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RESEARCH ARTICLE

HOMOEOPATHIC TREATMENT OF JAPANESE ENCEPHALITIS IN THE LIGHT OF RECENT SCIENTIFIC PROGRESS

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ARTICLE INFO

Article History:

Received 15th April, 2018
Received in revised form
20th May, 2018
Accepted 25th June, 2018
Published online 30th July, 2018

Keywords:

Japanese encephalitis,
Stage specific action of *Belladonna* in JE,
Belladonna, *Helleborus*, *Phosphorus*,
New Homoeopathic treatment outlook.

ABSTRACT

Background: Different studies proved that the homoeopathic medicine “Belladonna 200C” can abate the Japanese encephalitis virus infection in experimental models. The aim of this study is to find out the recent evidence based information which will be supportive to treat the Japanese Encephalitis virus infection according to severity of disease (JE) stratified in different stages.

Methods: A review of important recent studies regarding the treatment of Japanese encephalitis was made and analyzed for extraction of newer ways of homoeopathic treatment in JE. A final protocol for treatment in different stages of JE was formulated accordingly.

Results: After detailed analysis of all evidences, three homoeopathic medicines--Belladonna, Helleborus and Phosphorus were found specifically effective in three different stages according to severity and complications of the disease. Belladonna is useful in first stage of encephalitis without effusion. Helleborus is effective in the second stage of the disease with effusion, stupor, dragging of legs and developing paralysis. Finally the Phosphorus is indicated when complete paralysis appears due to inflammation and degeneration of brain cells.

Conclusion: This new outlook of treatment may decrease mortality and morbidity of JE virus infection besides reducing the complication and disability rates.

INTRODUCTION

The renown German homoeopathic physician (Dr. Hahnemann) who made the idea of “similarity” in medicine in a definite logical and scientific manner and administered first time in field of therapeutics. The review of present studies on homoeopathic curative treatment of Japanese encephalitis was done from different resources and based on all the information. The aim of this review is to find out those evidence based information and to treat the infectious disease likes Japanese Encephalitis in the light of scientific progress. An inspection of important recent studies regarding the treatment of Japanese encephalitis was made and analyzed for drawing out of newer ways of homoeopathic treatment in JE. A final protocol for treatment in different stages of JE was formulated accordingly. It has been noted in different studies that homoeopathic medicines can abate the Japanese encephalitis (JE) virus infection in Human and animal models. The homoeopathic practitioners and Government agencies traditionally used homoeopathic *Belladonna* for the treatment and prevention of Japanese encephalitis in epidemic and endemic area¹. Recently in 2016, Government of Manipur State, India implemented the

project *Belladonna-200C* for preventive purpose and distributed the medicine in 15 lakhs people in JE outbreak area but results are yet to be published². According to their observation the medicine can be used easily in their state as it is cost effective without any adverse effects and easily available in remote areas. There is an unavailability of effective conventional therapy for JE virus infection till date. The disease incidence and case fatality rates are increasing with spread of virus in new geographical areas. According to WHO, 68000 cases occur annually worldwide with 13,400-20,600 death occur per year. The children are the most vulnerable age group in JE infection³. The survivors of JE virus infection (~50%) suffers from different neurological problems with high disability rates. In India, situation is worse due to lack of consciousness about the disease including absence of suitable treatment and management. However, an alternative therapy appears to be essential to prevent as well as for survival from this fatal disease. In this study, our endeavor is to find out the effective homoeopathic medicines in different phases of JE (Early and late phases of the disease). This new treatment approach may entirely change the scenario of JE virus infection and disease can be alleviated to a great extent.

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Some encouraging results in recent decades: Michon, 1952 reported that the root preparation of *Atropa belladonna* was widely used in earlier period for the treatment of encephalitis,

parkinsonism and paralysis agitants in Bulgaria.⁴ Since conception, it is evident in homoeopathic literature as well as in recently published different scientific studies that *Belladonna* can abate the JE virus infection^{5, 6,7,8,9}. A comparative study was done between *Belladonna* and JE vaccine in treatment of JE virus infection in mice. The study reported that SA 14-14-2 live attenuated JE vaccine was somewhat more effective than *Belladonna* but difference was not statistically significant¹⁰. *Belladonna* can be safely used in JE prone area. The BCT (*Belladonna-Calcareea-Tuberculinum*) protocol was implemented to avert JE epidemic in Andhra Pradesh during 1999 -2003 with encouraging results¹¹, but the justification of specific time intervals during application of those three medicines is not clear. It has been observed that pharmacodynamics of *Belladonna* is very similar with the dynamic pathology of encephalitis. It may be the great cause for suitability of this drug in early stage of encephalitis without complications¹². The CCRH was deploying their medical expert team to control the JE epidemic in different parts of the Country from 1984 to 2010. After analyzing their selected medicines in JE epidemic; it was distinctly observed that *Belladonna* was effective as prophylaxis in most of the affected zone. The medicines like *Belladonna*, *Stramonium*, *Helleborus*, *Opium*, *Apis Mel*, *Rhus tox*, *Bryonia*, *Ars.alb* and *Gelsemium* were also used as prophylaxis or for the treatment¹³. A recent outcome in an exploratory observational comparative study conducted by CCRH has been published where homoeopathic medicine (H) was used with Institutional management protocol (IMP) in JE virus infection of humans in IPD (epidemic ward) of a hospital at Uttar Pradesh with encouraging results. The results revealed that there was marked diminution of mortality and morbidity (31.1%) in H plus IMP treated group in comparison to exclusively IMP treated group¹⁴. But the result of exclusively homoeopathic treatment group was essential here to compare the validity and legitimacy of homoeopathic treatment with the other group in JE virus infection on humans. Some recent study reported that genus *Atropa* has immense medicinal values and effective to treat the fever, conjunctivitis, encephalitis, peritonitis and acute inflammations^{15,16}. Bisignano *et al* isolated the bioactive material like colchicin, teniposide, combretastatin, podophyllotoxin, etoposide from *Belladonna* plant which have antimicrobial properties¹⁷.

Chemical composition of *Atropa belladonna*: From ancient times belladonna was used as poisonous as well as therapeutic agent¹⁸. Many historical incidents provide evidence on the poisonous effect of Belladonna on human and animals. The toxicological effect of Belladonna was confirmed and verified by different researcher from past to recent days^{19,20,21}. Basically the toxicological effect of belladonna depends on its tropane alkaloids. Hartman *et al* reported that 13 alkaloids are present in the root and 7 alkaloids are present in other parts of the plant which was above the ground following high resolution GLC and GLC-MS²². The parts of *Atropa belladonna* contain different alkaloids with various percentages²³ which showed in Table: 1:

Table:1 showing the % of Tropane alkaloid in different parts of *Atropa belladonna*

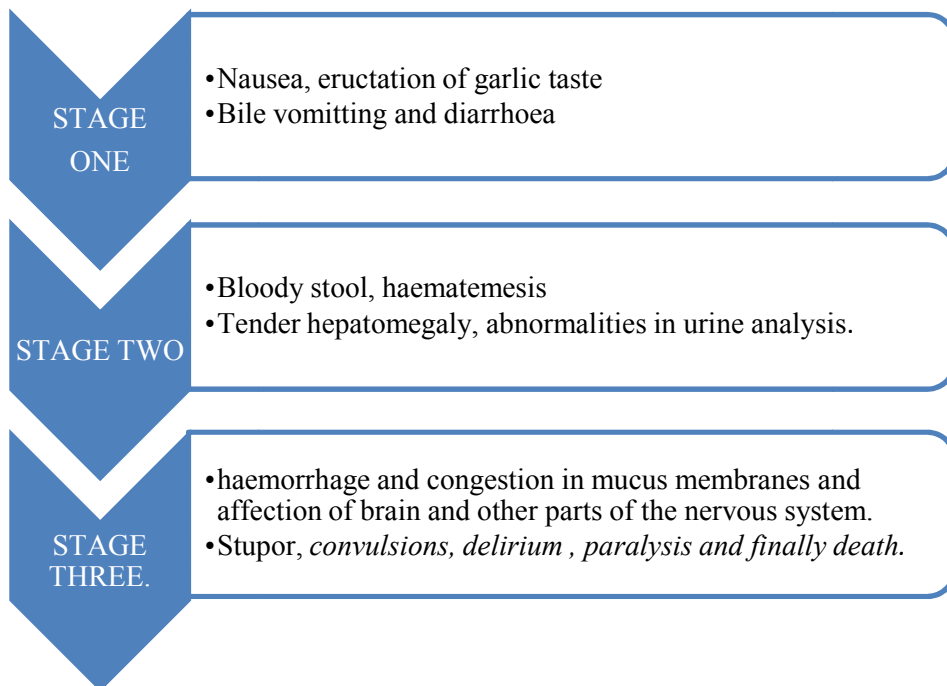
Name of prime alkaloids	Parts of plant	Percentage	Reference
Tropane alkaloids including hyoscyamine, atropine, apoatropine and scopolamine	Stalk	Up to 0.9%	Ratsch C, 2005
	Seeds	About 0.4%	
	Dried Root	0.3% to 1.2	
	Unripe Berries	Up to 0.8%	
	Ripe Berries	0.1% to 9.6%	
	Dried Leaves	0.2% to 2.0%	

Researchers reported that root is the main source of tropane alkaloid. The atropine, hyoscyamine, hyoscyne, apo-atropine (atro-pamine), belladadine, belladonnine, and cuscohygrine are present in root in various quantities and finally move in various parts of the plant²⁴. Wilson reported that the foliage and berries of this plant are extremely toxic, containing tropane alkaloids²⁵. The percentage of alkaloids is varied in natural plant when compared to the cultivated *Belladonna* plant. The production of alkaloids in plants was influenced by some extrinsic and intrinsic factors, atmospheric condition and seasonal changes. It has been found after HPLC analysis that the alkaloids percentages are highest at early night and early morning²⁶. The juice of belladonna plant was most active at the time of their bloom²⁷ and that's why according to HPI, the whole plant should be collected at the time of their blooming for the homoeopathic drug preparation²⁸. In fact the bio-active materials of genus *Atropa* has lots of medicinal properties like anticholinergic, muscarinic, mydriatic and anti-inflammatory effect. There are many diseases which can be treated by conventional and traditional system of medicines manufactured from genus *Atropa*²⁹. They also reported that genus *Atropa* has enormous remedial value for the treatment of parkinsonism and encephalitis. Arroo *et al* reported that the plant *Atropa belladonna* is commercially important for the natural production of atropine; hyoscyamine and scopolamine (hyoscyne) which had immense medicinal values³⁰. Ozcelik *et al* reported the anti-cholinergic agent atropine and scopolamine of *Atropa belladonna* has anti viral effect³¹. The anti viral properties of some natural compounds like atropine and caffeine was revealed by a novel work of Yamazaki *et al*, in 1980³². It has been observed from the result of experiment that atropine can inhibit the replication of some enveloped virus (either R.N.A or D.N.A virus) including Japanese encephalitis virus. Important bioactive materials like alkaloids, flavonoids and some trace elements are present in *Belladonna* extract which have remedial properties. So, it is very difficult to explain which bio active material has taken the leading role to inhibit the virus growth.

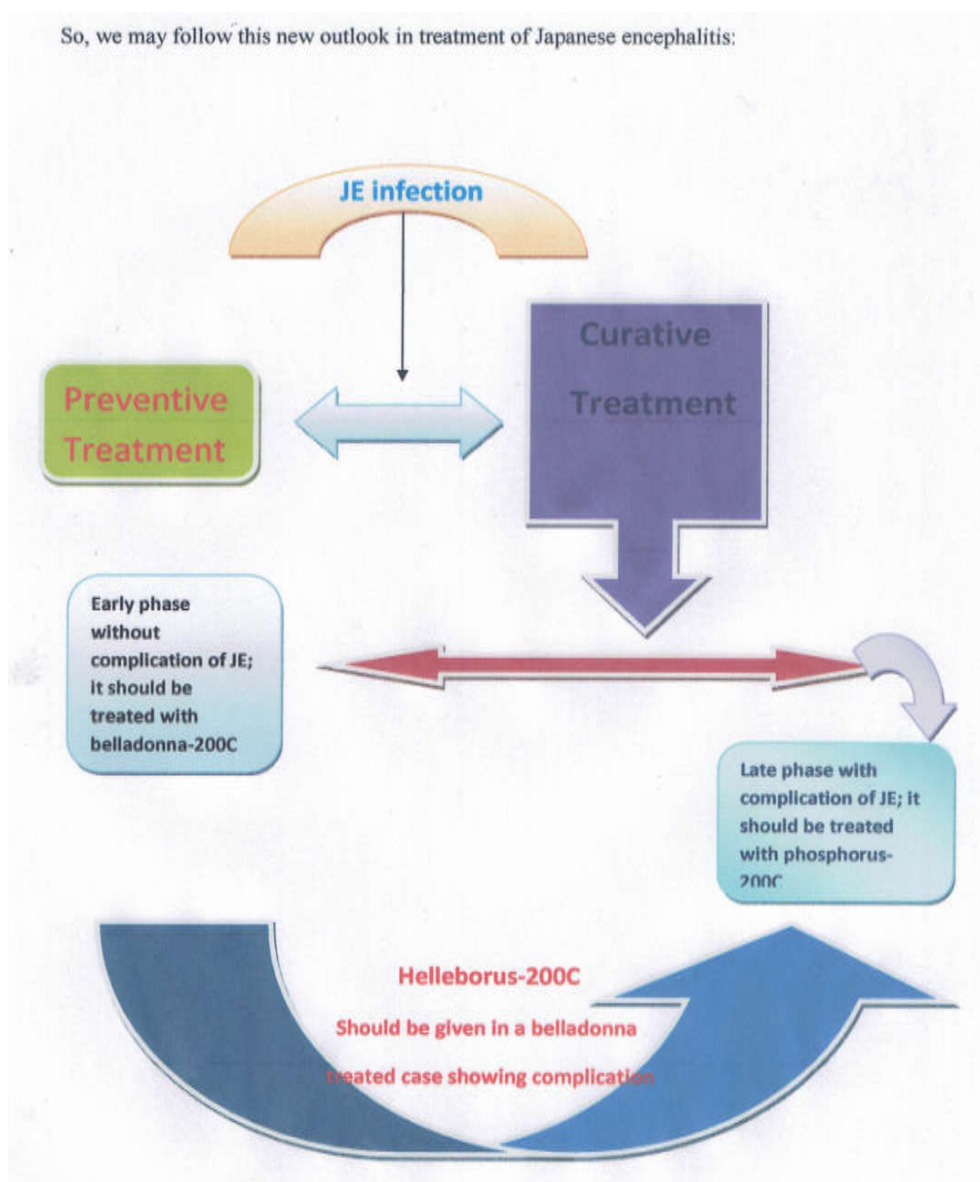
The effect of *Belladonna*, *Helleborus* and Phosphorus on Central nervous system: The Pharmacodynamics of *Atropa belladonna*, *Helleborus* and *phosphorus* on Brain and their suitable place of action in encephalitis¹² were observed in recent past.

Homeopathic observation on *Belladonna*: The Poisonous effect of Belladonna showed the acute cerebral congestion which is key note action of Belladonna in drug proving experiment. So in homoeopathic literature *Belladonna* is the 1st grade remedy for cerebral congestion among other cerebral remedies¹². Belladonna has been found very similar to the features of encephalitis when the congestion tends to an inflammatory irritation³³ in brain. In the arterial congestion of brain from almost any cause, the *Belladonna* is a very useful remedy²⁸. The action of *Belladonna* is unsuitable for meningitis when there is formation of "effusion" in brain in late phase of disease (Dr. Bahr and Dr. Hughes). The similar observation was found in famous literary work "Clinical Materia Medica" in "Solanaceae" (Lecture XXXIX) of Dr. E.A. Farrington where he mentioned that when exudation takes place in brain during inflammation, *Belladonna* must give place to other drugs. Belladonna is the main remedy in the first stage of the disorder, and not in the stage of "effusion" or collapse. All these phenomena of action of *Belladonna* (the pharmacodynamics of Belladonna,

Thus after analysis our main findings are arranged in the following two charts:



So, we may follow this new outlook in treatment of Japanese encephalitis:



i.e. congestion tends to inflammation) are very similar to the dynamic pathology of the encephalitis (inflammation produce congestion) and that's why *Belladonna* acts well in first stage of encephalitis but may not act well in the late stage of the disease.

Homeopathic observation on *Helleborus*: According to Lembke and others, *Helleborus* produces marked congestion in brain and helleborin, an alkaloid of *Helleborus* (glucoside) causes paralysis in animals. The alkaloid helleborin has narcotic effect and can produce paresis in both sensation and function in human³³. The congestion and extravasations of fluid in brain has been found after post mortem of cerebral meninges in animals¹². Teste reported that the medicine acts well on actual inflammation on brain and meninges. The drowsiness with fever in meningitis was the leading key note to prescribe the *Helleborus* in homeopathic practice. Another prominent feature of drug was one leg dragged on walking which have been observed in drug proving experiment on human being. This unique feature is very similar to second stage of JE in adult mice when mice were challenged with JE viral dilution (LD50 dose) intracerebrally after 3 dpi⁸. So, *Helleborus* is suitable for the second stage of encephalitis¹². It was also observed that *Helleborus* follow *Belladonna* well due to their close relationship. So, *Helleborus* is effective in second stage of the encephalitis at that time when in first stage of the disease was treated by *Belladonna*, otherwise it may not be acted (followed well" relationship)³⁴.

Homeopathic observation on *Phosphorus*: Japanese encephalitis is predominantly affecting on central nervous system mainly in brain. So our prime interest is to evaluate the toxicological profile of Phosphorus in CNS. Signs of neurotoxicity have been observed in a number of individuals ingesting a single dose of white *phosphorus*. These signs include lethargy, sleepiness, irritability, restlessness, hypo activity, coma, toxic delirium and psychosis, hyperesthesia, coarse muscle fasciculation, unresponsiveness to painful stimuli, and hemiplegia. Histological damage in the brain has also been observed in humans acutely ingesting white *phosphorus*³⁵. At post-mortem examinations in cases of phosphorus poisoning the blood-vessels of the piamater were found congested with blood, and yellow, opalescent lymph collected between the pia and arachnoids; the grey matter was softened. Phosphorus impairs the vitality of nervous centers and gives rise to paralysis¹². *Phosphorus* is truly treat the paralytic conditions which depend on lowered vitality or softening of centers according to symptoms similarity of medicine (in brain and spinal cord). These observations were supported by Dr. Gallavardin³⁵, Dr. Sorge and Dr. Trinks. So, it may help to minimize the degree of paralysis and complication in late stage of JE.

DISCUSSION

Japanese encephalitis is now a blazing global problem. The South- East Asian countries are affected by this fatal disease including India. The National Vector Borne Disease Control Programme (NVBDCP) has monitoring the outbreak of JE throughout the country. According to media report; Gorakhpur in Uttar Pradesh is the major JE affected area in the country. Large number of AES and JE cases were admitted and treated in OPD and IPD of BRD hospital, U.P. A large population in some district of North Bengal was also affected by JE virus

infection in last few years³⁶. Virtually there was no efficient anti-viral therapy against JE till now in spite of some promising candidate. Extensive research is needed to prove their efficacy. The disease is spreading worldwide despite of JE vaccine. During the occurrence of large epidemic, mass scale vaccination is not feasible due to climatic, geographical and socio- economical barrier. The competent health authority of the country should be interested to control the JE epidemic by using alternative therapy. Therefore, a review of important recent studies regarding the treatment of Japanese encephalitis was made and analyzed for extraction of newer ways of homeopathic treatment in JE. A final protocol for treatment in different stages of JE was formulated accordingly. The anti-viral properties of *Belladonna* on JE virus infection was confirmed by different studies mentioned earlier. To explore the protective mechanism of *Belladonna* against JE virus infection in mice, a study was done by some Indian researcher. In this study they determine the JE viral RNA level and genetic expression of IL-6, CCR-5, IFN- β , TNF, ISG 15, MX1, TLR-7 and IFIT1 in *Belladonna* treated survived mice in comparison with control group of survived mice. The result showed that *Belladonna*-200C was probably able to reduce the JE virus infection by its immune mediated mechanism in mice model³⁷. Sengupta *et al* reported that it is very difficult to ascertain the mechanism of action of specific bioactive material in *Belladonna* against JE virus infection in adult mice⁸. According to their postulation, the calystegines, a glycosidase inhibitor is present in belladonna showed glycosidase-mediated N-linked oligosaccharide trimming and most likely responsible to clear the JE virus infection by that special mechanism in adult mice⁸. There were many remedies in homeopathic literature having curative qualities against encephalitis. Some of them are used frequently like *Belladonna*, *Helleborus* and *Stramonium* in treatment purpose against JE. But our previous research experience on effect of homeopathic medicines on JE virus infection in mice model and also the observation of eminent clinicians revealed that those medicines act well in certain stage of disease which was peculiar character of that medicine. *Belladonna* acts well in first stage of JE without effusion¹². But when effusion starts to develop in brain in second stage of the disease with stuporous condition, *Helleborus* is the next drug of choice according to indication of medicine in curative purpose. In fact each homeopathic medicine is interrelated in different ways according to their curative action. As per remedy relationship *Belladonna* followed well by *Helleborus* when its action was localized in encephalon and serous effusion develop³⁴. So, *Helleborus* will be effective in second stage of the encephalitis at that time when first stage of the disease was treated by *Belladonna* and some residual symptoms remain, otherwise it may not act (this is the meaning of "followed well" relationship). *Belladonna*, *Hellebores* and *Phosphorus* are interrelated each other according to their symptomatology.

Conventionally *phosphorus* is not frequently applied for the treatment of JE. Nath *et al*. 2011 conducted a study on mechanism of Phosphine toxicity where they found the probable role of atropine to protect rats from phosphine toxicity. The probable cause was antagonistic action of atropine in *Belladonna* against the phosphorus toxicity³⁸. Actually we found from above study; the muscarinic acetylcholine antagonist atropine protects rats against phosphine exposure. indicating that acetylcholine signaling is an important component of phosphine toxicity³⁹. After repartorization on common symptoms of JE, we found some

homoeopathic medicines especially *Belladonna* is in first grade for treatment of encephalitis. But *Phosphorus* is found in second grade. This gradation was not always applicable and suitable during selection of drug in disease. However, after analyzing the symptoms of poisoning and the pathogenetic symptoms collected from drug proving of Phosphorus and Belladonna, it was found that their characteristics features are very similar to the certain stage of disease which arranged in *Materia Medica*. In case of JE, Belladonna will be applicable for prodromal and beginning of acute encephalitic stage but Phosphorus may be applicable for terminal part of acute encephalitic state of JE when Paralysis developed. *Phosphorus* is a potential remedy to treat the paralytic conditions due to lowered vitality or softening of nerve centers in brain and spinal cord. These observations were supported by Dr. Gallavardin⁴⁰, Dr. Sorge and Dr. Trinks. So, it may help to minimize the degree of paralysis and complication in late stage of JE. The precise place of hellebores was in between them during treatment of JE. The most alarming issue of this Flavivirus mediated disease is significant case fatality and disability rate. In homoeopathy, so many remedies are there to destroy this monstrous pathology. Belladonna, Helleborus and Phosphorus are well known homoeopathic remedies, proved and verified by legendary stalwarts and secured glorious place in the pages of Homoeopathic *Materia Medica*. From the above discussion it is quite clear that a remedy of this magnitude of action on human central nervous system can always come as our desired medicine in treatment of JE with a new outlook. But it is impossible to evaluate all aspects of this drug on which it can be tried in JE sufferers in this small space. However, we have seen its action and the individualistic features which were sufficient to make us understand the importance in the treatment of JE in a new stance.

Conclusion

The anti viral properties of *Atropa belladonna* against Japanese encephalitis has been established by several authorities from past to present days study. The bioactive material of *Belladonna* has been used in conventional as well as the traditional medicine since long for the treatment of several diseases. The mechanism of action of those materials has not been explored fully. So more research is warranted to know the actual pathway of its action on JE virus inhibition. The stage specific action of Belladonna, Hellebores and phosphorus in encephalitis were found in homoeopathic literature as well as in recent studies. Belladonna is useful in first stage of encephalitis without effusion. *Helleborus* is effective for the second stage of the disease with effusion, stupor, dragging of one leg and developing paralysis. Lastly the *Phosphorus* is indicated when full paralysis appears due to degeneration of brain cell. This new outlook in the treatment may reduce the mortality and morbidity of JE virus infection and also can control the neurological complication with disability rates.

Acknowledgement: We acknowledge Central Council for Research in Homoeopathy (CCRH), Under Ministry of AYUSH, New Delhi, India for the financial support. It is a pleasure to acknowledge with thanks to Dr. P.S. Chhkraborty, senior Scientist of DACRRI, Kolkata for his sustained support and specific suggestions in this work. We acknowledge the cordial help of all the staff and technicians of Virology Laboratory, Dr. Anjali Chatterjee Regional Research Institute for Homoeopathy, Kolkata, Under Central Council for

Research in Homoeopathy, New Delhi, Ministry of Ayush, Govt. of India

Conflict of interest: There is no conflict of interest of any Author.

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