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Research Article

A randomized clinical study to evaluate the efficacy and safety of OUTBREAK in mild and moderate COVID19 positive patients

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ABSTRACT
To evaluate the efficacy and safety of synthesized drug OUTBREAK, an Ayurvedic formulation for fever of viral origin in mild and moderate COVID19 positive patients. This is the prospective, randomized, multicentre, open label, parallel group interventional clinical endpoint study. Patients coming for the general outpatient department, were screened for viral fever by using the hematological, Biochemical and microbiological antibody assays. One Hundred patients who satisfied the selection criteria were enrolled in the study. Participants were randomized into 2 groups with 50 patients in each group. Patients were given standard treatment. In addition, Tab. OUTBREAK of Bageo Pharmaceuticals Pvt. Ltd., was administered to test groups. There is a highly significant improvement ($P<0.001$) in the subjects temperature, fever score, headache and SpO_2 suggesting a good Analgesic and antipyretic activity of OUTBREAK. There is asignificant improvement in platelet count in the OUTBREAK treated group ($P<0.01$) when compared to the control group, proving its efficacy intreating thrombocytopenia. The improvement ($P<0.01$) in the random Sugar level in the OUTBREAK treated group depicts the anti-diabetic property of OUTBREAK.The improvement ($P<0.01$) in the WBC count in the OUTBREAK treated group depicts the antiviral property of OUTBREAK. The overall quality of life was better in OUTBREAK treated group compared to the control group. There were no serious adverse events reported. OUTBREAK is safe and efficacious in reversing thrombocytopenia and thus normalizing the platelet counts and relieving the clinical signs and symptoms (fever, headache and SpO2) of viral fever associated with thrombocytopenia and other cases of viral fever without thrombocytopenia. OUTBREAK is having good anti-viral, anti-pyretic and immuno-modulatory property.

Keywords: OUTBREAK, COVID-19, Fever, SpO2

INTRODUCTION

Fever is a clinical feature that manifests due to an infection. The infection may be due to a virus, Bacteria or other microorganisms. Viral fever is a condition characterized by a temperature above 38.0 to 38.4°C (100.4°F to 101°F) associated with symptoms like sudden onset of fever, severe headache especially behind the eyes,severe joint and muscle pain, nausea and vomiting & sometimeaccompanied by body rash persisting for four to seven days afterinfection. Viral infections include Herpes, Chikungunya, Dengue, Influenza, etc [1-3].

There are no specific therapeutic options for the clinical management of many viral infections besides supportive care. Henceforth there exists an urgent need for development of alternative solutions for COVID19. Products obtained from various plant species have been reported with anti-dengue and other anti-viral properties. The various plant species are that of Carica papaya, Andrographis paniculata, Tinospora cordifolia, Piper nigrum, Melia azedarach, etc [4-11].

In a country like India we have a rich source of herbs having anti viral and antipyretic activity. In recent days we have started using many siddha formulations for various illnesses. Outbreak is one among
them which is a polyherbal formulation consisting of many ingredients. Composition of one OUTBREAK tablet includes extracts namely: Ocimum sanctum–25 mg, Curcuma longa–50 mg, Zingiber officinale–25 mg, Syzygium aromaticum–25 mg, Piper nigrum– 5 mg, Allium

sativum–25 mg, Andrographis paniculata–100 mg, Tinospora cordifolia–75 mg, Carica papaya–175 mg, Nigella sativa–125 mg, Phyllanthus niruri–50 mg, Azadiracta indica–50 mg, Adhatoda vasica–25 mg [4-11].

OUTBREAK is a proprietary of Ayurveda medicine. The individual used herbal drugs known to have variety of medicinal values against fever of viral origin and proven to have effective antipyretic, anti-viral and immunity boosting properties.

AIM & OBJECTIVES

1. To study the efficacy of OUTBREAK in fever due to viral origin.
2. To assess the safety of OUTBREAK by monitoring the occurrence of any adverse events and assess the quality of life.
3. To study the safety and efficacy of OUTBREAK in mild and moderate COVID 19 positive patients.

METHODOLOGY

The selected 100 participants were randomized into 2 groups with 50 patients in each group. Patients diagnosed as SARS CoV-2 infection received standard of care treatment (as per regulation) as per the WHO/ICMR guidelines. All key co-interventions were documented (control group). Patients diagnosed as SARS CoV-2 infection received standard of care treatment as per the WHO/ICMR guidelines. In addition, OUTBREAK tablets was given thrice daily after food for 14 days (test group) by oral. The study was conducted during the period of July to September 2021. Then they underwent general and systemicexamination followed by laboratory tests for hematology, blood biochemistry, blood microbiology, urine analysis, electrocardiogram (ECG) and chest X-ray for initial evaluation and werescreened for antibody assay for COVID-19.

RECRUITMENT OF PATIENTS

- Patients recruited in the study belonged to;

1. Either sex- between ages of 18 to 55 years, with an oral temperature of more than 38.0°C (100.4°F). With or without associated rash, body pain and joint pain, severe headache especially behind the eyes, nausea and vomiting.
2. With Viral fever accompanied by thrombocytopenia (in group1 and 2), with a platelet count between 80,000 /micro liter to 100,000/micro liter, along with stable vitals like pulse and blood pressure.
3. Female patients who tested negative for pregnancy (up totwo weeks prior tothestudy).

- Patients who were excluded from the study includes:

1. Patients with Dengue hemorrhagic fever grade III and IV
2. Patients with platelet countless than 80,000/microliter.
3. Pregnant or lactating women
4. Patients who have received blood or blood products transfusion during the current illness
5. Patients with thrombocytopenia Purpura (ITP), Leukemia, Hemophilia
6. Patients who were hypersensitive to any of the components of the formulation,

Patients were given standard treatment of care in all the groups. In addition, one tablet of OUTBREAK was administered thrice daily for two week, for the patients of test group 1. The patients were monitored on the day of entry, after 7 days and 14th day and parameters namely platelet count, haematocrit, random sugar level, SpO2 and WBC count were assessedfrom baseline. Clinical parameters namely temperature, fever score, headache and sugar level were assessed from baselineand on day 1 to day 7 and on day 14 (for all 100 subjects). Scoring of fever was done on a scale of 0-3 where 0≤99°F, 1≥99-100°F, 2≥101-102°F, 3≥102°F (for all 100 subjects). Similarly scoring for headache was done. The secondary outcome measures were to look for any adverse events during the study period and assess the quality of life using a pre- and post-feedback.

STATISTICAL ANALYSIS

The patient reports were compiled. Continuous data was reported using the descriptive statistics using Mean ± standard deviation (S.D.). Two-way ANOVA followed by Bonferroni's test was applied for statistical analysis of significance. The value of $P<0.05$ was considered as statistically significant.

RESULTS

The trial population consisted of 100 subjects, of which 50 adult subjects were diagnosed with viral fever associated with mild to moderate COVID 19 and 50 subjects were diagnosed with viral fever mild to moderate COVID 19. In addition, OUTBREAK tabs was given thrice daily orally after food for 14 days. Before the study initiation, the subjects were screened and selected according to their inclusion and exclusion criteria.

All 100 subjects completed the study. There were no serious adverse events recorded during the study duration.

Table 1: Demographic Data

Demographic details	Group 1 (Control) -Viral fever with Mild & Moderate COVID 19	Group 2 (OUTBREAK)– Viral fever with Mild & Moderate COVID 19
No. of subjects	50	50
Gender (M:F)	26:24	28:22
Mean Age	32.04±4.1	30.58±5.3
Mean BMI	22.5±2.3	23.1±4.7

Table 2: Analysis of patient's symptoms

Clinical symptoms	Scheduled visits	Group 1 (OUTBREAK)	Group 2 (CONTROL)
Temperature*	Screening	101.8±1.12	101.2±1.12
	Day7	99.4 ±0.42	100.2±0.35
	Day14	98.5 ±0.47	99.4 ±0.53
Fever score*	Screening	3±0.40	3±0.50
	Day7	1.56 ±0.26	2.04 ±0.50
	Day14	0.24 ±0.12	0.68 ±0.33
Headache score *	Screening	2.0±1.2	1.98 ±0.98
	Day7	0.98 ±0.79	1.10 ±0.91
	Day14	0.21 ±0.17	0.32 ±0.31
Random Blood Sugar Score*	Screening	2.0±1.2	1.98 ±0.98
	Day7	0.98 ±0.79	1.10 ±0.91
	Day14	0.21 ±0.17	0.32 ±0.31
SpO_2 level score*	Screening	3±0.40	3±0.50
	Day7	1.56 ±0.26	2.04 ±0.50
	Day14	0.24 ±0.12	0.68 ±0.33

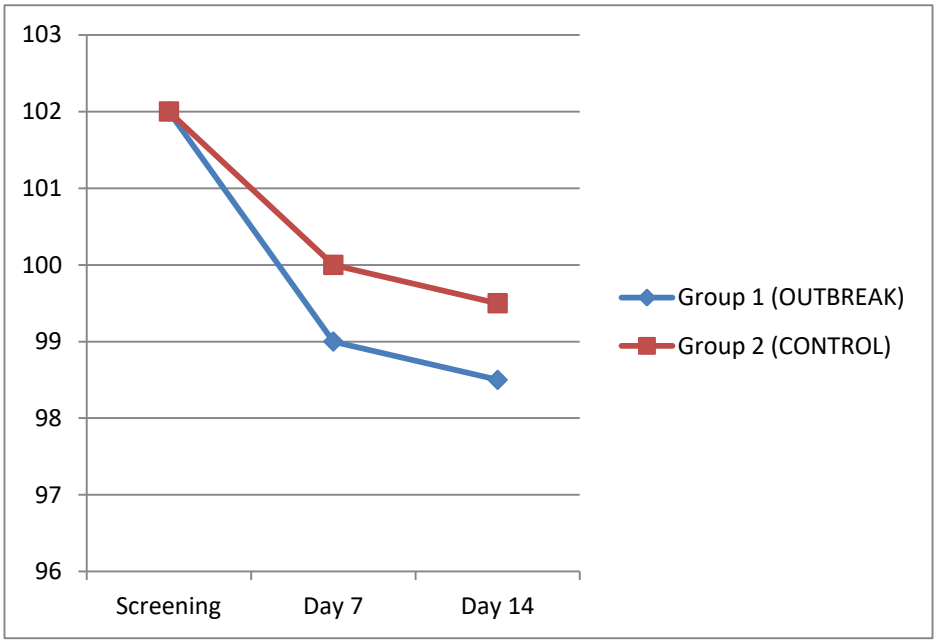

Fig.1: Reduction in Body Temperature

Table 3: Assessment of specific Efficacy Lab parameters

Specific Efficacy Lab parameters	Scheduled visits	Group 1 (Control)	Group 2 (Control) Viral fever with thrombocytopenia
Platelet cells/mm^3	Screening	84879.5±15654.2	93648.57±8547.3
	Day 7	110000.0 ±31831.5	84636.36±37092.5
	Day 14	258944.4 ±14945.4	198111.1 ±86415.3

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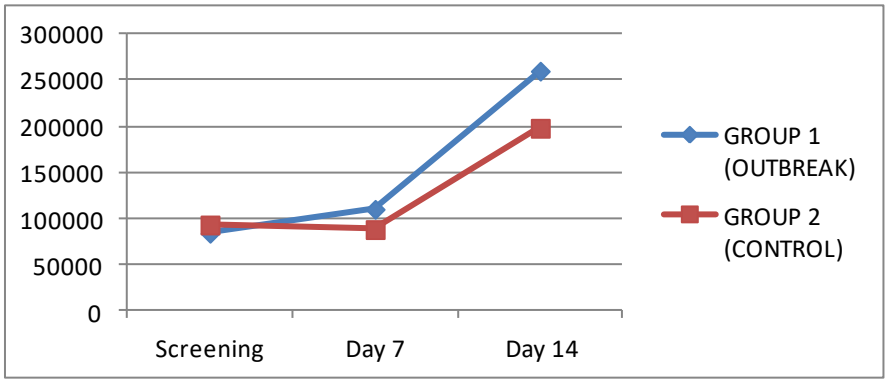

Fig.2: Improvement in Platelet Count

Table 4: Assessment of other Haematological parameters

Hematological Lab parameters	Scheduledvisits	Group 1 OUTBREAK)	Group 2 (Control)
Hemoglobin (%)	Screening	11.3±1.2	10.92±0.8
	Day 14	11.1±0.7	10.76±0.8
Total WBC count cells/mm$^{3\#\#}$	Screening	10409.1 ±1181.9	11533.3±1047.3
	Day 14	8621.6 ±2910.2	9541.6 ±1439.9
Neutrophils cells/mm$^{3\#\#}$	Screening	40.5±5.2	46.5±4.1
	Day 14	39.1±5.4	59.5±5.6
Lymphocytes cells/mm$^{3\#\#}$	Screening	54.7±7.3	51.2±3.9
	Day 14	48.6±4.7	52±4.4
Monocytes cells/mm^3	Screening	0.5±0.6	0.3±0.4
	Day 14	0.6±0.9	0.3±0.4
Eosinophils cells/mm^3	Screening	3.0±2.2	1.8±2.1
	Day 14	2.5±2.0	2.1±2.1
Basophils cells/mm^3	Screening	0.4±0.5	0.5±0.6
	Day 14	0.4±0.4	0.3±0.8

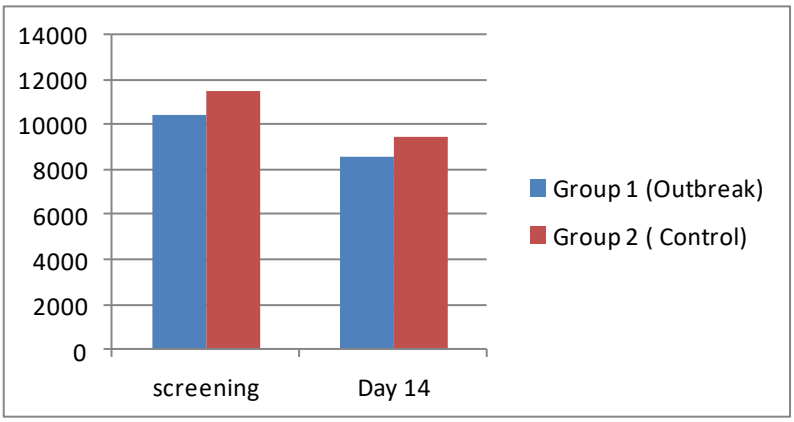

Fig.3: WBC count.

Table 5: Questionnaire assessment of quality of life

Groups		Group 1 (OUTBREAK)		Group 2 (Control)	
Questionnaire to assess quality of Life	Scale	Screening	Post study	Screening	Post study
Do you feel tired or fatigued?	Always	10 (83.3%)	0	12 (100%)	0
	Often	2 (16.7%)	0	0	0
	Sometime	0	6 (50%)	0	10 (83.3%)
	Never	0	6 (50%)	0	2 (16.7%)
Do you feel week?	Always	10 (83.3%)	0	12 (100%)	0
	Often	2 (16.7%)	0	0	0
	Sometime	0	6 (50%)	0	12 (100%)
	Never	0	6 (50%)	0	0
Do you get short of breath?	Always	0	0	0	0
	Often	0	0	0	0
	Sometime	6 (50%)	2 (16.7%)	8 (66.7%)	2 (16.7%)
	Never	6 (50%)	10 (83.3%)	4 (33.3%)	10 (83.3%)
Do you get dizzy?	Always	0	0	0	0
	Often	0	0	0	0
	Sometime	5 (41.7%)	2 (16.7%)	8 (66.7%)	2 (16.7%)
	Never	7 (58.3%)	10 (83.3%)	4 (33.3%)	10 (83.3%)
Have you experienced a rapid Heartbeat?	Always	0	0	0	0
	Often	0	0	0	0
	Sometime	10 (83.3%)	0	10 (83.3%)	0
	Never	2 (16.7%)	12 (100%)	2 (16.7%)	12 (100%)
Do you have numbness or coldness in your hands or feets?	Always	0	0	0	0
	Often	0	0	0	0
	Sometime	5 (41.7%)	0	2 (16.7%)	0
	Never	7 (58.3%)	12 (100%)	10 (83.3%)	12 (100%)
Are you irritable?	Always	0	0	0	0

	Often	0	0	0	0
	Sometime	2 (16.7%)	0	5 (41.7%)	5 (41.7%)
	Never	10 (83.3%)	12 (100%)	7 (58.3%)	7 (58.3%)
Do you feel sad or depressed?	Always	0	0	0	0
	Often	3 (25%)	0	6 (50%)	0
	Sometime	3 (25%)	5 (41.7%)	6 (50%)	6 (50%)
	Never	6 (50%)	7 (58.3%)	0	6 (50%)

Thus a significant improvement (quantitatively) in the Temperature, fever score, headache score, random blood sugar score and SpO_2 score ($P<0.001$)* was noted in the OUTBREAK treated group, when compared with the control group [Table 2]. There is significant improvement in the platelet count in both the group 1 [Table 3]. But it was more significant in the OUTBREAK treated group when compared with the control group [Figure 2]. There is significant improvement in the platelet count in both the group 1 [Figure 2]. But it was more significant in the OUTBREAK treated group when compared with the control group [Figure 2]. There is significant improvement ($P<0.01$) ## in the WBC score, Lymphocyte count and Neutrophil count [Table 4] in the OUTBREAK treated group when compared with the control group which is also evident from the Figure 3. This is mainly due to the antiviral property of OUTBREAK. There were no changes noted in the liver and renal parameters of all the subjects suggesting the safety of OUTBREAK. The quality of life was assessed in percentage based on the subject's response. The results shows that the quality of life (percentage scored) was better in OUTBREAK treated group compared with the control group at the end of the study.

DISCUSSION

In this study, there was a significant reduction in the mean score of all the clinical symptoms in both the groups, which was more prominent in OUTBREAK group. The platelet count was significantly normalized in OUTBREAK treated subjects earlier by 7^{th} and 14^{th} day when compared to the control group, were it was normalized on day 7 and above [Figure 3]. Thus, OUTBREAK has over turned thrombocytopenia and led to platelet level regulation.

From the study results, it is clear that the normalization ofbody temperature was evident on Day 7 onwards in OUTBREAK treatedgroup, compared to the control group were it was normalized after day 7 and 14. Thus, OUTBREAK is having a good anti-pyretic activity and suggesting a good Analgesic and anti-pyretic activity of OUTBREAK.

All the haematological and biochemical parameters were within the normal range with significant reduction in haematocrit and WBC count, suggesting the anti-viral property and immunomodulatory capacity of OUTBREAK against Dengue infectionsand other viral infectious fever conditions. Unaltered renal andliver function tests suggest the safety of OUTBREAK tablets at the recommended dose.

In this study, Proportion of patients with swabs negative for COVID 19 in RT-PCR at day 7 and 14, reduction in viral CT ratio. SpO_2 rate greater than 94%. Relief from cough and maintenance of above mentioned for more than 72 hours. Also normalization of pyrexia and body pain was observed.

There was a significant improvement in the quality of life of subjects in OUTBREAK group related to the fatigue, sense of feelingweek, dizziness and sense of feeling depressed, compared to that of baseline and control group. There were no clinically significant adverse events during the entire study period.

OUTBREAK, the Ayurvedic preparation made of herbs like Ocimum sanctum–25 mg , Curcuma longa–50 mg, Zingiber officinale–25 mg, Syzygium aromaticum–25 mg, Piper nigrum-5 mg, Allium sativum–25 mg, Andrographis paniculata–100 mg, Tinospora cordifolia–75 mg, Carica papaya–175 mg, Nigella sativa–125 mg, Phyllanthus niruri–50 mg, Azadiracta indica– 50 mg, Adhatoda vasica–25 mg.

Carica papaya is known for its anti-dengue and platelet augumentation activity. It is reported to be having enhancement of arachidonate 12 -

lipoxygenase and the platelet activating factor receptor gene expression which is responsible for increased plateletproduction. It also decrease peripheral platelet destruction by membrane stabilizing activity due to presence of many flavonoids and phenolic compounds, which could have facilitated the significant increase in platelet counts in OUTBREAK treated patients [4-5,7]. Andrographis paniculata is a medicinal plant which was reported to have anti-HIV, anti-pathogenic bacteria and immunoregulatory activities which also possess blood purifying activity and thus eliminates the toxic metabolites and have anti-inflammatory, anti-pyretic and analgesic activity [6, 8].

Limonoids from Melia azedarach fruits has been shown to have inhibitory activity on Flaviviruses and Mycobacterium tuberculosis [9, 10].

Tinospora cordifolia which is known to strengthen host immune system by activating macrophages, NF-kappa, beta translocation and cytokine production in addition its anti-pyretic, antiviral and hepato-protective activity [11].

Piper nigrum has shown to increase the bioavailability of drugs, protects the liver and neutralizes the endotoxins and detoxifies pathogenic remnants from liver and blood. It increases the immunity in your body and prevents the recurrence of fever. Piperine suppressed inflammation in the airways caused by asthma and seasonal allergies. It possesses immunomodulatory effect which prevent the disease occurrence could have potentially facilitated the significant reduction in clinical signs and symptoms of dengue fever associated with thrombocytopenia and in case of other viral fever patients [12].

Nigella sativa increases immune responses (activates antigen presentation system, and makes balance between Th1/Th2). Decreases inflammation (increases anti-inflammatory and anti-histamine responses), decreases oxidative stress (decreases MDA, increases SOD, GPx and Catalase), decreases comorbodities (decrease diabetes, hyperglycemia, CVD, PIMS, KLD, Hypertension, Bacterial Co-infection) [15].

Zingeber officinale dried rhizomes of ginger helps increase antibacterial action in the body and regularizes the digestive system [13-14]. Early research shows that taking ginger extract helps reduce runny nose as well as the prescription drug loratadine in people with hay fever. Reduces the time spent in intensive care units in people with sudden respiratory system a failure. Use in sudden and serious lung condition (acute respiratory distress syndrome or ARDS) The alkaloid irritant taste from ginger also aids in clearing respiratory issues thus it is also known to help preventing from COVID-19 [16].

Curcuma longa synthesized curcumin has been shown to reduce inflammation and decrease viral activity for COVID-19 [17]. Curcumin has been shown to modulate the NLRP3 inflammasome and main protease to reduce viral replication Recent studies have proven the medicinal uses of Turmeric for respiratory diseases, liver diseases, diabetes, cancer, Alzheimer's disease and AIDS. Thus the turmeric may have the potential effect against COVID-19 [18]. Curcumin widely used for the treatment of respiratory diseases and inflammatory diseases. Anti-thrombotic properties of Curcumin may also help in clearing the mucous in lungs so that relieving the oxygen supply to the entire body.

Phyllanthus niruri used to treat inflammation and pain. The tonsil inflammation of this herb helps to get good relief from the sore throat pain. It effectively fights against the bacterial, parasites, fungal, and viral infections.

Ocimum sanctum is used in bronchitis, rheumatic arthritis, and asthma. It is recorded in the research that tulsi plant has the binding property to destroy covid-19 deadly disease [19]. It has an anti-inflammatory properties help promote eye health by preventing viral, bacterial and fungal infections. A natural headache reliever which can also relieve migraine pain and treating fever Due to the presence of compounds like camphene, eugenol, and cineole, tulsi cures viral, bacterial, and fungal infections of the respiratory system. It can cure various respiratory disorders like bronchitis & tuberculosis.

Syzygium aromaticum is anti-viral, anti-microbial, anti-septic and anti-fungal agents. It clears the respiratory passages, acting as an expectorant for treating many upper-respiratory conditions including colds, bronchitis, sinus conditions, cough and asthma. It also helps in reliving the inflammation of pharynx and get relieved from severe cough. It controls the throat irritation. Its anti-platelet activities; which prevent the formation of a thrombus or a blood clotting, clove oil protecting against sudden death seen in some patients infected by Coronavirus (COVID 19), due to the acute pulmonary embolism associated with hypercoagulable state and marked increase levels seen in C-reactive protein, and D-Dimer, which considered the main cause of sudden death [20].

Allium sativum extract can be used as a source of antiviral against SARS-CoV-2, Extract has an inhibitory effect on avian bronchitis virus. Its antibacterial properties, help in treating throat irritations and fighting respiratory infections. Boost your immune system and helps ward off colds. It also thins the blood to prevent clots.

Helps to heal cold sores and reduce swelling.

Azadirachta indica has its extensive anti-microbial and anti-bacterial effects. These properties play a huge role in boosting immunity. It has anti-inflammatory properties and protective action on alveolar cells which may prevent lung fibrosis. They had the broad-spectrum of anti-viral action, anti-retroviral and antimalarial effects. Hence, its action on lungs acts as pro-inflammatory cytokine inhibitor and immuno-modulator effects. In molecular docking study, Neem shows high inhibitory action against corona virus. It's potential as a prophylactic treatment for the prevention of COVID-19 infection [21]. This study results clearly proves that Neem leaves as dietary supplement can inhibit COVID-19 [22].

Adhatoda vasica extract alters the cellular hypoxic response and modulates the inflammation-thrombosis axis to reduce lung injury, thrombosis and fibrosis. The various properties are useful in boosting immunity and alleviating the symptoms of COVID-19. Drug helpful in relieving symptoms in non COVID cases those who were quarantined or in lockdown pace thereby reducing pandemic panic and in confirmed asymptomatic or mild cases and its beneficial effects, particularly in bronchitis. A unique herb that helps support the bronchial function with bronchodilatory, expectorant and mucolytic properties [23] rich in anti-inflammatory, antibiotic and expectorant properties, Vasaka holds high significance in treating the common cold, cough and flu symptoms [24].

CONCLUSION

In conclusion, OUTBREAK is safe and efficacious in reversing thrombocytopenia and thus normalizing the platelet counts and relieving the clinical signs and symptoms of Mild and Moderate COVID 19 and other cases of control group. Thus OUTBREAK (poly-herbal combination) [25] is having good anti-viral, antipyretic, analgesic, anti-arthritic and immuno-modulatory property. OUTBREAK is having good anti-viral, antipyretic and Immuno-modulatory property. Hence, Outbreak should be used as add on drug in patients with viral fever with or without thrombocytopenia for a rapid recovery without any diverse effects. Outbreak, with its poly herbal ingredients shows a significant antiviral action against coronavirus (COVID-19) when given in addition to the medications suggested by WHO/ICMR, over a period of 14 days. On the treatment with OUTBREAK tablet 89% of patients turned out to be COVID 19 RT-PCR test negative on 7th day and 100% patients turned out be COVID 19 RT-PCR test negative on day 14. Henceforth, OUTBREAK can be used as an add-on drug in patients with COVID 19 to relieve the signs and symptoms of it and for a rapid recovery without any adverse effects.

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There is no fund given by the funding agencies.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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