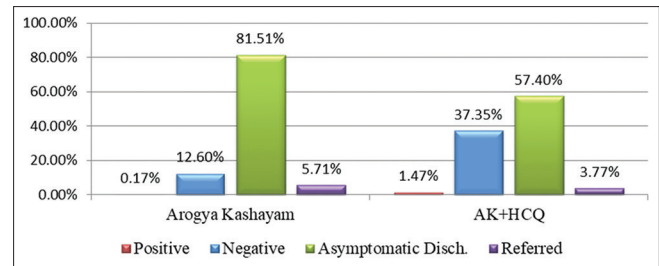


Figure 9: Result in female cases

recovered within due course of time and out of 1730 male cases who were under AK-20+HCQ treatment regimen, there was complete recovery reported in 1616 (93.40%) cases. However, 6.96% of the male cases in the AK-20 group and 05.49% of the male patients in the combination group required referral to higher centers [Figure 9]. As depicted in Figure 10, out of 4432 total cases, in this retrospective analysis, it was found that 1615 (36.39%) cases were treated with AK-20 alone, and among them, 1502 cases (93.00%) improved and were discharged from the hospital as per the ICMR guidelines. In other group, out of 2817 COVID positive cases, after intervention with HCQ and AK-20 together, 2653 (94.17%) cases improved and were discharged from the hospital. Although during the study period, posttreatment RTPCR testing was not mandatory (if the patient has completed 10 days isolation without fever for the last 3 days), but in the AK-20 alone group, 14% cases were tested for RTPCR posttreatment, and among them, 96.76% cases reported negative. Whereas in the HCQ + AK-20 treatment group, 39.99% of cases were tested for RTPCR and among them 97.36% of the cases tested negative.

Further 6.50% of the patients from AK-20 standalone group and 4.83% of patients from HCQ + AK-20 group were referred to higher centers/health facilities due to unsatisfactory health condition requiring intensive treatment [Figures 10 and 11].

Discussion

The retrospective analyses of 4432 COVID-19 positive cases showed that 36.43% of cases were treated with AK-20, out of these 93.00% cases recovered. Among these cases, 14.64% were tested for COVID-19 (RTPCR) and found that 3.63% of cases remained positive and 96.36% became negative after due course of time, i.e., 10 days. 6.50% of cases were referred

to higher centers. On the other hand, 63.56% of cases who were given HCQ along with AK-20, 94.17% recovered and were discharged. Among them, 39.99% of cases were tested for COVID-19 RTPCR and 2.63% remained positive while 97.36% became negative after due course of the time. 4.8% of cases were referred to higher centers. The Chi-square test was applied between the groups on their RTPCR test findings and found that comparison of the efficacy between the groups was statistically insignificant at a $P = 0.05$. It reveals that both the groups were equally effective on RTPCR findings irrespective of age and other criteria. According to the WHO media statement (March 08, 2020), 80% cases require hospital care and in India as on June 23, 2020, as per the economic times report on government official statements 15.34% cases required intensive care unit setting, 15.84% required oxygen support while 4.16% required ventilator support.

In the given circumstances and setup, it is clear that HCQ a well-recommended treatment for COVID-19 cases when supplemented with AK-20 (a poly-herbal formulation) showed a higher percentage of recovery rate (94.17%) and was almost equivalent (93.00%) to the standalone intervention with AK-20. Thus, it is clear that AK-20 has efficacy against COVID-19.

According to Ayurveda, the occurrence of the disease is a complex process in nature. The infectious disease COVID-19 shows predominance of *Vata* and *Kapha*. Initial symptoms of the respiratory system are aggravated due to the provocation of *Vata* by obstruction of a path by *Kapha Dosha*. This combination has *Trikatu* and *Yasthimadhu* which has got a better effect on *Kapha* by eliminating and pacifying it. The inflammatory process due to COVID-19 virus raises the body temperature resulting in febrile conditions ranging from mild-to-moderate temperature.

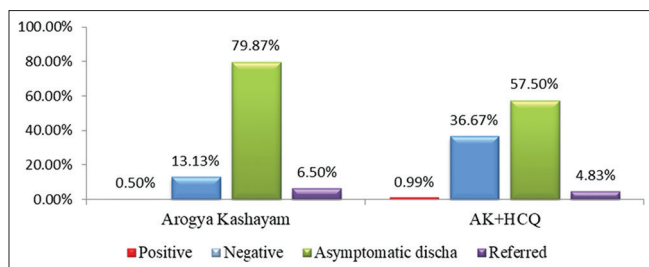


Figure 10: Overall result

Guduchi, *Bhumymlaki*, and *Yasthimadhu* due to *Vata-Pitta* pacifying action lowers the temperature by inhibiting the inflammatory process in the body.^[14,15] Studies showed that *Guduchi* extract could cause a significant increase in Immunoglobulin G antibodies in serum, along with macrophages activation besides promotion of humoral immunity and stimulation of cell-mediated immunity.^[16] It is also shown to result in upregulation of interleukin 6 (IL-6) cytokine, resulting in acute reactions to injury, inflammations, and activation of T-cells and B-cells differentiation.^[17] *AK-20* is a combination of seven herbs. These classical drugs are being used in practice since age. These have been proved to be nontoxic^[18-22] and effective on certain viral diseases scientifically. Most of the herbs are *Kapha-Vata* pacifying effect too. *Trikatu*, *Yasthimadhu*, and *Haritaki* are *Kapha-Vata Shamana*, *Guduchi* and *Bhumymlaki* have *Pitta* pacifying action and is good for febrile conditions. Out of these seven drugs, *Haritaki* and *Guduchi* are considered to be best *Rasayana* herbs in Ayurveda. The symptomatic management of COVID-19 cases is concentrated on antipyretic, anti-inflammatory, and immuno-enhancing properties of drugs. At the same time, there are huge efforts to have an effective antiviral drug to combat SARS-CoV-2. Analysis of efficacy of *AK-20* may show potential antiviral activity as already *Guduchi* has shown its antiviral activity against Swine flu^[23] and so also the *Bhumymlaki* and *Shunthi*.^[24-26] *Haritaki* and *Guduchi* were found to be immune-modulator in various studies.^[27-29]

Overall, the seven drugs of *AK-20* have different actions on various parameters of discomfort causing symptoms of COVID-19, thereby relieving the mild-to-moderate symptoms. Tested negative results of COVID-19 divulge the efficacy of this herbal formulation in swift reducing circumvents viral load in host cells.

Conclusion

The retrospective analysis showed that the treatment practices of *AK-20* standalone or in combination with HCQ applied in COVID-19 positive cases at COVID Care Centers in Madhya Pradesh were effective against SARS CoV-2 disease. A significant number of cases were tested negative or asymptotically discharged from both the groups of interventions. Moreover, *AK-20* alone has shown statistically

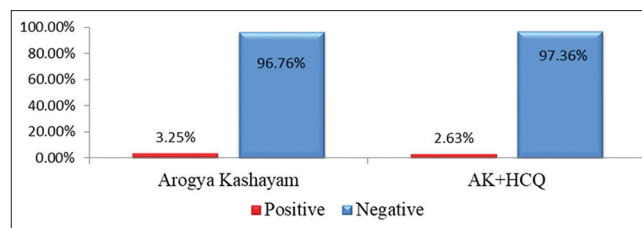


Figure 11: Tested cases

equal results to that when used in combination with HCQ therapy.

There were no adverse drug reactions reported by the centers in any case hence drug can be considered as safe for asymptomatic or mild to moderate COVID-19 cases. It is also to be mentioned that efficacy of intervention on co-morbid conditions could not be assessed; as maximum centers were the CCC where ordinarily cases with comorbidity were not admitted during the study period. Further, multicentric, randomized, controlled study can be planned to substantiate the scientific outcome.

Limitations

In the present analysis, bio-chemical tests such as IL-6, serum ferritin, and immunoglobulin assay were not done to assess the inflammatory changes and the response of treatment regimen on above biomarkers.

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Conflict of interest

There are no conflicts of interest.

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