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CHALLENGES IN THE ASSESSMENT AND AVAILABILITY OF HERBAL DRUGS FOR PUBLIC HEALTH: A PROPRIETARY AYURVEDIC FORMULATION FOR VIRAL DISEASE

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Abstract: *Herbal drugs are prominently used for therapeutic purposes in India, about 60% of Indian population relies on herbal formulations as traditional medicines, other countries which use traditional medicines includes Ethiopia, China, Chile etc. Viral diseases especially Japanese encephalitis, Rabies, and Chandipura encephalitis are the major concerns of India in terms of disease burden. Due to less toxicity the herbal formulations may play a significant role in disease treatment, if these are evaluated properly. ICMR has taken initiatives to handhold such herbal formulations developed by traditional practitioners. The evaluation studies are carried out with ICMR's support to examine the herbal formulations in accordance with regulatory guidelines like 'Schedule Y' and 'Section 3 (H)' of Drugs & Cosmetics act, 1940 and 'First Schedule' of Ayurvedic pharmacopeia of India.*

Keywords*: Herbal drugs, proprietary ayurvedic formulations, complementary & alternative medicine (CAM), viral disease, folklore folklore practice, Japanese encephalitis, Rabies, Chandipura virus, Intellectual property products, Drugs & Cosmetics, Schedule Y (DSA), Section 3H (DCA).*

Introduction: Traditional medicine, also known as indigenous medicine, folk medicine, or natural medicine (National Center for Complementary and Alternative Medicine) comprises knowledge systems that developed over generations within various societies before the era of modern medicine. The terms "Complementary Medicine" and "Alternative Medicine" (CAM) are also used inter– changeably with traditional medicines in some countries. They refer to a broad set of health care practices that are not part of country's own tradition and are not integrated into the dominant health care system [1].

Traditional medicine may include formalized aspects of folk medicine, healing practices and ideas of body physiology and health preservation known in a culture, transmitted informally as general knowledge, and practiced or applied by anyone in the culture having prior experience [2]. World Health Organization (WHO) defines traditional medicine as: "the sum total of the knowledge, skills, 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 in the prevention, diagnosis, improvement or treatment of physical and mental illness [3].

In India 70 percent of the population (See table) especially rural, depends on traditional medicine. In countries like Ethiopia, China and Chile approximately 90, 70 and 40 percent Population relies on traditional medicine respectively. A recent study of 2007 on 'Complementary and Alternative Medicines' (CAM) use in the U.S. population reported that almost 4 out of 10 adults had used some form of CAM within the past year. It was estimated that Americans spent 33.9 billion U.S. dollars (USD) out-of-pocket on CAM products and services during the prior year, accounting for 11.2 percent of total out-of-pocket health care expenditures. In other developed nations the use of CAM is equally extensive. According to WIPO document on Traditional Knowledge (TK), Traditional medical knowledge is receiving increased attention worldwide in light of global health care demand and it's significant role in the public health for developing countries and biomedical sector is increasingly investigating the potential

of genetic resources and traditional knowledge, therefore documenting and protecting these medicines is becoming a greater priority[4].

Table1. Use of Traditional Medicines in India

S N.	*Scientific name*	*Local name*	*Medical benefits*	*User Region*
1.	*Abrus precatorius*	karjari	Decocation prepared from fresh pods (50 gm.) three times daily in abortion.	Madhya Pradesh
2.	*Acacia catechu*	khair	Dye, on joints for rheumatism, blood dysentery, cough, sores and throat affection. Also known as antiviral, anti-inflammatory, hepatoprotective and spasmolytic.	Madhopur; Madhya Pradesh, U.P
3.	*Acacia chundra*	Kair	Paste of wood is applied locally for Leucoderma	Bhils, nayakas & other tribal communities of Gujarat
4.	*Albizzia lebbek*	khairi	Stomach troubles and dysentery	Bihar
5.	*Alysicarpus vaginalis*	Davai	Cough, root as an antifertility agent	Santhals of Santhal Pargana in Bihar
6.	*Atylosia scarabaeoides*	Banherwa	Post delivery tonic. Inflammation of legs, baldness	Raigarh (Aeppu) of Madhya Pradesh
7.	*Atylosia volubilis*	Gamble	Treatment of mumps	Orissa
8.	*Bauhinia purpurea*	Khairwal	Treatment of body pain and fever. Sores of small-pox, cancerous growth in stomach, antihelmintic , diuretic , astringent , carminative and for diarrhoea treatment. Leaf – paste of this plant mixed with latex of *Jatropha curcas*is to cure jaundice..	Raigarh. Santhals, Bhumij, Birhors and Kherias of West Bengal, Nagaland, Tamil Nadu
9.	*Bauhinia vahlii*	Sehar	Bone Fracture	Sisrangha (Raigarh) of Madhya Pradesh the Korwa tribal people
10.	*Bauhinia variegata*	Guiral	As an astringent, carminative, alterative, anthelmintic, antidote to snake poison and laxative and used for dysentery, diarrhoea, skin disease, ulcer, piles and leprosy. bark used for malaria	Garhwal, Himalayas
11.	*Butea monosperma*	Palas	Root decoction for urinary troubles, bark decoction for loose motions, roots for tuberculosis. It is also known as depurative, aphrodisiac, astringent, anthelmintic, antidote to snake bite and it is also used for diarrhoea, piles, tumours, dysentery and herpes.	Oraon and Korwa tribes of Madhya Pradesh. Andh, Bhil, Gond, Halba, and Malhar tribes of Khandala region in Maharashtra. Santals of Santal pargana in Bihar
12.	*Caesalpinia pulcherrima*	Puraiphul	Used as an abortifacient, febrifuge, purgative, emmenagogue, tonic, stimulant and for asthma, bronchitis and malarial fever. Decoction of its fresh seeds for pain in gums due to inflammation. It is also used as tonic, purgative, stimulant, abortifacient, emmenagogue, febrifuge and also used for bronchitis, asthama and malarial fever.	Kondh, Bhumij and Saora tribes of Orissa
13.	*Cassia auriculata*	Anwal , Avaram	Root extract for rheumatism pain. Seed extract for asthma. As astringent and anthelmintic, used for urinary complaints, skin affection, diabetes, and ophthalmia.	Maharashtra, Eastern Rajasthan
14.	*Cassia occidentalis*	Dhendheni	Twigs as tooth brush	Kundi (Surgiya) of Madhya Pradesh
15.	*Cassia sophera*	Raw Asan	Relieves itching and pain in piles, diuretic, purgative and antidote to snake bite and used for ring worm and bronchitis.	Bhoxa of Uttar pradesh
16.	*Allium sativum*	Garlic	Hypertension, antibiotic, cough syrup, *tripa ida*	Maharashtra, Rajasthan, Gujarat, Madhya Pradesh
17.	*Artemisia absinthium*	Wormwood	Worms, colic, diarrhea, cramps, *bilis, empacho*	Kashmir
18.	*Eucalyptus obliqua*	Eucalyptus	Coryza, asthma, bronchitis, tuberculosis	Andhra Pradesh, Goa, Tamil Nadu, Gujarat
19.	*Verbascum*	Mullein	Cough suppressant, asthma, coryza, tuberculosis	Himalayan region
20.	*Matricaria discoidea*	Chamomile	Nausea, flatus, colic, anxiety; eyewash	Uttar Pradesh, Punjab, Jammu & Kashmir
21.	*Origanum vulgare*	Oregano	Coryza, expectorant, menstrual difficulties, worms	Kashmir, Sikkim
22.	*Passiflora*	Passion Flower	Anxiety, hypertension	Kerala, Nagaland, Himachal, Nilgiris
23.	*Salvia officinalis*	Sage	Prevent hair loss, coryza, diabetes	Jammu, Kashmir
24.	*Mentha piperita*	Peppermint	Dyspepsia, flatus colic, *susto*	Uttar Pradesh, Punjab, Haryana.
25.	*Aloe vera Mill.*	Aloe Vera	External - cuts, burns Internal - purgative, immune stimulant	Uttar Pradesh, Madhya Pradesh, Rajasthan

Folklore Practice against Viral Diseases: The most important viral diseases in our country are JE, Rabies and Chandipura Encephalitis. Maximum reported numbers of JE cases are in UP i.e. 3,291 in 2014 followed by 2,317 in West Bengal, 2,194 in Assam and 866 in Bihar. At least 272 persons have died in Assam after being diagnosed of having Encephalitis this year [5]. No specific treatment for Japanese encephalitis is supportive, with assistance given for feeding, breathing or seizure control as required [6].

Rabies is another major challenge for us. An estimated 45% of all deaths from rabies occur in south-eastern Asia [7]. The global human mortality due to rabies is estimated to be over 60,000 per annum whereas, in Asia, human mortality due to endemic canine rabies exceeds 30,000 per annum; Africa is not far behind with 23700 deaths per annum. Within Asia, India is reported to have the highest incidence of rabies globally (20565 deaths per annum). Rabies is fatal with no cure, but there are preventive interventions to reduce its burden, although they are not well adopted in India. As a result, India has the largest contribution to worldwide rabies mortality.

Chandipura virus (CHPV) is another fatal disease; the virus was named after the site of its first isolation from Chandipura region of Maharashtra [8] and prevalent in Andhra Pradesh and neighboring countries like Srilanka, Nigeria and Senegal. In 2010, 31 deaths were registered, of which 15 had tested positive for CHPV. Rest had died of encephalitis. In 2011, the total number of death was 12, with 3 cases positive for CHPV [9]. No antiviral therapy or antiviral agent available.

It would be evident from the foregoing health challenges that there is an acute need of suitable economical an easy to use composition which have requisite efficacy and spectrum to cover intended antiviral applications; especially against Rabies, Chandipura and Japanese Encephalitis, with minimum side effects for humans.

Although traditional practitioners have come up with the novel herbal remedies but it requires more work to accomplish the fully tested quality products. The ICMR has received the request of folklore practitioner who has developed herbal formulation by using traditional knowledge with a preliminary antiviral activity which needs further evaluation studies to reconfirm the observational findings of folklore practitioners. The ICMR has supported such kind of folklore practice for antiviral therapy. This antiviral herbal formulation has claimed benefit for Rabies, Chandipura, Japanese Encephalitis, HSV1 and enterovirus. These claims on antiviral activity were based on traditional knowledge practicing in remote areas of Eastern India for more than 50 years. Traditional practitioner prescribed the medication orally in empty stomach mixed with jaggery for 3 subsequent days after dog bite. For complete medication about 6-7 plants roots are required.

Support for Valuation by ICMR: To assess the evidence based anti-viral herbal preparation as a lead for rabies, influenza and Japanese encephalitis **,**the ICMR has supported in two ways, first to carry forward the evaluation studies provided the technical help and secondly examined the legal and administrative criticalities and supported accordingly to carry forward the traditional knowledge for value edition.

IPR related Support: The ICMR received the material after execution of Material Transfer Agreement (MTA) as the traditional practitioner has filed the patent as an independent inventor. This is the most essential step to carry forward the traditional knowledge. The salient feature of the agreement were on status of preexisting IP, data generated after receiving the material, modalities IP status after receiving the TK, Definition of Material etc. Formulation of Non disclosure Agreement was the another major step due to the reason that ICMR was proposing to conduct multi centric studies for other institutes and restrict the sharing of important data with participating institutes only, therefore NDA is the major component to carry forward the studies up to product development. Based on the stage of evaluation the ICMR has proposed to enter into Product development agreement with stakeholders and ultimately the licensing agreement.

Technical Help in the Evaluation and Proof of Principle: After resolving these IP related criticalities multi centric studies were needed for extraction, purification and characterization of active principle from the herbal preparation. The Exert group has been constituted by ICMR to examine the suitability of this folklore medicine for further up scaling through ICMR support. The Expert group suggested carrying forward the findings in disease specific institutes where expertise technical manpower will examine the potential of this herbal formulation. For multi-centric studies for evaluation of this herbal

formulation the ICMR has sanctioned the projects for multi-centric study at three centers of viral studies. Further to supply standard herbal extract, semi-purified/purified fractions for in vitro antiviral tests against viruses i.e Japanese Encephalitis , Rabies and Chandipura virus and other viruses such as Herpes Simplex Viruses-1&2 and Enterovirus-71**.** The ICMR has supported this claimed knowledge in terms of financial grant and intellectual input. One of our institutes is regularly involved in conducting the in vitro and in vivo studies for JE and Chandipura Following studies were undertaken

a. Extraction, Purification and Characterization: The extraction, purification and characterization studies have been started. The herbal roots bark were dried and powdered and different solvents were used to obtain various extracts like petroleum ether, absolute alcohol, cold aqueous, hot aqueous extracts. Phytochemical screening and HPLC Profiling was carried out. Polarity graded extractions with different solvents was done and coded with various fraction for antiviral in vitro testing. The extract with specific solvent was subjected to column chromatography for further fractionation and subjected to HPLC profiling and *in vitro* antiviral screening.

b. In Vitro and in Vivo Antiviral Testing for Rabies, JE and Chandipura and other Viruses: The extract on specific medium of the herbal compound was found effective against Herpes Simplex Virus (HSV)-1, Rabies Virus and Japanese Encephalitis Virus (JEV). Antiviral activity was confirmed by using the methods: CPE based, MTT based and Immunofluorescent based during in vitro studies. The In vivo antiviral activity on JE and CHPV of the herbal product done by oral and intraperitoneal route administration

c. In Vitro and in Vivo Antiviral Testing Data for Rabies: One specific fraction has shown antiviral property in sub toxic concentrations in vitro experiments. This fractions inhibited viral replication for up to 6 hours post infection. Their efficacy was observed in vivo experiments on mice aged 4-6 weeks old. It was found that same specific fractions were ineffective in killing the virus in all the routes of inoculation tested.

III. Intellectual Property Status: These research works shows novelty and industrial applicability therefore these findings were protected through patent and patent of addition at Indian Patent office. The upscaling evaluation studies both in-vitro and in-vivo were included in the patent document. Formulation for pre-exposure as a preventive for the Viral Diseases, a substitute for Immunoglobulin used for viral neutralization in case of real time and post exposure cases, for the treatment of hydrophobic animals or humans, for the treatment of Flu-Viruses for humans and animals and for the treatment of Flu-viruses for humans and animals are the possible outcome after industrial collaboration. Antiviral formulation can also be explored against Chandipura, HIV, Japanese Encephalitis, Entero Virus, H1N1 (swine) and other Influenza Virus including pandemic Viruses.

IV. Action Plan for Product Development: The studies on JE has shown promising results therefore, further plan of action was focused on Ayurvedic proprietary product development for JE has been initiated as fast track mode with the support of AYUSH and strategies are being explored by involving the Private Company as a Public-Private Partnership mode (PPP) Programme and also to overcome the bioavailability issues in Rabies. All essential regulatory requirements were needed for the Ayurvedic Product approval. Two impotent milestones need to achieved to make Aurvedic product; Firstly to conduct safety and stability studies of finished product on rodents and secondly preparation of dossier.

a. Advertisement Placed on Website: A web advertisement for JE and Rabies was placed with technical support from AYUSH on ICMR website done for stability and toxicological studies of hydro-alcoholic extract and finished product. The key feature of the advertisement was on studies should be on oral toxicity as acute and sub-acute as per schedule Y of Drug and Cosmetic Act for hydro-alcoholic extract and finished product (Box 1). Acute studies should be done in two rodent species i.e. Rat and Mice mode while sub-acute studies should be done in 1 rodent (Rat) and 1 non rodent (rabbit) model. Further accelerated stability studies of hydro-alcoholic extract and finished product need to be done as per the standard guidelines of Ayurvedic Pharmacopea.

The experts also suggested while examining the results on multicentric studies that the drug formulation is possible as a proprietary Ayurvedic drug only for JE and rabies as the results are quite encouraging in vitro and in vivo. Further as the invention is protected as patent and patent of addition. Drug formulation is possible as a proprietary Ayurvedic drug as

defined in the Section 3(h) of Drugs & Cosmetics Act, 1940 and Drugs & Cosmetics Rule 158-B provide the guidelines for issue of license (Box 2). The proposed drug in wholesome form can be licensed as Ayurvedic product for commercial manufacturing, if the ingredient is specified with new indication different from the ones mentioned in the authoritative Ayurvedic texts listed in "THE FIRST SCHEDULE" of the Drugs & Cosmetics Act (Box 3). Safety study and proof or evidence of effectiveness is also required either in the form of published literature or scientific data. It is advisable to have multiple indications for the proposed drug to make it commercially viable since JE incidence is limited to certain areas and mainly to the children population. For regulatory approval of proprietary Ayurvedic drug, toxicological studies are essential while safety studies are optional. After placing the advertisement on ICMR's website for a month and received the proposals from the companies for safety and stability studies. For considering the interested company the company should be GLP certified, valid certificate from State Licensing Authority during the safety and stability study period and undertaking from company indicating that studies will be conducted as per schedule Y of Drug and Cosmetic Act and standard guidelines of Ayurvedic Pharmacopea these proposals need to be examined by the experts to fast track the product development.

b. Preparation of Dossier: The technology dossier is under preparation in consultation with AYUSH, evaluating institute and potential licencee for development of anti-encephalitis and anti-rabies Ayurvedic product as the herbal formulation has showed promising results. It contained the information on collecting /cutting /washing / drying herbal root material, preparation of herbal root bark powder; preparation of hydro-alcoholic extract; lab scale preparation of oral suspension along with specific use for JE & Rabies for immunomodulatory and anti-inflammatory. The dossier should contain the information on broader applicability on product development and it should refer as sugar based syrup or oral liquid suspension. The dossier should contain the detail in the line of rule 158 (b) of the Drug and Cosmetic Act (Box 4) which deals with proof of safety, effectiveness etc. for hydro-alcoholic based formulation. The classical description of the plants along with pictures should be mentioned in the dossier along with other details like use of technology, existing gaps and how this technology help bridging the gaps, patent status, market segment and demand of technology in the dossier. The dossier should be based on the format of National Medicinal Plant Board in accordance with state licensing authority.

c. Technology Transfer to Potential Licensee: To examine the suitability of the companies to license the technology for manufacturing tested formulation the ICMR has established the set of criteria in terms of essential and desirable. These criteria cover capacity for absorption of the technology to be assessed by infrastructure, human resource and clear defined plan for further development and commercialization. The company including its partnering group should have the financial capability in terms of technology of interest for co-development, if necessary for further. The company should have adequate knowledge on market demand. This criterion comes under essential criteria. The desirable criteria covers the registration status in India with relevant in house R and D laboratory recognized by DSIR, certification of Bio Safety Committee (IBSC) for carrying recombinant R&D activities, NABL (National Accreditation Board for Testing and Calibration laboratories), accreditation from DST for GLP for the company/ partner group, animal house with compliance to Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), experience of downstream work for development of products, information about working with Govt. and/or Public sector Clients, products available in market, record of Intellectual property rights ownership in terms of patents, trademarks or other IP, compliance to ISO standards like ISO 9000 (Quality management) etc. One public sector company has shown the interest to manufacture the herbal formulation. It was informed about the execution of NDA and licensing agreement on a non-exclusive basis only after the technology dossier is ready.

Current Status of Herbal Formulation: Currently two proposals are supported by ICMR, one for antirabies activity and other for product development as ayurvedic formulation. For ayurvdic formulation safety and stability studies is essential and ICMR has received the proposals for carrying out safety and stability studies on specific medium and finished product (syrup suspension) as per schedule Y of Drug and

Cosmetic Act. and reconfirming the details on GLP, State Licensing Authority certification etc. After completion of toxicology and stability studies, the technology can be transferred to companies selected by ICMR.

Conclusion: Herbal formulations are commonly used for the treatment of various diseases in India, China, Chile, Ethiopia and USA etc. Acknowledging the efforts of folklore practitioners, they must be supported by the government to facilitate the reach of these efficacious alternate treatments to the public. The ICMR has taken initiatives for hand holding in the research, validation, IP protection and product development of such folklore alternatives in accordance with regulatory framework of the Govt. of India. The ICMR is in the process of preparing ayurvedic proprietary formulations with the support of AYUSH well indicated in the 'Ayurvedic Pharmacopeia' and 'Drugs & Cosmetics Act, 1940' of India.

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