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Immunostimulant- Adjuvant Therapy For Influenza A (H1N1)

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ABSTRACT

Swine flu is an acute respiratory disease of pigs caused by tiny spheroid virus that is H1N1 virus that belongs to the influenza A virus group. This virus spread the infection in to the people through sneezing, coughing, splitting, inhaling infected droplets. Oseltamivir is now drug of choice for the swine flu, but it has several side effects. The primary infection of H. influenza to the host stimulates the host immune system. Immunostimulant property of herbal drugs proved to stimulate T cell and macrophages that can be used as adjuvant therapy for Swine flu treatment to stimulate the low host immune system. This review is an attempt to discuss the role of immune-stimulant as adjuvant therapy for H1N1.

Keywords: Swine flu, influenza A virus, Immunostimulant.

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INTRODUCTION

Swine flu is new disease caused due to H1N1 virus. Up to 24th July 2009, 94000 cases of H1N1 influenza have been registered across 135 countries in the world; there have been 475 deaths across the globe. Up to 7th august 2009 in India 150 cases of H1N1 have been registered. H1N1 virus spreads from person to person probably in much the same way that regular seasonal influenza virus spread. Influenza is an infectious disease that affects birds, mammals and pigs and it is often referred to as the flu. The flu is a contagious respiratory illness caused by influenza virus. H1N1 virus was originally referred to as Swine Flu virus because laboratory testing showed that many of the genes in this virus were very similar to influenza virus that normally occur in pigs in North America but further study has shown that this new virus is very different from what normally circulate in North American pigs . It has two genes from flu virus that circulate in pigs in Europe and Asia and avian genes and human genes, scientist called this a ‘Quadruple reassortant’ virus¹. This new virus is first detected in people in April 2009 in the united state.

Swine flu virus generally circulates throughout the year, but the disease mostly occurs during the late fall and early winter season. It has major economic impact on the swine industry in the United State as it causes high mortality and morbidity in pigs resulting in the financial losses². The most commonly circulating strains of swine flu virus isolated from pigs in the United States are H1N1, H1N2, H3N2, H3N1, which belong to the influenza A sub type^{3,4,5}. In the past, the Center for Disease Control and Prevention (CDC 2009) have received reports of approximately one human swine influenza virus infection every one to two years in the United States but a sustained pattern of human-to-human transmission has been seen to occur only recently, raising a pandemic alarm⁶.

Swine flu virus, a respiratory virus initially known to cause infection in pigs, belongs to the orthomyxoviridae family of viruses that include influenza A, influenza B, influenza C and thogotoviruses^{7,8}. It is RNA type of virus⁹, that virus particles are usually spherical or ovoid in shape and are usually 80 to 120 nm in diameter and approximately 500 molecules of Hem agglutinin (HA) 80%. Hem agglutinin is that function in the attachment of the virus to the host cell. The remaining 20% is neuraminidase is used to release newly produced virus particle from the host cell. On the inside of the influenza virus is an antigenic protein lining which contain 8 pieces of single stranded RNA (A and B).The RNA is packed with nucleoprotein in to helical ribonucleic form with 3 polymerase peptide for each RNA segment.

STRUCTURE

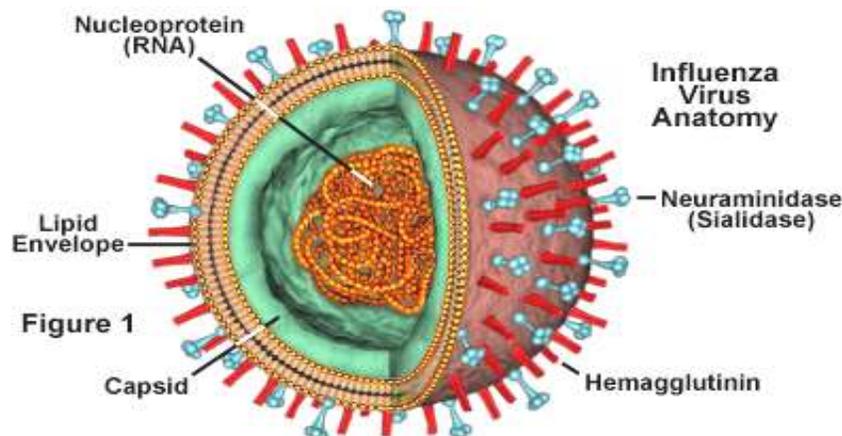


Figure 01

Hem agglutinin (HA) is found on the surface of the influenza viruses, it is an antigenic glycoprotein. The name 'Hem agglutinin' comes from the protein ability to cause red blood cells to clump together (agglutinate) in vitro HA has two primary function¹⁰.

1. HA bind to silica acid containing receptor which is present on the surface of its target cell.
2. Allowing the entry of the viral genome into the target cells by causing the function of host endosome membrane with a viral membrane. Influenza virus is destroyed by specified heat in addition germicides including chlorine and alcohols.

Pathophysiology

An influenza virus enters via respiratory tract¹¹. These viruses then bind through hem agglutinin to monosaccharide silica acid which is present on surface of its target cell. This causes the viral particle to stick to the cell surface typically in the nose, throat and lungs of mammals and intestine of bird. The cell membrane then engulfs the virus and the portion of the membrane that encloses it pinches off to form a new membrane bound compartment within the cell called an endosome, which contain the engulfed virus. In this way virus enter into the human body and produces infection.

Two account mechanism for clearance of primary influenza virus infection found in human¹².

1. Cytotoxic T cell kill virus infected cell.
2. Intracellular anti-influenza protein (MX1) is induced in macrophages by the cytokines interferon alpha and interferon beta.

Signs and Symptoms

The symptoms of the flu are similar to those of the common cold, but tend to be more severe. Symptoms can happen quickly and can start suddenly after one or two days of infection.

Symptoms include Fever, headache, fatigue, muscle weakness, pain, sore throat, cough, extreme coldness, redness of eyes, irritated watering eyes, diarrhea and vomiting, anorexia leading to loss of weight, lethargy, ocular nasal discharge¹³. Abortion and preterm birth have also been reported among pregnant women, especially those with pneumonia¹⁴.

Transmission

H1N1 virus can be spread in three main ways by direct transmission when an infected person sneezes mucous into the eyes, nose or mouth of other person, through a people inhaling the aerosols produced by infected people coughing, sneezing and spitting¹⁵. Through hand shaking with infected person. Trough hand to mouth transmission from either contaminated surface or direct personal contact. H1N1 virus is not transmitted through freshly prepared well cooked food.

TREATMENT FOR SWINE FLU

There are four different antiviral drugs for the treatment of influenza these are as follows-

A) Neuraminidase inhibitors- Oseltamivir , Zanamivir

B) Inhibitors of viral uncoating- Amantadine, Rimantadin.

The most recent H1N1 influenza virus isolated from humans are resistant to Amantadine & Rimantadine. Recently, Oseltamivir is the drug of choice for swine flu treatment.

MECHANISM OF ACTION OF OSELTAMIVIR

Oseltamivir is an ester type pro-drug and it is activated by the hepatic esterase. It is analogue of sialic acid and a neuroaminidase inhibitor¹⁶. It interferes with the action of neuroaminidase which is essential for the release of new viral particles. Thus Oseltamivir by inhibiting neuroamidinase interfere with the flu viral reproduction.

Immunomodulators

An immunomodulators may be defined as a substance, biological or synthetic, which can stimulate, suppress or modulate any of the components of immune system including both innate and adaptive arms of the immune response.^{17,18} Immunostimulant are used to enhance body resistance against infections. These agents are inherently nonspecific in nature, but they can act to the innate and adaptive arms of immune response.

The reported natural immunostimulant

1. Natural product - *Matricaria recutita*, *Azadirachta indica*, *Aspragallus racemosus*, *Allium sativum*.
2. Rasayana - *Aspragallus racemosus*, *Shilajit*, *Withania somnifera* ,*Praval*, *Suvarnamakshika*, *Makarandhvaja*.

3. Adaptogens - *Withania somnifera*, *Ocinum sanctum*, *Panax ginseng* , *Sida cordifolia*

MECHANISM OF ACTION OF HERBAL IMMUNOSTIMULANTS

The immunostimulants are introduced into the body which activates the macrophage and granulocytes there by increasing the phagocytosis of infected cell. It may be stated that irrespective of the primary targets of the immunostimulants, be they T or B – lymphocytes or the complement system, an increasing in phagocytosis by macrophages (macrophagocytosis) and granulocytes (microphagocytosis) plays a central role in immunostimulation. The major role in amplification of the nonspecific immunological defense is played by lysosomal enzymes secreted by activated macrophages, the component of compliment, interferon, lymphokines, macrophage migration inhibition factor (MMIF) and prostaglandin¹⁷. Rasayana is the therapeutics which promotes dhatus- tissue of body and increases strength and immunity against diseases¹⁹. Adaptogens are those natural substances which increases the non specific resistance of organism against different type of stressors. The natural immunostimulants given in table no.1 are reported to enhance the T-cell and macrophages of immune system, which if given as adjuvant therapy with other treatment available for swine flu can be beneficial to the patient in term of fighting against swine flu.

Table 1

Sr. no.	Plant Name	Immunostimulant Activity
1	<i>Azadirachta indica</i>	Activate macrophages
2	<i>Echinacea purpurea</i> <i>Echinacea angustifolia</i>	Increases in phagocytic action, enhancement of TNF secretion, stimulation of macrophage and also non specific T cell stimulant activity.
3	<i>Tinosporacordifolia</i>	Activation of macrophages
4	<i>Arniea nontana</i>	Stimulate phagocytosis
5	<i>Laminaria japonica</i>	Stimulate phagocytosis
6	<i>Eupatorium perfoliatum</i>	Stimulate phagocytosis

DISCUSSION

H1N1 is the pandemic alarm. Swine influenza virus has been shown to be resistant to standard antiviral drugs such as amantidine and rimantidine. In these era of resistance to known drugs, natural stimulation of host immune system to stimulate T-cell, which kill the virus infected cell and macrophages which induces intracellular anti-influenza protein by cytokinines, interferon alpha and interferon beta can be considered. Our review thus suggest that immunostimulants can be probably used as adjuvant therapy for influenza A (H1N1) with its standard treatment options.

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