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Evaluation of the efficacy of an Ayurvedic intervention (Chyawanprash) in the prevention of COVID-19 pandemic among Health Care Personnel – An open label single arm prospective study

Clinical Research Proposal

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Background

COVID-19 has emerged as the latest pandemic that erupted in the Wuhan City of People's Republic of China in December 2019, which is affecting human health and economy across the world. 1 133758 cases has been reported globally as on April 5, according to the WHO Coronavirus disease 2019 (COVID-19) Situation Report – 76. The occurrence of the ongoing COVID-19 in developed countries also highlights the fact that developed countries and rich populations are not immune to the outbreaks of infectious diseases. Coronaviruses (CoVs) belong to the family Coronaviridae and are enveloped, single-stranded, positive-sense RNA viruses. The SARS-CoV-2 belongs to the beta CoV genus which also includes the SARS-CoV-1 and the MERS-CoV. The lack of approved effective drug therapeutic protocols for CoVs would be a challenge for the treatment of the newly emerged COVID-19 infections worldwide.

Drug repurposing, which is defined as identifying alternative uses for approved or investigational drugs outside their defined indication, could be a possible way to overcome the time limitation of research and development needed to design a therapeutic drug to combat the pathogen. The drug repurposing or repositioning approach thus can facilitate prompt clinical decisions at lower costs than de novo drug development. Though drug repurposing is sometimes based on chance observations, target-based repurposing of drugs depends on prior understanding of the precise molecular or cellular element that is recognized by the proposed drug,. Ayurveda and traditional systems of Medicine in India have been treating diseases of infectious and non-infectious origin equally with expansive success rates, treating the patients through an individualized person to person approach depending upon the presentation of clinical symptoms in each.

Chyawanprash (CP) is a 5000 year old Ayurvedic multi-herbal jam considered to be a *Rasayana* for all the tissues of the body. *Rasayana* translates to "path of essence" as it promotes systemic rejuvenation of the mind and body. *Rasa* is a Sanskrit term meaning "essence" and *Ayana* means "path." The term *Rasayana* not only refers to the science of prolonging life span but also to the herbal remedies used to promote optimal health and reverse aging. Chyawanprash is a potent antioxidant paste, prepared through the synergistic blending of around 50 herbs and spices. Chyawanprash falls, by virtue of its consistency and form of dosage, under the category of Awaleha (electuaries/herbal jams), a group of Ayurvedic formulations.

Health benefits-
Antioxidant-rich spices, botanicals and herbs are combined in a meticulous and specific manner with ghee, black sesame oil and honey to create a delicious jam that can be taken every day to support overall health and vitality.

Respiratory Health- Protect and Strengthens the Respiratory System
A regular intake of *Chyawanprash* strengthens the tracheo–bronchial tree and hence improves the immunity and functioning of the respiratory system. It helps to treat respiratory infections, allergic cough, asthma, bronchospasm, rhinitis, seasonal or non seasonal respiratory disorders, common cold, and tuberculosis, and thus strengthens the respiratory system. It is also used as an adjunct to antitubercular drugs to augment their bioactivity and prevent their side effects. "Pippali, Kantakaari, Kakdasingi, Bhumyamalaki, Vasa, Pushkarmul, Prishnaparni, Agnimanth, Shalparni, sesame oil, and Amla help to nourish the respiratory system." In a randomized controlled trial (RCT), 90 pulmonary tuberculosis patients were treated with *Chyawanprash* 10 g, twice daily as an adjunct to antitubercular drugs. *Chyawanprash* augmented the bioactivity of antitubercular drugs and prevented their side effects. Cough, expectoration, weakness, loss of appetite, loss of weight, fever, edema aches, and hemoptysis disappeared almost completely in the treated group, along with improvement in the hemoglobin (Hb) levels and effective healing as evidenced through chest X-ray post-therapy.' Another observational study on 99 newly diagnosed pulmonary tuberculosis patients revealed that concomitant adjunct use of CP with antitubercular drugs significantly abated the symptoms and improved bioavailability of isoniazid and pyrazinamide.

Antioxidant, Adaptogenic, and Immune-Booster
Chyawanprash is best known for its support of the immune system, which is why it is such a popular tonic during the fall and winter months. Amla Berry, also known as Amalaki, is the main ingredient and base of Chyawanprash. It has a tart, sour taste and is an extremely rich source of vitamin C. Stress and poor lifestyle habits such as smoking, drinking and poor dietary habits can all deplete the body's stores of vitamin C and weaken the immune system. Several studies have shown vitamin C to have a positive effect on bolstering immunity. In addition, amla berry has been shown to have adaptogenic properties, which help the body adapt to stress and regulate immunity.
The combination or cocktail of phytocompounds (as in CP) offers better antioxidant effects than single antioxidant therapy. The adaptogenic characteristics of CP are attributable to its excellent antiaging and anxiolytic supplement. The revitalizing and tonic effects of CP could be due to its rich antioxidant composition, bioactive phytoconstituents, such as carotenoids, flavonoids, tannins, and phenolic compounds "", though supportive experimental and clinical evidence is scarce. Recent investigations have ascertained that polyphenols (gallic acid, catechin, epicatechin) in CP exert key antioxidant potential and is known to possess potent neuroprotective, cytoprotective, and antioxidant properties. 'Piperine content in *Chyawanprash* act as a bioavailability enhancer. *Chyawanprash* is an effective adaptogenic. Some clinical reports do support the adaptogenic and antioxidant effect of *Chyawanprash* on normal and depressive subjects.
A study evaluated and ascertained highly potent free radical scavenging, based on the synthetic DPPH (1,1-diphenyl,2-picrylhydrazyl) scavenging and antioxidant activities of ethyl acetate

extracts of several market brands of *Chyawanprash*. The findings were proximate to the standard ascorbic acid (IC 50 20.69 _g/mL). Another study found potent DPPH radical scavenging ability and antioxidant effects of ethanolic extracts of *Chyawanprash*. *Chyawanprash* strengthens immunity and facilitates the healing process. Due to the rich Amla percentage, *Chyawanprash* is loaded in high vitamin C, polyphenolics, including flavonoids, and exhibits evident antioxidant and free radical scavenging activity, enhances the immune system, and fights infections. Vitamin C also helps to revive and restore the energy loss of the human body. Vitamin C conjugates to gallic acid molecules and reducing sugars and facilitates the development of intricate synergistic effects with other phytoconstituents. Polyphenols are acknowledged to be more effective antioxidants in vitro than vitamin E and C on a molar basis. Polyphenolic compounds in several herbs and natural honey in *Chyawanprash* are found beneficial in various human degenerative diseases, cardiovascular disorders, and diabetes. Several natural antioxidants, especially flavonoids, exert multiple bioactivities, including antibacterial, antiviral, anti-inflammatory, antiallergic, antithrombotic, and vasodilator effects.
In a 6-month-long randomized, open labelled, prospective, multicenter, clinical study in children (5–12 years), CP was shown to lead to significant improvement in immunity, energy levels, physical strength, vigor, and quality of life assessed through KIDSCREEN QOL-27 questionnaires in children.

An experimental study showed that *Chyawanprash* pretreatment significantly reduced plasma histamine levels and serum immunoglobulin E (IgE) release when rats and mice were challenged with allergen-and ovalbumin-induced allergy, respectively. This suggests the antiallergic potential of *Chyawanprash*. Natural killer (NK) cell activity was significantly (versus dimethyl sulfoxide) increased in different concentration ratios of NK cells and target cells by *Chyawanprash* treatment. On treating dendritic cells with *Chyawanprash*, a significant increase in the secretions of tumor necrosis factor-alpha (TNF-Alpha) and macrophage inflammatory protein-1 alpha (MIP-1alpha), stimulation in interleukin-1 beta (IL-1beta) levels, and rise in phagocytic activity were observed. The augmented immunity marker levels (TNF-alpha, IL-1beta, and MIP1alpha), as well as enhancement of NK cells and phagocytic activity support the immunomodulatory properties of *Chyawanprash*. Clinical studies also support the immune-booster role of *Chyawanprash* as demonstrated by reduced disease symptoms of seasonal influences, modulated IgE and immunity markers C3 and C4 levels, improved pulmonary functions, decreased cortisol levels, and increased quality of life (QoL).
The minute quantities of spice components of *Chyawanprash* are also known for their wide range of health benefits by their antioxidative, chemopreventive, antimutagenic, anti-inflammatory, immune-modulatory effects on cells and several beneficial effects on the gastrointestinal, cardiovascular, respiratory, metabolic, reproductive, neural, and other systems.

Strength and Energy
The ingredients in Chyawanprash promote healthy muscle mass by supporting protein synthesis and the absorption of nutrients. Chyawaprash's ability to bolster the immune system and remove damaging toxins and free radicals, lends itself to supporting the general strength and energy of the body. It supports healthy muscle mass and tones all the tissues of the body.

Health workers are at the front line of COVID 19 outbreak response and as such are exposed to hazards that put them at risk of infection. In spite of use of PPE and hand sanitizers/hand rubs

and other preventive aspects, morbidity among exposed health care workers are much more than that of general Public and hence this study was conceived.

METHODS

Study Type	**: single arm, interventional**
Purpose	: prophylactic use.
Masking	**:** Nil
Control	**:** None
Timing	**:** Prospective
No. of Groups	: One

Number of Patients to be completed in the clinical trial (Sample Size): 50

The participant of the study will be given Chyavanprash as per the dose schedule. They will follow the Standard Preventive Regimen (Standard precautions, Hand hygiene, Personal protective equipment (for healthcare workers), Respiratory hygiene and cough etiquette).

* Any other home remedies or other preventive measures taken by participants such as gargling with hot water, golden milk etc. shall be recorded)

TIMELINES:

- **Study duration** : 2 months
- **Pre-trial preparation & medicine procurement** : 15 days
- **Duration of intervention** : 30 days
- **Statistical analysis** : 15 Days

Inclusion criteria:

- All healthcare professionals and supporting staff of all age groups willing to participate, who were negative for SARS- Cov-2 at screening, (tested by RT-PCR), at identified hospitals dealing with COVID-19, with or without co-morbid condition with exposure/chance of exposure to COVID 19 positive cases.
- All healthcare providers and supporting staff deputed for Covid-19 outbreak response and willing to participate and give signed informed consent for the same.

Exclusion criteria:

- Pregnant and lactating females.
- Known case of Carcinoma lungs, CRF and CHF.
- Participants with any immunosuppressive medication or in an immune compromised state or hematological disease.
- DM uncontrolled with medications.
- Any other criteria, as per the investigator would jeopardize the study.

Withdrawal Criteria

- The participant may be withdrawn from the trial if there is
  - Any major ailment which necessitating the institution of new modalities of treatment.

OR

  - Non-compliance of the treatment regimen (minimum 80% compliance is essential to continue in the study).

****The decision to withdraw a participant from the trial would be taken only by the Principal Investigator, who will then have to set out a detailed justification and also indicate the line of further management-if needed. The same needs to be informed to the Sponsor and the Ethics Committee within two working days.**

Interventions

Conventional guidelines for health care workers as per the WHO plus *Chyawanprash* as intervention medicine for prophylactic use.

***Chyawanprash*-**

Dose	**:** 12 g twice daily.
Dosage form	**:** *Avaleha* (Jam like paste).
Route of Administration	**:** Oral.
Time of Administration	**:** Twice in a day- On empty stomach in the morning at least 1 hour before breakfast and two hours after dinner at night.
Anupana	**:** Warm water.
Duration of therapy	**:** 1 month.

All the healthcare workers and supporting staff (including Doctors, Nursing Staff, Post Graduate Students, Interns, Nursing Orderly Sanitation Staff, Security Guards and other staff of essential services like kitchen, PWD etc delivering services) deputed for dedicated Covid ward of the hospital will be included for the study.

OBJECTIVES

To assess the impact of ***Chyawanprash*** **in SARS-CoV-2 (COVID-19) infection prevention in health care personnel exposed to COVID-19 positive cases.**

OUTCOMES

Primary outcome measure

- Percentage of participants with SARS- Cov-2 positivity as estimated by RT-PCR of nasopharyngeal swab

Secondary outcome measure

- Safety profile of the intervention as estimated by LFT, KFT and other hematological & biochemical investigations.
- Presence or absence of AE/ADR and their level of tolerability
- Number of participants who developed any infective diseases during the trial period (bacterial /viral/ fungal / etc.) and percentage of participants with Upper respiratory tract illness during the period.
- Immune and inflammatory markers (IgG, IgM, IgE, Hs-CRP TNF - α,IL6, IL10) baseline and end of treatment.

SAFETY RECORDING

a. Adverse Events

All adverse events observed or reported by patients will be recorded in the CRF with information about severity (i.e., whether mild, moderate or severe) and possible relation to the study medication. **Any serious adverse effects will be notified immediately to the study monitor.**

STATISTICAL METHODS

Clinical symptoms, Subjective parameters and Laboratory parameters will be subjected to Univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) 15.0 version with appropriate statistical methods.

DEVIATION FROM THE PROTOCOL:

The trial should be conducted in compliance with the protocol. **Deviations from the protocol should not be made except when necessary to alleviate an immediate hazard to trial patients. All the deviations** from the protocol, including unplanned changes to interventions, examinations, data collection and method of analysis **should always be reported to sponsors and IEC** at the earliest along with the exact reason for that deviation.

In view of novel coronavirus, Guidelines are frequently updated by the Government and ICMR. In view of it, the deviation from protocol (if any) will be informed to the IEC and Sponsor at the earliest.

ADVERSE EVENTS –

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

ADVERSE DRUG REACTION (ADR):

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.(WHO, 1972). An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

Any adverse event, if observed during treatment period or during follow up visits should be clearly documented and its appropriate and timely management should be done. The Principal Investigator should report the same to the Ethics committee and the sponsor(s) at the earliest.

DRUG COMPLIANCE

If there is more than or equal to 80% compliance, the participant would be continued in the trial. The compliance needs to be assessed at each follow-up by investigator on the admitted patients.

CONCOMITANT MEDICATION

A concomitant medication (con-med) is a drug or biological product, other than a study drug, taken by a subject during a clinical trial.

Participants registered under the trial will be issued treatment cards with the entire treatment regimen written on it. They will be instructed to avoid the use of any other drugs on their own for any ailment and will be clearly instructed to consult the treating Investigating physician for any symptom or complaint, or if they feel anything unusual. The Investigating physician will record any medication(s) he / she may prescribe to alleviate their ailments.

RESCUE MEDICATION

Rescue medication / Quick-acting medication / Fast-acting Medication - A medication intended to relieve symptoms immediately. This is in contrast to preventive medications, which are taken over a long period of time to prevent or manage symptoms.

To alleviate any emergency, the use of rescue medication is permitted as per the wisdom / discretion of the Principal Investigator and ICMR guidelines in respect to Covid-19. . However, the same need to be documented in appropriate column in the Case Record Form.

DROP-OUTS

An attempt shall be made to record the reason for drop outs, if any during the clinical trial.

ETHICS

The trial will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki for biomedical research and ICMR ethical guidelines involving human participants (2006), and that are consistent with Indian / ICH Good Clinical Practice (GCP) guidelines.

INSTITUTIONAL ETHICS COMMITTEE:

Prior to commencement of the trial, the protocol, the participant information sheet and the consent form must be submitted to the Institutional Ethics Committee. Written approval of the same must be obtained from the IEC. Protocol amendments are also to be approved by the IEC according to the usual procedure.

PATIENT INFORMATION AND CONSENT FORM:

Prior to any trial related activity, the Principal Investigator will give the patient verbal and written information about the trial in a form the participant can read and understand. The Investigator would ensure that the participant is fully informed about the aims, procedures, discomforts and expected benefits of the trial. It must be emphasized that participation is voluntary and participants have the right to opt out of the trial at any time without any prejudice. A voluntary, signed witnessed Informed Consent should be obtained from the participant prior to any clinical trial related procedure.

CO-ORDINATION OF TRIAL

Co-ordinating Centre:

DATA DOCUMENTATION AND ANALYSIS

Clinical symptoms, Subjective parameters and Laboratory parameters will be subjected to univariate and multivariate analysis using Statistical Package for Social Sciences (SPSS) 15.0 version with appropriate statistical methods. All information regarding clinical trial should be properly documented, carefully handled and meticulously stored in order to ensure its accurate interpretation and verification. Analysis will be done by **CCRAS's statistical Unit.**

Study schedule

	Screening	Baseline	7th Day	15th day	30th Day
Informed consent & PIS	**Y**				
Medical history		**Y**			
Laboratory Investigations (RT-PCR)	**Y**				**Y**
Chest X-ray		**Y**			**Y**
Laboratory Investigations CBC, LFT, RFT		**Y**			**Y**
Immune and inflammatory markers		**Y**			**Y**
Clinical Examination		**Y**	**Y**	**Y**	**Y**
Concomitant Medication		**Y**	**Y**	**Y**	**Y**
Assessment of ADRs		**Y**	**Y**	**Y**	**Y**
Assessment of other infections		**Y**	**Y**	**Y**	**Y**
Assessment of Medication compliance			**Y**	**Y**	**Y**

Laboratory Examination:

- **Haematology**
  - Haemoglobin : _____ g/dl
  - T.L.C. : _____ / cu.mm.
  - D.L.C. : N ____ % E ____ % B ____ % L ____ % M _____ %
  - Absolute lymphocyte count_____
  - E.S.R. : _____mm (at the end of 1st hour)
  - Blood Sugar :Fasting _____ mg%
  - HbA1c: _____%
- **Bio-chemistry:**
  - Blood Urea : _____ mg/dL
  - Serum Uric Acid: _____mg/dl.

- Serum Creatinine : _____ mg/dL
- S.G.O.T.(A.S.T.) : _____ IU/L
- S.G.P.T. (A.L.T.) : _____ IU/L
- Total protein: _____ gm/dl
- S.Albumin: _____gm/dl
- S.Globulin: _____gm/dl
- A/G ratio: _____
- Serum Bilirubin:
    - Conjugated bilirubin _____mg/dl
    - Unconjugated bilirubin _____ mg/dl
- Serum Alkaline Phosphatase: _____ IU/L
- Urine Routine and microscopic test
- Hs-CRP
- IL-6
- IL-10
- TNF-α
- Immunoglobulins(IgG,IgM and IgE)
- Chest X-Ray-PA view_____

Note:, *covid-19 testv, hematology and biochemistry, Renal Function tests and liver function tests will be done at baseline and 30th day in all 50 participants.*

However, the investigations like Hs-CRP, IL-6,IL-10, TNF alpha and immunoglobulin's like Ig G, IgM and IgE will be done in every 3rd patient.(17 patients only)