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Yellow Fever: Epidemiology, Symptoms, Pathology and Treatment including role of Potential herbs and Biotechnological Products

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Abstract

The yellow fever virus belongs to the family of Flaviviridae whose vector is Aedes aegypti. The virus showed its impact mainly in the African region and the South American region. To immune one from its infection, live attenuated vaccines were made which can provide immunity in 30 days. However, these vaccines have some side effects therefore a search for antiviral activity was needed. Hence the activity of sofosbuvir and some adjuvants were observed against this virus. Also, plants based antiviral chemical was searched and observed against this virus to see the efficacy. The role biotechnology was also exploited for making non-infectious vaccines which can elucidate the immunity. Here as for precaution and preventive measures different essential oils activity was studied against the larva of the vector.

Keywords: Yellow Fever; Aedes aegypti; Flavivirus; Sofosbuvir; E. chlorantha

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Introduction

Yellow fever is caused by the virus belonging to the family Flaviviridae [1] and the virus is a single-stranded RNA with a spherical nucleo-capsid surrounded by a lipid envelope. The envelope is embedded with envelope protein (E) which was thought to regulate the binding of yellow fever virus (YFV) and membrane protein (M) [2]. It is transmitted through Aedes and Haemagogus species of mosquito.The disease is widely spread in South America and Africa.4 The clinical symptoms observed may be varying like self-limited, mild febrile illness to severe hemorrhage, and liver disease. Since it is observed that this disease is accompanied by jaundice hence it is named “yellow fever” [3]. Surprisingly even after so many centuries and so many deaths, there is no antivirals medicine for this disease, but an effective vaccine is there to provide little immunity. Apart from that preventions are the best and only way to avoid the yellow fever.

Epidemiology

The yellow fever virus (YFV) is a mosquito-borne virus that is transmitted by Aedes spp. Genetically seven genotypes of YFV were identified in which five are found in Africa and two in South America. Up to date, there were two outbreaks in Angola and surprisingly the strain which caused the 2016 outbreak was genetically identical from the 1971 Angola outbreak strain [4-5].

South America

The first yellow fever epidemic was reported in yucatan peninsula in 1648 which involved many Caribbean islands from 1647-1649. To understand the YF epidemiology

in 1900 Reed and the yellow fever commission working in Cuba reported that a filterable agent transmitted by Aedes aegypti mosquito is causing yellow fever.

In 1946 Pan American health organization started a program that was successful in preventing the YF. In 1942 the last urban epidemic was reported in South America, after that in Trinidad small outbreak were observed in 1954 and 1979, it was evidence that A. aegypti was not the vector in these cases (Figure 1).

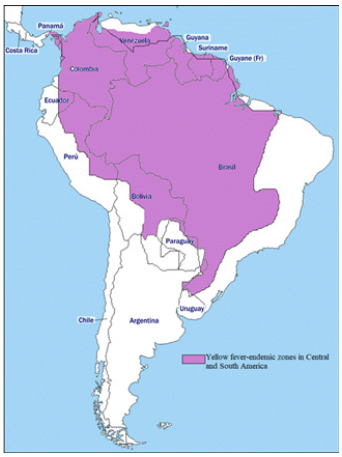

Figure 1: Endemic affected area due to in South America.

Africa

Worldwide around 200,000 cases of yellow fever are registered annually out of which 90% of cases are from Africa. The first epidemic of yellow fever in Africa was reported among the British troops in 1778 in St. Louis de Senegal. But the major outbreak was reported in West Africa, it was observed that epidemic was not that explosive as the American outbreak, the fatality case was also quite low compared to America. To study the disease an African YF Commission was established by Rockefeller Foundation in 1925. Which lead to the many discoveries like the isolation of YF virus from mildly infected human who was from Asibi. The first YF vaccines in 1931 were also developed by them after that many other vaccines were made by them which were used widely to control YF (Figure 2).

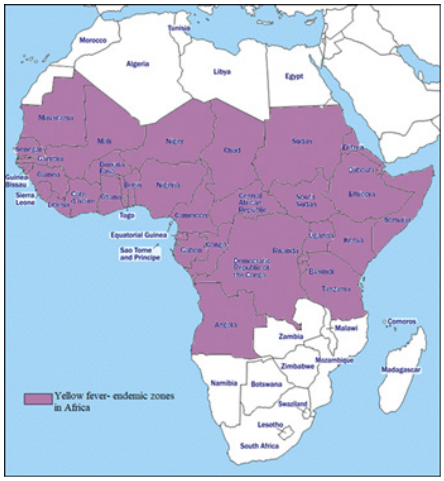

Figure 1: Endemic affected area due to yellow fever in Africa.

Symptoms

After the infection, the virus incubates in 2-3 days longer the virus live in blood higher chance of sever condition will occur. In our study, three phases of yellow fever are described. Phase-I is normally characterized by fever, malaise, myalgia, nausea, vomiting, irritability, dizziness, and toxic appearance. Laboratory abnormalities which were observed were leukopenia on the onset of illness and at day2-3, high serum transaminase level is observed just before the onset of jaundice.

Phase-II in the majority of cases in this phase the improvement is observed like lowering of fever but it lasts up to 48 hours. In some cases, the patient's health is recovered without developing jaundice. Phase-III this phase is characterized by a reoccurring of fever along with nausea, vomiting, jaundice, and bleeding diathesis and was observed in ?15%. In the blood, as the antibodies bind with virus antigen the virus count down gets lower resulting in the appearance of antibodies and the disappearance of the virus from the blood. Different organs like the liver, kidney, gastrointestinal tract, central nervous system were seen to get affected. The severity of the disease is directly proportional to the serum transaminase level; were relatively elevated in the second week of illness in patients who recovered.

In mice, it is found that genetic factors are crucial during the susceptibility and immune response to flaviviruses but these factors are not well studied in humans.

Pathophysiology

They enter into the host cell by receptor-mediated endocytosis. Many different primary receptors and low-affinity co-receptor which help their entry had been identified. Acidifying the endosomal vesicle triggers a conformational change in virion which further leads to the fusion of the viral and cell membranes and particle disassembly which lead to the release of genetic material in the cytoplasm. The positive sense of RNA of virus translate into a single polyprotein which by the help of viral and host protease is converted into co- and post-translationally polyprotein.

This polyprotein i.e. the virus assembly anchor on the lumen side of the endoplasmic reticulum(ER). Through ER structural protein along with the newly synthesized RNA is released which is then transported in the trans-Golgi network (TGN). At this point, the viral particles are immature and are non-infectious. Though the host protease furin the immature virion particles and subviral particle are cleaved which leads to the matured and infectious particle. By the exocytosis, the mature virion and subviral particles are released.

Treatment

Vaccination

The live attenuated yellow fever vaccines were produced from the Asibi strain which leads to the discovery of two lineages of vaccines 17D and 17DD.The major difference in Asibi strain and 17D vaccine is the 10,862- nucleotide which are found in

the envelope (E) protein gene. The envelope protein plays an important role in the transmission of the virus in the host cell since the 17D vaccine have enough enveloped protein gene that can activate the immune response without causing the harm. The envelope protein covers most of the surface of the virion. But currently, it's not possible to identify which mutation in the E protein resulted in the deletion of viscerotropism of YFV-17D [6-10].

Recent studies

Role of adjuvants formulation

Due to the serious adverse effect caused by vaccine, the need for adjuvants formulations is needed. Adjuvants work through several different mechanism ones which is influence the innate immunity response. Here different adjuvants of a different class that is antigen carriers (Al(OH)3 and Addavax) and immune potentiators (Flagellin) had been studied to see which one is showing the best result for the evolution of an inactivated yellow fever virus vaccine (IYFV). Through the test, it was observed that 100% protection was given by the combination of IYFV+ addavax after the 2 dose regimen against 25% survival was induced by alum formulation. However, it can be seen that the best survival rate was achieved when Al(OH)3 was used which was 78%. From these data, it can be concluded that even though addavax is a reassuring candidate however further studies on addavax and alum based formulation is needed to understand their mechanism of action in this model.

Herbal source

Plants always played an important role in the idea of developing novel drug compounds. Traditionally plant products were always used to treat the different pathological conditions and even now in developing countries mostly plant-based products are used16. Most medicinal plants which were screened for their antimicrobial activity appear in the literature but the evaluation was not done adequately.

From long time plants, algae, lichens, tissue culture, or cell culture providing the necessary source for the antiviral agents. Animal models, animal protection studies, egg inoculation studies, and cell methods were the different screening methods which are used to screen plants and their extracts to identify the antiviral activity. Plants secondary metabolites don't have any necessary function in the development of plants however these secondary metabolites can have activity against bacteria, fungi, and some viruses. The therapeutic activity can be observed when these plants product gets accumulate in them.

The activity of enantia chlorantha extract

The water extract of the bark of enantia chlorantha was made to test its anti-viral activity against the yellow fever virus. The bioactivity of the extract of E. chlorantha was previously reported against the microbes as it showed a broad-spectrum antibiotic activity. It was observed that at the minimum inhibitory concentration (MIC) of 0.025mg/ml E. chlorantha showed 100% inhibition of yellow fever virus against the Vero cells. The results were obtained when the plant sample was used in 2 model systems: 2 YFV in Vero cells and reproduction of 2 vaccine strains of YFV in mice brain. Interestingly both oral and subcutaneous administration the plant extract showed anti-YFV activity.

The activity of sulfated galactomannas

Galactomannan is the second most abundant polysaccharides which are present in the higher plants especially in the legume seeds. They possess different molecular mass, degree of side-chain, and fine structure32-36. Sulfated polysaccharides in vitro antiviral activity were investigated and it was observed that the negatively charged sulfate groups inhibit the adsorption of virus to the host cells.

Through different studies, the activity of two galactomannas which were extracted from the seeds of Mimosa scabrella (BR) and Leucaena leucocephala (LL) and later sulfate were observed against the yellow fever virus. When the sulfated extracts Mimosa scabrella (BRS) and Leucaena leucocephala (LLS) were given into the mice it was observed that the BRS and LLS gave 87.7 and 96.5% resistance against death in mice also it was seen that the LD50 value at 37.5 of YFV was similar to LD50 value at 25 for formaldehyde inactivated YFV. From these studies, it was concluded that the sulfated galactomannans affectivity against the YFV.

Role of Biotechnology

The YFV has surface proteins lead a key role in the expression of virus-neutralizing and mounting protective immunity this factor makes them an essential target for the evolution of YF subunit vaccine. In this study, we tried to engineer and produce YFE protein in N. betnthamiana as a stand-alone subunit, and as LicKM fusions and its immunogenicity and protective efficacy were evaluated on mice and non-human primates. Through the studies, it was observed that the vaccine produced by this method resulted in the production of virus-neutralizing (VN) antibody response and protect over 70% of the mice and non-human primates from serious yellow fever infection from these results it was indicated that it was possible to produce a non-infectious YF vaccine from these YFE subunit antigens. It is also important to note that even though the booster dose of these YFE subunit vaccines was given the response was not equivalent to 17DD vaccine which suggests that more studies on different things like adjuvants, vaccine dose regimen, and detailed immunological evaluation needed for the evolution of YFE based subunit vaccine.

Precautions

Larvicidal activity of Neem oil (Azadirachta indica)

It was observed that the median lethal concentration (LC50) of the Neem formulation was found to be 1.7ppm even at high temperature the value did not deviate much. When the dose is applied at the rate of 140 mg a.i. /m2 in different breeding sites it was observed that the 95.1% and 99.7% reduction in Aedes larva was there on day 1 and day 2 and by day 7 100% larva control was observed. Hence these studies suggest that neem oil formulation was very effective in controlling the mosquito larva in their

natural breeding site.

Larvicidal Efficacy of five cucurbitaceous plant leaf extract

The crude hexane, ethyl acetate, petroleum ether, acetone, and methanol extract were made from the leaves of five species of cucurbitaceous plants Citrullus colocynthis, Coccinia indica, Cucumis sativus, Momordica charantia, and Trichosanthes anguina. The extracts were tested on the early fourth instar larvae of Aedes aegypti and it was observed that all the extracts showed some level of Larvicidal activity. Interestingly extracts of petroleum ether extract of C. colocynthis, methanol extracts of C. indica, C. sativus, M. charantia, and acetone extract of T. anguina showed the highest level of Larvicidal activity with LC50 value 74.57, 309.46, 492.73, 199.14, and 554.20 ppm. From the data, it can be said that the activity of C. colocynthis and M. charantia extracts are most effective in comparison to other cucurbitaceous extracts. Hence, these extracts can be used to control the vector Aedes aegypti.

Activity of selected plant essential oils against larva of yellow fever

During this experiment 14 plant essential oils were used against the Aedes aegypti and only 9 showed toxicity against the Aedes aegypti larvae. Those essential oils are from the heartwood, sapwood, bark, leaf essential oils of C. japonica; the heartwood, bark, leaf essential oils of C. formosana; the heartwood essential oil of T. cryptomerioides; and the leaf B essential oil of C. osmophloeum. These nine essential oils had the LC50 value as follows 72.0, 82.7, 48.1, 37.6, 75.2, 51.8, 56.3, 79.8, and 86.8 µg/ml from this data it can be concluded that leaf and bark essential oil of C. japonica showed the most potent Larvicidal activity against A. aegypti larvae as its LC50 = 37.6 µg/ml and LC50 value of bark of C. japonica was found to be 48.1 µg/ml. Therefore, from the data obtained it can be concluded that essential oil of leaf and bark of C. japonica are reassuring as Larvicides against A. aegypti larvae.

Larvicidal activity of botanical extracts against yellow fever mosquito

We tried to observe the activity of different botanical extracts against the larva of A. aegypti and it was observed that out of 8 botanical extracts only 5 showed the highest Larvicidal activity. Two plant extracts Delonix regia , Limonia acidissima showed 100% mortality at dose 2mg/ml during the screening test. However, to get more accurate data LC50 was done and it was observed that S. cumini gave the highest LC50 value that is 0.85 mg/ml and the second-highest mortality was given by J. curcas which was LC50 at 0.85 mg/ ml. Hence from these data, it can be concluded that the extract of Delonix regia and S. cumini are the most promising candidate.

Brazilian plants Larvicidal Activity

In total 18 plants, extracts or oils were assayed against the larva of A. aegypti however it was interesting to note that only 6 plants met the passing criteria which were>50% lethality at 500 µg/l. The most active sample was cashew nut (A. occidentalis) oil as it has an LC50 value 14.5µg/l. The other plant extract or oil was from the Annonaceous plant's species like (Annona muricata, Annona crassiflora, and Annona squamosa amongst others) these plants have chemical acetogenins which have many biological properties including antibiotic, anti-tumor, anti-malarial, anti-parasitic and insecticidal activities. If we compare the Brazilian plant oil A. occidentalis, C. langsdorffii, C. guianensis and C. winterianus, and the stem extract of A. glabra with neem oil we observe that the LC50 value of these Brazilian plants oil or extract is much lower than the neem. Hence it can be concluded that these plants have good Larvicidal activity against the A. aegypti larva.

Activity of South American plants on the larva of A. aegypti

From 9 South American plants 11 extracts were made and their activity was observed against the larva of A. aegypti. Interestingly 8 extracts out of 11 showed lethality against the larvae at LC50 < 500µg/ml. However, out of those 8 extracts, two extracts showed superior Larvicidal activity. The first extracts are the dichloromethane extract of A. grandifolia, with an LC50= 2.6 µg/ml which is basically 2 times higher than the natural bio insecticide β- asarone and the second one is the dichloromethane extract of M. setosa with an LC50 value = 9.2 µg/ml. These data indicate that the extract of M. setosa and A. grandifolia, can be used as larvicides.

Repellent activity of citrus plants against the female A. aegypti mosquito

The activity of 8 essential oils from citrus plant species as mosquito repellent were tested and compared with the chemical repellent (IR3535 12.5 w/w; Johnon's Baby Clear Lotion) and it was observed that the highest repellent activity was shown by C. aurantifolia The order 8 essential oils based on their activity will be as C. aurantifolia > C. microcarpa > C. maxima > C. reticulate > C. sinensis > C. hystrix > C. aurantium >C. medica var sarcodaclylis. It is also important to note that all essential oil has a period of protection time higher than the IR3535 (3.0±0 minutes). Hence it can be concluded that essential oils from citrus plants can be used as green or bio mosquito repellent.

Conclusion

The yellow fever virus is one of the most deadly viruses which caused many deaths to prevent its spread studies were carried out and to form a live attenuated vaccine called 17DD which can provide immunity against the YFV. However, this vaccine had its serious side effect to deal with these side effects a search for antiviral treatment was done by studying different chemical compounds like sofosbuvir, adjuvants activity, or a plant-based antiviral chemical. Some results obtained after the studies suggest that some chemical compounds, adjuvants, or plant-based chemicals are potent candidates against the YFV. The biotechnological studies were also carried out to make a potent candidate and at last, it was concluded that further studies are necessary to develop a highly potent YFV vaccine with fewer side effects. Here we also studied different plant extracts or essential

oils on activity on Aedes aegypti mosquito larva and the results obtained from that suggest that these extracts and essential oils can be used as a precaution to safeguard one from infection.

Conflict of Interest

The authors have no conflicts of interest to declare.

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