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HERBAL, PHARMACOLOGICAL AND ADVANCED APPROACHES FOR THE TREATMENT OF SWINE FLU- A REVIEW

CH. B. Praveena Devi*, B. Vyshnavi, J. V. C. Sharma and P. Sirisha

Department of Pharmaceutical Chemistry, Joginpally B.R. Pharmacy College, Yenkapally (V), Moinabad (M), Hyderabad, Telangana, India, 500075.

***Corresponding Author: CH. B. Praveena Devi**
Department of Pharmaceutical Chemistry, Joginpally B.R. Pharmacy College, Yenkapally (V), Moinabad (M), Hyderabad, Telangana, India, 500075.

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ABSTRACT
Swine flu also known as Influenza A (H1N1), is a pandemic infection caused by swine flu influenza virus (SIV). There are many marketed preparations available for the treatment of swineflu. The treatments for the disease include ayurveda, unani and pharmacological medications. There are few pharmacologically active anti-viral drugs like Oseltamivir (Tamiflu), Zanamivir (Relenza) were available in the market. The scope of herbal treatments over the allopathic drugs in treating swine flu is becoming more popular because of the less adverse effects**.** Among them, Tulsi, Neem, Garlic, Aloevera, Liquorice are the common ayurvedic plants for the treatment of the disease. As the H1N1 strain is resistant to few anti-viral medications, there is a lot of scope for research on the advanced approaches to act on this resistant strain.

KEYWORDS: Swine flu, H1N1, Influenza virus, herbal remedies, Ayurveda and allopathic drugs.

INTRODUCTION
Swine flu, also known as Influenza A (H1N1), pig influenza, hog flu and pig flu is a new influenza virus causing illness in people.[1] It is an infection caused by several types of swine influenza viruses. It infects the respiratory tract and result in nasal secretions, cough and decreased appetite. Swine influenza virus (SIV) is any strain of the influenza family of viruses that is endemic in pigs. There are many thousands cases of swine flu in the present day.

Nowadays, we have more number of medications available for the treatment of swine flu which includes ayurveda, unani and allophatic formulations. Presently, two classes of antiviral drugs have been approved by the US Food and Drug Administration (FDA) in treating or preventing influenza virus infections: M2 ion channel blockers and neuraminidase inhibitors (NAIs). The M2 blockers, amantadine and rimantidine, are effective against influenza A viruses, but not influenza B viruses, which lack the M2 protein. However, use of the M2 blockers has been associated with the rapid emergence of drug-resistance mutations of the M2 protein among human influenza A viruses of H3N2 subtype and H1N1 subtypes circulating in certain geographic areas.[2]

The herbal formulations are becoming more popular in recent days because of the safety when compared to the synthetic drugs that are regarded as unsafe to human and environment. It has been estimated that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as China and India, the contribution is as much as 80%. Ayurveda, Siddha, Unani and Folk (tribal) medicines are the major systems of indigenous medicines. Among these systems, ayurveda is the most developed and widely practiced science in India.[3] Unlike many diseases, swine flu is an infectious disease caused by RNA viruses of the family Orthomyxoviridae (the influenza viruses), that affects birds and mammals.

Transmission of virus to human
Transmission of the virus from pigs to humans is not common and does not always lead to human influenza, often resulting only in the production of antibodies in the blood. If transmission does cause human influenza, it is called zoonotic swine flu. People with regular exposure to pigs are at increased risk of swine flu infection. The meat of an infected animal poses no risk of infection when properly cooked. Like most viruses, it enters the body through the mucous membranes - the eyes, the nose or the mouth. Swine flu is spread just like the regular seasonal flu spreads. It goes from person to person through close contact and direct touch, indirect touch, or respiratory droplets that carrying the virus. Infected person may be able to infect others beginning one day before symptoms develop and up to seven or more days after becoming sick. Swine influenza viruses are not transmitted by food. Every virus, bacteria or pathogen of any time has a certain incubation period. Like all,

influenza pathogens the average incubation period are two days. However, individual periods may range between one to seven days.[4]

Structure of influenza virus

It is an orthomyxo virus that contains the glycoprotein's Haemagglutinin (HA) and Neuraminidase (NA) (Fig.1).[5]

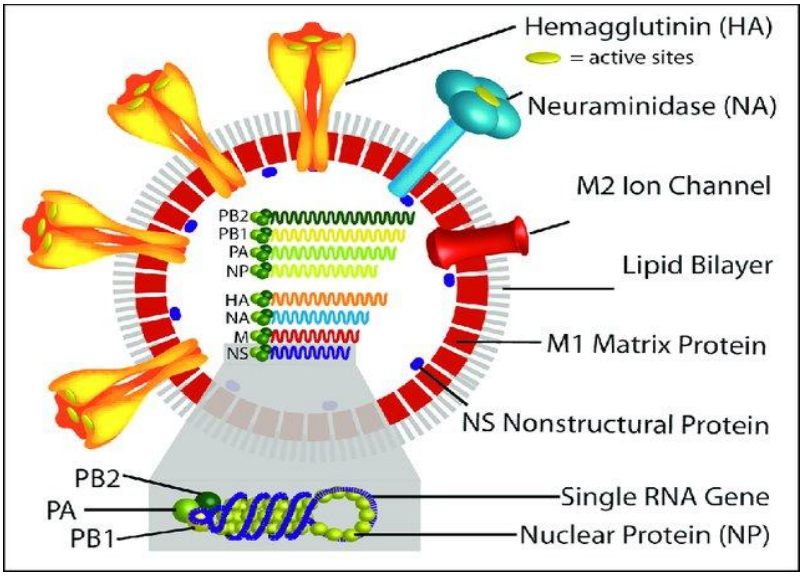


Fig. 1: Structure of influenza Virus.

Signs and symptoms

In pigs, influenza infection produces fever, lethargy, sneezing, coughing, difficulty breathing and decreased appetite.[6] In humans, symptoms include fever, cough, sore throat, body aches, headache, and chills and fatigue.[7,8] Influenza viruses are transmitted from person to person primarily through contact with infected respiratory secretions, especially airborne droplets generated by coughing and sneezing. Viral replication and shedding are key considerations in the timing of treatment, infection control, and chemoprophylaxis.

In general, the incubation period for influenza is estimated to range from 1 to 4 days with an average of 2 days. Influenza virus shedding (the time during which a person might be infectious to another person) begins the day before illness onset and can persist for 5 to 7 days, although some persons may shed virus for longer periods, particularly young children and severely immune compromised persons. The amount of virus shed is greatest in the first 2-3 days of illness and appears to correlate with fever, with higher amounts of virus shed when temperatures are highest. For these recommendations, however, the infectious period for influenza is defined as one day before fever begins until 24 hours after fever ends.[9]

Patients who have severe, complicated, or progressive illness or who are hospitalized

Treatment is recommended for patients with confirmed or suspected 2009 H1N1 influenza who have severe, complicated, or progressive illness or who are hospitalized. The recommended duration of treatment is 5 days. Hospitalized patients with severe infections (such as those with prolonged infection or who require intensive care unit admission) might require longer treatment courses. Even though treatment is most effective when started in the first 48 hours of illness, limited data from observational studies of hospitalized patients suggests treatment of persons with prolonged or severe illness reduces mortality or duration of hospitalization even when treatment is started more than 48 hours after onset of illness. Antiviral doses recommended for treatment of 2009 H1N1 influenza in adults or children 1 year of age or older are the same as those recommended for seasonal influenza. Some experts have advocated use of doubled doses of oseltamivir for some severely ill patients, although there are no published data demonstrating that higher doses are more effective. For patients unable to take oral medication or in whom oral medication appears to be ineffective, peramivir for intravenous administration is available from the CDC under an FDA EUA, although studies of efficacy and safety are limited.

Patients at Increased Risk for Complications

Prompt empiric antiviral drug treatment is recommended for persons with confirmed or suspected influenza who are at increased risk for serious morbidity and mortality. Based on currently available data, approximately 70% of persons hospitalized with 2009 H1N1 are in one or more of the following groups:

- Children (see below) younger than 2 years old.
- Adults 65 years of age or older.
- Pregnant women and women up to 2 weeks postpartum (regardless of how the pregnancy ended [live birth, pregnancy termination, preterm birth, miscarriage, fetal death])
- Persons with certain medical conditions, described below.

Children
Children younger than 2 years of age are at higher risk for influenza-related complications and have a higher rate of hospitalization compared to older children. Children aged 2 to 4 years are more likely to require hospitalization or urgent medical evaluation for influenza compared with older children and adults, although the risk is much lower than for children younger than 2 years old.

Adults aged 65 years and older
Even though persons aged 65 years and older are less likely to become ill with 2009 H1N1 influenza compared to younger persons, when they do acquire influenza, they are at higher risk for severe influenza-related complications.

Pregnant women
Pregnancy increases the risk of complications, hospitalization, and severe disease. One study estimated the risk of hospitalization for 2009 H1N1 to be four times higher for pregnant women than for the general population (Jamieson DJ, et al. Lancet. 2009; 374: 451-458). While oseltamivir and zanamivir are "Pregnancy Category C" medications, meaning no clinical studies have been conducted to assess the safety of these medications for pregnant women, available data suggest pregnant women with suspected or confirmed influenza should receive prompt antiviral therapy, and pregnancy should not be considered a contraindication to treatment with oseltamivir or zanamivir.

Oseltamivir is preferred for treatment of pregnant women because of its systemic activity. Anecdotal reports suggest postpartum women, similar to pregnant women, might be at increased risk for severe complications and death from 2009 H1N1 influenza. The transition to normal immune, cardiac, and respiratory function occurs quickly, but not immediately after delivery. Therefore, the increased risk associated with pregnancy should be considered to extend for 2 weeks postpartum regardless of the outcome of the pregnancy (including live birth, premature birth, termination of pregnancy, miscarriage, fetal death). Prompt empiric antiviral treatment is indicated for suspected or confirmed 2009 H1N1 influenza in women who are up to 2 weeks postpartum regardless of how the pregnancy ended.[9]

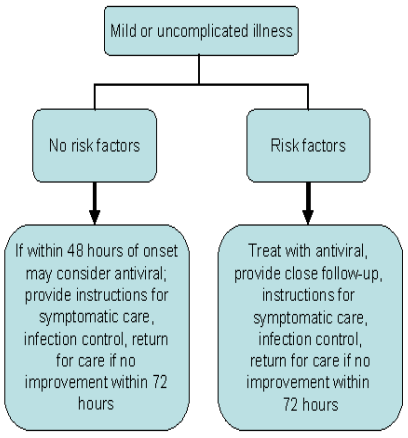
Medical conditions
The following medical conditions have been associated with increased risk of complications from influenza:

- Asthma
- Neurological and neuro-developmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury].
- Chronic lung disease (such as chronic obstructive pulmonary disease [COPD] and cystic fibrosis)
- Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
- Blood disorders (such as sickle cell disease)
- Endocrine disorders (such as diabetes mellitus)
- Kidney disorders
- Liver disorders
- Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
- Weakened immune system due to disease or medication (such as people with HIV or AIDS, or cancer, or those on chronic steroids)
- People younger than 19 years of age who are receiving long-term aspirin therapy

Local public health authorities might provide additional guidance about prioritizing treatment within groups at higher risk for severe infection.[9]

Clinical Assessment
While most persons who have had confirmed or suspected 2009 H1N1 influenza have had a mild, uncomplicated self-limited respiratory illness similar to typical seasonal influenza and while persons not considered to be at increased risk of developing severe or complicated illness may not require treatment, they can be considered for antiviral treatment. Benefits of treating such patients might include a reduced duration of illness. However, based on experience with seasonal influenza treatment, patients not considered to be at increased risk of developing severe or complicated illness and who have mild, uncomplicated illness are not likely to benefit from treatment if initiated more than 48 hours after illness onset. Clinical judgment is always an essential part of treatment decisions.

Clinical algorithm for consideration in the assessment of persons with mild or uncomplicated influenza illness



Diagnosis

The diagnosis of swine flu is not easy like that of other diseases. The Centers for Disease Control and Prevention (CDC) recommends real time RT-PCR as the method of choice for diagnosing H1N1. This method allows a specific diagnosis of novel influenza (H1N1) as opposed to seasonal influenza. Other methods are Rapid Antigen Tests, virus isolation, virus genome sequencing.[10]

Prevention

Prevention of swine influenza has three components namely prevention in swine, prevention of transmission to humans, and prevention of its spread among humans.[11] Methods of preventing the spread of influenza among swine include facility management, and vaccination.[12]

Treatment

The following are the different treatment strategies for treating the disease. Few vaccines have also been developed to protect against the virus that causes swine flu.

Ayurvedic Treatment

Ayurveda promotes the concept that if one's immune system is strong, then even if the body is exposed to viruses, one will not be affected. During a pandemic or an epidemic, Ayurveda emphasizes on the immunity of people living in regions affected by viruses. This branch of medicine promotes the intake of special herbs or decoctions to increase the immunity level of the people. Ayurvedic remedies comprise pure natural herbs which are effective in preventing swine flu. Moreover, the herbs are used to relieve swine flu symptoms, and boost the immune system against the H1N1 virus.

Basil: *Ocimum sanctum* and *Ocimum basilicum* also known as Tulsi (Hindi) and Holy Basil (English), is an aromatic plant of the family Lamiaceae. The plant, as a whole, is a treasure house of potent compounds with its leaves, seeds, and roots, as well as flower being medicinally important and is considered divine by the Hindus. Ayurvedic practitioners claim that basil not only keeps the nasty swine flu virus at bay, but it also assists in the fast recovery of an affected person. They claim that basil improves the body's overall defense mechanism, thereby increasing its ability to fight viral diseases. *Ocimum* extracts are used in ayurvedic remedies for common colds, headaches, stomach disorders, inflammation, heart disease, various forms of poisoning, and malaria. For the control and prevention of swine flu, basil must be consumed in the fresh form. The paste or juice of a minimum of 25 leaves (medium size) should be consumed twice a day. Moreover, it should be had on an empty stomach. O. sanctum is considered to be an adaptogen par excellence.[13,14] It harmonizes different processes in the body and is helpful in acclimatizing to stress. The main chemical constituents of O. sanctum are oleanolic acid, ursolic acid, rosmarinic acid, eugenol, carvacrol, linalool, and β-caryophyllene.[15]

Ginger: *Zingiber officinale* is a plant which belongs to the family Zingiberaceae. *Zingiber officinalis* is one of the natural remedies for swine flu prevention. It boosts the body's immunity level and helps protect the body. The characteristic odor and flavor of ginger root is caused by a mixture of zingerone, shogaols, and gingerols, volatile oils that comprise of about one to three percent of the weight of fresh ginger.

Garlic: *Alium sativum*, also known as Lahsan (Hindi) and Garlic (English), belongs to family Alliaceae. *A. sativum* has been used throughout recorded chronicles for both culinary and medicinal purposes. It has a characteristic pungent, spicy flavor. Allium sativum on the other hand is a powerful natural antibiotic. Garlic has natural antiviral, antibacterial, and immuneboosting properties. It is known to kill influenza virus *in-vitro*.[16] An extract of A. sativum called ajoene, which appears to protect CD+ cells from attack by HIV early in the viral life cycle. At low concentrations, the drug appears to have little toxicity, and its anti-HIV activity is 45 times more powerful than the drug dextran sulfate. Ajoene is found only in fresh A. sativum and is not readily procurable. Recent investigations reveal that A. sativum impairs the activity of the liver enzymes that process protease inhibitors and raises the protease inhibitor levels. The *in-vitro* antiviral activity of A. sativum extract (GE) on human cytomegalovirus (HCMV) was also evaluated in tissue cultures, plaque reduction, and early antigen assay.

Gooseberry: *Phyllanth usemblica*. The Indian gooseberry (*Phyllanth usemblica*, syn. Emblicaofficinalis) is a deciduous tree of the Euphorbiaceae family. It is also known as Amlaka (Sanskrit) and Amla (Hindi). In traditional Indian medicine, dried and fresh fruits of the plant are used. All parts of the plant, including the fruit, seed, leaves, root, bark, and flowers, are used in various Ayurvedic/Unani Medicine herbal preparations. As gooseberry is rich in Vitamin C, it helps raise the body's resistance to flu viruses. If fresh gooseberry is not available in the market, then the form of jam or juice is also great. Methanolic extract of the fruit of Emblica officinalis has potent inhibitory action against human immunodeficiency virus-1 reverse transcriptase. Emblicaofficinalis aqueous extracts are used in Cuban traditional medicine for their antiviral activity against Hepatitis B virus and A&B influenza virus. The cytotoxicity of the extract was tested by means of colony-forming ability and growth-inhibition assays, as well as by measuring the mitotic index. Apoptosis induction and cell-cycle kinetics were analyzed by cyto fluorimetric methods.[17]

Aloevera: Aloe Vera is an easily available plant and is also beneficial to boost immunity. One should consume a

teaspoon of gel with water on a daily basis for the treatment of many diseases.

Camphor and Eucalyptus Oil: Camphor has a great ability to keep different air borne diseases under control. It is available in the form of camphor oil, which can be burnt in the room or office all the time. Inhaling the steam of Eucalyptus oil is also good. This helps to clear the nasal track and promotes the health of the respiratory tract.

Giloy: *Tinospora cordifolia*, also called Guduchi, is an herbaceous vine of the family Menispermaceae indigenous to the tropical areas of India, Myanmar, and Sri Lanka. An herbal preparation prepared by taking one foot Long Branch of Giloy herb (Amta) and seven leaves of Tulsi. Mix them and extract juice of this mixture in a vessel. Boil this juice and drink it. This herbal juice will increase body resistant up to three times and prevent infection of swine flu It has Anti-periodic, Anti-pyretic, Alterative, Diuretic, Anti-inflammatory properties. It is a constituent of several compound preparations. The plant has immense potential for use against novel H1N1 flu since it is a potent immune stimulant. It is used in fever, urinary disorders, dyspepsia, general debility and urinary diseases. It is also used in treatment of rheumatism and jaundice. Therefore it is very often included in comprehensive Ayurvedic formulas, since such toxins interfere with all bodily functions and are a factor in almost all diseases. It clears out brain toxins that hinder mental activity.

Liquorice: *Glycyrrhiza glabra* also known as Yashtimadhu (Sanskrit), Mulathee (Hindi), and Licorice (English), Glycyrrhizaglabra (Papilionaceae) derives its flavor principally from a sweet-tasting compound called anethole ("trans"-1- methoxy-4-(prop-1-enyl) benzene). Additional sweetness in licorice comes from glycyrrhizic acid, an antiviral compound significantly sweeter than sugar.[18] Powdered licorice root is an effective expectorant, and has been used for this purpose since ancient times, especially in Ayurvedic medicine. The roots of the plant have been used for throat and upper respiratory tract-related infections and contain many phenolic compounds such as flavonoids and their glycosides, coumarin, and cinnamic acid derivatives. One study found that licorice root (through glycyrrhizin) protects cells from infection with Influenza A virus and in already infected cells, caused a drastic reduction in the number infected cells.[19] Liquorice root has also been shown to help with sore throats.

Andrographis: *Andrographis paniculata* (Kalmegha in Hindi) is an herbaceous plant in the family Acanthaceae, native to India and Sri Lanka. It is sometimes called "Indian Echinacea" because it is believed to provide much the same benefits as Echinacea. Andrographolide, the major constituent of the extract is implicated towards its pharmacological activity. Studies have been conducted on the cellular processes and targets modulated by andrographolide treatment of immune cells. Andrographis has anti-inflammatory, antipyretic, anti-viral, and immune-stimulatory properties and studies have found that taking andrographis supplements upon feeling symptomatic relieves symptoms, leads to quicker recovery, and prevents post influenza complications.[20]

Ashwagandha: *Withania somnifera*, Ashwagandha is a tonic herb, similar to ginseng, which is belongs to family Solanaceae which is recommended to increase energy and endurance, strengthen immune function, and help the body overcome imbalance caused by mental or physical stress, poor diet, lack of sleep, or environmental toxins.[21] It has Stimulant for the immune system, also a very potent adaptogen. It's principally compounds include like anaferine, anahygrine, beta-sisterol, chlorogenic acid, cysteine, cuscohygrine, pseudotropine, scopoletin, somniferinine, withaferin α, withanine, withananine, and withanolides. Researchers who studied Ashwagandha along with other Ayurvedic plants found that it stimulated the immune system and had no toxic effects. Ashwagandha is available in powdered form, capsules, and as a liquid extract. A traditional dose is 1-2 g of the dried, powdered root, taken one to three times daily, or a standardized extract dose is 100-200 mg twice per day.

Turmeric: *Curcuma longa* is also known as turmeric. This compound is highly used in Ayurvedic and Chinese medicine to address many health concerns. It helps to stabilize the body and is a strong antioxidant with anti-inflammatory properties as well. It has also been found to guard against free radical damage, protects the liver from toxic compounds, prevents blood platelet aggregation, stimulates the gallbladder, detoxifies the body and boosts the immune system. Curcumin in Turmeric is responsible for these effects.[22]

Isatis: Both the leaf and the root of this Chinese plant have been used to treat various infections, including influenza and upper respiratory infections. Studies have shown the root extract to be antibacterial, antiviral and anti- parasitic against many different types of viruses and bacteria. This is likely because Isatis increases white blood cell and lymphocyte counts in the blood. It is also has cooling effects which is used to reduce fevers.

Neem: *Azadirachta indica* (Neem in Hindi) is a tree in the mahogany family Meliaceae. Three bitter compounds that have been extracted from neem oil are nimbin, nimbinin, and nimbidin, respectively.[23] The seeds contain a complex secondary metabolite azadirachtin. All parts of the plant yield β sitosterol. The antiviral activity of azadirachtin, nimbin, and nimbidin has been reported. *Azadirachta indica* extracts possess anti-diabetic, anti-bacterial, and anti-viral properties. *In vitro* antiviral activity of aqueous neem leaves extract, assessed in cloned cells of larvae of Aedesalbopictus cells employing virus inhibition assay, showed inhibition in a dose dependent manner.[24] The effect of A. indica leaf

extract and pure compound (Azadirachtin) on the replication of Dengue virus type-2 has also been reported. Thus, neem can serve as a source of promising future antiviral drugs.[25]

Bael: *Aeglemarmelos* also called Bael (Hindi) belongs to family Rutaceae. It contains primarily alkaloids, coumarins, and steroids. The leaves contain skimianinc, sterol, and aegelin. The active constituent of the fruit is marmorosin, which is identical to imperatorin. Coumarins contained in the fruits are also imperetorin and β sitosterol. Roots of the tree have been found to contain psoralin, xanthotoxin, scopoletin, and tebamide. A. marmelos from India is reported to possess imperetorin[26], which has certain interesting biological properties such as analgesic, anti-inflammatory, anti-bacterial, and anti-viral properties.

Ajwain: *Trachy spermumammi* called as Ajwain in Hindi and Bishops weed in English is a member of the family Apiaceae. The principal constituents of the essential oil from the fruit are the phenols, mainly thymol and some carvacrol. The oil possesses p -cymene, g-terpinene, α- and β-pinenes, and dipentene, minute amounts of camphene, myrcene, and careen.[27] It is used internally in the treatment of colds, coughs, influenza, and asthma. The essential oil is also added to various cough medicines as well.[28]

Mentha: *Mentha piperita*, family Labiatae, is an herbaceous rhizomatous perennial plant widely used in Ayurveda.[29] It contains about 1.2%–1.5% essential oil. The volatile oil, also known as menthaepiperitaeaetheroleum, contains 30–70% free menthol, menthol esters and more than 40 other compounds. The principal components of the oil are menthol (29%), menthone (20%– 30%), and menthyl acetate (3%–10%). Mentha piperita has significant antiviral activity.[30]

Harde: *Terminalia chebula*, is a deciduous tree of family Combretaceae native to Southern Asia from India and Nepal east to Southwestern China (Yunnan), and south to Sri Lanka, Malaysia, and Vietnam. It is regarded as a universal panacea. The dry nuts peel from this plant is used to cure cold-related nagging coughs. The bark/peel of the nut is placed in the cheek and this generates a huge amount of saliva as the material does not dissolve. The resulting saliva, bitter in taste, is believed to have medicinal qualities to cure cold related coughs. Its fruits possess digestive, anti-inflammatory, anthelmentic, cardiotonic, aphrodisiac, and restorative properties and are additionally beneficial in cough and colds.

Green Tea: *Camellia sinensi* is a type of tea made solely from the leaves of Camellia sinensis that has undergone minimal oxidation during processing. Green tea is particularly rich in polyphenolic compounds and catechins. Catechin derivatives have shown pronounced antiviral activity, observed for derivatives carrying moderate chain length (7–9 carbons). The derivatives exerted inhibitory effects for all six influenza subtypes tested including three major types of currently circulating human influenza viruses (A/H1N1, A/H3N2, and B type), H2N2 and H9N2 avian influenza virus. The compounds strongly inhibited adsorption of the viruses on red blood cell (RBC).[31] The disease preventive properties of green tea are mainly due to the presence of polyphenols like epigallocatechin- 3-gallate (EGCG), epicatechin, epicatechin-3-gallate, and epigallocatechin (EGC).

Ginseng: *Panax quinquefolius* commonly known as American Ginseng is an herbaceous perennial in the ivy family that is commonly used in medicine. American ginseng contains dammarane-type ginsenosides as the major biologically active constituents. Studies have been done on Panax to reveal that they effectively provide immunity to individuals against influenza.[32] These medicinal herbs mainly act via two basic approaches against H1N1 infection, namely enhancement of overall immunity of the individual or by acting against the virus by preventing viral replication or by inhibiting viral signal transduction.

Purple Coneflower: *Echinacea purpurea* belongs to family Asteraceae. Pleschka S et al., used a standardized alcohol extract of fresh Echinacea purpurea herb (95%) and root (5%) was *used in-vitro* infection model Five influenza A strains were investigated: H3N2 (e.g. Hong Kong flu—or seasonal influenza), H5N1 (e.g. bird flu—human pathogen), H7N7 (e.g. avian influenza, also human pathogen), H1N1 (human influenza) and H1N1 (e.g. Mexico influenza— swine flu, current pandemic). Almost 100% of the viruses were resistant to the conventional antiviral drugs like Tamiflu after the third treatment cycle. Even these resistant influenza strains were inhibited over 99.9% by the Echinacea fresh-plant extract.[33] Sharma M *et al*., showed that *Echinacea purpurea* fresh alcohol plant extract can block the replication of relevant respiratory tract pathogens *in-vitro*.[34]

Brazilian Propolis: Brazilian Green propolis is derived mainly from vegetative apices of *Baccharis dracunculifolia* (alecrim plants).[35] Suggestions have been made that probable sources of Brazilian propolis that have been suggested are Araucaria heterophylla, Clusia major, Clusia minor and species of Baccharis, Araucaria angustifolia, Baccharisdracunculifolia and Eucalyptus citriodora.[36,37] Shimizu T *et al*., found the ethanolic extract of Brazilian propolis at a dose of 10mg/kg, p.o significantly reduced virus yields in the broncho alveolar lavage fluids of lungs in infected mice in compared to oseltamivir at 1 mg/kg twice daily from day 1 to day 4 after infected with influenza virus. The extract was given for seven successive days after infection.[38]

Litchi Chinensis: It is also called as Lychee fruit belongs to the family Sapindaceae. Leila Gangehei *et al*., found that Oligonol, a low molecular weight polyphenol of obtained from lychee fruit extract inhibits proliferation of influenza virus by blocking reactive oxygen species-dependent ERK.

Japanese Wasabi: It is also called as *Wasabia Japonica* belongs to the family Brassicaceae. Kyo M *et al*., studied the ethanolic extract of summer harvested leaves of Japanese wasabi for anti-influenza activity where winter harvested leaves were used for foods and spice. They investigated 70% ethanolic extract of leaves harvested in July have activity (98% or higher replication inhibition) against H1N1 influenza along with simple influenza viruses. Therefore, such extracts are expected to be a promising source of a novel anti-influenza virus agent.[39]

Pharmacological treatment

The Government also stored medicines in the designated hospitals for treating the patients. It is strongly advisable not to take any medicines on the patient's own will, as it will lowers the immunity and the disease becomes worse.

Neuraminidase inhibitor antiviral medications

These medications target the early phase of the infection. However, this strain is resistant to the adamantanes class of drugs, such asamantadine and rimantadine.[40]

Oseltamivir (Tamiflu): It is a prodrug that is hydrolysed by the liver to its active metabolite, oseltamivir carboxylate, with an elimination half-life of about 6–10 h. The mechanism of action is by a neuraminidase inhibitor, serving as a competitive inhibitor of sialic acid, found onthe surface proteins of normal host cells. By blocking the activity of the neuraminidase, oseltamivir prevents new viral particles from being released by infected cells.[41] Adverse effects occur more commonly in children and adolescents which are nausea (severity is less, ifoseltamivir taken with food), vomiting, transient neuropsychiatric events (self-injury or delirium).[42]

Dose: Tamiflu (75-mg capsule) should be taken twice a day for 5 days.

Zanamivir (Relenza): The bioavailability of the drug is 10–20% by inhalation, compared with 2% by oral administration. The elimination half-life in serum of zanamivir is about 2–5 h. The mechanism of action is similar to oseltamivir. The later may be preferred over zanamivir for young children because zanamivir therapy requires the patient to voluntarily inhale through the device, so it is quite difficult for the children to administer this drug by this route. The main adverse effect includes Cough, diarrhoea, dizziness, headache, nausea, sinus inflammation, sore throat, stuffy nose and vomiting.

Dose: Two inhalations (5mg each) of Relenza should be administered twice in a day (i.e. 20 mg/day) for 5 days.

Precaution: It is not recommended for treatment for patients with chronic airway disease or asthma as it can induce bronchospasm.[43] In the U.S., on April 27, 2009, the FDA issued Emergency Use Authorizations to make available Relenza and Tamiflu antiviral drugs to treat the swine influenza virus in cases for which they are currently unapproved.[44]

Peramivir: A third neuraminidase inhibitor peramivir formulated for intravenous (IV) administration is an investigational product currently being evaluated in clinical trials. As of October, 2009, safety and/or efficacy data from 1,891 patients with acute uncomplicated seasonal influenza A has been submitted to the FDA. Efficacy and safety have not been evaluated in hospitalized patients. Even though the data are insufficient to allow FDA approval, the FDA issued an EUA for treatment with peramivir of hospitalized patients with 2009 H1N1 influenza who have potentially life-threatening suspected or laboratory confirmed infection. Peramivir IV is available through the CDC upon request of a licensed physician. Under the EUA, treatment of adult patients with IV peramivir is approved only if: (1) the patient has not responded to either oral or inhaled antiviral therapy; (2) drug delivery by a route other than IV is not expected to be dependable or is not feasible; or (3) the clinician judges IV therapy is appropriate due to other circumstances. Treatment of pediatric patients is approved if either of the first two criteria applies.

Advanced Treatment Approaches

Vaccines are also used in the treatment and prevention of swine flu. There are various types of vaccines, which are used to provide immunization. Live attenuated vaccines contain live microbe which has been weakened hence they are not capable to cause the disease. They provide lifelong immunity since they have a very strong cellular and antibody response.[45] Hence it requires 1 or 2 doses to develop immunity. The microbe used has a tendency to mutate, which might lead to microbe virulent hence it's a severe drawback to use live attenuated vaccines. This type of vaccines cannot be given to people with a weak immune system. The other limitation of this type of vaccine is that it needs to be continuously refrigerated while shipping and storage for a long time which is difficult.

Inactivated vaccines contain dead microbes in vaccines. The microbes are killed by exposing them to chemicals, radiation or heat. This type of vaccine is a safer approach to use because the microbes cannot mutate as they are dead. Hence there are no chances to regain its virulence. Most of the inactivated vaccines do not require refrigeration since they are kept and delivered in the lyophilized [desiccated] form.[46] This vaccine type has a weaker response to immunity because of the large number of doses are required to develop a stronger immune response. It may not always be feasible to visit the place to take regular doses of vaccine. The efficacy

of inactivated influenza vaccine depends on the age, similarity between the viruses in circulation and the viruses in vaccines and the immune-competence of the vaccine recipient.[47] Subunit vaccines include only the antigen, which is responsible to provide the best immune response. Since this type of vaccine has only the antigen and not the molecules, the possibilities of antagonistic reactions are happened least. A subunit vaccine can receive 1 to 20 or more antigens. The process to identify and isolate specific antigen that provide the immune response is a very time consuming phenomenon. Recombinants DNA technology may be used to manufacture the antigen to such vaccines are termed as recombinant subunit vaccines.

Toxoid vaccine is of significance when the toxins are being generated by the causative agent. The toxins can be deactivated, but treating it with formalin such deactivated toxins are termed as taxis. The body learns how to defend natural toxins by locking on the toxin and blocking its action. Conjugate vaccine is used when the disease causing agent has an outer coating of polysaccharides since it can easily mask its antigens. The toxoids or antigens are linked in such a way that the body's immune system can recognize its antigen.[48] The vaccine protecting against influenza type B is of this type. DNA vaccines may be used when the complete genetic composition of the virulence imparting organism is known. It helps induce a strong immune response. It is easy to prepare, less expensive not causing the disease.[49]

Naked DNA vaccines are used to provide immunity against influenza virus. Such vaccines contain DNA as their constituent and are administered using a needle and syringe or high pressure gas which helps the particles to enter the targeted cells easily. Sometimes DNA of the antigen is coupled with other components that help to enhance its permeability and immunizing ability. Recombinant vector vaccines are correlative to the DNA vaccines, but they utilize attenuated virus to access the DNA into the body. Vector is the bacteria or virus which is being used as a carrier. They closely resemble to a natural infection, hence produce a very strong immune response. For HIV infection the recombinant vector technique using bacteria as well as the virus has been studied since the structure of swine flu virus is similar to HIV. This approach may work in providing immunization against swine flu.

Some of the marketed vaccines available for swine flu are included in the **Table 1.**[50, 51]

S.no.	Brand name	Manufacturer	Forms available
1	Agripal	Chiron Panacea [Panacea Biotech Ltd]	Injection
2	Fiurax	Glaxo Smithkline Pharmaceuticals Ltd	Injection
3	Influgen	Lupin Laboratories Ltd	Injection
4	Influvac	Solvay Pharma India Pvt Ltd	Injection
5	Nasovac	Serum Institute of India Ltd	Injection
6	Vaxigrip	Sanofi Pasteur	Injection

Novel Drug Delivery Treatment Approaches to Vaccines

Colloidal drug delivery systems for vaccines is of immense importance since using a conventional vaccine delivery system has severe drawbacks which include problems associated with toxicity, hypersensitivity reactions, etc. Colloidal drug delivery systems are considered to be more safe and effective. It can be used to provide immunization by oral and transmucosal routes. This type of drug delivery system has better immune recognition. It uses particles in the range of 1 to 1000 micrometers.[52] Liposomes are particles made up of phospholipids and cholesterol. This imparts vesicle integrity and helps to achieve a closely packed structure. These liposomes are highly biocompatible and biodegradable and hence have better acceptance when used in the form of vaccines. They provide a better mucosal, systemic and transcutaneous immunization. In case of trivalent vaccines for H1N1 and H2N2 virus the liposomes are used to enhance the immune recognition.

Niosomes have two layers which are made up of non-ionic surfactants and cholesterol thereby making them more stable and preventing auto-oxidation. They are used to deliver antigens against common virulence causing organisms.[53] However, its response against swine flu virus is under research.

Archaeosomes are self-assembled units prepared by using polar phospholipids which are derived from an archebacteriae known as Sulfolobus acidocaldariu. These are prepared by aggregation of the archebacteriae below its critical micelle concentration.[54] This kind of approach is of great significance while choosing oral route for vaccine administration. It helps in enhancing the mucosal immunization. They are stable at high temperatures, alkaline pH and have better immune adjuvant properties.

Spherulites are vesicles made up of amphiphilic lipids, which are biocompatible and do not show the presence of any aqueous core. They have unique structural configuration which makes them more stable as well as increasing its microencapsulation efficiency.[55] This helps to protect the antigen in the virus from the external environment. Spherulites are commonly used when the parenteral route of vaccine administration is preferred as systemic immunization is enhanced.

Transfersomes are also known as elastic liposomes.[56] They contain phospholipid, cholesterol and an edge activator which is commonly ethanol. The edge activator provides flexibility which allows them to change their shapes and thus provides better penetration. They are used in oral as well as the transdermal route to induce immunity.[57] This approach is used for delivery of vaccines in HIV. Since the virus structure of H1N1 is similar to HIV this approach is being studied to develop a more effective vaccine for swine flu.

Microspheres are spherical in shape and are made up of synthetic and natural biopolymers. They help to impart immunity against infectious diseases when the choice of route is oral administration. The natural polymers like gelatin, pectin, chitosan etc. are used in microspheres. Polylactic acid [PLA], Poly caprolactone is synthetic polymers which are generally used in the preparation of microspheres.[58] It had been discovered that environmentally safe microspheres enclosed with vaccine antigen help to provide long lasting immunity. Since swine flu is a highly progressive disease, hence imparting long-lasting immunity could help hence microsphere approach for its vaccine is being studied.[59] Here the particle size of microspheres decides the immune response; larger particles will not be able to enter the tissues targeted and the optimum particle size required for microspheres is below 125 mm. Biodegradable microspheres are commonly used for mucosal immunization. Microspheres comprising of synthetic polymers like polylactic acid are used when the vaccine delivery is from oral or systemic routes.[60] Microspheres prepared from chitosan are commonly used in vaccines for influenza and are also proved to be successful in nasal route for vaccine delivery in case of influenza where FluMist® is the first nasal vaccine, which had been developed by a company known as Medimmune Inc.

Virus like particles and virosomes consists of viral envelope which is self-assembled and does not have any genetic material and non-infective particles.[61] These types of particles have better permeability through the cellular membranes. They are easy to prepare and have a higher antigen loading capacity. Virosomal vaccines are preferred for influenza. Inflexal® V is the vaccine developed by Berna Biologics [Bern, Switzerland] with virosomes to treat flu symptoms and seasonal flu. Invivac® for nasal flu was developed by Solvay Pharma Registered in the Netherlands, Switzerland uses virosomal approach to treat flu. NasalFlu® for the curing nasal flu was made using virosomes by Berna Biologics Marketed in Switzerland. Virosomes have excellent adjuvant properties which make them evoke better immune recognition.

Protozoans are similar to transmembrane proteins and are hydrophobic in nature. They act as carriers for delivering antigens, polypeptides and lipopolysaccharides. They are commonly used when the nasal route of administration of vaccine is used. They are site-specific hence have a wider range of targets. They adhere to the surface of T-cells and initiate the immune response. They can be used for oral, topical as well as parenteral route of vaccine delivery. Nasal vaccines are highly effective in case of influenza viruses.[62] Hence proteosomal approach can be used to target swine flu virus.

Immuno-potentiating Reconstituted Influenza Virosomal Carriers [IRIVS] are comprised of spherical hexagonal single laminar vesicles. They are safer, non-toxic and free from any adverse reactions. They contain phospholipids along with phosphatidylcholine [PC] and phosphatidylethanolamine [PE] which are the components which help to attain immunity.[63] They are used in the oral mucosal immunization process for influenza HIV. Thereby can be used to target swine flu virus and acquire immunity against it. The vaccine H5N1 virus is prepared with this technique and is administered through the sub-lingual route.

Antigen cochleates contain calcium ions which aid in delivering the antigen. They can be obtained by infusion of calcium ions with the phospholipids and cholesterol. Calcium gives the particles a jelly roll like structure. They have the best compatibility, stability, target species and hence are most preferred. They are used for subunit and multiple unit vaccines, which are administered via oral mucosal, nasal or parenteral route.[64] Cochleates have been used in preparation of vaccines for HIV, which help to boost the mucosal immunity. Hence cochleates are being researched for its ability to impart immunity against swine flu. The other lipid based carriers available currently involve triglyceride emulsions, micellar systems, solid-lipid nanoparticles [SLNs] and self-emulsifying drug delivery systems [SEDDS]. These lipids based carriers with the use of gut associated lymphoid tissues can easily enter the lymphoid tissue and induce oral immunization.[65] This type of approach has already been studied for HIV but for swine flu virus this kind of approach is still under development.

Dendrimers are highly branched molecules comprising of various small units known as monomers which are bonded covalently with each other. Each monomer unit is termed as Dendron. The inner part of the dendrimer is hydrophilic, which assists in the encapsulation of vaccine antigens. The external branches are hydrophobic, which eases the penetration in the immune recognition cells. Poly [amidoamine] [PAMAM] dendrimers and Poly [propyleneimine i.e. PPI] are explored for such approach. Since penetration is enhanced using this approach it is being studied for its immunizing activity in case of swine flu.[66]

Carbon nanotubes are the allotropes of carbon. These are used for vaccine delivery since it has a very hollow internal structure and greater surface area. They can easily permeate through the membranes and are non-

toxic. The surface of the carbon nanotubes is easy for adsorption of antigens. These antigens bind the surface of carbon nanotubes via hydrophobic interactions and Vander Waals forces.[67,68] These are highly stable molecules they resist degradation and provide controlled release of antigen at specific target sites. This kind of approach might prove to be important in developing swine flu vaccine.

Current Research Guidelines as per WHO

The most important recommendations regarding the further research were suggested by WHO in the following areas:

• Increased learning to check the capacity of the anti-virals and supporting medications which are existing as well as which are under investigation, which also include regional products used for severe complicated influenza illness.

• Usage of post-septic sera/plasma or monoclonal antibodies in problematic illness is because of influenza virus infection by increasing the analysis to assess its efficacy.

• To conduct comparative studies of clinical trials of neuraminidase inhibitors, which are utilized for the medication of influenza for all the population's. Special attention has to be provided to the parenteral neuraminidase inhibitors, which are mostly for critically ill patients, and also enhancing the safety and comparative efficacy.

• The clinical and laboratory virological limitations which are used to evaluate the consequences of such assessments conducted should be standardized.

• Special care to denote dosage, safety and competence of all the anti-virals used for the treatment for children under one year and particularly for neonates diagnosed with influenza infection.

• Build-up of administering oseltamivir and zanamivir by different routes, especially for neonates diagnosed with virus infection and for severely ill patients should be encouraged.

• Studies of different combinations that can be used for treatment, longer durations of the dose action in the system, loading of the doses, and higher doses.

• Improved pharmacodynamic and pharmacokinetic studies regarding the correlation between the doses and the routes of administration, and the viral amount in the lower respiratory tract with the influenza infection.

• Accurate knowledge regarding the medication of influenza mainly in gestating females, patients dealing with obesity, the immunosuppressed [in addition to the HIV] infected individuals as well as people in higher risk groups.

• Better definitions to be developed for patients who are at a greater risk for chronic or severe influenza sickness such as HIV infected groups [adults as well as children], pregnant women and obese individuals.

• Progressive studies on the different methods of action and a clinical condition which improves the protection from the antiviral medications is likely to develop.

• Evolution and improvement of a durable surveillance system to monitor the influenza antiviral resistance.

DISCUSSION

There are many anti-viral herbal drugs mentioned in different websites, articles and news forum that they can prevent swine flu. Most of literature also has given much emphasis on mainly anti-viral herbs and immunity booster herbs. The pharmacologically active anti-viral drugs like Oseltamivir (Tamiflu), Zanamivir (Relenza) were also available in the market which was also administered in emergency cases. The scope of herbal treatments over the allopathic drugs in treating swine flu is becoming more popular because of the less adverse effects**.** Among them Tulsi (Ocimum sanctum)[69], Neem (Azadirachtaindica)[70], citrus fruits[71] and common ayurvedic plants. Researchers should have a closer look to various chemical composition and pharmacological profile of these herbal drugs to obtain definite anti-swine flu herbal drugs. It can be possible to make an effective herbal formulation of various drugs by elaborate phytochemical studies of these drugs. By this way it can have cost effective, lesser side effect and potent herbal choice for endemic swine flu.

CONCLUSION

The treatments available which are either the herbal, pharmacological or the vaccination remedies suggested for the current swine flu pandemic, any new scope in controlling the disease helps the society. The fact that an established medicinal plant with a known, multiple spectrum of effect is also discovered to have a direct anti-viral effect against swine flu and other influenza viruses is surprising. Even though, there are few anti-viral drugs available in the market for treating this wide spread infectious disease due to their immense side effects, scientists are now, turn their attention towards herbal therapy for a safer option.

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