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The Influenza a Virus Subtypes H1N1, H1N2 and H3N2, Hdfx: a Novel Immunomodulatorand Potential Fighter against Cytokine Storms in Viral Flu Infections-*Carica Papaya* Linn

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Introduction

The influenza A virus subtypes H1N1, H1N2 and H3N2 are prevalent in pig populations worldwide. All scientific data point towards swine as the key host species for new human influenza pandemics, which have been suggested to evolve in pigs from viral genes of avian, human and porcine origin. Therefore, it is of major importance to record the evolution of swine influenza viruses in pigs, and in particular monitor hallmarks of adaptation to humans. The scope of this thesis was to increase the understanding of the genetics of swine influenza virus (SIV), and to investigate the importance of different viral gene markers in association with differences in pathogenicity of two viruses of H1N2 subtype in pigs. The results from this study demonstrate, for the first time, natural reassortment in H1N2 viruses in the pig populations of Sweden. These H1N2 viruses have an avian-like SIV H1N1 hemagglutinin (HA) and a European H3N2 SIV-like neuraminidase (NA). Nucleotide sequence comparison revealed significant differences between the two consecutive H1N2 isolates. To be able to understand the genotypic differences observed in the genomes of these H1N2s, and to identify the genetic markers responsible for the differences, a reverse genetic system was developed. Four recombinant SIV H1N2 viruses were constructed that displayed differences in virulence in mice, r1021 (more virulent) and r9706 (less virulent), as well as the same viruses with swapped PB1 segments. Interestingly, the current findings showed that the replacement of the PB1segment of r9706 by that of r1021 increases the virulence of the virus that replicate with higher titer in mice lungs, while the opposite is true when PB1 r9706 is introduced into r1021. This study demonstrates that differences in virulence of swine influenza virus subtype H1N2 are attributed at least in part to the PB1 segment. The findings presented in this thesis support the observations concerning the continuous reassortment processes of SIVs in pigs, resulting in repeated and independent emergence of certain HA/NA combinations. This may lead to emergence of new viral variants of severe pathogenicity of pigs. Continuous and efficient surveillance and further detailed genetic and phenotypic analysis can help to identify such novel viral variants, having more potential to cross species barriers and to pose health risks even to humans and to other host species

A disturbing trend in antimicrobial-antiviral resistance is the advent of “superbugs” which often complicates the treatment of flu-immunocompromised patients. To this must be added the numerous hospitalizations and increased morbidity from contaminated meats, vegetables, seafood’s, and dairy products.

Many of the emerging types of avian flus [e.g. H1N1, H2N2, H3N2, A (H10N8)] have a very serious haemorrhagic component to them which complicates effective treatment. Any new, effective treatment against severe flu infections should be able to prevent these types of haemorrhages, particularly in the lungs.

Government resources are being overstretched and often remain powerless to combat flu plaque-like assaults.

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Papaya (Carica papaya Linn) is commonly called as paw-paw and it belongs to the family Caricaceae. Papaya is commonly known for its food and nutritional values throughout the world. The properties of papaya fruit and other parts of the plant are also well known in traditional system of medicine. During the last few decades considerable progress has been achieved regarding the biological activity and medicinal application of papaya and now it is considered as valuable nutraceutical fruit plant. Papaya possess excellent medicinal properties for treatment of different ailments. The different parts of the Carica papaya plant including leaves, seeds, latex and fruit exhibited to have medicinal value. The stem, leaf and fruit of papaya contain plenty of latex. The latex from unripe papaya fruit contain enzymes papain and chymopapain. This review focuses on different properties of papaya as a multi-faceted plant..

• Dengue, a viral disease transmitted by the bite of the Aedes mosquito, has reached alarming proportions in the past few years. Today endemic in over 125 countries, it infects nearly 50-270 million people every year, resulting in a sizable number of deaths. [1] In fact, dengue appears to be overtaking malaria in terms of morbidity and economic impact of the disease.[2]

• Unfortunately, due to lack of adequate surveillance systems in the underdeveloped and developing countries, the exact extent of the problem is not known.[1] Travellers from non-endemic areas to the dengue-affected areas are also exposed to the possibility of infection.[3] This makes it an international public health concern, affecting individuals from countries even where the disease is not prevalent.

A herbal medicine being investigated to control the mammoth problem of dengue is the extract of the leaves of the papaya plant, Carica papaya. There have been conflicting reports on the effectiveness of this extract in the treatment of dengue. In this article, we present a brief overview of dengue and a review of available literature regarding the use of the papaya leaf extract for the treatment of this condition.

Materials and Methods

The literature search was carried out independently by the two authors using PubMed, Google and the library database. The keywords used for the search included dengue treatment, dengue herbal treatment, dengue papaya leaf extract, dengue C. papaya. A search in PubMed was conducted for relevant articles over the last 10 years, from 2002 to 2013. A Google search was done using the same keywords to identify articles that were not indexed in PubMed. In addition, the authors also did a detailed search in the library database for relevant articles in journals not indexed in PubMed. A total of 7 studies were selected for this review, which included one animal study, one case

Authors	Subjects/animals	Article type	Article title	Key message
Patil, Shetty, Bhide, Narayanan	*n*=24 (4 groups with 6 animals in each)	Placebo controlled	Evaluation of platelet augmentation activity of Carica papaya leaf aqueous extract in rats	Increased platelet counts and reduced clotting time by Carica papaya leaf aqueous extract in cyclophosphamide-induced thrombocytopenic rat model
Hettige	*n*=12	Case series	Salutary effects of Carica papaya leaf extract in dengue fever patients-a pilot study	Papaya leaf juice elevated total white cells and platelets in dengue patients
Ahmad, Fazal, Ayaz, Abbasi, Mohammad, Fazal	*n*=1	Case report	Dengue fever treatment with Carica papaya leaves extracts	Carica papaya leaves extracts increased platelets over 5 days
Yunita, Hanani	*n*=80	Randomized clinical trial (dengue not confirmed)	The effect of Carica papaya L. leaves extract capsule on platelet count and hematocrit level in dengue fever patient	Carica papaya L. leaves extract increased platelets and hastened recovery
Kumar	*n*=2	Case series (rapid response)	Dengue: An escalating problem	Increase in platelets within 12 h and 2 days respectively
Kala	*n*=5	Case series	Leaf juice of Carica papaya L.: A remedy of dengue fever	Increase in platelets by 24 h
Subenthiran, Choon, Cheong, Thayan, Teck, Muniandy *et al.*	*n*=228	Open labeled randomized control trial	Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue hemorrhagic fever	Increase in platelets after 40 h of the first dose

report, three case series and two randomized controlled trials. The studies were published in the years 2008 or later. A brief summary of the included in vivo studies is listed in Table-1

Discovery and Unique Characteristics of HDFx

Approximately 85 years ago, the first flu vaccine was made by Jonas Salk and Thomas Francis after it was discovered that viruses (influenza virus types A, B, and C rarely) cause flu [see 1, for review]. It was first utilized to protect the U.S. military forces against the flu in World War II [1]. The most dangerous (virulent) influenza , the 1918 H1N1 Spanish flu, pandemic infected about 5% of the world's population and killed approximately 2% of the world's population. In an attempt to prevent a pandemic, and an increased risk of Guillain-Barre syndrome (i.e. Approximately one to nine cases per million doses), 25% of the people, in 1979, in the U.S.A. were given the vaccine [2]. Since that time, influenza vaccines have been vastly improved in design. Highly pathogenic avian influenza viruses of the H5 subtype are a current, serious problem for poultry and human health. Despite the advent of drugs like oseltamivir, and other antiflu therapies, severe influenza still kills tens of thousands in the U.S. A. every year and millions worldwide

Details of the studies included in the review

Numerous pathophysiological responses, in the body, take place after infection by flu viruses [3]. The classical clinical signs are high fevers, coughs, headaches, muscle and joint pain, and severe fatigue. However, when the lungs become severely inflamed, by an overproduction of a host of mediators (primarily by respiratory epithelial cells and alveolar macrophages), i.e., cytokines or chemokines (e.g., interferons, tumour necrosis factor, interleukins, macrophage factors, etc.), this gives rise to what is termed a "cytokine storm" [4]. These "cytokine storms" often proceed, unabated, to cause severe tissue damage and haemorrhages, followed by death which is preceded by multiple organ failure triggered by a spill over of the cytokines and chemokines into the general circulation, particularly in the lungs, kidneys, and cardiovascular system [4-6]. These inflammatory responses are triggered as the infected cells die via apoptosis and necrosis. It must be noted, here, that surgically-operated hospitalized patients are often at great risk for developing influenza infections which result in severe "cytokine storms", particularly among the elderly population. These deadly scenarios have intensified immunological research into devising new therapies that could be utilized to either prevent or stem the course of events leading to massive release of diverse cytokines [7-9]. Pharma laboratories, for more than 30 years, have been working on a new approach to develop host-defense factors that stimulate various arms of the innate and adaptive immune systems. To this end, we have discovered a new host-defence factor we have termed "HDFx", that is a conserved protein found , so far, in rats, mice, guinea-pigs, rabbits, dogs, and subhuman primates [10-14].

HDFx

About 135 years ago, Elie Metchnikoff, the father of immunology, hypothesized that the body, under stressful conditions, would manufacture/release molecules that could stimulate various arms of the immune system and serve to protect the host against major injuries, insults and diseases [15]. Metchnikoff's early studies pointed to the importance of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and viruses. During these past 30- 40 years, a vast body of information and studies , derived from animals and people, have demonstrated a strong relationship between the functional (physiological) state of the microcirculation, macrophages, leukocytes, natural killer (NK) cells,and "pit cells" in the liver to host-defence and resistance to pathogens, trauma, circulatory shock, haemorrhages, infections of diverse types, and sepsis [16-23].

A great many experiments, carried out on thousands of animals, in our laboratories have clearly shown that "HDFx" is protective (to varying degrees) against a variety of systemic bodily insults, ranging from hemorrhage, trauma, combined injuries, endotoxins, a variety of lethal bacteria (e.g., E.coli, S. *enteriditisC.welchii*, among others), fungi (e.g., A. fumagatus, C. albicans), and centripetal forces to septic shock [10-14, 24-28]. A unique attribute of "HDFx" is its ability to protect against "cytokine storms" in animals that are septic or administered several different endotoxins [10, 13, 14, 23, 25, 28, unpublished findings]. "Cytokine storms" are clearly known to be a major cause of lethality in hospitalized patients infected with numerous types of bacteria, viruses, or fungi who become resistant to antibiotic treatment [3, 4, 6]. To our knowledge, no other host-defense factor, except for "HDFx" , can stem the dissemination in the body of cytokines and chemokines in sepsis, at least in experimental animals.

Septic shock, as occurs in severe flu infections, accounts for about 10% of all human deaths in the U.S.A.

each year, and is a major cause of battlefield deaths and farm animal deaths each year.

"HDFx" has the unique ability to induce a "supercharged effect" in macrophages, NK cells, lymphocytes, Kupffer cells, as well as "pit cells" in the liver, at least in all animals we have investigated to date [10,13,14, 23, 25, 28,unpublished data]. But, for this kind of effect to take place, in an expeditious fashion, we believe the microcirculation, in the various critical circulatory regions in the body (i.e., lungs, liver, spleen, heart) must perforce produce optimal blood flows and stem the bleeding that occurs in severe flu infections. Fortunately, we have identified "HDFx" as being a protein molecule that possesses such vasoactive propertiesthat manipulates the microcirculation and curtails bleeding, even in the lungs (e.g., after endotoxin administrations)[10-14, unpublished findings].

Dengue-Brief Overview

Dengue is a viral infection caused by four closely related, but antigenically distinct serotypes of the Flaviviridae family, which are designated as dengue virus (DENV) DENV-1, DENV-2, DENV-3 and DENV-4. Many cases of dengue are asymptomatic, especially in children and in adults with a first infection. In other cases, it may appear as self-limited, undifferentiated fever or classic dengue fever.[3] An incubation period varying from 3 to 14 days is followed by a febrile illness consisting of sudden-onset fever, headache, myalgia, arthralgia and rash. Thrombocytopenia is a common feature of the illness.[4] The patient develops hemorrhagic manifestations such as petechiae and bleeding through the nose, gastrointestinal tract and gums. A number of atypical manifestations have also been reported in the literature, which include encephalitis, encephalopathy, myocarditis, hepatitis and cholecystitis.[5]

Deaths due to dengue are usually a consequence of patients developing complications like dengue hemorrhagic fever and dengue shock syndrome.[6] Dengue hemorrhagic fever, if untreated, has a mortality rate of 10-20%. It occurs due to progression of thrombocytopenia and development of increased vascular permeability and plasma leakage. It progresses to dengue shock syndrome, which is again associated with high mortality.[4]

Treatment for dengue is usually symptomatic. Some cases require platelet transfusions and fluid management.[3] One of the most disturbing aspects of the problem of dengue is that there are no effective antiviral agents available to treat dengue complications. Though symptomatic treatment works in most mild cases, some cases progress to complications very fast and this often make it difficult to save the life of the patient.

Attempts to develop an antiviral agent for dengue have met several hurdles. Dengue is caused by four distinct serotypes which often undergo mutations.[7] Like in other ribonucleic acid (RNA) viruses, these mutations are due to the error-prone nature of RNA polymerase, which results in the formation of quasispecies. It is currently unclear which viral genome results in a higher viral titre. [8] An antiviral would have to be effective against all the serotypes. The current mouse model for dengue (AG129) is inefficient due to low viral load and short period of viremia.[7]

A lot of hope rests on the development of effective vaccines, many of which are undergoing clinical trials.[2] Besides vaccines, every other possible treatment including traditional medicines are being investigated to test their usefulness in controlling this problem. A recent *in vitro* study demonstrated the possible effectiveness of cocktail extracts prepared from four species of phyllanthus against the DENV.[9]

Mechanism of Thrombocytopenia in Dengue

Dengue hemorrhagic fever is characterized by a thrombocyte count of <100,000 cells/mm3.Two mechanisms have been suggested that could be responsible for dengue-induced thrombocytopenia-impaired thrombopoiesis and peripheral platelet destruction. In support of the theory of impaired thrombopoiesis, studies have suggested reduced megakaryopoiesis at the onset of infection, which is normal at the time of clinical recovery. This effect could be due to a direct effect of the virus on the megakaryocytes, or an effect on the stromal cells which are responsible for the release of cytokines and control of megakaryopoiesis. Studies have also indicated altered proliferative capacity, inhibition of differentiation and megakaryocytic progenitor apoptosis as possible mechanisms of thrombocytopenia.

The other main mechanism proposed for thrombocytopenia is the increased peripheral platelet destruction by the DENV. This could be due to an autoimmune reaction, where antibodies produced by the host against the DENV bring about activation and destruction of platelets. Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction. Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients may also be responsible for the

destruction. Recent studies indicate a direct infection of the platelets by the DENV. Increased levels of mediators like tumour necrosis factor-α and interleukin-1β were associated with the thrombocytopenia.[10]

Use of Papaya Plant in Medicine

The papaya plant or *C. papaya* has been used since ancient times for the treatment of a number of disease conditions. Various beneficial effects of extracts from the leaves, fruit and seeds have been suggested through scientific studies. The chymopapain and papain extracts of the leaves are useful in the treatment of digestive disorders. The extracts from fruits and seeds have bactericidal properties.[11] The fruit juice and leaf extract have been demonstrated to have a wide variety of properties including anticancer, antioxidative, anti-inflammatory, anti-bacterial, nephroprotective, hepatoprotective, hypoglycemic and hypolipidemic effects, and anti-sickling effect in sickle cell disease. The ripe fruit has been used against ringworm, whereas the green fruit has been used to lower blood pressure, as an aphrodisiac and to induce abortion.[12] The leaf extract has also been shown to have larvicidal properties against the *Aedes aegypti*mosquito, the vector of the DENV.[12]

Possible Mechanism of Action of Papaya Extract in Dengue

The papaya plant possibly brings about its effect in dengue by treating the thrombocytopenia associated with the condition. A study has reported membrane stabilizing properties of *C. papaya* L. leaf extracts in *in vitro* studies. The study found that C. papaya L. leaf extracts inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and individuals with dengue infection; the effect was observed at the lower concentrations of the extracts. Thus, the extracts are likely to possess membrane-stabilizing properties and protect blood cells against stress-induced destruction. This property may be useful in patients with dengue infection where the leaf extracts could possibly prevent platelet lysis. The authors postulate that this effect could be due to the presence of flavonoids and other phenolic compounds in the papaya leaves.[12]

Studies in Animals

A study in mice found an increase in thrombocyte counts in mice administered 15 mg of powdered papaya leaves/kg body weight between 1 and 12 h following dosing.[13] Another study found that the C. papaya leaf aqueous extract at concentrations of 400 mg/kg and 800 mg/kg significantly increased the platelet counts in cyclophosphamide-induced thrombocytopenic rat model. It also reduced the clotting time in the treated rats.[14]

Studies in Humans

Treatment of dengue using *C. papaya* leaf extract in humans has been reported in very few studies conducted in Asia. A pilot study was conducted in Sri Lanka on 12 patients suspected of suffering from dengue. The patients had a platelet count of <130,000/cu mm, but only six patients were serologically confirmed to be suffering from dengue. The patients received 2 doses of papaya leaf extract at intervals of 8 h. They also received standard symptomatic care for dengue. The study found an increase in platelet count and total white blood cell count in patients administered papaya leaf extract within 24 h of treatment with the extract.[15]

A case report from Pakistan described the effective treatment of dengue in a truck driver with papaya leaf extract. The patient received 25 mL of papaya leaf extract twice a day for 5 days. A steady increase in the platelet and white blood cell count was observed after 2 days of treatment. However, the results of the study have to be interpreted with caution, taking into consideration the vague and incorrect details mentioned in the report. For example, the report states that the driver was bitten by a "mosquito carrying Dengue virus", 24 h after which he started developing symptoms. These and similar other statements raise questions regarding the credibility of this report.[16]

A study conducted in Indonesia used C. papaya L. leaves extract capsules (CPC), which contained 70% ethanol extract of C. papaya leaves. The 80 patients included in the study had high continuous fever for 2-7 days, thrombocyte count of <150,000/μL and hematocrit of 20% or more. They were randomized into two groups; one group received CPC in addition to standard treatment, whereas the other group received only standard treatment for dengue. The study found that platelets in patients with dengue increased faster in those who were administered the CPC. The authors thus conclude that treatment with CPC can hasten recovery of patients and therefore reduce hospitalization. However, there is no clear mention if any of the patients including those in the control group died due to dengue. The study also does not confirm the diagnosis of dengue in these patients.[17]

A report in the British Medical Journal website

described the rapid recovery of platelet counts in two children suffering from dengue. These cases were proved to be positive for dengue by the demonstration of the dengue antigen in the serum. The boys, aged 10 years and 14 years, were administered a spoonful of ground papaya leaves paste every 4 hourly. A dramatic increase in platelet counts was observed; in one case within 12 h of initiating treatment, the count increased to 100,000. In the second case, it increased within 2 days to 250,000. The duration of treatment was not mentioned in the report. [18]

A study in the journal of Medicinal and Aromatic Plants reported an increase in platelet counts in five patients within 24 h who had taken papaya leaf extract for dengue. However, no other details have been provided – whether the dengue was confirmed in these patients, what other treatment was given and whether the increase in platelet count is significant. Furthermore, the response in platelet count beyond 24 h has not been described.[19]

A study conducted in Malaysia had a more systematic approach in evaluating the use of papaya leaf juice in the treatment of dengue. The juice was obtained from the papaya leaves under hygienic conditions from trees that were grown without insecticides or pesticides. An open-labeled randomized controlled trial was conducted on 290 patients between the ages of 18 and 60 years with platelet counts ≤100,000/μL. The patients were confirmed to be suffering from dengue using a rapid dengue bedside test. Patients in the intervention group were administered fresh juice from 50 g of C. papaya leaves once a day 15 min after breakfast for 3 consecutive days. In addition, they received the standard treatment for dengue. The controls only received the standard treatment. The final analysis was conducted on 111 patients from the intervention group and 117 controls. The study found that there was a significant increase in the platelet counts in the intervention group at the end of 40 h when compared to the counts 8 h after the intervention began. This significant increase was not observed in the control group. An increase in arachidonate 12-lipoxygenase and the platelet-activating factor receptor gene expression was also observed in the intervention group. These genes are associated with increased platelet production.[7]
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4071726/table/T1/

Discussion

From the various reports published in scientific literature, it appears that C. papaya L. leaf extract does have beneficial properties in dengue. It has been shown to bring about a rapid increase in platelet count. This could be possibly attributed to its membrane-stabilizing property. The flavonoids and other phenols present in the extract have been suggested to provide the beneficial effects. One study found that the leaves of papaya plant are rich in several minerals. The researchers suggested that these minerals may balance the mineral deficiency caused by the virus and strengthen the immune cells against it.[20]

However, the picture is not entirely clear. First of all, there are very few cases reported in literature. Many of the reports have presumed that the patients suffer from dengue due to the presence of thrombocytopenia and have not confirmed the diagnosis. This may have been due to the high cost of the test, which is often unaffordable to people in the underdeveloped and developing countries, where most of these studies were conducted. Therefore, it cannot be proved based on these case reports that the extract is conclusively effective in dengue. It is possible that the extract may be beneficial in other cases of thrombocytopenia as well. Thus, it is first important to diagnose the cases correctly and prove beyond doubt that the patient indeed suffers from dengue infection.

Most of the cases were given a crude leaf extract prepared by grinding the papaya leaves. The amount of extract given also differed among the studies. Thus, the active principle needs to be identified and the dosage standardized to conduct clinical studies on it to prove its efficacy in dengue beyond doubt. It is also necessary to conduct pharmacokinetic studies to ensure that the active principle is absorbed from the digestive tract.

In addition to its effect against the virus, the papaya plant also appears to be effective against the *Aedes*mosquito. Thus, if proved to be effective, this plant could control dengue at two levels, at the level of transmission as well at the host level.

Papaya extract no doubt offers a cheap and possibly effective treatment for dengue. However, currently, it is also necessary not to rely entirely on the leaf extract and ignore standard treatment for dengue until the benefits are established. Large scale randomized clinical trials in dengue-confirmed patients is necessary to establish their usefulness

Medicinal Uses: *Athletes Foot/Ringworm *Circulation * IBS * Parasites/worms* South American

Properties: *Antioxidant * Antiparasite * Diuretic

Parts Used: fruit, seeds

Constituents: leaf: beta-carotene, calcium, carpaine, fats, flavonols, niacin, papain, tannins, and vitamin c. fruit: papain

How to Use: Papaya

Papaya fruit offers not only the luscious taste but is a rich source of antioxidant nutrients such as carotenes, vitamin C and flavonoids; the B vitamins, folate and pantothenic acid; and the minerals, potassium and magnesium; and fibre. Together, these nutrients promote the health of the cardiovascular system and also provide protection against colon cancer. The fruit is valued for its proteolytic enzymes including papain, which is used like bromelain, a similar enzyme found in pineapple, to treat sports injuries, other causes of trauma, and allergies. The milk like juice from unripe fruit called latex, contains the most concentration of papain, enough some people say to remove freckles. Papaya leaf is used in herbal medicine to remove intestinal worms. Papaya leaf has less of the protein- dissolving papain than the fruit, so it is less likely to "dissolve" the worms, but it contains tannins that the fruit does not. These tannins protect the intestine from reinfection by "tanning" proteins in the lining of the intestinal wall so that worms cannot attach themselves.
Preparation Methods &Dosage: Papaya is an edible fruit, and the leaf can be brewed as a tea. Often taken in extract and capsule form.

• 1N1 is a subtype of the type a influenza virus that causes an illness commonly known as the flu. There are three types of influenza virus (A, B, and C), and each type may have various subtypes. New strains may develop when the virus mutates. The H1N1 subtype currently holds much interest because an ongoing pandemic involves a novel (new) strain of the virus. This outbreak began in late March of 2009 in Mexico and is predicted to continue into the regular flu season of 2009-10.

• This novel strain was originally referred to as "swine flu" because it appeared similar to influenza viruses that normally infect pigs (swine) and rarely infect humans. There was widespread concern that eating pork or coming into contact with pigs would increase the risks of contracting the novel H1N1 flu. Because people began to avoid pork for fear of catching H1N1, the pork industry suffered. Travel to Mexico was restricted, which also had negative economic effects. In late April 2009, 300,000 pigs were slaughtered in Egypt in an effort to curb the disease, even though no cases of H1N1 had been reported in Egypt at that time.

• Later studies showed that this novel H1N1 strain (henceforth, H1N1 or novel H1N1) is quite distinct from influenza viruses that normally infect pigs. It appears that the virus is derived from multiple viruses that may have originated in swine. Novel H1N1 is spread from humans to humans and is not known to be transmitted by eating pork or from close contact with swine. It has not yet been identified in pigs in the United States, and only isolated herds of swine have been infected around the world. Thus, the term "swine flu" is somewhat of a misnomer. Nonetheless, it is still currently used to refer to novel H1N1.

• According to the U.S. Centers for Disease Control (CDC), as of September 2009, around 9,000 people in the United States have been hospitalized due to novel H1N1 infection, and fewer than 600 deaths are linked to this new virus. It is estimated that a total of one million people have contracted H1N1 flu in the United States. This is far less than the number of cases caused by seasonal flu viruses, which infect an average of 5-20% of the U.S. population (up to 60 million people) each year. Annually, seasonal flu viruses cause around 200,000 severe cases (requiring hospitalization) and 36,000 deaths. However, what makes H1N1 influenza unique is that infections peaked outside of the regular flu season, and it is currently the predominant strain of the influenza virus worldwide.

• Another unique feature of novel H1N1 influenza is that more infections occur in people under age 60. With seasonal flu, the above-60 population is usually considered to be at high risk. However, the elderly seem to be more resistant to novel H1N1 infection, perhaps because previous exposure to similar viruses has increased their immunity to this new strain. However, people with lower immunity are still at increased risk of infection for any strain of flu, as well as serious complications. This includes young children and those with certain health conditions that hinder the immune system, including cancer, human immunodeficiency virus (HIV), and acquired immunodeficiency syndrome (AIDS). Children also easily spread the virus to others due to poor hygiene, such as sneezing without covering the nose.

• As with seasonal influenza viruses, novel H1N1 flu is transmitted through the air in tiny droplets when someone with the infection coughs, sneezes, or talks. Individuals are then exposed to the virus through inhalation, or by contact with objects such as telephones, door handles, railings, or computer keyboards. An infection may occur when the virus is then transferred to the eyes, nose, or mouth.

• The symptoms of novel H1N1 flu are similar to those of seasonal flu. In fact, novel H1N1 has thus far caused milder symptoms than seasonal flu. Treatment for the flu, regardless of strain, includes bed rest and plenty of fluids, along with symptomatic treatment, such as drugs to fight viral infections, reduce fever, and help with sore throat and cough. An annual influenza vaccine may offer protection against some strains of the influenza virus. Other forms of prevention include frequent hand washing, avoiding touching the nose or face, and avoiding contact with infected individuals.

• When a flu epidemic occurs, specific populations are infected with a type of influenza virus that has not been encountered before. Epidemics may be restricted to one locale (an outbreak), or they may be more general (an "epidemic") or even global (a pandemic). Because novel H1N1 influenza is causing infections globally, it is currently classified as a pandemic. However, the rates of infection have been far less than well-known pandemics, such as the 1918 "Spanish flu" pandemic that killed between 50 and 100 million people worldwide. Both the current pandemic and the 1918 pandemic are attributed to the H1N1 subtype. Therefore, global health experts are advising caution for the upcoming flu season.

• In the southern hemisphere, the seasonal flu period is between April and November. By late August of 2009, the levels of influenza (including H1N1) had returned to normal in the southern hemisphere, according to the World Health Organization.

.Taxonomy, Morphology and Distribution

Botanical Classification

Domain: Flowering plant
Kingdom: Plantae
Sub Kingdom: Tracheobionta
Class: Magnoliopsida
Subclass: Dilleniidae
Superdivision: Spermatophyta
Phyllum: Steptophyta
Order: Brassicales
Family: Caricaceae
Genus: Carica
Botanical Name: Carica papaya Linn [2]

2.3 Botanical Description Plant

Papaya plant is a large, single–stemmed herbaceous perennial tree having 20–30 feet height). The leaves are very large (up to 2½ feet wide), palmately lobed or deeply incised with entire margins and petioles of 1-3 feet in length. Stems are hollow, light green to tan brown in colour with diameter of 8inches and bear prominent of scars [4]

Fruit

The fruits are big oval in shape and sometimes called pepo–like berries, since they resemble melon by having a centra seed cavity. Fruits are borne axillary on the main stem, usually singly but sometimes in small clusters. Fruits weigh from 0.5 up to 20 lbs, and are green unlike ripe, turning yellow or red orange. Flesh is yellow-orange to salmon (pinkish orange)at maturity. The edible portion surrounds the large central seed cavity. Individual fruits mature in 5-9 months, depending on cultivator and temperature. Plants begin bearing fruits in 6-12 months [4].

Flowers

Papaya plants are dioecious or hermaphroditic, producing only male, female or bisexual (hermaphroditic) flowers. Papaya as are sometimes said to be “trioecious” meaning that separate Plants bear either male, female, or bisexual flowers .Female and bisexual flowers are waxy, ivory white, and borne on short penducles in leaf axils, along the main stem. Flowers are solitary or small cymes of 3 individuals. Ovary position is superior. Prior to opening, bisexual flowers are tubular, while female flowers are pear shaped. Since, bisexual plants produce the most desirable fruit and are self–pollinating, they are preferred over female or male plants. A male papaya is distinguished by the smaller flowers borne on long stalks. Female flowers of papaya was pear shaped, when unopened Whereas, bisexual flowers are cylindrical [4].

Conclusions

The discovery of a new, biologic host-defense protein, “HDFx”, may provide a unique way to ameliorate and prevent the “cytokine storms” and haemorrhages seen in severe influenza infections noted in the civilian population, hospitalisedpatients, as well as in military personnel.

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