EVIDENCE-BASED RESEARCH IN AYURVEDA AGAINST COVID-19 IN COMPLIANCE WITH STANDARDIZED PROTOCOLS AND PRACTICES

Acharya Balkrishna

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Evidence-Based Research in Ayurveda against COVID-19 in Compliance with Standardized Protocols and Practices

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Message

Ayurveda is a rich legacy that we as Indians are fortunate to have inherited from our ancestors. However, the lack of proper guidelines has kept this system of medicine less organized and limited its spread for a long time. To streamline such precious knowledge, the Ministry of AYUSH has organized India's traditional systems of medicine under one umbrella with tangible, pragmatic guidelines to align them with other medicinal systems across the globe. Several aspects of this book by Acharya Balkrishna orient Ayurveda in a direction that holds promise to bridge the gap between modern and traditional systems of medicine. This precise effort of bridging the gap is evident from the meticulous scientific affirmation generated by Patanjali Research Institute, in support of Ayurvedic remedy for COVID-19. This excellent compendium of preclinical and clinical data has the potential to serve as a general guide for developing Ayurvedic formulations into modern forms of medications.

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FOREWORD

The COVID-19 pandemic has emerged as a global health emergency of international concern since its first identification, resulting in millions of deaths and economic disruption. The healthcare systems across the globe are at the hilt and being tested for effective management against COVID-19. Employing our ancient traditional system and integrative approach, our nation has dealt with this bolstering virus competently, which is evident from the significantly low mortality rates in India. Param Pujya Acharya Ji, with his sheer dedication, astute guidance, pragmatic approach, and deep knowledge of the ancient Indian traditional system of medicine, has written a new success story by developing an effective medicine against COVID-19.

Patanjali Research Institute, Haridwar, Uttarakhand, is a lineage representative of ancient Indian Vedic and sage traditions. A team of dedicated scientists at Patanjali Research Institute has worked relentlessly to develop Ayurvedic formulations into effective medicine by screening close to 1500 phytochemicals from more than 200 medicinal plants. This was a path-finding journey with experiences shared in this book titled **"Ayurveda against COVID-19"**. We hope that this body of work will serve as a capstone of guidance to develop a new series of Ayurvedic formulations into medicines that would be acceptable to the modern medical and scientific fraternity worldwide.

By sharing our research through this book, we wish to reach a greater and wider readership and, in the process, hope to materialize our humble efforts towards ensuring the well-being of humankind worldwide.

May this excellence of scientific practice in Ayurveda find its due destination!

Swami Ramdev

President and Co-founder
Patanjali Yogpeeth
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PREFACE

The year 2020 has posed a grave challenge for humankind in the form of a new coronavirus, SARS-CoV-2. The outbreaks witnessed by the world back in 2002 and 2012 due to SARS and MERS, respectively, now appear to be insignificant in front of the current pandemic. The virus was officially named coronavirus disease 2019 (COVID-19) by WHO in March 2020, after due diligence of the first case being reported in Wuhan, Province of China. This pandemic has divided the current age into two eras: pre-COVID-19 and post-COVID-19, in every respect, some of which are obvious immediately, like, healthcare and finance, while others, like education and politics, are yet to be revealed. All these changes are primarily adaptive, and yet we are still not well-adapted to this selection pressure. The world as one entity has stood up in solidarity to face this challenge in all spheres of life, healthcare, and medicine being at the forefront. While on field, it is the medical personnel who are relentlessly fighting an apparently never-ending battle against COVID-19. In the laboratories, it is the scientists putting their heart and soul to find a solution to end this battle that is draining humankind both physically and emotionally.

We still do not have a cure for COVID-19 despite the fact that the etiology and pathology of this disease have been thoroughly worked out. Modern medicine is grappling to cope with the current situation with no specific treatment against COVID-19. Our hopes for the re-purposed modern medicines fell flat with unfavorable outcomes of clinical trials conducted involving them. So, after a transient flash of hope for a potential cure for COVID-19, we are apparently, still in the darkness as at the beginning of this year. Alternative medicines are coming up with promising reports but establishing a medicine from an alternative system is difficult with no standard operating protocols to do so in place.

The ancient Indian medicinal system, Ayurveda, is at the core of the working mandate of Patanjali Research Institute (PRI), governed by Patanjali Research Foundation Trust (PRFT), Haridwar, India. PRFT has been following the rapid evolution of COVID-19 very closely right from the day when the first case was reported. Probably, that is the reason, today, PRFT can confidently declare that it has found a way to fight COVID-19, although the solution is only recognized as an immunity booster, preliminary and interim outcomes from surveys, observational clinical studies, and completed and continuing clinical trials speak more favorably towards this solution being a cure rather than a mere prophylactic in the form of an immunity booster. This book is a chronicle of this journey of PRFT from fields (medicinal herbs) to clinics (medicines being used in clinical trials) via research laboratories at Patanjali Research Institute (PRI) for developing solutions for COVID-19. Additionally, this work is also expected to be a capstone to guide how one can develop traditional medicines into forms acceptable by modern medical practitioners worldwide.

PRFT has been actively involved in finding a cure for COVID-19 since WHO expressed its concern last January, even before declaring this to be an outbreak. In fact, computational studies from PRFT after coming into the public domain as pre-prints triggered several groups to take up similar studies that have now resulted in a huge database of phytochemicals with predicted antiviral potentials against SARS-CoV-2. Even before this, revered Swami Ramdev Ji recommended the use of decoctions of herbs (which were later used in these medicines) as a home remedy for protection against COVID-19. These recommendations were based on Ayurvedic medicines prescribed for ailments with corresponding etiologies. So, it is evident that what we have offered humankind in the form of a Coronil kit is the outcome of our deep-rooted traditional scientific knowledge. We believe that this piece of work would be like a

beacon to whosoever wishes to develop our ancient Ayurvedic prescriptions into a form acceptable to the practitioners of modern medicine.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 1

Virtual Screening and Computational Study

Abstract: This chapter discusses the virtual screening of phytochemicals and computational validation of identified ones as potential antiviral agents against the SARS-CoV-2 virus. In addition, we have provided an outline of how to conduct virtual screening and computer validation to identify potential lead compounds for further studies, including their formulation, chemical characterization, validation, and licensing, which have been addressed in the next chapter.

Keywords: ACE 2, Molecular docking, Molecular dynamic simulation, RBD, SARS-CoV-2, Scutellarein, Tinocordiside, Withanone.

1.1. SARS-COV-2 OUTBREAK AND HELPLESSNESS OF MANKIND

On 8th December 2019, a pneumonia case of unknown cause was reported in Wuhan, province of China, and hence, started the COVID-19 nightmare (Lu *et al.*, 2020). By the first week of January 2020, a new strain of coronavirus was identified by the Chinese Centre for Disease Control and Prevention (CCDCP), which was never associated with humans earlier (Kruse, 2020; Zhu *et al.*, 2020). Soon after, on 10th January 2020, the World Health Organization (WHO) acknowledged this report and tentatively referred to the novel coronavirus as 2019-nCoV. Within just three days, the first case of the new disease was reported in Thailand. The disease started spreading like wildfire, and by the end of the month, on 30th January 2020, WHO recognized it as a Public Health Emergency of International Concern and, on 11th March 2020, exactly one month after naming the disease as COVID-19, WHO declared it as a pandemic. With its anniversary just shy of a month, the COVID-19 situation, if anything, has become more rampaging.

The opening remarks of Dr. Tedros Adhanom Ghebreyesus, the current Director-General of WHO, in a media briefing on COVID-19 on 26th October 2020, are far from putting our minds at ease. According to him, the third week of October 2020 witnessed the highest number of COVID-19 cases worldwide. Several countries in the Northern Hemisphere are experiencing a concerning rise in the active COVID-

19 cases that require hospitalizations, filling up the intensive care units to the capacity in some places (WHO, 2020). Initial ripples created in the global economic matrix due to preventive shutdown measures against COVID-19 have now multiplied to a colossal magnitude. The pandemic has plunged the global economy into a severe contraction. The World Bank has forecasted a 5.2% shrinkage in the global economy this year, making it the deepest recession since the Second World War (The World Bank, 2020). Another lockdown would, for sure, swallow the world economy in a never-to-be-recovered abyss. The magnitude of this shock keeps mounting with the continued lack of a specific cure for COVID-19.

1.2. MOLECULAR ETIOLOGY OF COVID-19

SARS-CoV-2 is recognized as a member of the sister clade of the prototype human and bat Severe Acute Respiratory Syndrome Coronaviruses (SARS-CoVs) (Gorbalenya *et al.*, 2020). Coronaviruses are zoonotic pathogens that can transmit from animals to humans. They are large positive-stranded RNA viruses, with host specificity among avian and mammalian species and are responsible for ailments of the central nervous system, upper and lower respiratory and gastrointestinal tracts (Huynh *et al.*, 2012; Yu *et al.*, 2015; Salata *et al.*, 2019; Gralinski and Menachery, 2020). There are seven coronaviruses identified so far, out of which, OC43, 229E, HKU1, and NL63 are mild ones, whereas SARS-CoV, MERS-CoV, and SARS-CoV-2 are extremely virulent in humans. SARS-CoV and MERS-CoV appeared in 2002 in China, causing Severe Acute Respiratory Syndrome, and in 2012 in Saudi Arabia, causing Middle East Respiratory Syndrome, respectively (Ksiazek, 2003; Stadler *et al.*, 2003; Zaki *et al.*, 2012; Zeng *et al.*, 2018). The epidemiological and clinical knowledge base of COVID-19, although building up fast, still falls behind the swift evolution found in the virus (Huang *et al.*, 2020s; Hui *et al.*, 2020). Therefore, the whole world is left with the only option of employing stringencies, like social distancing and lockdowns, to face this challenge until a cure or a vaccine against it is developed. The present COVID-19 pandemic has put us in a war-like situation, requiring strategic planning in all areas. Developing treatments, identifying cures, and formulating intervention strategies to fight back the COVID-19 outbreak has become our most important concern. Fortunately, studies, by now, have confirmed the molecular pathway of COVID-19 virulence that involves ACE-2, AT1, and TMPRSS2. Many studies have been reported, and several others are ongoing to find a cure using these target molecules.

Coronaviruses enter the target animal cells by binding to cell-surface-associated receptors. During viral infection, entry of the virus into the host cell is a critical

step that can be exploited for antiviral therapy (Bupp and Roth, 2005). So, entry inhibition by targeting viral receptor binding through neutralizing antibodies (NABs) is an obvious option that works well in most cases. There are also certain small molecules (like RFI-641 and VP-14637) that inhibit the entry of several viruses, including respiratory syncytial virus (Razinkov, *et al.*, 2001; Douglas, *et al.*, 2003). SARS-CoV entry into the host cell is mediated by the Receptor-Binding Domain (RBD) of its spike glycoprotein (S-protein). S-protein binds to the host cell receptor Angiotensin-Converting Enzyme-2 (ACE-2) (Prabakaran, *et al.*, 2006; Adedeji, *et al.*, 2013). The coronavirus S-protein is a structural protein conferring the crown-like morphology to the virus particles. It is ~1200 aa long, belongs to Class-I viral fusion proteins, and contributes to the cell receptor binding, tissue tropism, and pathogenesis (Millet and Whittaker, 2015). It contains several conserved domains and motifs, and the trimetric S-protein is processed at the S1/S2 cleavage site by host cell proteases. The protein is cleaved (or primed) at a conserved sequence AYT↓M (located 10 aa downstream of SLLR-ST) into an N-terminal S1-ectodomain that recognizes a cognate cell surface receptor and a C-terminal S2membrane-anchored protein involved in viral entry (Bosch, Bartelink and Rottier, 2008; Matsuyama *et al.*, 2010; Millet and Whittaker, 2015). The SARS-CoV S1-protein contains a conserved RBD, which recognizes the host ACE-2. The interacting interface of RBD of S1 and ACE-2 implicates 14 aa in the S1 of SARS-CoV (Li *et al.*, 2005). Among them, 8 residues are strictly conserved in SARS-CoV-2 S protein, supporting the observations that SARS-CoV-2 uses the SARS-CoV receptor ACE-2 for entry and the serine protease TMPRSS2 for S protein priming (Lan *et al.*, 2020; Wan *et al.*, 2020). The receptor-binding domain (RBD) of viral coat spike (S) protein binds to transmembrane ACE-2. Viral coat fuses with host cell membrane only after the viral coat S protein gets primed, that is, cleaved at S1/S2 and the S2' sites by host cellular serine protease, TMPRSS2 (Hoffmann *et al.*, 2020). The RBD of SARS-CoV-2 S protein differs largely from the SARS-CoV at the C-terminus, but the difference does not affect its capability to engage the ACE-2 receptor (Tian *et al.*, 2020). Therefore, RBD has been an attractive target for researchers to abrogate coronavirus infection. Reports suggested that certain human antibodies recognized RBD on the S1 domain of SARS-CoV and inhibited the viral infection by blocking its attachment to ACE-2 (Anand *et al.*, 2003; Dau and Holodniy, 2009). Consequently, three possible mechanisms, namely, targeting ACE-2 receptor, RBD of S protein, and the interaction between ACE-2 and RBD are proposed, which are schematically depicted in Fig. **(1.1)**, through which SARS-CoV-2 entry/infusion can be abrogated.

CHAPTER 2

Formulation, Licensing, Chemical Characterization, and Validation of Ayurvedic Medicine

Abstract: This chapter, besides sharing the story behind the formulation and development of Ayurvedic medications acceptable in modern medicine, provides a detailed standard operating procedure for developing Ayurvedic drugs. To fight the COVID-19 infection, caused by the SARS-CoV-2 coronavirus, Patanjali Research Institute (PRI), Haridwar, developed the Divya Swasari Coronil kit. It contains Coronil Tablet, Divya Swasari Vati, and Divya Anu Taila. Divya Pharmacy, Haridwar, India, has obtained a manufacturing license from the Ayurvedic & Unani Department of Uttarakhand, Dehradun (License No.: 13-71-72/D-431/2020-2021) for Coronil and Swasari Vati tablets. Divya Coronil tablet has been formulated from a blend of Giloy, Ashwagandha, and Tulsi, whereas Divya Swasari Vati and Divya Anu Taila were prepared according to the classical recipe mentioned in traditional Ayurvedic texts. Analytical methods have been developed to identify and quantify the active phytoconstituents present in these blends and tablets. Sophisticated techniques are used in the manufacturing of these tablets, like liquid chromatography, equipped with single quadrupole, colloisan cell and time of light (UPLC/QToF MS), high-performance liquid chromatography (HPLC) equipped with PDA detector and high-performance thin layer chromatography (HPTLC) with automatic spotting, in which developing and scanning chambers are used for the identification and quantification of herbs. The methods have been validated in-house using ICH-Q2 (R1) and pharmacopoeia guidelines to demonstrate the repeatability, reproducibility, and reliability of the data generated. There are stringent quality checks for the authentication of raw material used in the manufacturing of the tablet, along with in-process checks and the final release of the batch. The herbs used during the manufacturing of these products have been authenticated, and voucher specimens have been stored in a government-approved depositary. The synergistic effect of these tablets has been studied by Patanjali Research Institute (PRI) for their immunity-boosting properties and the restoration of health of SARS-CoV-2 infected patients.

Keywords: CoP, HPTLC, Manufacturing license, Pharmacopoeia guidelines, Raw material selection and sampling, UPLC/QToF MS.

Acharya Balkrishna

SELECTION OF RAW MATERIAL

For any formulation, selecting the right quality raw material is of prime importance. In Ayurvedic preparations, raw material is mainly herbs or their standardized extracts. In the Coronil tablet, extracts of Ashwagandha, Tulsi, and Giloy were used. Likewise, Divya Swasari Vati is a traditional formulation comprising of 9 herbs.

Coronil tablet is a new formulation; therefore, all the three plants used for manufacturing went through stringent quality check parameters. However, Divya Swasari Vati, being a traditional formulation, already had its herbal constituents authenticated, and the quality check parameters were already established. The stringent quality parameters were applied for every batch of herbs procured from outside sources. Being a natural product, many factors are responsible for the selection of the right quality raw material. The below-listed factors are considered during the selection of the right quality of raw material:

i. Geographical location: It plays a major role in deciding product quality. Herbs grown at high altitudes will have different constituents compared to herbs grown in dry places like deserts or humid conditions that exist near a sea shore.
ii. Maturity period: The maturity period of the crop is another important criterion for selection.
iii. Season of harvesting.
iv. Drying condition: Sun drying, shade drying, air drying, drying under controlled temperature, *etc.*, play a major role in deciding the quality of the material.
v. Storage: Temperature, humidity, light, *etc.*, affect the quality of raw material.
vi. Protection from insects and pests.
vii. Supply chain: Herbal material may be forest collected or farm cultivated. The supply chain plays a major role not only in selecting the quality but also in ensuring contamination-free raw material. A schematic representation of the supply chain used in India is shown in Fig. (**2.1**).

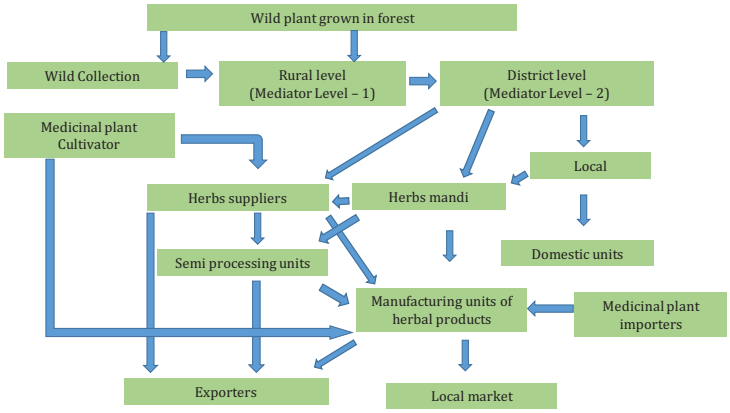

Fig. (2.1). Supply chain map used in India.

SAMPLING OF RAW MATERIAL

A sampling of raw material is one of the most important criteria for approving the right material quality. The reliability of any conclusions drawn from the analysis of a sample will depend upon how well the sample represents the whole batch. General recommendations for the sampling of pharmaceutical materials in connection with quality control are provided in the 39th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Because of the specific characteristics of herbal materials, in particular their lack of homogeneity, special handling procedures are required in relation to sampling.

RECOMMENDED PROCEDURES OF SAMPLING

Sampling of Material in Bulk

As per WHO (WHO, WTR; 2005) guidelines, for bulk raw material, like herbs which consist of roots, stem, leaves, or whole plant, the first requirement is a physical inspection of each container or packaging material. The second step is to check if the label matches the specification, monograph, or other packaging and labelling criteria. Checking the condition of the package gives us information about the quality, quantity and stability of contents (loss during transportation, physical damage, increase in water content, *etc.*).

If the initial finding confirms that the batch is uniform, sampling should be initiated, and the whole material has to be quarantined to ensure that no unwanted insects or pests are being carried. As per the guidelines that detail the sampling procedure, if a batch consists of five or lesser containers or packaging units, a sample should be taken from each unit. From a batch of 6–50 units, a sample is

CHAPTER 3

Understanding the Mode of Action of the Medicine through *In-Vitro* Studies

Abstract: This chapter deals with the scientific authentication of the formulated Ayurvedic medicine. . Scientific research for mechanistic insights into the functionality is not a regulatory requirement for developing a herbal drug. Nevertheless, the outcomes from such scientific research works have been included in this chapter. Such scientific evidence on modes-of-actions of the herbal medicines helps in generating awareness among the end users, who could be from both scientific and non-scientific backgrounds. In this chapter, we have shared our scientific observations from the laboratory validations of the medicines, Coronil and Divya Swasari Vati,that have been developed. We have also discussed the modes of action of these medicines against the SARS-CoV-2 virus, as gathered from ***in-vitro*** experiments. Biochemical studies have shown that the medicines formulated by Patanjali Research Foundation Trust against the SARS-CoV-2 virus are capable of inhibiting the physical interactions between viral spike (S) protein and host ACE2 receptor protein. This interaction between S protein and ACE2 receptor is critical for COVID-19 infection. Our medicines were found to be effective in disrupting this interaction regardless of the initial mutation, like, D614G, that the SARS-CoV-2 virus has undergone to increase its infectivity. These medicines could also rescue the lung epithelial cells from S protein- and pseudovirus-induced cytokine storms. Pseudoviruses are non-pathogenic study viruses used for experimental purposes to understand the host entry mechanisms in viruses. In this case, the non-pathogenic viral genome was encased with SARS-CoV-2 S protein so that we can follow the S protein and ACE2 interactions. Besides, these pseudoviruses also had reporters inside them that helped us to monitor their entry into host cells. We found that cells, when treated with our medicines, showed lesser internalization of the viruses, suggesting that the medicines are preventing the virus entry. During COVID-19 pathogenesis, the pro-inflammatory cytokines put the immune response into an overdrive by inducing each other. We tried to mimic this *in-vivo* condition ***in-vitro*** by inducing inflammation in the lung epithelial cells with one pro-inflammatory cytokine and then checked the levels of others and how the treatment with our medicines altered this response. We observed that cells, when exposed to one pro- inflammatory cytokine showed an increase in the levels of others and interestingly when these cells were treated with Ayurvedic medicines, the cytokine levels reduced. Taken together, these *in-vitro* observations revealed that these Ayurvedic medicines disrupted physical interaction between viral S protein and host ACE2 receptor and attenuated the cytokine storm, implicating their potential in managing acute respiratory distress syndrome (ARDS), one of the prime causes of COVID-19 associated mortality.

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Keywords: SARS-CoV-2 pseudovirus, ACE2-S protein interaction, S^{D614G} protein, S^{W436R} protein, ELISA, RT-PCR.

3.1. EXPERIMENTAL VALIDATION OF COMPUTATIONAL OBSERVATION

ACE-2 is a single-pass type I membrane protein, with its enzymatically active domain exposed on the surface of cells in lungs and other tissues (Hamming *et al.*, 2004). The binding of the spike S protein of SARS-CoV-2 to the enzymatic domain of ACE-2 on the surface of cells results in endocytosis and translocation of both the virus and the enzyme into endosomes located within cells (Fig. **3.1 A**). This entry process also requires priming of the S protein by the host serine protease TMPRSS2, the inhibition of which is under current investigation as a potential therapeutic (Hoffmann, *et al.*, 2020).

Computational studies from our and other groups have shown that withanone can target ACE-2 and Receptor Binding Domain (RBD) of SARS-CoV-2 viral spike (S) protein interaction, SARS-CoV-2 main protease (M^{pro}) and TMPRSS2 (Kumar, Dhanjal, Bhargava, *et al.*, 2020; Kumar, Dhanjal, Kaul, *et al.*, 2020; Balkrishna, Pokhrel, *et al.*, 2021) (Fig. **3.1B**). However, experimental evidence has been lacking. Through an ELISA-based method, we have checked the effect of pure withanone on the interaction between human ACE-2 protein and RBD of SARS-CoV-2 viral spike (S) protein (Fig. **3.1 C**). In this method, overexpressed truncated S protein of SARS-CoV-2 expressing only the RBD was used while the human ACE-2 (hACE-2) used was full length. ELISA wells were coated with viral RBD to which biotinylated hACE-2 was added along with different concentrations of withanone. An inhibitor of ACE-2-RBD interaction provided with the kit was used as a positive control, while the reaction without any inhibitor was taken as a negative control. Inhibition of ACE-2-RBD interaction was calculated with respect to the negative control assuming the interaction to be 100%. The interaction was detected using HRP- conjugated streptavidin against biotinylated ACE-2 (Fig. **3.1 D**). We observed that withanone exhibited a dose-dependent inhibition of ACE-2-RBD interaction (IC_{50} = 0.33 ng/ml) (Fig. **3.1 E**). In the physiological context, this will translate into therapeutic efficacies of pure withanone. To validate this speculation, we treated the zebrafish model presenting COVID-19 pathologies with leaf extract from *W. somnifera* (Ashwagandha) enriched in withanone (WiNeWsE) (Fig. **3.1F**). WiNeWsE treatment relieved these fishes from pathological symptoms, like, behavioural fever (Balkrishna, Pokhrel, *et al.*, 2021).

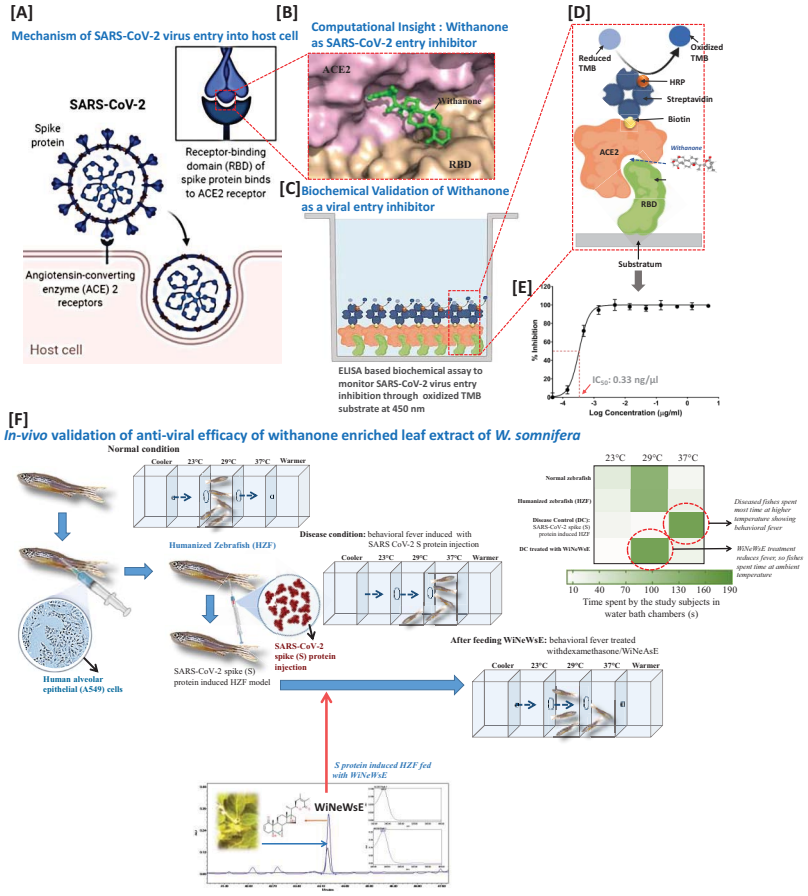

Fig. (3.1). Experimental validation of the viral entry inhibitory effect of withanone. **[A]** Schematic representation of the molecular mechanism of SARS-CoV-2 entry into the host cell. **[B]** withanone binds at the ACE-2-RBD interacting interface (demarcated with a red open box in the cartoon) as shown in a magnified view of the molecular docking visualization. **[C]** Pictorial depiction of the experimental procedure employed in evaluating the inhibitory effect of withanone on the biochemical interaction between host ACE-2 and viral RBD. **[D]** Biotinylated ACE-2 bound to RBD, immobilized to the substratum, is detectable through HRP-conjugated streptavidin due to oxidation of 3,3',5,5'-Tetramethylbenzidine (TMB). **[E]** Dose-response curve exhibiting the inhibitory effect of withanone on the interaction between human ACE-2 and RBD of SARS-CoV-2 S protein. IC_{50} is found to be 0.33 ng/ml. **[F]** *In-vivo* validation of the efficacy of *W. somnifera* leaf extract enriched with withanone (WiNeWsE) showing the induction of disease pathology in the zebrafish, subsequent treatment with WiNeWsE and concomitant amelioration of behavioural fever. Withanone enrichment in WiNeWsE was validated through HPLC *[Courtesy:*(Balkrishna, Pokhrel, *et al.*, 2021)*; Under CCBY License]*.

CHAPTER 4

Use of *In Vivo* Models in Preclinical Drug Discovery and Development

Abstract: This chapter deals with the *in vivo* preclinical studies involving the COVID-19 zebrafish model conducted on the Ayurvedic medicines mentioned in the last chapter to further validate their efficacy against COVID-19. Animal models are needed in order to understand the disease's progress and associated symptoms. While it is possible to understand the disease characteristics based on historical evidence and previous research on similar disease-causing organisms, newer species of disease-causing agents have been recently discovered. These newer organisms without any previous history, pose the biggest challenge in drug discovery and development. In these cases, the use of relevant animal models of disease becomes important in order to understand the disease progression as well as the interaction of the body with the disease-causing agent. In the current SARS-CoV-2 infections, the virus is potentially lethal in humans. In such cases, the danger of using humans to test new drugs becomes ethically unacceptable unless the drug has been tested in animal models against the virus. The use of higher primates, like monkeys, or small animals like dogs and rodents, which are generally accepted pre-clinical models of drug discovery, has a myriad of ethical concerns. Despite this, several different models of SARS-CoV-2 infection are currently in use, ranging from non-human primates, such as rhesus macaques (Rhesus monkey), and rodent models, such as transgenic mice and hamsters. While it is difficult to incorporate all the different pathological features of the disease in a single model, it is important to choose the correct model animal in order to answer the primary question that the investigator seeks. For example, rodents lack the coagulopathy component, which is often seen in severe SARS-CoV-2 infections. By the same token, the narrow spectrum of viral infectivity and the inability to the cross-species barrier by the virus is an important consideration while studying the disease pathology. This was seen in a rhesus monkey model where no overt clinical signs were detected even though prolonged viral shedding was detected in the upper respiratory tract of animals. With these issues in mind, we developed a humanized zebrafish model to test the efficacy of Coronil and Divya Swasari Vati in decreasing the pathogenic characteristics associated with SARS-CoV-2 spike protein expression. Zebrafish has proven to be a solid model system for investigating human viral pathophysiology, and various human viruses, including chikungunya and influenza, can colonize zebrafish, making it an appealing and alternative model system. Zebrafish have well-defined innate and adaptive immune systems that are strikingly comparable to those of humans. Unlike mouse models, zebrafish have swim bladders as buoyancy organs, and human cells could be transplanted into swim bladders to create xeno-transplanted humanized models for respiratory disorders, such as SARS-CoV-2 infection. The implantation of human lung cells into the zebrafish's air bladder increases the model's relevance and

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gives human-equivalent methods of inquiry. Different groups have successfully employed this strategy to replicate lung cancer in zebrafish as well as COPD and Pseudomonas aeruginosa pathogenesis. Results obtained from treating the humanized zebrafish model injected with the S protein of SARS-CoV-2 with either Coronil or Divya Swasari Vati are shared in this chapter, along with a proposed mode of action for both of these Ayurvedic formulations.

Keywords: Behavioural fever, Cytokine response, Humanized zebrafish, *In vivo* studies, Preclinical, SARS-CoV-2 S protein-induced inflammation.

4.1. RATIONALE FOR THE USE OF *IN VIVO* MODELS

Animal models are needed in order to understand the disease's progress and associated symptoms. While it is possible to understand the disease characteristics based on historical evidence and previous research on similar disease-causing organisms, newer species of disease-causing agents have been recently discovered. These newer organisms without any previous history pose the biggest challenge in drug discovery and development.

It becomes important for researchers to use relevant models of disease or induce disease in small animals to replicate the disease progression and to understand the interaction of the body with the disease-causing agent. Once such a model has been developed and successfully used, the process of drug discovery can start.

The introduction of unknown chemical agents to humans is fraught with danger, and therefore, it is ill-advised to test drugs directly in humans. Even if a particular drug was previously cleared for human use, it is important to understand the interactions between the drug and the new disease it is being tested against. This has many reasons, the most important being the potential transformation of the drug by the pathogen into a newer metabolite which could cause untold damage to the human body. For this reason, animal testing forms an integral part of drug discovery and development.

In the current SARS-CoV-2 infections, the virus is potentially lethal in humans. In such cases, the dangers of using humans to test new drugs become ethically unacceptable unless the drug has been tested in animal models against the virus. In the case of newer pathogens for which medications are not available, patient management to prevent mortality takes the center stage rather than outright eradication of the pathogen. Symptomatic treatment for the changes seen as a result of the viral infection is important so that the body’s immune system is not over-burdened and can fight back on its own, or with a little help from various drugs that give symptomatic relief. Therefore, the immediate use of untested

drugs in patients with active infections becomes a double-edged sword, wherein the drug may pose an unnecessary burden on the patient while having minimal to no effect on disease eradication.

4.2. WHY ZEBRAFISH?

The use of higher primates like monkeys, or small animals like dogs and rodents, which are generally accepted preclinical models of drug discovery has a myriad of ethical concerns. Despite this, several different models of SARS-CoV-2 infection are currently in use, ranging from non-human primates such as rhesus macaques (Rhesus monkey), and rodent models such as transgenic mice and hamsters. While it is difficult to incorporate all the different pathological features of the disease in a single model, it is important to choose the correct model animal in order to answer the primary endpoint that the investigator desires. For example, rodents lack the coagulopathy component, which is often seen in severe SARS-CoV-2 infections. By the same token, the narrow spectrum of viral infectivity and the inability to cross the species barrier by the virus is an important consideration while studying the disease pathology. This was seen in a rhesus monkey model where no overt clinical signs were detected even though prolonged viral shedding was detected in the upper respiratory tract of animals.

Keeping these concerns in mind, we employed a humanized zebrafish model to see if Coronil and Divya Swasari Vati may help reduce the pathogenic characteristics associated with SARS-CoV-2 spike protein expression. For researching the human viral disease, zebrafish has proven to be a reliable model system. It is a small and adaptable organism that is very easy to manipulate, and the signalling pathways, interactions with chemical modifiers, and host-virus communications on mucosal tissues may all be studied in great detail. Zebrafish have well-defined innate and adaptive immune systems that are strikingly comparable to those of humans. Furthermore, the interaction of viral glycoproteins with olfactory sensory neurons in the fish nasal area is well understood. The loss of olfactory sensibility is one of the early clinical indications of established SARS-CoV-2 infection, hence such an interaction model is required.

Several human viruses, including chikungunya and influenza, can invade zebrafish, making it an appealing and novel model system. Unlike mouse models, zebrafish have swim bladders that serve as buoyancy organs, and human cells could be implanted in them to create xenotransplanted humanized models for respiratory disorders like SARS-CoV-2 infection. The transplantation of human lung cells into the swim bladder of the zebrafish enhances the relevance of the model and provides a human equivalent means of investigation. This approach

CHAPTER 5

Importance of Studying Adverse Effects of High Doses of Drugs Using Toxicology Studies

Abstract: This chapter highlights the requirements for conducting an adverse effect study involving laboratory animals. Though this study is not required for Ayurvedic formulations, we are conducting these studies to follow the requirements in order to make the medicinal formulation acceptable by modern medical practitioners. The maximum tolerance limit for the formulation needs to be tested in toxicology studies using a rat and a rabbit model under the 'New Drugs and Clinical Trials Rules,' Ministry of Health and Family Welfare, Government of India, and the 'Organization for Economic Co-operation and Development (OECD)' guidelines. These two animals are the species accepted by regulatory agencies for conducting safety and toxicity studies. The acute toxic class method is a stepwise procedure using 3 animals of a single-sex per step. Depending on the mortality and/or the moribund status of the animals, on average, 2-4 steps may be necessary to allow judgement on the acute toxicity of the test substance. This procedure is reproducible, uses very few animals, and can rank substances based on their toxicity. The acute toxic class method is based on biometric evaluations with fixed doses, adequately separated to enable a substance to be ranked for classification purposes and hazard assessment. The objective is to determine the possible health hazards of the formulation after repeated daily oral administration for 28 consecutive days. In a second set, the animals were allowed to recover for a further 14 days after a 28-day drug administration to test for reversibility, persistence, or delayed occurrence of toxic effects. The study will provide information on major toxic effects, target organs, if any, and determine the No-Observed- Adverse-Effect-Level (NOAEL) of the Ayurvedic formulation. We tested Coronil and Divya Swasari Vati in both rats and rabbits. Preliminary studies showed that either formulation did not show any toxic effects for 28-day administration followed by a 14-day recovery period. We will present data obtained in the toxicity studies in an appropriate forum once the study is completed. This chapter mentions the protocols and standard procedures to be followed while conducting such studies. This is critical since the clearance for clinical studies is based on these toxicological observations, as is described in the next chapter.

Keywords: Acute toxicological study, Sub-acute toxicological study, NOAEL, New Drugs and Clinical Trials Rules, Organization for Economic Co-operation and Development' (OECD) guidelines.

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5.1. BACKGROUND

After conducting lots of research to establish the efficacy of our investigational Ayurvedic formulation through pre-clinical studies as per different guidelines, methods, and protocols, we proceeded for safety/toxicity evaluation as per Central Council for Research in Ayurvedic Sciences guidelines. However, our case is exempted from such requirements (as per page no: 6, The Gazette of India: Extraordinary (Part II-Section 3-Sub-section (i)). Since this book is intended to serve as a comprehensive guideline for developing Ayurvedic formulations into medicines acceptable by modern practitioners, so, continuing along the sequence of requirements, we conduct toxicological studies as per Organization for Economic Co-operation and Development (OECD) and Drugs and Cosmetics Act, Government of India, following the principles of Good Laboratory Practices (GLPs) in compliance with Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. This chapter mainly aims to lay out the prerequisites for conducting an adverse effect study. The guidelines for a 28-day repeated dose toxicity study in rats are as per the OECD guideline for testing chemicals, No. 407, titled 'Repeated Dose 28-Day Oral Toxicity Study in Rodents'. The guidelines for repeated dose toxicity in rabbits are as per the guidelines of 'Schedule Y' of the Drugs and Cosmetics Act, 1945, Govt. of India. The toxicology studies are also in line with the International Council of Harmonization (ICH) guidelines 'M3R2'.

5.2. RATIONALE BEHIND THE USE OF TOXICOLOGY STUDIES

Once the efficacy of the Ayurvedic formulation was tested by *in vitro* and *in vivo* studies, the maximum tolerance limit for the formulation needs to be tested in toxicology studies using a rat and a rabbit model. These two animals are the species accepted by regulatory agencies for conducting safety and toxicity studies.

The repeated dose toxic class method is a stepwise procedure using 3 animals of a single-sex per step (Schlede *et al.*, 2005). Depending on the mortality and/or the moribund status of the animals, on average, 2-4 steps may be necessary to allow judgement on the acute toxicity of the test substance. This procedure is reproducible, uses very few animals, and is able to rank substances based on their toxicity. However, for an Ayurvedic formulation, such a ranking system has not been established and, in most cases, may not be needed or relevant. The repeated dose toxicity method is based on biometric evaluations with fixed doses, adequately separated to enable a substance to be ranked for classification purposes and hazard assessment. The method, as adopted in 1996, was extensively validated *in vivo* against LD_{50} data obtained from the literature, both nationally and internationally. When the method was adopted, it replaced the oral LD_{50}

method. As such, in the case of using Ayurvedic formulations, specific guidelines for LD_{50} data might not be relevant. However, the oral LD_{50} test is no longer accepted by the OECD, the European Union, and the USA, making the use of alternatives to the oral LD_{50} test mandatory.

The objective is to determine the possible health hazards of the formulation after repeated daily oral administration for 28 consecutive days. The study will provide information on major toxic effects, target organs, if any, and determine the No-Observed-Adverse-Effect-Level (NOAEL) of the Ayurvedic formulation.

In a second testing set, the animals will be observed for further 14 days after 28-day drug administration to evaluate reversibility, persistence, or delayed occurrence of toxic effects.

5.3. INSTITUTIONAL REQUIREMENTS

The testing for toxicity of a test drug, or in this case, a formulation, must be performed by experts of the field under some very strict guidelines. These guidelines ensure that all parameters of toxicity can be adhered to and carried out in a way such that no ambiguity exists, either in the testing conditions or in the results obtained. All the certifications for the facility have to be current before the start of such toxicity studies.

(i) All the study procedures must be carried out based on standards set forth by the government of India, under the 'New Drugs and Clinical Trials Rules, Ministry of Health and Family Welfare, Government of India (Department of Health and Family Welfare), Gazette of India, (extraordinary) Part-II, Section 3(i) vide G.S.R. 227(E), dated 19th March 2019.

(ii) In addition, the toxicity study will have to comply with 'Good Laboratory Practice' (GLP) norms set out by 'Organization for Economic Co-operation and Development' (OECD) [(revised 1997, issued January 1998) ENV/MC/CHEM (98) 17 Environment Directorate, Organization for Economic Co-operation and Development, Paris, 1998].

(iii) The facility where such testing is carried out has to be a certified GLP laboratory under the principles set by the 'National GLP Compliance Monitoring Authority' (NGCMA), Department of Science & Technology, Govt. of India, for compliance to OECD-GLP.

(iv) Clearance from 'Committee for the Purpose of Control and Supervision of Experiments on Animals' (CPCSEA) must be obtained for conducting

CHAPTER 6

Designing Clinical Research: Application on Evidence-based Practice

Abstract: This chapter is a guide on designing and executing clinical trials for traditional medicines. It includes the guidelines to be followed during protocol designing and study execution. Patanjali Research Institute combines deep therapeutic and scientific knowledge of Ayurvedic medicines with unmatched clinical trial design execution. Every patient who participates in a clinical trial plays a critical role in conquering disease and discovering cures for COVID-19 on behalf of all of us. Thus, with an in-depth understanding of the issues related to the clinical trial, Patanjali Research Institute has conducted human clinical trials and studies as per the ethical codes of biomedical research.

Keywords: Clinical study, Trial design, Clinical trial document, CTRI, Randomized clinical trial, Observational study.

6.1. BACKGROUND TO CLINICAL RESEARCH

Owing to millions of cases and thousands of deaths that have occurred due to this present devastating pandemic, COVID-19, the healthcare system is at the hilt and being tested for effective management of COVID-19. Understanding the importance of clinical trials as a premier method for validating new drugs and therapies, Patanjali Research Institute has been working proactively in advance due to the evident public concern since late February 2021. We take pride in addressing the fact that we had developed a formulation when no specific vaccine or treatment was approved for COVID-19. After conducting preclinical studies as per the standard procedures while addressing all the challenges, we moved forward with the quest of conducting clinical studies in order to find an effective treatment regime against a virus.

The meaning of clinical research may appear to be self-evident. However, some researchers have narrowly defined clinical research to refer to clinical trials (*i.e.*, intervention studies in human patients), while others have broadly defined it to include any research design that studies humans (patients or subjects) or any materials derived from humans. Altogether with the above considerations, clinical

studies are also conducted with the aim to obtain knowledge on the safety, efficacy, and mechanism of action of investigational new drugs on human subjects and to obtain regulatory approval. Numerous statements describe clinical research, some of which are valid and while some are not. We have opted for a 'middle of the road' approach that comprehends the term **'patient-oriented research**,' which is defined as research conducted with human subjects or on human-derived material, in which the investigator directly interacts with the human subjects at some point throughout the initiation to termination of the study (Hoffmann *et al.*, 2020).

Clinical research, in essence, serves as a connection to bridge the gap between research and clinical practice, which is handled with our evidence-based approach (EBP). The EBP framework entails the amalgamation of research findings with clinical knowledge and traits, values, and preferences, and so serves as an important basis for undertaking clinically relevant research as well as empiric research based on sensitive clinical practice (Hershenberg, Drabick, and Vivian, 2012), which is reproduced in evidence-based practise (EBP) (Fig. **6.1**).

6.1.1. Patanjali Research Institute Quest to the Map-Design

With the above background, our major purpose at the clinical research division is to reduce assumptions and seek universal truth. In fact, little, if anything, is clear in science, and the interpretation of data does not imply truth but rather an opinion on what the data signify. Nonetheless, in our quest, this is the standard body of knowledge, and this may raise additional questions that will invariably generate further research. Recently, in our ongoing research with COVID-19, we have addressed all the aforementioned components for the development of therapeutic management that can address the gap between research and practice (Fig. **6.2**).

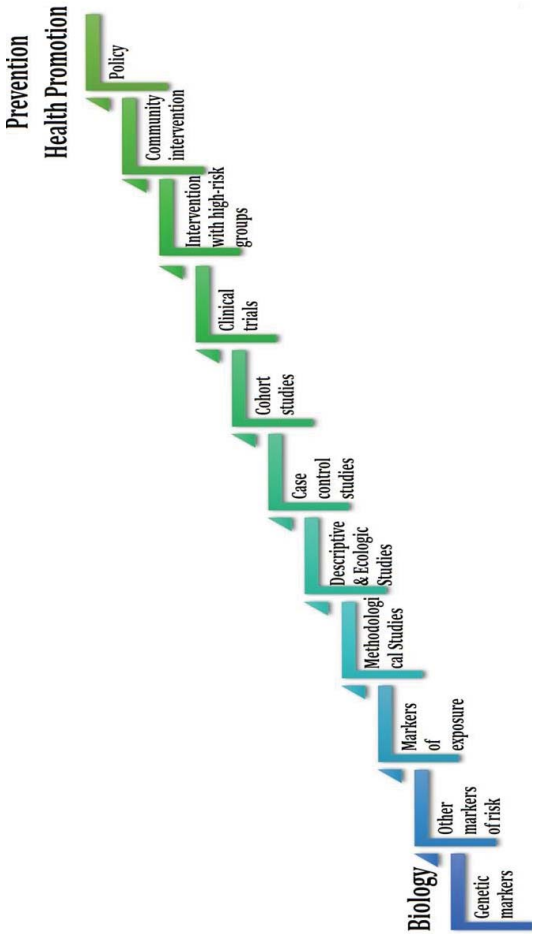


Fig. (6.1). Bridge which Patanjali Research Institute encompasses under term "clinical research".

CHAPTER 7

Public Health Research and Development

Abstract: This chapter essentially discusses the contribution of Patanjali Research Institute, Haridwar, in conducting research for human ailments in general and COVID-19 in particular. We strive to enhance the quality and understanding of healthcare and traditional medicine globally. We are committed to harnessing the power of Ayurvedic knowledge resources in order to discover, comprehend, and resolve unmet public health requirements. It can be assumed that by harnessing the power of Human Data Science, we can create new approaches to solving the world's most challenging health problems.

Keywords: Correlation matrix, Demographic variables, HR-QoL, Human Data Science, Public health, Psychosomatic study, TSQM.

7.1. BACKGROUND OF PUBLIC HEALTH

As a cutting-edge research institute, Patanjali works to enhance the quality and understanding of healthcare and traditional medicine globally. Patanjali Research Institute is dedicated to playing its part by pooling resources and expertise to find, comprehend, and resolve unmet public health issues. We think that by combining the power of scientific research with tried-and-true disease-prevention strategies, we can envision new ways to solve the world's most difficult health problems and improve people's lives.

From a precautionary perspective, public health highlights a complicated relationship between the state/country, its policies, and society, involving individuals and organizations (Fig. **7.1**).

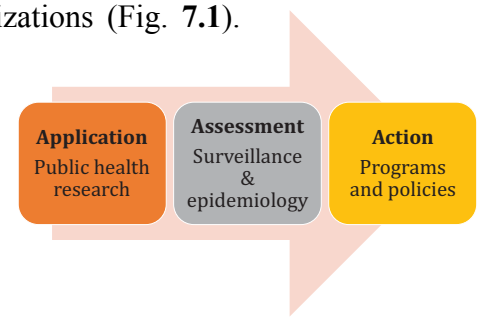


Fig. (7.1). Integrative approach in Public Health.

Ethics in public health apply to both practice and research, which rely on epidemiology and other methodologies to improve societal conditions and lead to healthier lives.

As a result, public health protects both individuals and the general public because the benefits and risks affect not only individuals but also communities, populations, and the environment. It is crucial to understand that public health interventions have the ability to reveal and exploit the vulnerabilities of communities and populations.

We firmly believe that public health research investigations and interventions should therefore be conducted through a process of ethical reflection, together with the establishment of appropriate protections, oversight procedures, and governance mechanisms. We have recently started interdisciplinary work to understand the impact of Ayurvedic formulations as health-related quality of life predictors and other critical health matters. We develop a research plan to understand health situations and assess health trends, as well as setting norms and standards.

7.2. PRINCIPLES OF PUBLIC HEALTH RESEARCH ETHICS

We strongly believe in the following concepts, which are outlined in the Indian Council of Medical Research (ICMR) guidelines for public health research:

- ***Principle of respect for autonomy, right, and dignity*:** Autonomy is a Latin word that means 'self-rule,' which gives the right of decision, confidentiality, and respect to human dignity. Because the interests of an individual as part of Public Health Research and the society as a whole are related, the principle of respect for autonomy is relational. As a result, individual autonomy may not always be appropriate as a stand-alone concept for use at the community level. Understanding this superlative connection, all individuals should be respected in terms of individuality to outreach and inter-relate the whole community. The method to address this principle is the informed consent process which should be addressed from one to all in addition to ethical committee approval (Mathur and Swaminathan, 2018).
- ***Principle of beneficence:*** Public health research attempts to fulfil a moral commitment by maximizing social benefit over individual benefit while maintaining an adequate risk/benefit balance.
- ***Principle of non-maleficence:*** This principle entails a responsibility to minimize the harm caused to persons, such as the community, particularly in the collecting of data and the conduct of any interventional pharmacological trial.

As noted in the guidelines, "harm" can take the form of stigma, poverty, and discrimination that affect people living with diseases, such as HIV, mental illness, and the current COVID-19 pandemic, among other things. There should be safeguards in place to ensure secrecy, as there could be indirect harm to the individual, community, or relationships, as well as a loss of benefits. The ideas listed below may overlap with those in public health and research.

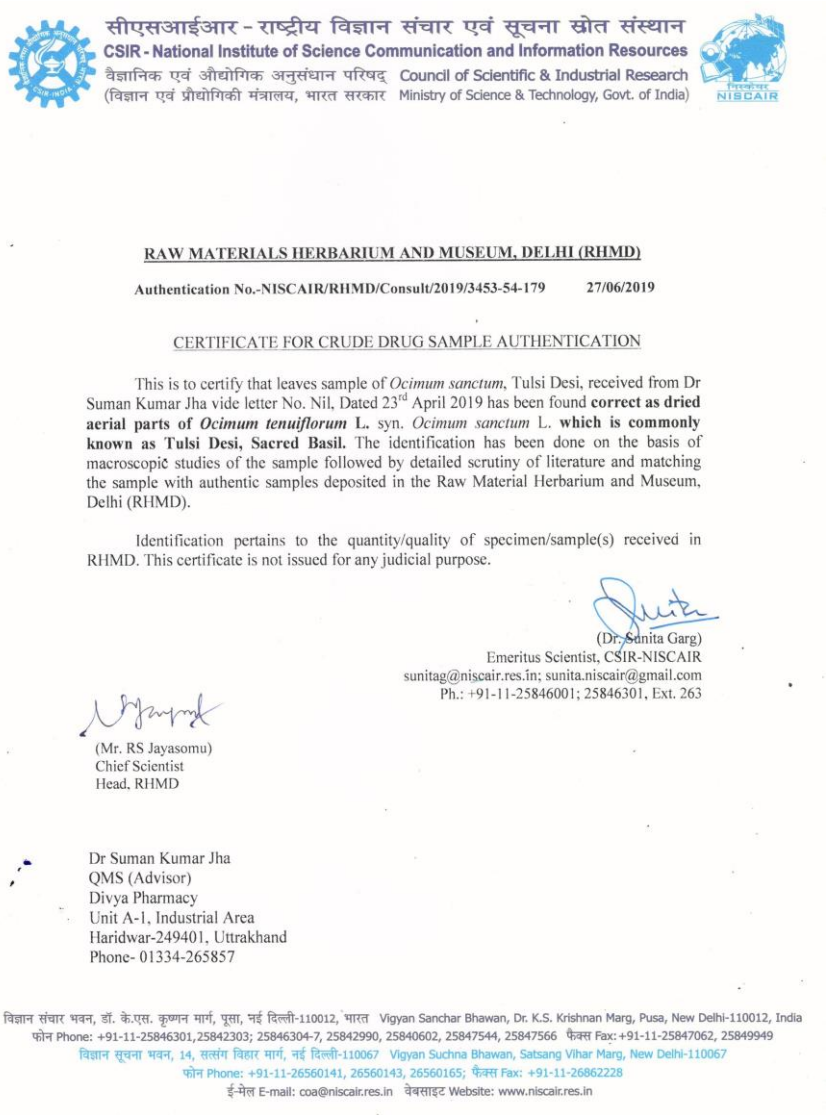
- Harm principle: If an individual's or a group's liberty is rightfully restrained against their choice to protect others, the choice should be supported by solid ethical reasons. In short, one person's actions should be limited to not damage other people.
- **Principle of least infringement**: When liberty is restricted, the least restrictive measures should be used as much as practicable.
- **Principle of proportionality**: This principle demands public health officials to reduce risks and improve public health. Individual autonomy and privacy should be weighed against the likelihood of public benefits and the necessity of such intervention. It must justify the costs borne by participants and communities.

- ***Principle of social justice***: As a result of this principle, public health authorities are required to reduce hazards and promote public health. Individual liberty and privacy should be weighed against the potential public good and the need for such intervention. It should justify the hardships that participants/communities have to bear.
- ***Principle of reciprocity:*** This principle urges public health officials to reduce dangers while also promoting public health. Individual autonomy and privacy should be weighed against potential public advantages and the necessity of such intervention. It must justify the costs borne by participants/communities.
- ***Principle of solidarity:*** Intra- and inter-dependence as a key principle based on sharing both the benefits, such as wealth and the burdens equally among members of communities, leading to solidarity for collective welfare or the common good, should be respected in public health research.
- ***Principle of accountability and transparency*:** The conduct of research must be open, honest, and transparent in every aspect. The outcomes should be made available to the general public.

According to the ICMR guidelines, PRI being a public health representative, strictly follow these guidelines. For conducting any research, these principles should be stringently followed during the conduction of any public health research (Mathur and Swaminathan, 2018) (Fig. **7.2**).

APPENDICES

Appendix - 2.1



सीएसआईआर - राष्ट्रीय विज्ञान संचार एवं सूचना स्रोत संस्थान
CSIR - National Institute of Science Communication and Information Resources
वैज्ञानिक एवं औद्योगिक अनुसंधान परिषद् Council of Scientific & Industrial Research
(विज्ञान एवं प्रौद्योगिकी मंत्रालय, भारत सरकार Ministry of Science & Technology, Govt. of India)

RAW MATERIALS HERBARIUM AND MUSEUM, DELHI (RHMD)

Authentication No.-NISCAIR/RHMD/Consult/2019/3453-54-179 27/06/2019

CERTIFICATE FOR CRUDE DRUG SAMPLE AUTHENTICATION

This is to certify that leaves sample of *Ocimum sanctum*, Tulsi Desi, received from Dr Suman Kumar Jha vide letter No. Nil, Dated 23rd April 2019 has been found **correct as dried aerial parts of *Ocimum tenuiflorum* L.** syn. *Ocimum sanctum* L. **which is commonly known as Tulsi Desi, Sacred Basil.** The identification has been done on the basis of macroscopic studies of the sample followed by detailed scrutiny of literature and matching the sample with authentic samples deposited in the Raw Material Herbarium and Museum, Delhi (RHMD).

Identification pertains to the quantity/quality of specimen/sample(s) received in RHMD. This certificate is not issued for any judicial purpose.

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(Mr. RS Jayasomu)
Chief Scientist
Head, RHMD

Dr Suman Kumar Jha
QMS (Advisor)
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Appendix - 2.2

सीएसआईआर - राष्ट्रीय विज्ञान संचार एवं सूचना स्रोत संस्थान
CSIR - National Institute of Science Communication and Information Resources
वैज्ञानिक एवं औद्योगिक अनुसंधान परिषद् Council of Scientific & Industrial Research
(विज्ञान एवं प्रौद्योगिकी मंत्रालय, भारत सरकार Ministry of Science & Technology, Govt. of India)

RAW MATERIALS HERBARIUM AND MUSEUM, DELHI (RHMD)

Authentication No.-NISCAIR/RHMD/Consult/2019/3453-54-15 **11/06/2019**

CERTIFICATE FOR CRUDE DRUG SAMPLE AUTHENTICATION

This is to certify that roots sample of *Withania somnifera*, Ashwagandha, received from Dr Suman Kumar Jha vide letter No. Nil, Dated 23rd April 2019 **has been found correct roots of *Withania somnifera* (L.) Dunal which is commonly known as Ashwagandha, Punir, Asgandh.** The identification has been done on the basis of macroscopic studies of the sample followed by detailed scrutiny of literature and matching the sample with authentic samples deposited in the Raw Material Herbarium and Museum, Delhi (RHMD).

Identification pertains to the quantity/quality of specimen/sample(s) received in RHMD. This certificate is not issued for any judicial purpose.

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Appendix - 2.3

सीएसआईआर - राष्ट्रीय विज्ञान संचार एवं सूचना स्रोत संस्थान
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(विज्ञान एवं प्रौद्योगिकी मंत्रालय, भारत सरकार Ministry of Science & Technology, Govt. of India)

RAW MATERIALS HERBARIUM AND MUSEUM, DELHI (RHMD)

Authentication No.-NISCAIR/RHMD/Consult/2019/3453-54-63 18/06/2019

CERTIFICATE FOR CRUDE DRUG SAMPLE AUTHENTICATION

This is to certify that stem sample of *Tinospora cordifolia*, Giloy, received from Dr Suman Kumar Jha vide letter No. Nil, Dated 23rd April 2019 **has been found correct as stem pieces of *Tinospora cordifolia* (Willd.) Hook.f. & Thoms. which is commonly known as Giloy, Giloe, Guduchi, Amrita, Golancha.** The identification has been done on the basis of macroscopic studies of the sample followed by detailed scrutiny of literature and matching the sample with authentic samples deposited in the Raw Material Herbarium and Museum, Delhi (RHMD).

Identification pertains to the quantity/quality of specimen/sample(s) received in RHMD. This certificate is not issued for any judicial purpose.

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(Mr. RS Jayasomu)
Chief Scientist
Head, RHMD

Dr Suman Kumar Jha
QMS (Advisor)
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Phone- 01334-265857

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विज्ञान सूचना भवन, 14, सत्संग विहार मार्ग, नई दिल्ली-110067 Vigyan Suchna Bhawan, Satsang Vihar Marg, New Delhi-110067
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ई-मेल E-mail: coa@niscair.res.in वेबसाइट Website: www.niscair.res.in

Appendix - 2.4

प्रेषक,

लाइसेंसिग अधिकारी,
आयुर्वेदिक एवं यूनानी सेवाएँ,
उत्तराखण्ड, देहरादून।

सेवा में

मैसर्स दिव्य फार्मेसी यूनिट–।।,
खसरा नं0 210, 211 पतंजलि फूड एवं हर्बल पार्क,
लक्सर रोड, ग्राम पदार्था हरिद्वार।

संख्या–1371-72 /डी–431/2020–2021 दिनांक 12 जून,2020

विषय– **अतिरिक्त योगों के निर्माणार्थ अनुमति दिये जाने के सम्बन्ध में।**

महोदय,

उपर्युक्त विषयक आपके पत्रों दिनांक 06.06.2020 एवं दिनांक 09.06.2020 के साथ प्राप्त अतिरिक्त औषधियों की सूची इस पत्र के साथ संलग्न करते हुए निवेदन है कि औषधि नियंत्रक/लाइसेसिग अधिकारी, आयुर्वेदिक एवं यूनानी सेवायें उत्तराखण्ड देहरादून द्वारा प्रेषित औषधि निर्माणार्थ लाईसेन्स संख्या **UK.AY-274/2013** में उल्लिखित शर्तों एवं प्रतिबन्धों के अधीन कमांक 01 से कमांक 03 पर अंकित स्वानुभूत योगों को आयुर्वेदिक औषधि के रूप में निर्माण करने की अनुमति प्रदान की जाती है।

1- DIVYA CORONIL TABLET
2- DIVYA SWASARI VATI 540MG
3- DIVYA SWASARI VATI 350MG

भवदीय

(डॉ0 यतेन्द्र सिंह रावत)
लाइसेंसिग अधिकारी

संख्या एवं दिनांक तदैव।

प्रतिलिपि–औषधि निरीक्षक/जिला आयुर्वेदिक एवं यूनानी अधिकारी हरिद्वार को उक्त की एक प्रति इस पत्र के साथ संलग्न करते हुए सूचनार्थ एवं आवश्यक कार्यवाही हेतु प्रेषित।

(डॉ0 यतेन्द्र सिंह रावत)
लाइसेंसिग अधिकारी

Appendix - 2.5

National Accreditation Board for Testing and Calibration Laboratories

NABL

CERTIFICATE OF ACCREDITATION

CENTRAL LABORATORY, PATANJALI FOOD & HERBAL PARK PVT. LTD.

has been assessed and accredited in accordance with the standard

ISO/IEC 17025:2017

"General Requirements for the Competence of Testing & Calibration Laboratories"

for its facilities at

VILLAGE PADARTHA, LAKSAR-HARIDWAR ROAD, HARIDWAR, UTTRAKHAND, HARIDWAR, UTTARAKHAND, INDIA

in the field of

TESTING

Certificate Number: TC-7269

Issue Date: 18/05/2020 Valid Until: 17/05/2022

This certificate remains valid for the Scope of Accreditation as specified in the annexure subject to continued satisfactory compliance to the above standard & the relevant requirements of NABL.
(To see the scope of accreditation of this laboratory, you may also visit NABL website www.nabl-india.org)

ame of Legal Identity : Companies Act

Signed for and on behalf of NABL

N. Venkateswaran
Chief Executive Officer

Appendix - 2.6

AYUSH/Divya Pharmacy/Haridwar/03/2020-DC (Unit-II)
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(AYUSH Section)

FDA Bhawan, Kotla Road
New Delhi-110002
Dated: 05 NOV 2020

To,

M/s. Divya Pharmacy (Unit-II)
Khasra No.-210,211, Patanjali Food & Herbal Park,
Padartha, Laksar Road, Haridwar,
Uttarakhand -249404.

Subject: Issuance of additional Certificate of Pharmaceutical Product (CoPP) of Divya Coronil Tablet as per WHO Certification scheme – reg.

Sir,

With reference to your application on the subject matter, please find herewith the additional Certificate of Pharmaceutical Product (CoPP) dated of Divya Coronil Tablet as per WHO certification scheme.

Please acknowledge the receipt.

Yours faithfully,

(Dr. V.G. Somani)
Drugs Controller General (I)

Copy to: **1.** Dr. DC Katoch, Advisor (Ay.), AYUSH Bhawan, 'B' Block, GPO Complex, INA, New Delhi 110023.

2. Dr. Yatender Singh Rawat, Licensing Authority (Ay.), Directorate of Ayurvedic & Unani Services, Danda Lakhond, PO Gujradda, near IT Park, Sahastradhara Road, Dehradun, Uttarakhand.

Appendix - 2.7

Government of India
Directorate General of Health Services
Ministry of Health & Family Welfare
Central Drugs Standard Control Organization

Certificate of Pharmaceutical Product (Herbal)

(This certificate confirms to the format recommended by the World Health Organization.)			
No. of certificate		:	WHO-GMP/COPP/DP-II//70/2020
Exporting (certifying) country		:	INDIA
Importing (requesting) country		:	As per Appendix –I
1.	Name and dosage form of product	:	**DIVYA SWASARI VATI**
1.4	Active ingredient(s) and amount(s) per unit dose for complete composition including excipients sees attached.	:	As Per Appendix- II
1.2	Is this product licensed to be placed on the market for use in the exporting country?		YES
1.3	Is the product actually on the market in the exporting country? (If the answer to 1.2 is yes, continue with section 2A and omit section 2B.If the answer to 1.2 is no, Omit section 2A and continue section 2B)		YES
2. A.1	Number of product license And date of issue	:	Licence. Number: UK.AY-274/2013 Granted on 13.12.2013, Valid up to 12.12.2023
2. A.2	Product license holder (Name and address)	:	M/s Divya Pharmacy (Unit-II), Khasra No. 210-211, Patanjali Food & Herbal Park, Padartha, Laksar Road, Haridwar-249404, Uttarakhand, India.
2. A.3	Status of product-license holder*	:	A. The Applicant is the manufacturer.
2.A.3.1	For categories b and c the name and address of the Manufacturing producing the dosage form is:	:	Not Applicable
2. A.4	Is summary basis of Approval appended?	:	Not Applicable
2. A.5	Is the attached, officially approved product Information completed and consonant with the License?	:	YES
2.A.6	Application for certificate if different from license Holder: (Name and address)	:	Not Applicable
2.B.1	Applicant for certificate (name and address)	:	Not Applicable
2.B.2	Status of applicant* a / b / c	:	Not Applicable
2.B.2.1	For categories b and c the name and address of the Manufacturing producing the dosage form is*	:	Not Applicable
2.B.3	Why is marketing authorization lacking?	:	Not Applicable
2.B.4	Remark:	:	--------


Greenland
Iceland
Finland
Sweden
Norway
Russia
Canada
United States
Mexico
North Atlantic Ocean
Mongolia
China
Japan
South Korea
Afghanistan
Pakistan
India
Libya
Egypt
Saudi Arabia
Sudan
Chad
Colombia
Brazil
Peru
Bolivia
Argentina
DRC
South Africa
Madagascar
Indonesia
Papua New Guinea
Australia
New Zealand
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Southern Ocean

Appendix – 5.1

Pentagrit
Speed Unmatched

To whomsoever it may concern **11/6/2020**

This is to confirm that Pentagrit will be offering facility for the study of, including, but not limited to Animal Modelling.

Study: "Humanized Zebrafish Covid-19 Spike Protein Model"
For:
Patanjali Research Foundation,

The study has been reviewed by us, in house Institutional Animal Ethics Committee and conducted with compliance to ICH harmonization principles for animal housing and handling.
IAEC Study No: 223/Go062020/IAEC.
Member of IAEC Pentagrit

1) Dr.Bibas Kar - Advisor at Center for Genetic Studies & Research, MMM
2) Dr. Kannan Maharajan – Professor, International Medical University, IMU
3) Dr. Charles Dhorni – National Institute of Nutrition, ICMR
4) Mr. Benin Joseph – Scientific Lead, Member of Institutional Animal Ethic Committee, Pentagrit
5) Ms. Kalaichitra – Registered Dietician & Scientific Director, Pentagrit
6) Mr.Preston Richard – Indian Patent Attorney
7) Mr.Manglesh – Group Leader for Animal and Environmental Welfare, CRY, NIZHAL

About Pentagrit: Pentagrit is a drug discovery and screening focused company with expertise in zebrafish and "Clinical Zebrafish Models". Academic research is a core principle in innovation towards being a scientific leader in drug discovery. Current services include ADMET, BABE and Animal Models for over 120 models offered to Academia/Research Institutions only as "Not for Profit" services. Currently for profit, clients include Biotech and Pharma outsourcing companies globally.

PENTAGRIT Chennai - 100

P.Kalaichitra
Scientific Director

Pentagrit Research
87, 3rd Floor Radhanagar First main road, Perumbakkum, Chennai-100
0091 8056156420, kal@pentagrit.com, www.pentagrit.com.

Appendix – 6.1

NIMS UNIVERSITY RAJASTHAN, JAIPUR

Fully empowered & incorporated as a regular & full-fledged University under NIMS UNIVERSITY ACT, 2008 duly recognized by Government of India under the provisions of the Sections 2(f)and 22 of the UGC Act, 1956.

FACULTIES:• Medicine • Dentistry • Engineering • Advanced Engg. •Management • Law • Pharmacy • Nursing• Science & Technology • Physiotherapy • Allied Health Sciences • Fashion • Media • Mass Comm. • Hospitality • Aviation • Education • Library Sciences • Physical Education • Films & Television etc. • ***multi-specialty 1130-bedded tertiary level Hospital on campus***

INSTITUTIONAL ETHICS COMMITTEE
NIMS UNIVERSITY RAJASTHAN, JAIPUR (INDIA)

Ref. No.: NIMSUR/IEC/2020/036 Date: 04th May, 2020

To:

Name: **Prof. (Dr.) Ganpat Devpura**

Department of **Medicine**

Sub: **IEC (Institutional Ethics Committee) Approval for research project**

Institutional Ethics Committee had reviewed and discussed the research project titled **"Impact of Indian traditional Ayurvedic treatment regime for nCoV-2 (COVID-19)."** After review and discussion, members decided to accord ethical clearance and allowed the study to be undertaken at National Institute of Medical Sciences and Research, Jaipur (NIMS University Rajasthan, Jaipur).

This approval is valid till the completion of the study, please inform us in case of any serious event observed during the conduct of the study.

From:

Member Secretary

Institutional Ethics Committee,

NIMS University Rajasthan, Jaipur

FULL DETAILS (Read-only) -> Click Here to Create PDF for Current Dataset of Trial

CTRI Number	**CTRI/2020/05/025273** [Registered on: 20/05/2020] **Trial Registered Prospectively**
Last Modified On:	20/05/2020
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Ayurveda
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	Impact of effect of Ayurvedic treatment on novel Corona virus disease
Scientific Title of Study	Impact of Indian traditional Ayurvedic treatment regime for nCoV-2 (COVID-19)
Trial Acronym	
Secondary IDs if Any	Secondary ID: NIL; Identifier: NIL
Details of Principal Investigator or overall Trial Coordinator (multi-center study)	**Name**: Dr Ganpat Devpura **Designation**: Professor Medicine **Affiliation**: National Institute of Medical Sciences **Address**: Professor Department of Medicine National Institute of Medical Sciences and Research, Jaipur India 303121 NH 11 C Jaipur Delhi Highway Nims University Campus Jaipur Rajasthan India Jaipur RAJASTHAN 303121 India **Phone**: 9829069669 **Fax**: **Email**: gdevpura@yahoo.co.in
Details of Contact Person Scientific Query	Name: Dr Abhishek Sharma **Designation**: Assistant Professor Medicine **Affiliation**: National Institute of Medical Sciences **Address**: Professor Department of Medicine National Institute of Medical Sciences and Research, Jaipur India 303121 NH 11 C Jaipur Delhi Highway Nims University Campus Jaipur Rajasthan India Jaipur RAJASTHAN 302021 India **Phone**: 9828816135 **Fax**: **Email**: dr.abhisheksharma1987@gmail.com

CLINICAL TRIALS REGISTRY - INDIA
ICMR - National Institute of Medical Statistics

PDF of Trial
CTRI Website URL - http://ctri.nic.in

Clinical Trial Details (PDF Generation Date :- Thu, 24 Sep 2020 07:14:13 GMT)

CTRI Number	CTRI/2020/09/027882 [Registered on: 17/09/2020] - **Trial Registered Prospectively**
Last Modified On	17/09/2020
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	A Clinical Trial to Evaluate the effect of an Ayurvedic Regimen administered in (COVID – 19) Patients
Scientific Title of Study	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the effect of an Ayurvedic Regimen administered in nCoV-2 (COVID – 19) Patients

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Dr Shirobhi Sharma
Designation	Assistant Professor,Department of Medicine
Affiliation	Subharti Medical College and Hospital
Address	Subharti Medical College and Hospital, Subhartipuram, NH 58, Meerut bypass (Delhi Haridwar Road) Meerut UTTAR PRADESH 250005 India
Phone	9456206192
Fax	
Email	shirobhisharma@yahoo.in

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	Dr Shirobhi Sharma
Designation	Assistant Professor,Department of Medicine
Affiliation	Subharti Medical College and Hospital
Address	Subharti Medical College and Hospital, Subhartipuram, NH 58, Meerut bypass (Delhi Haridwar Road) Meerut UTTAR PRADESH 250005 India
Phone	9456206192
Fax	
Email	shirobhisharma@yahoo.in

Details Contact Person (Public Query)

Details Contact Person (Public Query)	
Name	Dr Gaurav Kapil
Designation	Assistant Professor,Department of Pharmacology
Affiliation	Subharti Medical College and Hospital
Address	Subharti Medical College and Hospital, Subhartipuram, NH 58, Meerut bypass (Delhi Haridwar Road) Meerut UTTAR PRADESH 250005 India

Appendix – 6.2

World Health Organization

International Clinical Trials Registry Platform
Search Portal

Home Advanced Search List By Search Tips UTN ICTRP website REGTRAC Contact us

Back to Search

Export to CSV Export results to XML

1 trial found for: Impact of Indian traditional Ayurvedic treatment regime for nCoV-2 COVID- 19 (What is this?)

Show 10 records per page

Display synonyms

Recruitment status	Prospective Registration	Main ID	Public Title	Date of Registration	Results available
Not Recruiting	Yes	CTRI/2020/05/025273	Impact of effect of Ayurvedic treatment on novel Corona virus disease	20-05-2020	

Disclaimer: Trials posted on this search portal are not endorsed by WHO, but are provided as a service to our users. In no event shall the World Health Organization be liable for any damages arising from the use of the information linked to in this section. None of the information obtained through use of the search portal should in any way be used in clinical care without consulting a physician or licensed health professional. WHO is not responsible for the accuracy, completeness and/or use made of the content displayed for any trial record.

Copyright - World Health Organization - Version 3.6 - Version history - For crawlers

Snapshot from World Health Organization-International Clinical Trial Registry Platform exhibiting global accreditation of our Randomized Clinical Trial conducted for Ayurvedic medicines against COVID-19 positive patients

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[http://dx.doi.org/10.3109/1547691X.2013.832444] [PMID: 24099633]

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[http://dx.doi.org/10.1016/j.resuscitation.2016.04.015] [PMID: 27155545]

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