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Research Article

A Pilot Clinical Study to Evaluate the Safety and Efficacy of ZingiVir-H, Herbo-Mineral Drug in Patients with Viral Fever

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Abstract

A viral infection develops when an organism's body is attacked by pathogenic viruses, and infectious virus particles attach to and enter susceptible cells. There are a few antiviral medicines available to manage the viral infection. The objective of this pilot clinical study was to demonstrate the preliminary evaluation on the efficacy and safety of ZingiVir-H, a herbomineral Ayurvedic preparation in hospitalized adults diagnosed with viral infection. A total of thirty patients above 18 years of age presenting with fever were enrolled from 3rd October 2019 to 28th December 2019 for conducting the pre-test and post-test clinical trial. All the patients were administered with ZingiVir-H tablet (500 mg) orally every 4th hour along with lukewarm water after light meal. The intervention was continued until the body temperature became normal. Body temperature, Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (C-RP), Liver Function Test (LFT), and Renal Function Test (RFT) were recorded after treatment, first follow-up (on 7th day of discharge) and 2nd follow-up (on 30th day from first follow-up date). LFT and RFT were observed before treatment and 2nd follow-up (on 30th day from first follow-up date) and the results obtained were analyzed statistically. Repeated measurements with ANOVA recorded a significant decrease in body temperature (within an average of 4.3 days), CBC, ESR, C-RP after the intervention. The LFT and RFT parameters before and after treatments were within the recommended clinical range which established the hepato-renal safety of the ZingiVir-H in the study subjects. This study proved that ZingiVir-H is highly effective and safe in managing viral fever (*jwara*).

Keywords: ZingiVir-H; Viral fever; Antipyretic; Herbo-mineral drug

Introduction

Ayurveda, the science of life considers *jwara* (fever) as a separate disease. But in modern medicine, they consider it as a symptom of an infection or an ongoing pathology. *Acharya Charaka* introduces *jwara* (fever) as an ailment causing *Deha-Indriya-Manas-Santapa* [1] (rise in body temperature felt with the impairment of sensory and mental functions) and *Sarvaroga agraja* [1] (supreme among diseases). Ayurveda states that one gets fever during birth and encounters the same during the life time according to the *bala* (strength) till death [2]. The *samprapti* (patho-physiology) of *jwara* most probably starts from a specific *nidana* (causative factor) which may be external or internal (*nija* or *aganduka*) [3], that leads to the formation of *ama* (intoxication). This eventually leads to *agni mandhya* (malfunctioning of digestive fire) and shows signs and symptoms with its differential factors [4]. The clinical features of *jwara* have been stated as *santapa* (increase in body temperature), *aruchi* (tastelessness), *thrisna* (excessive thirst) [3]. Nowadays, even for mild elevation in body temperature, anti-pyretic medications are used to overcome the fever and associated symptoms. In fact, appropriate medical attention for *jwara* (fever) is *deepana* (digestive) and *pachana* (carminative) formulation that has the ability to carry out *samprapti vighatana* (reversal of pathophysiology) [5-9].

Fever is a common symptom found in many infectious conditions. According to studies of healthy individuals from 18-40 years of age, the mean oral temperature is 36.8° ± 0.4°C (98.2° ± 0.7°F) [10]. The maximal normal oral temperature is 37.2°C (98.9°F) at 6 am and 37.7°C (99.9°F) at 4 pm; these values define the 99th percentile for healthy individuals. In light of these studies, an am temperature of > 37.2°C (> 98.9°F) or a pm temperature of > 37.7°C (> 99.9°F) would define a fever [11], and this may be due to any sort of (that may include either epidemic or pandemic) infections affecting our body. An epidemic is a rapidly spreading viral or microbial outbreak of disease within a confined region. A pandemic is in fact an epidemic that occurs over a wide geography and affecting an exceptionally high proportion of the population. Unluckily, the prevalence rate of viral fevers is high in India due to its density in population. Vaccinations are available for most of the epidemics and hence many are prevented. However, at present, novel microorganisms or mutated versions of existing microorganisms are emerging continuously and creating major health hazards to the people worldwide. While modern medicine is concentrating on developing vaccines for newly identified infections, *Ayurveda,* by nature, mainly focuses on immunity, immune response, and breaking the disease pathology. The available classic Ayurveda formulations used to manage *jwara* are limited because apart from the infections, an underlying disease could also show the signs of *jwara* in some cases. Considering the limitations and the developing crisis, it is the need of the hour to develop an ideal formulation having *deepana* (digestive) and *pachana* (carminative) property which can even fight against almost all microbial infections affecting humans.

Treatment principles like *ama pachana* (restoration of normal digestive physiology), *jwarahara* (anti-pyretic), *kasa-swasahara* (antitussive) can be effectively utilized for the management of fever. Various herbal and herbo-mineral formulations are available in the market to prevent and manage pyrexia. The present pilot study is aimed to evaluate the efficacy and safety of ZingiVir-H, a herbo-mineral drug designed and developed by Pankajakasthuri Herbals India Pvt. Ltd. Poovachal, Thiruvananthapuram, against viral fever. *Agantu jwara* (fever due to exogenous factors) is associated with *swasa* (breathing difficulty) and *kasa* (cough) is having vata *kapha* predominance [12]. All viral fevers can be correlated as *agantu* (external) caused by *bhoota abhishanga* (microbial infection) [13] which aggravates all the three doshas. To treat such a manifestation where both *pranavaha* (Respiratory tract) and *rasavaha srotodhusthi* involving the *abhyantara rogamarga*, the medicine should have *deepana-pachana* (restoration of normal digestive physiology)*, vata kaphahara* and *jwarahara* (antipyretic) properties. The trial drug viz. ZingiVir-H was formulated using Adraka (*Zingiber officinale*), Lavanga (*Eugenia caryophyllus*), Parpata (*Hedyotis corymbose*), Musta (*Cyperus rotundus*) and Ajamoda (*Trachyspermum ammi*) along with two purified minerals as per Ayurvedic principles i.e. Hingula-HgS (Mercuric sulphide) and Haratala-As_2S_3 (Arsenic trisulphide). The ingredients used for formulating the trial drug are expected to have an overall property required for treating *jwara* as discussed above. Hence, the present pilot study was conducted to evaluate the role of ZingiVir-H in managing viral infection. The study further aimed to assess the safety profile of the study drug, ZingiVir-H.

Methodology

The study was conducted among patients who attended the OPD of Pankajakasthuri Ayurveda Medical College Hospital & PG Centre, Killy, Kattakada, Thiruvananthapuram, Kerala, India. The study design was single group pre-test and post-test clinical trial with a sample size of 30 patients presenting with fever. The study was cleared by IEC with vide approval number (PKAMC/IEC/46/2019) and was carried out as per the International conference of Harmonization Good Clinical Practices Guidelines (ICH-GCP).

Study Drug

ZingiVir-H, an Ayurvedic herbo-mineral preparation in tablet form for oral administration, is the study drug. Pankajakasthuri Herbals India Pvt. Ltd., located in Poovachal, Thiruvananthapuram, Kerala, India, manufactures ZingiVir-H (500 mg) tablets on a

GMP-approved production line.

Inclusion Criteria

The following are the inclusion criteria of the study:

- Patients of either gender above 18 years, irrespective of demographic status and characteristics.
- Patients with classical signs of viral fever.
- Patients willing to sign the Informed Consent Form.

Exclusion Criteria

The following are the exclusion criteria of the study:

- Patients diagnosed with chronic obstructive pulmonary disease, malignancy, chronic liver disease, a recent history of cardiovascular event, renal disease and autoimmune disorders.
- Pregnant or lactating women.
- Substance abuse (use of illegal non-prescribed (NR_x) drugs)
- Subjects with known allergy to contents of the trial drug.

Intervention

All subjects were administered with ZingiVir-H tablet (500 mg) orally every 4th hour along with lukewarm water after light meal, making a total of 6 doses (3 g) daily. The intervention was continued until the body temperature became normal.

Assessment Criteria

Body Temperature, Complete Blood Count, Erythrocyte Sedimentation Rate, C-Reactive Protein, Liver Function test, and Renal function test are the variables assessed at (i) BT (before treatment) to AT (after treatment) (ii) BT to FU7 (follow up on 7^{th} day) (iii) BT to FU30 (Follow up on 30^{th} day) and (iv) AT to FU30 in this pilot study.

Observation Period

Body temperature (axillary) of the subjects was recorded using a digital thermometer before treatment and on a daily basis at 6:00 AM, 10:00 AM, 4:00 PM and 10:00 PM until the date of discharge. Temperature monitoring was also performed on 7^{th} day of discharge (first follow-up date) and on 30^{th} day from first follow-up date (second follow-up date). After the treatment, blood parameters were assessed before the treatment, first follow-up and on second follow-up date. LFT and RFT were observed before treatment and on second follow-up date.

Results

This pilot study includes 30 patients to study the efficacy of ZingiVir-H tablet in patients suffering from viral fever. Analysis of variations in temperature of 30 patients receiving ZingiVir-H tablet based on 4 time points was done. The assessment was done by comparing the data of body temperature, blood parameters, CRP, LFT and RFT at these time points.

Effect of ZingiVir-H on body temperature

Out of the 30 patients studied, the temperature has shown a dip in its curve for 3 patients on day 3, for 17 patients on day 4 and 10 patients on day 5 (Figure1). The temperature of all patients became normal by the 5^{th} day. Friedman chi-squared = 35.475, df = 9, p-value = 0.00004911. On an average, the trial drug showed an overall recovery time of 4.3 days in the study subjects. The Friedman's test result showed a significant difference existed in temperature over the time point (p-value = 0.00004911 < 0.05). Pairwise comparisons using Wilcoxon signed rank test was also recorded a significant difference between each pair of observations. As the p-value of the paired Friedman's test was found to be less than 0.01, it was inferred that the mean body temperature of patients decreases significantly after the intervention with ZingiVir-H tablet, during each time point and in comparison, to each other time points.

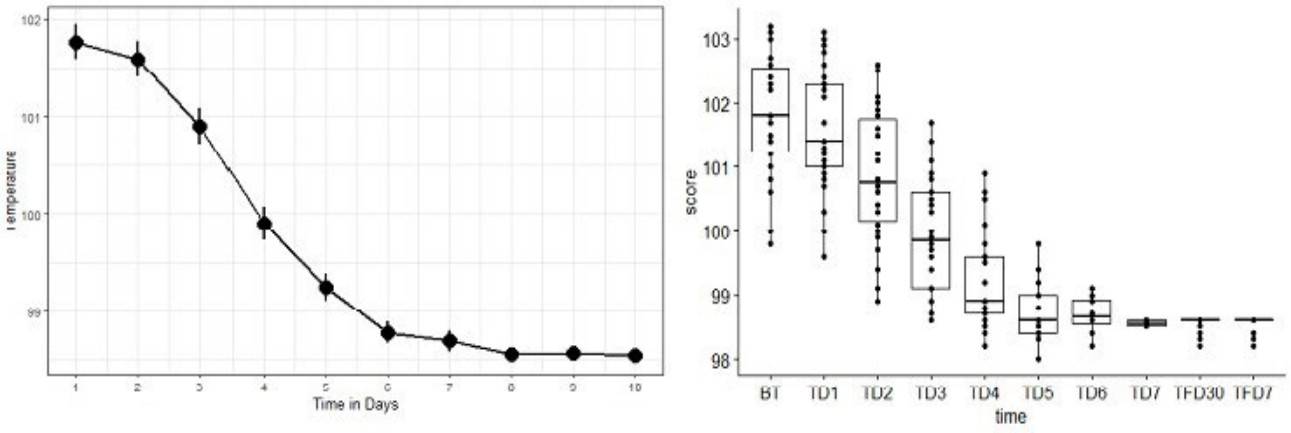

Figure 1: Effect of ZingiVir-H on body temperature.

Effect of ZingiVir-H tablet on the blood parameters

Effect on hemoglobin

Figure 2A showed the hemoglobin's growth curves of the hemoglobin, in which the first one considered the complete data in each time point and observed a gradual increase in the hemoglobin count. ANOVA results showed that there does not exist any interaction effect (p-value = 0.8383 > 0.05). So, a separate analysis was performed for each of the categorical variables based on the scores of Hemoglobin. In addition to this, the Figure 2A showed that hemoglobin has significantly changed over different time points (p-value = 0.0187 < 0.05). As the p-value of the two-way ANOVA test was found to be less than 0.05, it was inferred that mean hemoglobin of patients increased significantly after the intervention with ZingiVir-H tablet, during each time point and in comparison, to each time point.

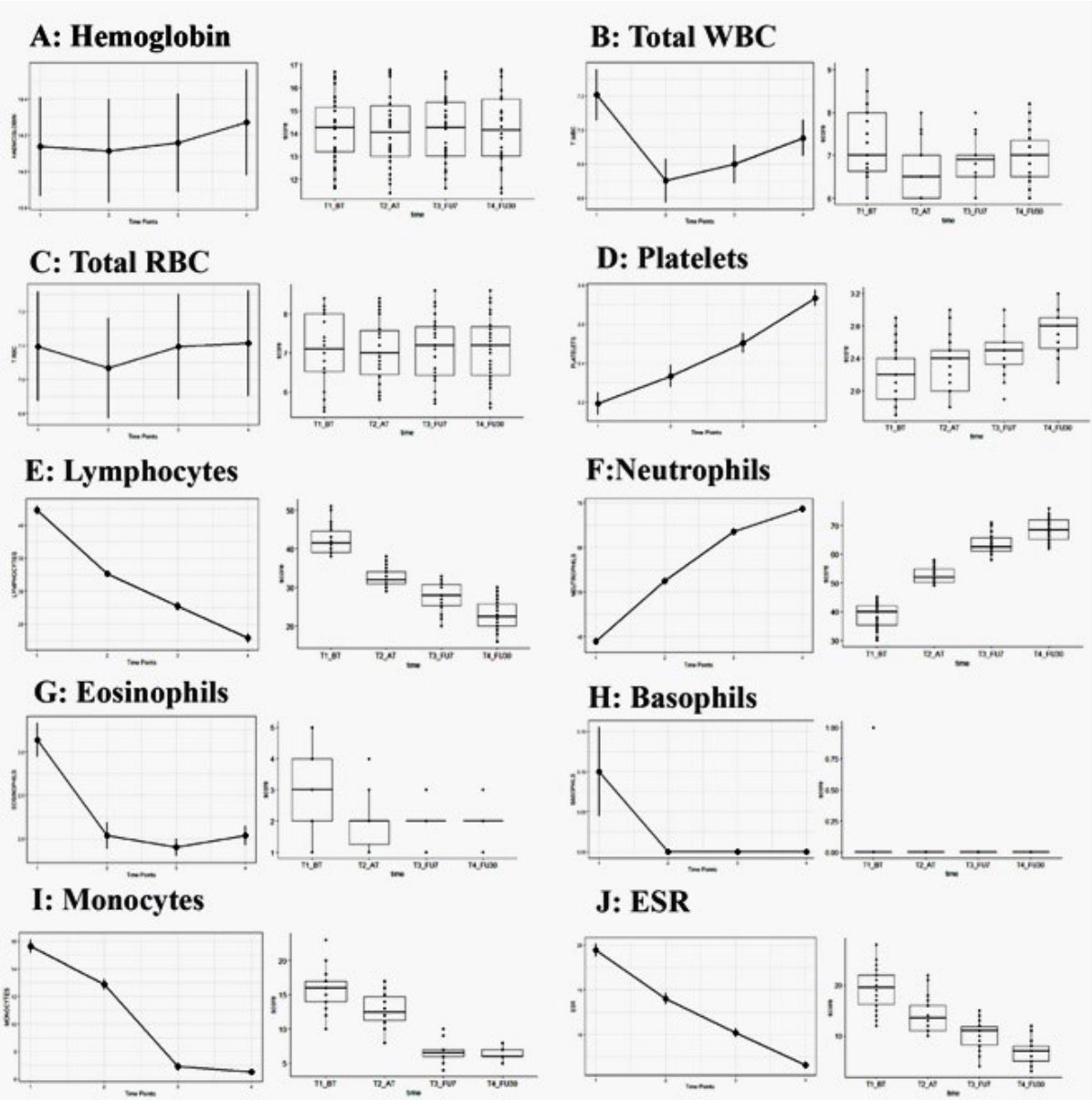

Figure 2: Effect of ZingiVir-H on the blood profile.

Effect on Total WBC (T.WBC)

The figure shown in 2B considers the complete data in each time points and it was observed a fall in T.WBC count for the time point 2 and a steady increase happened with the rest points. In Figure 2B, based on the mean (on left hand side plot) and the other based on median (on the right-hand side plot), indicated that the change in T.WBC from After Treatment (AT) to Follow up (FU7) on 7th day is highly differing in the subjects. The ANOVA result showed that there does not exist any interaction effect (p-value = 0.083653 > 0.05). So, a separate analysis was performed for each of the categorical variables based on the scores of T.WBC. Further, the Figure 2B showed that T.WBC count has significantly changed over different time points (p-value < 0.05). . The Post-Hoc analyses over the time points showed that a significant change has happened between the time points (i) BT to AT (ii) BT to FU7 (iii) BT to FU30 and (iv) AT to FU30 and in the other cases, no significant changes were observed.

Effect on Total RBC (T.RBC)

The figure shown in 2C considers the complete data in each time points and it can be observed a fall in T.RBC count on the time point 2 and approximately the same for all other points. The ANOVA showed that there does not exist any interaction effect (p-value = 0.161 > 0.05). So, a separate analysis was performed for each of the categorical variables based on the scores of T.RBC. The Figure 2C also showed that T.RBC does not significantly change over different time points (p value = 0.397 > 0.05). As the p-value of the two-way repeat ANOVA test was found to be greater than 0.05, it was inferred that there was no significant change in the T.RBC before and after the intervention with ZingiVir-H tablet during each time points and also in comparison to each time points. Since the mean T.RBC count being within the normal clinical limits, it was inferred that there was no direct relation of the intervention with T.RBC count.

Effect on platelets

The Figure 2D showed the growth curve of the platelets and there was a steady increase in the count of platelets during the treatment period. The Post-Hoc analyses over the time points showed that a significant change happened between all the pair of time points. As the p-value was found to be less than 0.05, it was inferred that the platelet counts of patients increased significantly after the intervention with the study drug, during each time points.

Effect on lymphocytes

The Figure 2E showed the growth curve of the lymphocytes. Here, we can observe a steady decrease in the amount of lymphocytes. The ANOVA showed that there does not exist any interaction effect (p-value = 0.32440 > 0.05). So, a separate analysis was performed for each of the categorical variables based on the scores of lymphocytes. The Figure 2E also showed that Lymphocytes have a significant change over the different time points (p value < 0.05). The Post-Hoc analyses over the time points showed a significant decrease in mean lymphocyte count between all the pair of time points.

Effect on neutrophils

The Figure 2F showed the growth curve of the parameter neutrophils, where an increase in the count of neutrophils can be observed. The ANOVA showed that there does not exist any interaction effect (p-value = 0.20789 > 0.05). So, separate analysis can be performed for each of the categorical variables based on the scores of Neutrophils. Neutrophils have a significant change over the different time points (p-value < 0.05) (Figure 2F). The Post-Hoc analyses over the time points showed a significant increase in mean Neutrophil count in between all the pair of time points.

Effect on eosinophils

The Figure 2G showed a steady decrease in the mean eosinophils count. The ANOVA showed that there does not exist any interaction effect (p-value = 0.77171 > 0.05). So, a separate analysis can be performed for each of the categorical variables based on the scores of eosinophils. Eosinophils have a significant decrease over the different time points (p-value < 0.05) Figure 2G. The Post-Hoc analyses over the time points showed that a significant decrease happened between Before treatment-After treatment, before treatment- Follow up on 7th day and Before treatment -Follow up on 30th day pair of time points.

Effect on basophils

The Figure 2H showed the growth curve of the parameter basophils, in which we can observe a decrease in the mean basophil count. The Basophil count during all the time points was within the normal clinical limit (Figure 2H). There was no significant change in the basophil counts before and after treatment.

Effect on monocytes

The Figure 2I showed the growth curve of the parameter monocytes, in which we can observe a decrease in the amount of monocytes. The ANOVA results showed that there exists an interaction effect (p-value = 0.039041 < 0.05) Figure 2I. A significant interaction indicates that the effect of different time points on the monocytes is different at different values of the other gender. The Two-way ANOVA showed that monocytes significantly decrease over the different time points p-value < 0.05).

Effect on ESR

The Figure 2J shows the growth curves of the parameter ESR, in which the first one considers the complete data in each time points and we can observe a decrease in ESR. The ANOVA result showed that there does not exist any interaction effect (p-value = 0.77928 >0.05) (Figure 2J). So, a separate analysis was performed for each of the categorical variables based on the scores of ESR. ESR had a significant decrease over the different time points (p-value < 0.05). Here we can observe a significant change overall the pair of variables, since p-value is less than 0.05 in all combinations.

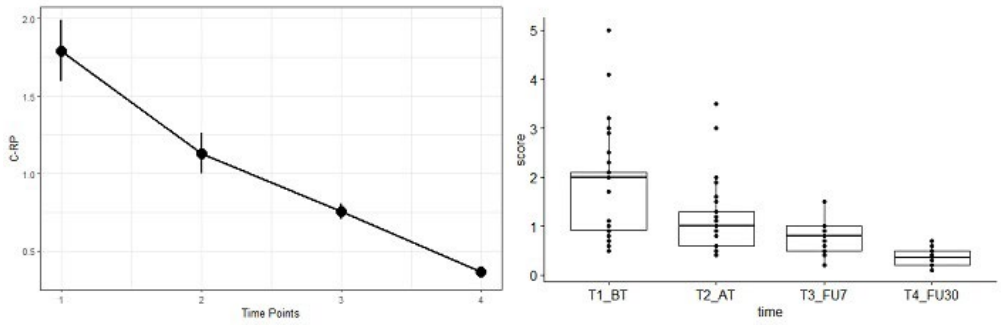

Figure 3: Effect of ZingiVir-H on C-RP.

Effect on C-RP

The growth curve of the parameter C-RP showed a steady decrease in the amount of C-RP. ANOVA showed that there does not exist any interaction effect (p-value = 0.22254 > 0.05). So, a separate analysis was performed for each of the categorical variables based on C-RP scores. The Figure 3 also showed that C-RP significantly decrease over the different time points (p-value < 0.05). Here we can observe a significant decrease over all the pair of variables, since p-value is less than 0.05 in all combination. It showed the combination is very much effective for a wide range of infections and also may be a proof for synergetic effect exerted by the herbo-mineral combination (Figure 3).

Effect on LFT

The data analysis corresponding to LFT was done either using the Paired T-test or Wilcoxon signed-rank test based on the validation of assumptions. If the data satisfies, we will perform the normality assumption first with the Paired T-test and if this fails, we will perform the Wilcoxon signed-rank test to get an accurate result. Corresponding to the Paired T-test, the mean difference and its 95% confidence interval are reported and if it is Wilcoxon signed-rank test, the median difference and its 95% confidence interval are reported. The p-value less than 0.05 reports a significant difference in the variable before and after the treatment and if the p-value is greater than 0.05 leads to a conclusion of non-significant difference. Alkaline phosphates recorded a significant decrease before and after treatment (p-value = 0.02073 < 0.05), with a mean difference of 1.16333 and 95% confidence interval (0.190771, 2.135896). Bilirubin (Conjugated) recorded a significant decrease before and after treatment (P-value = 0.004764 < 0.05), with a median difference of 0. Bilirubin (Total) recorded a significant decrease before and after treatment (p-value = 0.004376 < 0.05), with a median difference of 0.1 and 95% confidence interval (0, 0.1). SGOT (AST) recorded a significant decrease before and after treatment (p-value = 0.0000809 < 0.05), with a median difference of 0.7 and 95% confidence interval (0.1, 1.1). SGPT (ALT) recorded a significant decrease before and after treatment (p-value = 0.00016 < 0.05), with a median difference of 1.05 and 95% confidence interval (0.7, 2.1). Total Protein recorded a significant decrease before and after treatment (p-value = 0.002639 < 0.05), with a mean difference of 0.4066667 and 95% confidence interval (0.153803, 0.65953). Albumin recorded a significant decrease before and after treatment (p-value = 0.0017 < 0.05), with a median difference of 0.2 and 95% confidence interval (0.1, 0.2). A/G Ratio (0.241), Bilirubin (unconjugated) (0.4767), and Globulin (0.5331) does not recorded any significant differences before-and-after the treatment.

Effect on RFT

The data analysis corresponding to RFT is done either using the Paired T-test or Wilcoxon signed-rank test based on the validation of assumptions. If the data satisfies, we will perform the normality assumption first with the Paired T-test and if this fails, we will perform the Wilcoxon signed-rank test to get an accurate result. Corresponding to the Paired T-test, the mean difference and its 95% confidence interval are reported and if it is Wilcoxon signed-rank test, the median difference and its 95% confidence interval are reported. The p-value less than 0.05 reports a significant difference in the variable before and after the treatment and if the p-value is greater than 0.05 leads to a conclusion of non-significant difference. Uric acid showed a significant decrease before and after treatment (p-value = 0.02189 < 0.05), with a median difference of 0.15 and 95% confidence interval (0.1, 0.3). Urea showed a significant decrease before and after treatment (p-value = 0.01283 < 0.05), with a median

difference of 1.095 and 95% confidence interval (0.24, 1.49). Sodium showed a significant decrease before and after treatment (p-value = 0.00007496<0.05), with a mean difference of 1.3333 and 95% confidence interval (0.74176, 1.924906). Potassium showed a significant decrease before and after treatment (p-value = 0.009792 < 0.05), with a mean difference of 0.1733 and 95% confidence interval (0.045127, 0.30154). Phosphorus showed a significant increase before and after treatment (p-value = 0.004748 < 0.05), with a median difference of -0.05 and 95% confidence interval (-0.14, -0.02). Creatinine showed a significant decrease before and after treatment (p-value = 0.000001801 < 0.05), with a median difference of 0.105 and 95% confidence interval (0.06, 0.16). Chloride showed a significant decrease before and after treatment (p-value = 0.0006633 < 0.05), with a median difference of 0.55 and 95% confidence interval (0.18, 1.05). Bicarbonate showed a significant decrease before and after treatment (p-value = 0.0001716 < 0.05), with a mean difference of 0.46 and 95% confidence interval (0.241695, 0.678305). Calcium (0.6717), does not showed any significant differences before-and-after the treatment.

Discussion

The present study attempted to find out the efficacy of ZingiVir-H tablet in the management of viral fever and to understand its safety by assessing the blood parameters, LFT and RFT. This study revealed many positive and promising results which fulfill the study objectives. All the ingredients used in the formulation of ZingiVir-H tablet have proven antipyretic properties along with antiseptic, anti-inflammatory and bronchodilatory action, especially Haratala [14], Hingula [15], *Hedyotis corymbose* [16], *Cyperus rotundus* [17], *Eugenia caryophyllus* [18]. The antiviral activity of *Syzygium aromaticum* has been reported against different viruses such as herpes adenovirus, poliovirus, and coxsackie virus [19]. The antiviral activity of *Zingiber officinale* has been demonstrated against influenza virus [20]. In this study, we observed the improvement in hemoglobin level, which was contributed by the *raktha vardhaka* property of *Cyperus rotundus* [17], *Eugenia caryophyllus* [18], *Trachyspermum ammi* [21], *Hedyotis corymbose* [22] present in the study drug. There was a significant improvement in the WBC count which may be due to the immune boosting and immune modulatory effect of hingula [15], *Hedyotis corymbose* [23] and *Cyperus rotundus* [17]. There was no statistically significant change in the total RBC count and was within the clinically normal limits. So, it was inferred that there was no direct effect of the trial drug with RBC count. Even though the ingredients of the trial drug do not directly affect the Platelet count, *Zingiber officinale* has proven anti-thrombotic and prevents platelet agglutination thereby reducing blood coagulation. *Zingiber officinale* possesses an anti-thrombotic property probably through inhibition of platelet function. Regular consumption of *Zingiber officinale* may therefore confer protection against thrombotic diseases [24]. The aqueous extract of *Zingiber officinale* possesses anticoagulant properties through prevention of coagulation process and clot formation [25]. The reduction in lymphocytes may be due to the immunomodulatory effect of *Trachyspermum ammi*. It is already proven that proteins and polysaccharides in *Trachyspermum ammi* Lam. differentially activates B cells and macrophages, which play independent roles in innate immune responses and the production of antibodies [26]. The volatile oil of *Zingiber officinale* influences both cell-mediated immune response and nonspecific proliferation of T lymphocyte and may exert beneficial effects in several clinical conditions, such as chronic inflammation and autoimmune diseases [27]. Mean Neutrophil and Eosinophil count has increased due to the immunomodulatory effect of Hingula, *Cyperus rotundus*, and *Hedyotis corymbose*. A decrease in ESR and C-RP showed that the combination is very effective for a wide range of infections and may prove the synergetic effect exerted by the herbo-mineral combination. A meta-analysis study suggests that *Zingiber officinale* supplementation significantly reduces serum CRP and improves glycaemia indexes and lipid profile. Random-effects meta-regression revealed that changes in serum CRP levels were independent of the dosage of *Zingiber officinale* supplementation [28]. Regarding the effects of ZingiVir-H on LFT & RFT to evaluate safety of patients, gives evidence to rule out any hepatic and/or renal discrepancy. Present study indicated that, patients' condition has improved and the bilirubin, serum alkaline phosphatase, serum albumin and total protein level have reduced but within recommended range as the progression of the treatment. All changes in parameters of LFT and RFT were within the normal clinical limits.

Conclusion

This pilot study has proved the efficacy and safety level of the trial drug, ZingiVir-H. It has been established that ZingiVir-H effectively treats *viral fever* in the therapeutic dosage and frequency. None of the patients developed any hepatic or renal complications during the trial, and it also showed its capacity as a safe remedy for *jwara.* There was no incidence of adverse drug reaction during the trial intervention.

The outcome of the clinical study

ZingiVir-H is a new herbo-mineral formulation that has clinically proven its capacity to combat viral infection associated fever with a high safety profile to the liver and kidney.

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