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AYUSH Systems and Corona Virus:
Assessing R&D in Viral Diseases

Introduction

In the aftermath of the Novel Corona Virus-2019 (COVID-19) pandemic, the Ministry of AYUSH, in collaboration with the Ministry of Health and Family Welfare (H&FW), has launched clinical trials of certain Ayurvedic medicines for COVID-19 infection.[1] The scientific studies on Ayurvedic interventions as preventive prophylaxis and as an add-on to standard care to COVID-19 are a joint initiative of Ministries of AYUSH and H&FW and Council of Scientific and Industrial Research (CSIR) with technical support of Indian Council of Medical Research (ICMR). Given that the study will be carried out in 25 states covering approximately five lakh population, the outcome of the study will provide a boost to understanding and reaffirming the potential of AYUSH systems during viral epidemics like COVID-19 through scientific evidence. In this context, this policy brief looks at the rationale, status and issues connected with clinical trials and AYUSH systems.

During the last one hundred years or so, the world has been successful in containing most infectious diseases and eradicating at least one, namely, small pox. However, new epidemics keep on occurring from time to time. Even during the current century, we have had the SARS-Cov (Severe Acute Respiratory Syndrome - Corona Virus) outbreak in 2003 and the Ebola virus disease (EVD) in 2014-2016. The ongoing COVID-19 pandemic is the latest and one of the severest and most widespread since the Spanish Flu caused by H1N1 virus in 1918. This reemphasises the role of viral diseases as one of the major causes of human morbidity and mortality leading to significant threat to health and economic security in India and across the world. Governments have launched extraordinary public-health responses. The immediate focus has been on critical care capacity, providing ventilators, building stocks of critical medical supplies including medical care equipments. Efforts for avoiding recurrence include large scale testing, sophisticated real time surveillance, rigorous contact tracing, and rapid targeted quarantine to isolate cases and contacts. Due to the unavailability of effective and validated therapies, several initiatives have been

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launched across countries to find effective preventive and curative medicines to control the viral infection. As in the case with all health emergencies, the present crisis has also activated scientific enquiries into nature of viral diseases that would help humanity to foresee and prevent recurrence of pandemics in the future. Branches of science like bio-technology and digital technology contribute significantly in this endeavour.

The absence of any specific drug for this viral infection in Allopathy also opens the field of traditional medicine systems for exploring solutions. These systems have long experience with viral pandemics dating back to more than two millennia. Many traditional medicine systems like the Indian Systems of Medicine (ISMs) developed into systematised knowledge systems during this period. Over the course of their history, systems like Ayurveda have acquired much knowledge on the pathogenesis of such pandemics. Emergence of new viral strains like Covid-19 is an opportunity for intensifying their research into the general causes of the diseases, from their system's principles and finding effective preventive and treatment protocols and therapies. It also gives these traditional systems an opportunity to re-establish their scientific credentials.

Rationale of R&D in AYUSH Systems

The AYUSH systems of Ayurveda, Siddha, Unani, etc. fall under the category of traditional, complementary and integrative medicine in the World Health Organisation programmes. It defines, traditional medicine as "the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not used in the maintenance of health as well as the prevention, diagnosis, improvement or treatment of physical and mental illness."[2] The elements mentioned in the definition are primarily drawn from folk or local traditions of medicine indigenously developed in various parts of the world; it does not present the proper image of the systematised knowledge like Ayurvda, which continues to grow through enquiry and experimentation, like any other branch of science. Systems like Ayurveda or Siddha are not moribund but living systems. Certainly as a science it has to be an eternal quest for new knowledge. Research in these systems mostly is limited to making improvements in existing medicines and whenever they come out with new drugs, they do not get much attention since Allopathy medicines would be there in the mainstream of healthcare. COVID-19 epidemic gives ISMs a chance to work on a frontier area of viral pandemics for which no drug exists as of today.

Another reason for R&D in these systems is that new pathogens always warrant novel approaches. Minor modifications by the pathogens can result in new manifestations of diseases. What kind of dietary and life style regime and drug administration protocol positively impact controlling the diseases caused by new pathogens necessitate new R&D. It may be possible that in some of these cases, certain existing drugs or therapies may be effective, but that needs to be proved through new research and experiments. Only with such an open attitude and approach, ISMs can claim their rightful place and become universally accepted systems of medicine.

The third reason is that another well established system like the Traditional Chinese Medicine (TCM) has been into R&D on handling new pandemics. In the treatment of an earlier epidemic, namely, SARS, China has claimed to have effectively utilised TCM for treatments. Policy support for utilisation of TCM in such viral epidemics is coupled with a push for dedicated R&D in emerging pathogenic related health pandemics. In the

current outbreak, it has asserted to have treated 60,107 confirmed COVID-19 patients (85.20 per cent of total confirmed cases) with TCM.[3]

Fourth, practitioners of the systems base their prescriptions on principles and formulae in ancient texts that have stood the test of time. While good many patients accept the systems as such because of practice and use, many modern patients and new users would ask for 'scientific' validation of the medicines and therapies. Policy makers also would demand the same. The pandemic has given an opportunity for ISMs to get new validations using generally accepted principles of research. Such validations will enable the ISMs to reach out to more people, both within and outside India.

Fifth, the WHO has welcomed scientifically proven traditional medicine for Covid-19 treatment. However, such medicines should be tested for efficacy and adverse side effects.[4] This testing can be done only through proper R&D. Since Covid-19 pandemic is accepted as a new pathogen generated disease, argument that ISMs medicines have been in use for centuries alone will not suffice. This could be considered a golden opportunity for the systems to establish their credentials through R&D, if handled properly.

Viral Pandemics, Drug Repurposing and Role of Traditional Medicines Globally

When crisis like the Covid-19 comes up, focus is on new drug development, if required. A new drug development is always a time consuming one. But research and development (R&D) can also effectively look into re-uses or 'repurposing' of drugs, especially in the case of viral pandemics which are related. As scientists around the globe race to find solutions, the fastest approach to finding a treatment may be to repurpose existing drugs in the hopes of avoiding having to start from "square one" on the drug development pathway. There are dozens of existing drugs in modern medicine currently being evaluated for treating COVID-19 and its symptoms, ranging from a failed Ebola treatment to arthritis and diabetes medications. In order to understand the issues with current research in disease control, we need to understand the nature of viral pathogens.

The nature of viral pathogens could account for the challenges associated with R&D for prevention and treatment; there is a continuous evolution of new virus. In the 1970s, and for years afterwards, progress in development of new vaccines, antibiotics and other treatments and technologies, led to a proclamation of a victory over microbes. However, since 1970more than 1,500 new pathogens were discovered.[5] Between 2011 and 2018, WHO tracked 1,483 epidemic events in 172 countries. At present, out of the priority diseases listed by WHO, namely, COVID-19, Crimean-Congo haemorrhagic fever, Ebola virus disease and Marburg virus disease, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever and Zika,[6] majority are diseases caused by viral pathogens. Zoonotic pathogens, accounting for 70 per cent of budding infections of humans, emerge and re-emerge in more virulent forms, as time progresses. Treatment is therefore a challenge.

In view of the lack of specific therapy for most viral infections, including the COVID 19, the repurposing potential of existing or candidate drugs has been viewed as an effective strategy for the development of ready-to-use antiviral agents as well as for the identification of new paths for intervention. In the 80 clinical trials that have been recently launched to test corona virus treatment, drug repurposing or repositioning for COVID-19 is also included. Traditional medicine usage has also been

documented as part of the drug repurposing though it includes only Traditional Chinese Medicine (TCM). The Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)[7] includes TCM as a priority research area for therapeutics

It is interesting to note that a search in March 2020 of the clinicaltrials.gov database identified 24 clinical trials, involving more than 20 medicines, such as human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, and bevacizumab, and also TCMs[8]. TCMs were already used for SARS-CoV infection in 2002 as coadjuvant therapy.[9]

As of 1 March 2020, a total of 303 ongoing clinical trials aiming to evaluate the efficacy and safety of treatments for COVIF-19 patients have been launched in China. Among them, 50 trials (16.5 per cent) are about the use of TCM, including 14 cases (4.6 per cent) to examine the effect of combined treatment with TCM and Western medicine. The research priority accorded to TCM in treatment of global viral pandemics by international health platforms like WHO legitimises the utility of traditional medicine, albeit only that of China.

Relevance of Viral diseases R&D in India

During 2017, the Integrated Disease Surveillance Programme (IDSP) network[10] reported a total of 1,683 outbreaks of infectious diseases. The analysis of data showed that 71 per cent of these outbreaks were caused by viral pathogens. Nearly 72,000 individuals were affected in these outbreaks, and amongst them, 60 per cent had a viral aetiology.[11] Respiratory viral infections, arboviral infections and bat-borne viral infections represent three major categories of emerging viral infections in India. Pandemic influenza H1N1pdm09, highly pathogenic avian influenza (AI) infection (H5N1) and the Middle East respiratory syndrome coronaviruses (MERS-CoV) represent three pathogens posing severe threat in this category.[12] Arthropod-borne viruses have consistently been the reason of emerging and re-emerging diseases in the Indian subcontinent, including Crimean-Congo haemorrhagic fever (CCHF), dengue, Chikungunya, Japanese encephalitis and Kyasanur forest disease (KFD).[13]

Yet, India's R&D landscape on viral pathogens and innovations has been limited. Along with issues of funding, appropriate industry-academia partnership, interdisciplinary collaboration among biologists, microbiologists, chemical and material scientists, engineers and clinical researchers, lack of research/knowledge of disease burden and tools required for molecular epidemiology or appropriate research ecosystem and lack of translational research in the field are key inhibiting factors.

Vaccine research and development would make a strong impact on the fight against viral epidemics. But even as India produces more than 60 per cent of the world's vaccines and is a member of the governing council of International Vaccine Institute, with a commitment of US$ 500,000 every year[14], new indigenous vaccine development is limited with the exception of the development of rotavirus vaccine.

The Biotechnology Industry Research Assistance Council (BIRAC) of the Department of Biotechnology has started many initiatives to support research programmes on new vaccines and many new programmes under BIRAC are nurturing industry-academia partnerships. Recent efforts towards facilitating virus research also include establishing and strengthening the network of laboratories, i.e. Virus Research and Diagnostic Laboratory (VRDLN),[15] across the country to create infrastructure for timely identification of viruses causing outbreaks or related to significant morbidity/mortality. This

network is also intended to provide virological diagnosis to patients attending tertiary health care facilities (medical colleges) and thereby help in generating surveillance data on common viral diseases from different parts of the country. The last 10-15 years have seen the establishment of a number of world class educational and research institutions such as the Indian Institute of Science Education and Research (IISERs), Translational Health Science and Technology Institute, National Institute of Biomedical Genomics and National Institute of Animal Biotechnology in addition to several new All India Institute of Medical Sciences and the Indian Institute of Technology. CSIR-Institute of Microbial Technology at present is focussed on anti-viral therapeutics against dengue / flavivirus only.

Status of Viral Diseases R&D in AYUSH

Infectious diseases in general have been well referenced in Indian Systems of Medicine. In the *Atharva Veda* references to microbes and infectious diseases have been made. The concept of micro-organisms is well emphasised in Ayurveda with reference to *krimi, bhuta* and *graha*. The concept of epidemic diseases and their management has been also elaborated by *Charaka Samhita* . Further, management of infectious diseases has also been described in a manner similar to modern microbiology. These include avoiding factors responsible for causation of the disease (*nidanaparivarjanam*), removal of micro-organisms from the affected sites (*apakarshanam*) and bringing change in the environment (*prakriti vighata*) as suggested by *Charaka* for the management of infectious diseases. Further, the role of *Rasayana* for immunity boosting has been highlighted by several scientific studies. AYUSH systems can play a significant role in fighting viral epidemics/pandemics like the corona virus with the right R&D support.

Clinical validation of Ayurvedic formulations/therapies in certain identified diseases/conditions of national importance, include infectious diseases, viz. *Visamjwara* (Malaria) and *slipada* (Filariasis). Till date, 12 technologies including Ayush 64 for Malaria, Ayush SG for Rheumatoid Arthritis, Ayush 82 for Diabetes mellitus have been developed and commercialised. R&D on other viral diseases and drug development has been documented by the Central Council for Research in Ayurvedic Sciences (CCRAS) for Chikungunya and NIPAH virus. Validation of classical drugs in the management of jaundice caused by Viral Hepatitis has also been documented. However, R&D in AYUSH systems for treatment for emerging viral epidemics, or even preventative, curative and anti-viral properties of Ayurvedic medicinal plants or formulations has been limited though literature on anti-viral properties of medicinal plants list as many as 17 antiviral compounds derived from plants.

Being ancient systems which emerged during pre-modern scientific age, documentation of the R&D, that presumably might have gone into the classical medical formulations and practices, has not come down to the current practitioners, except what is recorded in the commonly accepted ancient texts. The Drugs and Cosmetics Act, 1940, as amended from time to time, gives a list of 55 such ancient texts and the Ayurvedic Formulary of India and its parts and Ayurvedic Pharmacopoeia of India and its parts for Ayurveda, 29 ancient texts and Siddha Formulary and its parts and Siddha Pharmacopeia and its parts for Siddha, and 11 ancient texts and National Formulary of Unani Medicine and Unani Pharmacopoeia of India.

It is true that research is there in these systems. They generally fall under the following categories:

- Literary and Conceptual Research
- Clinical and Therapeutic Research, and
- Drug Development Research.

The third category includes standardisation of in-use drugs and development of new drugs. The new drugs follow the formulae so far as their ingredients are concerned in the basic texts and these new ones are categorised as Patent or Proprietary Medicines under the Drugs and Cosmetics Act, which in the context of these three systems is defined as "all formulations containing only such ingredients mentioned in the formulae described in the authoritative books of Ayurvedic, Siddha or Unani Tibb systems of medicine specified in the First Schedule, but does not include a medicine administered by parenteral route and also a formulation included in the authoritative books ..." [Section 3(h) of the D&C Act].

All the above forms of research are common for all systems including modern medicine, but in the area of new drug development, which is the one which gets more into public attention, the ISMs are sluggish. The R&D will have to focus certainly on the science of the system and also in the therapeutics. They add to the basic foundations of the system.

Even though time-tested evidences vouch immense therapeutic benefits for Ayurvedic herbs and formulations, several important issues are required to be resolved for successful implementation of Ayurvedic principles to present drug discovery methodologies.

Ayush R&D: Challenges and Way Forward

Adhering to the basic principles of the system

Each system has its own basic epistemology. Ayurvedic approach to treatment is cure the factors that cause the disease and make the patient's body generate the antigens that fight and overcome that disease or where the disease is caused by the shortage of a vitamin or an enzyme make the body produce the same. The *tridosha* (three humours) and *panchamahabhhoa* (five basic elements) theory is fundamental to Ayurveda. The R&D will have to be in keeping with this epistemology. Since the R&D is to be on a new or existing medicine in a system different from the modern medicine, it necessarily will have to follow a different protocol, in keeping with the conceptual differences.

Adapting to the requirements of randomised clinical trials

During the second half of the twentieth century, consequent on concerns about the safety of certain Allopathic drugs randomised double blind clinical trials were made mandatory in most countries before grant of approval for marketing and drug administration. ISM medicines were being practised for centuries and had not recorded any serious adverse effects in the literature. Therefore, the issue of clinical trials was not there. But the current times which place very high premium on verifiable facts and objectivity and replicability, demand that ISMs also satisfy these criteria. The WHO has advocated that traditional medicine "research should use methods, which are generally accepted in the evaluation of health services, including comparative effectiveness studies and mixed method designs."[16]

Level playing field with Allopathy / obtaining facilities for research including clinical trials such as access to patients

The initial reaction of health establishment to the COVID-19 outbreak in India was to exclude all systems other than Allopathy from treating the epidemic although that system did not claim to have any effective drug or vaccine for the infection. This prohibition of ISM practitioners from attending to the patients prevented them from observing, understanding the symptoms, diagnosing and collecting disease progress data

in patients which are necessary for designing treatment and research protocols. Patient data is a must for any clinical research. Although there is some relaxation in the situation, valuable time was lost. The ISM practitioners should not be debarred from doing research and clinical trials in future as and when new viral pandemics arise. They should also be part of the "*India COVID-19 Clinical Research Collaborative Network*" coordinated by the Indian Council of Medical Research.

Following the Ethical Guidelines of ICMR for clinical trials[17]

Ayush related clinical trial also will have to strictly follow all the legal provisions as incorporated in the New Drugs and Clinical Trials Rules, 2019, especially the Ethical Guidelines. The Ministry of AYUSH has well recognised this fact and in its order dated 21 April 2020 permitting research in the AYUSH systems it has specified the conditions which should be complied with, one of which is compliance to ICMR's National Ethical Guidelines for Bio-medical and Health Research on Human Participation (2017).

Obtaining finances for R&D

Clinical trials are an expensive activity. Pharmaceutical companies claim that the cost of such trials run into billions of dollars. Whilethe trials in respect of drugs in ISMs may not be so expensive, they can still cost much. The ISM drug firms are not so large that they can afford many such trials. Since most are MSMEs, they may have to be supported or fully funded by the government. It is, therefore, necessary, significant public finance should be made available for the same. Such funds can be given as either outright grants or soft loans or subsidies, on case to case basis.

R&D into ISM medical devices

An aspect generally ignored in ISM research is the need for R&D into the medical instruments used in the diagnosis and treatment by ISM practitioners. They use both devices mentioned in the authoritative texts and also those used by modern medicine like Stethoscope or Thermometer. The sector requires research to develop new devices in accordance with the basics of the systems, which will facilitate diagnosis and treatment and also to adapt existing devices to modern times.

R&D in therapeutic procedures and protocols

If the systems are to adapt to the modern scientific age and to create confidence in the minds of people without exposure to such systems, they should also develop therapeutic procedures and protocols which appeal to the modern mind. R&D is required for this.

Conclusion

There is urgent need of a common vision and plan of action for leveraging the latest advances in scientific research, emerging technologies and new data sources in the fight against viral pandemics like COVID-19. The call for interdisciplinary approach to RNA virus research creates substantial space for AYUSH systems, specially Ayurveda owing to its holistic approach to disease management. AYUSH systems' potential is yet to be tapped even as other traditional medicine systems are being effectively harnessed through systematic R&D policy in countries like China. What is required is an objective treatment of the systems, encouraging them to adapt some of the methods of modern science and adopt the rigour of clinical trial regimes in developing new drugs and medical instruments as well as in drug repurposing. The government will have to support and encourage such efforts through policies and programmes, regulations and also through financing. The launch of interdisciplinary studies on AYUSH interventions in COVID 19, including clinical research, is a step in the right direction.

Endnotes

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12 *Ibid.*

13 *Ibid.*

14 Medigeshi GR, Fink K, Hegde NR. Position Paper on Road Map for RNA Virus Research in India. *Front Microbiol*. 2018;9:1753. Published 2018 Jul 31. doi:10.3389/fmicb.2018.01753

15 The detailed list of VRDLN currently functional in India is available at http://112.133.207.124:82/vdln/vdls.php

16 WHO, 2013.*WHO Traditional Medicine Strategy 2014 – 2023.* P. 46.

17 https://thsti.res.in/pdf/ICMR_Ethical_Guidelines_2017.pdf.

About FITM: The FITM has been established in the RIS with the participation of the Ministry of AYUSH as a common platform for all actors and stakeholders to contribute to pragmatic policy-making in the area of Traditional Medicine (TM) and Traditional Knowledge and to develop pro-active policies and strategies. The broad objectives of the FITM are to: undertake/ commission studies on various issues pertaining to Indian TMs, IPRs and regulatory frameworks for traditional medicinal knowledge; examine trade policy with reference to TMs; prepare cogent and coherent policy and strategy responses on emerging national and global developments; provide critical inputs such as policy briefs, briefings and reports to the Government of India in a continued and sustained way; and to facilitate interactions with experts and stakeholders and policy-makers from India and abroad. It would also provide Fellowships and Scholarships for studies in the area of TMs, arrange invited talks by national and international experts, and organize periodic consultations.

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