REVIEW ARTICLE

EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT OF CHIKUNGUNYA - A REVIEW

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ABSTRACT

Chikungunya is a viral disease transmitted to humans by infected mosquitoes. Like most mosquito-borne infections, the virus can only be transmitted by blood-to-blood contact, through a mosquito bite or transfusion with infected blood. The disease is characterized by the common symptoms involving rashes, nausea and headache. In addition to this, it also causes intense joint pain and fever, which is known as arthralgia. It is widely spread in America, Africa and all over the world. The onset of chikungunya fever is more intense and the period of illness is shorter than that of dengue fever. Recently, chikungunya has become a serious public threat. The chikungunya symptoms are usually self-limiting and prophylactic treatment is currently unavailable to cure the disease, although various allopathic medicines, such as NSAID's, analgesics, steroids, DMARDs and some anti-viral drugs claim to treat the disease. However, these medicines provide only symptomatic relief with serious side effects. Nowadays, researchers focus more towards an alternative treatment. The present review aims to highlight the epidemiology of chikungunya, treatment options available, and potential of alternative medicines for its treatment.

Keywords: Chikungunya fever, *Aedes aegypti,* diagnosis, pathogenesis, alternative medicines

INTRODUCTION

Chikungunya fever is an acute febrile viral disease[1] transmitted by chickungunya virus (CHIKV), which is a single stranded positive RNA arbovirus[2] (arthropod borne virus) belonging to the family Togavirdae[3] with genus *alphavirus.* The name chikungunya is derived from the African Makonde word, which means bent joints with severe arthralgia. The disease is transmitted to humans through the bite of viremic mosquitoes especially *Aedes aegypti* and *Aedes albopictus*[4,5]. The illness produced by the CHIKV involves the development of joint pain, especially of ankle, knee, toes, fingers, wrist and elbows. In 1953, it was first identified in Tanzania[6] and Africa as a human pathogen, later on it was found in many countries of world[7, 8].

During the transmission period, CHIKV is maintained in two defined transmission cycles. In Asia, chikungunya is primarily maintained in a mosquito–human–mosquito urban cycle, and transmitted by *A. aegypti,* where as in Southern Africa it is transmitted by sylvatic cycle between forest dwelling mosquitoes such as *A. furcifer* and humans[9, 10]. After transmission, the virus starts to infect the human body and onset of symptoms arises in the form of high fever, rashes, nausea, polyarthralgia, vomiting and headache, which are difficult to differentiate from dengue and zika virus fever. This makes the diagnosis of CHIKV difficult, since many patients are co-infected by CHIKV, DENV and ZIKV[11]. It has been recently observed that, ocular and neurological manifestations are also developed by the CHIKV, including optic neuritis, retrobulbar neuritis, keratitis, unilateral papillitis, granulomatous uveitis congenital infections, encephalitis, Guillain-Barré syndrome and myelitis[12,13]. However, the infection is limited and the symptoms may resolve within 2-3 weeks but the polyarthralgia may last up to one year. Morbidity rate of the disease has been increasing day by day, but till date there is no specific prophylaxis or treatment available. A range of medicines are used to inhibit the viral replication *in vitro*

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or to target the host factor for reducing the susceptibility of the infection, but they only provide symptomatic relief.

The present review aims to spotlight the structure and replication of the virus, pathogenesis of the disease, clinical phases of infection and treatment available, including herbal and allopathic treatments.

Geographical spreading of CHIKV

In 1952, the first identified outbreak of chikungunya virus was reported in Newala and Masisi districts of Tanzania[14,15]. In early 1953, it was first isolated from the blood of febrile patients and various species of mosquitoes such as *A. aegypti and A. albopictus*. In the beginning of 2004, a large epidemiological burden of the disease was reported in Kenya[16], and nearly a half million of population affected from this. During the year 2005 to 2007, the virus produced a serious threat for the public and had traversed near about 60 countries across the world including Africa, Asia, Europe and Pacific Ocean and various islands of the Indian Ocean[17]. At the end of 2013, the first emergence of infection caused by CHIKV was reported in America and at the end of 2014 it was spread to near about 45 countries of Caribbean, Northern America, Central America, and Southern America[18,19]. Due its high transmission rate in recent years, CHIKV has become a serious public threat and there is an urgent need to identify the preventive measures to control the disease.

Structure and replication of CHIKV

Chikungunya is a virus having a positive sense, single stranded RNA of length 12kb with two open reading frames, namely, 5'ORF and 3'ORF[20,21]. 5'ORF encodes the four non-structural proteins (nsP), namely, nsP1, nsP2, nsP3 and nsP4. 3'ORF encodes the polyprotein that is processed into three structural proteins namely, capsid C, envelopes E1 and E2 with molecular weight of 36000, 56000 and 52000 respectively. The 5'ORF gets translated from the genomic RNA and 3'ORF gets translated from the sub-genomic RNA[22, 23]. The viral particles are spherical in shape with a diameter of approximately 70nm. It is formed by the various copies of capsid protein and is surrounded by a lipid bilayer composing envelope, as shown in Fig. 1[24]. E1 and E2 glycoproteins form 80 trimer shaped spikes which are inserted in the envelope[25].

The replication cycle of CHIKV is nearly same as that of other alpha viruses[26]. Virus enters the target cells through various receptors such as prohibitin (PHB), integrin alpha V (ITGAV), b1 integrin (ITGB1) dimer and phosphatidylserine (PtdSer)-mediated virus entry-enhancing receptors (PVEERs), which mediate the endocytosis[27,28]. After the formation of endosome change in p^H occurs. In the envelope, conformational changes get triggered by the p^H changes. This leads to the fusion of viral and host cell membrane. After fusion, virus releases its genetic material into the host cytoplasm. The precursors of the non-structural proteins are generated by the translation of viral RNA from the mRNA. Non-structural proteins further mediate the synthesis of the negative strand of RNA intermediate. This works for the synthesis of the both genomic (49S) and subgenomic (26S) RNAs as a template[29]. Glycoproteins pE2 and pE1 (precursor of E2 & E2) generate after the release of capsid. These precursor proteins undergo post-transductional modification to form heterodimers of E1 and E2 when transported to the endoplasmic reticulum and Golgi complex. Both E1 and E2 proteins are important for viral replication. E1 plays an important role in membrane fusion, whereas with the help of E2, virus enters the cell by endolysis[19]. After the transportation of these proteins into the host cell membrane, viral envelope spikes are developed and the assembled alpha virus particle buds at the host cell membrane and gets free from the host cell.

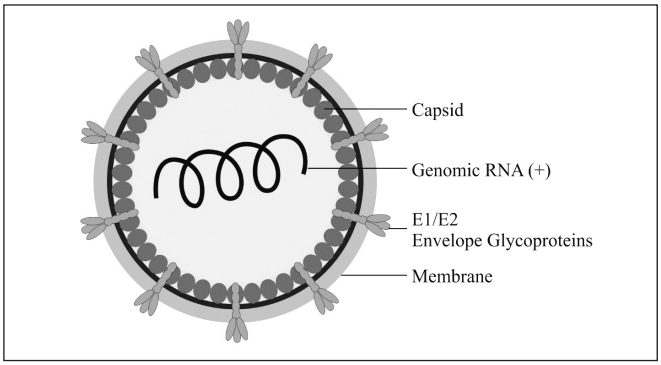

Fig. 1: Structure of Chikungunya virus[30]

Pathogenesis of disease

Aedes mosquito transmits the virus through the skin along with the salivary molecules, including proteins and nucleic acid. This salivary component alters the host hemostasis for blood feeding purposes and enhances the pathogen transmission by modifying immune processes toward TH2 response, by suppressing the TH1 cells and antiviral cytokines[31].

For the host control of CHIKV infection; both hematopoietic and non-hematopoietic cells are involved. Some cells are more susceptible to the virus and allow the CHIKV to replicate. The cells involved in virus replication include, local endothelial, epithelial cells, monocyte derived macrophages and primary fibroblasts, while lymphoid, monocytoid cell and monocyte derived dendritic cells are

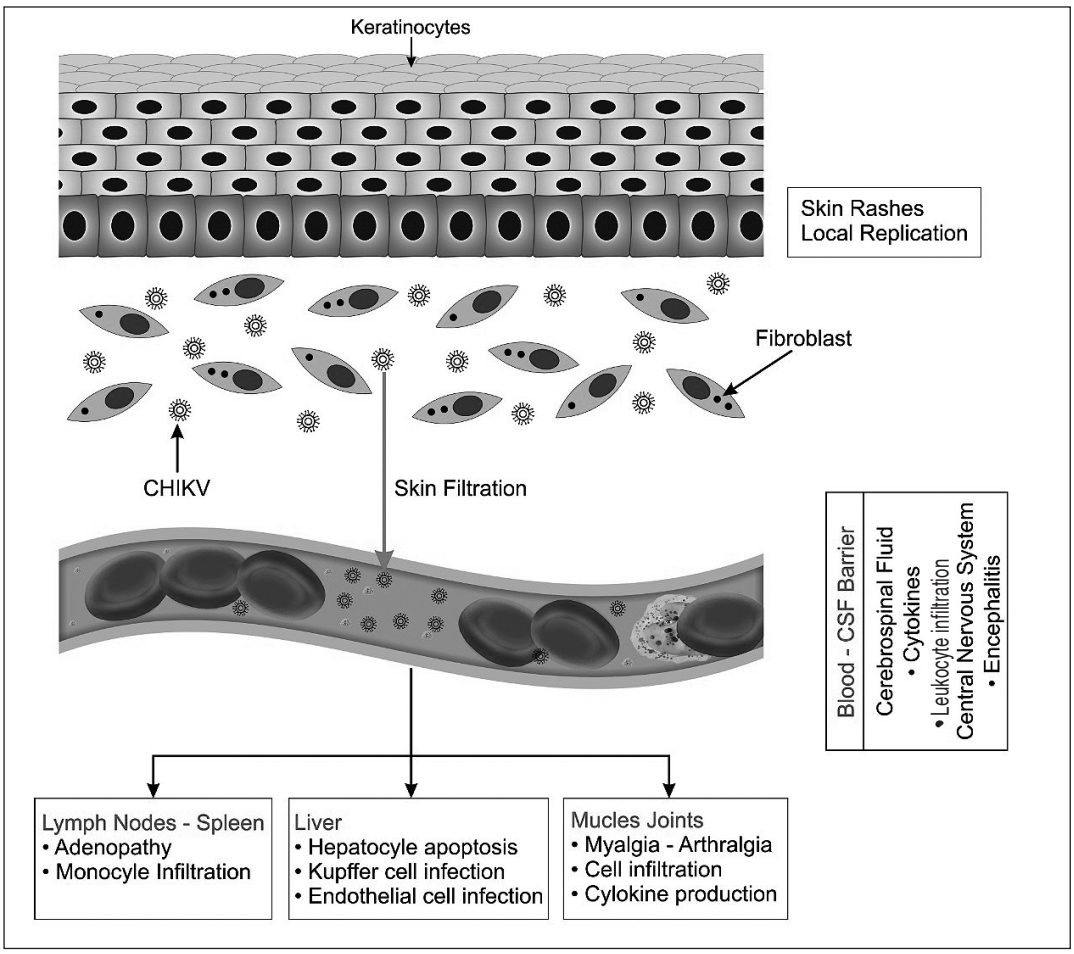

Fig. 2: Pathogenesis of chikungunya virus[37]

not involved in the CHIKV replication[21]. The pathogens associated with molecular pattern are recognised by receptors such as toll like receptor and retinoic acid inducible gene I-like receptors. After the recognition and binding, the virus-receptor complex mediates the immune response and releases the inflammatory cytokines[32]. In the initial period of viral infection, the concentration of CHIKV is increased in the blood stream and viraemia develops due to the activation of interferon and interleukin-6. Some other cytokines and chemokines such as CCL_2, CCL_4 also become activated and start to boost host immune system for the clearance of viral particles from the host body by $CD8^+$ and natural killer cells within one week. Thus, PCR is recommended before the seventh day of infection, as after the seventh day virus becomes undetectable[33, 34]. In post-acute and chronic phase, the concentration of the cytokines and chemokines such as, IL-4, IL-10, IL-6, interferon-α, interferon-β interferon-γ, TNF-α, monocyte chemo-attractant protein-1 and interferon gamma-induced protein 10 starts increasing[35]. The susceptibility of the disease depends upon the levels of the chemokines and interferons. With the high titer of interferons, the impression of the prostaglandins increases and develops arthralgia associated with the CHIKV. Infected cells drain into the lymphatic circulation through lymph nodes and now cells are in lymphatic replication phase. After endocytosis, the virus particles are circulated into the blood stream through the lymph. The virus then replicates in the blood and disseminates in other tissues of the body involving liver, muscles, joints, and brain as shown in Fig. 2[25]. The chronic condition of arthralgia may be related to the viral burden in the synovial cavity[36, 37].

Clinical phase of CHIKV Infection

The person suffering from CHIKV infection may experience three different phases of the disease. These three phases are: acute phase, post-acute phase and chronic phase.

Acute phase: This phase generally includes the first three weeks of the disease i.e. first 21 days of onset of infection, as shown in Fig. 3[38]. Then, the incubation period starts, which is of 4-7 days duration[39]. In the acute

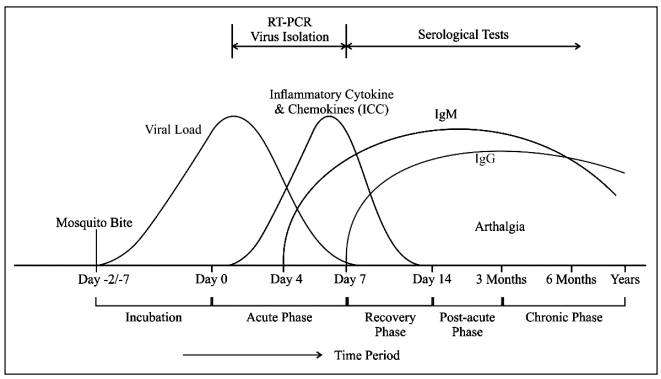

Fig. 3: Clinical phases of chikungunya infection[44]

phase, the infected individual exhibits symptoms like high fever, poly-arthralgia, rashes and intense myalgia. Poly-arthralgia generally represents poly-arthritis, which involves multiple joint aches, tenderness and inflammation of joints of ankles, knees, fingers, elbows and wrist. Other symptoms like nausea, vomiting, myalgia, headache, back pain, edema of the face and polyadenopathies may also arise. In case of children, in addition to these symptoms, two problems like gingival bleeding and epistaxis may also arise[2, 40].

Post-acute phase: This phase starts from the 21st day i.e. from fourth week and ends up to the third month of the onset of disease. In this phase, generally stiffness of the joints during the morning occurs. Other complications like neuropathic pain and peripheral vascular phenomena such as Raynaud syndrome may persist[41]. The most common symptoms that may arise during this phase include change in the colour of skin, metabolic disorders, alopecia, anxiety and depression[42].

Chronic phase: This phase starts after the third month i.e. after the post-acute phase[2]. This phase proceeds when clinical manifestations become more severe after three months of infection and joints of fingers, ankle, knee and shoulders are the main targets in this phase of the disease. The symptoms in this phase involve severe joint pain, fatigue in some cases, tingling and numbness[43].

DIAGNOSIS OF CHICKUNGUNYA INFECTION

Following methods are generally used to assess the severity of the disease:

Detection of viral particles: The viral particles are detected by Reverse Transcription Polymerase Chain Reaction (RT-PCR) and Reverse Transcription Loop Mediated Isothermal Amplification (RT-LAMP). Both the methods are closed system techniques and are generally used because of their sensitivity and chances of less contamination. RT-PCR test is generally recommended after the arising of symptoms and/or before the seventh day of onset of symptoms. This method proves to be very useful for the early diagnosis of the infection and plays an important role in the success of the treatment[45].

Antibody test for the detection of IgM and IgG: Various techniques are used for the determination of IgM and IgG in serum of infected individuals, such as, Enzyme Linked Immuno-Sorbent Assay (ELISA), immune-fluorescent method and neutralizing techniques. Antibody test is not recommended in the first week from the onset of the disease. In some cases, antibody takes more time to appear, approximately 6-12 weeks. When sufficient concentration of antibodies develops, then ELISA is recommended for the detection of the severity of the disease[46, 47].

a) Presence of viral ribo-nucleic acid (RNA) in acute phase serum.

b) An increase in the concentration of virus specific IgG antibodies in samples collected at least three weeks apart[48].

Treatment of chickungunya infection

A range of drugs is available to treat chikungunya infection, which only provide symptomatic relief than cure. There is no specific prophylaxis or treatment available for the disease. Generally, symptomatic treatment is recommended after observing the symptoms of infection.

In acute condition of the disease, symptomatic treatment is commonly recommended. For a normal adult of weight more than 60 kg, dipyrone is recommended at a dose of 1g for every 6 h. Paracetamol is used to reduce the fever and is given at a dose of 50-750mg every 4-6 h, not exceeding the maximum dose of 4 g day^{-1} [49]. It is not recommended with interferons and vinblastine, as it causes liver complications, most commonly hepatotoxicity[50]. NSAIDs like ibuprofen and naproxen can also be recommended for the management of arthritic pain. Tricyclic anti-depressants, anti-epileptic drugs and tramadol are used to treat the neuropathic pain caused by CHIKV[36].

For the post-acute condition of the disease, NSAIDs are the first line therapy and can be used for 5-7days. Commonly used NSAIDs for post-acute condition are ibuprofen (400mg for every 8h), nimesulide (100mg day^{-1}), and meloxicam (7.5-15 mg day^{-1}) [2]. One can also prescribe tramadol hydrochloride at a dose of 50–100 mg every 6 h by oral route and codeine at a dose of 30 mg every 6 h with paracetamol (500-750 mg), as shown in Fig. 4.

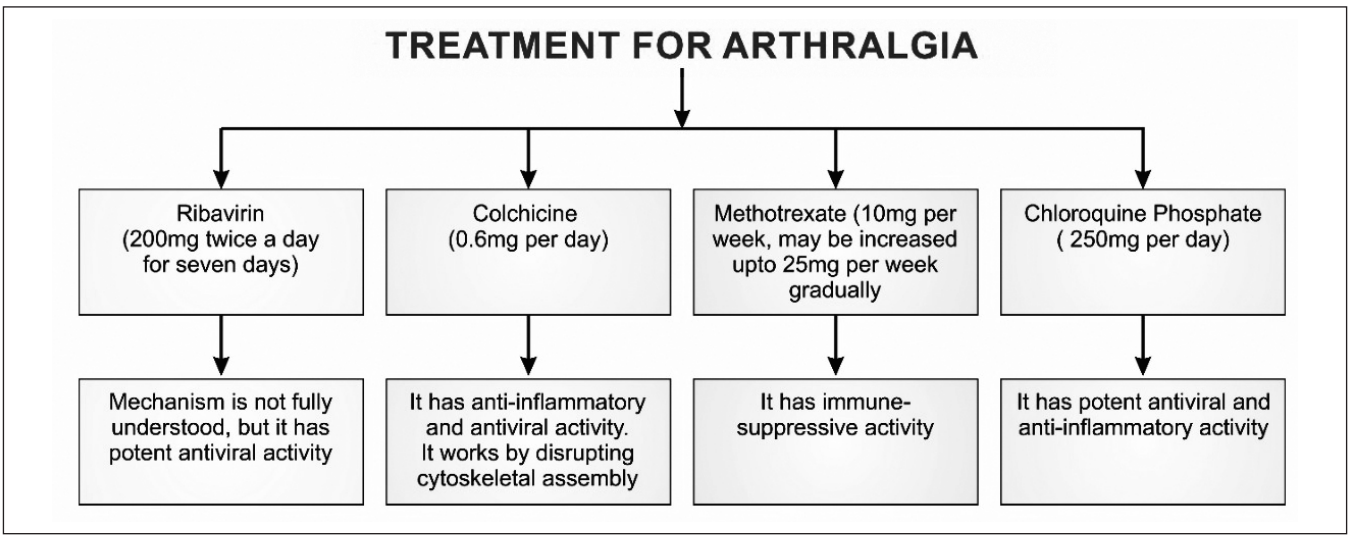

Fig. 4: Treatment for CHIKV induced arthralgia[49]

Treatment of CHIKV in case of pregnant women

Pregnant women are advised to take plenty of fluids and rest. First safest option for pregnant women is to take paracetamol[51]. NSAIDs including aspirin are contraindicated in the 24th week of the gestation period, due to the risk of foetal renal failure and closing of the ductus arteriosus, which may lead to fetus death in uterus[19]. *Touret* et al.[4] reported the maximum maternal–foetal transmission of chikungunya virus at 12th and 15th week of gestation due to deep trophoblast invasion[52, 53]. All of these resulted in fetal death. When the symptoms of CHIKV infection are reported at the end of pregnancy, the infected patient is suggested to consult with an obstetrics specialist.

Treatment of CHIKV in case of new-borns and children

When the mother is suspected with chikungunya infection, the neonate of that mother should be under 7-day monitoring after the birth. In neonates and infants, the major symptoms are skin rashes, high fever, diarrhea, febrile convulsion, poor breast feeding and limb edema. In children, the main symptoms are muscular pain, fever, photophobia, skin rashes and headache. However, arthralgia is uncommon in children. Codeine should not be recommended to children having the age of less than 12 years. In case of infants younger than the 3 months of age, NSAIDs should be avoided[53].

Treatment of CHIKV induced arthralgia

Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as, hydroxychloroquine, sulfasalazine, methotrexate, chloroquine, Interferon 1 and ribavirin are the most commonly used drugs to treat post-chikungunya chronic arthritis. Steroids drugs like prednisone at a dose of 0.5 mg per day per kg of body weight are also recommended for the treatment of CHIKV induced arthralgia during sub-acute phase of the disease for the management of moderate to severe arthritis pain. However, their use is contraindicated in various pharamacological conditions such as diabetes, hypertension and bipolar disorders[54,55]. Chloroquine, which is an anti-malarial drug, has proved to be very effective in the chronic phase of the infection. From the results of recently conducted trials, chloroquine at a dose of 250 mg day^{-1} in the acute phase of the infection has proved to be effective[56,57]. Ribavarine is another drug used at a dose of 200 mg twice a day for seven days. This drug represents an inhibitory activity against the genetic material of the virus[58]. Methotrexate at a dose of 10 mg week^{-1} (to be increased to 25 mg week^{-1} in gradual steps,), alone or in combination with sulfasalazine, is found to be very effective for the management of chronic CHIKV arthritis[59, 60], as shown in Fig. 4[61].

Chikungunya virus vaccine

Vaccine is a preparation containing killed and/or living attenuated microorganisms, which provides immunity against a particular infection[62]. A wide variety of CHIKV vaccines have been tested in animal models to ensure clinical efficacy and safety of the treatment. Some of these are based on live attenuated virus, chimeric virus, subunit vaccines, inactivated virus, nucleic acid vaccine and virus like particles (VLPs). Erasmus et al. (2017)[63] developed a chimeric virus, in which CHIKV structural protein encoding gene is cloned as cDNA of insect-specific Alphavirus Eilat virus (EILV). This newly developed vaccine is found to be effective only in case of mouse models and non-primates,

Table I: Botanical name and active constitutents of herbs responsible for anti-CHIKV activity

Sr. No.	Botanical name	Active constituent	References
1	*Tinospora cordifolia*	Berberine, mangoflorine	65, 66, 67
2	*Andrographis paniculata*	Andrographolide, kalmeghin, deoxyandrographolide	68, 69
3	*Carica papaya*	Chlorogenic acid, protocatechuic acid	70, 71, 72
4	*Curcuma longa*	Curcumin	73, 74, 75
5	*Berberis vulgaris*	Berberine	76, 77, 78
6	*Trigonostemon howii*	Trigowiin A	79, 80
7	*Camellia sinensis*	Epigallocatechin-3-gallate	81, 82, 83
8	*Croton mauritianus*	12-*O*-Decanoylphorbol-13-acetate, 12-*O*-decanoyl-7-hydroperoxy-phorbol-5-ene-13-acetate	84, 85
9	*Euphorbia dendroides*	9,14-Dioxojatropha-dienes	86, 87
10	*Trigonostemon cherrieri*	Trigocherrin B	88, 89
11	*Hyptis suaveolens*	Pentacyclic triterpenoids	79
12	*Anacolosa pervilleana*	B-Amyrone, lupenone	90
13	*Silybum marianum*	Silimarin, silydianin	91, 92
14	*Cynodon dactylon*	Luteolin and apigenin	93
15	*Stillingia lineata* ssp.	Tonantzitlolones	94, 95
16	*Glycosmis pentaphylla*	Isovaleric acid and avicequinone-C	96
17	*Zingiber officinale*	[6]-Gingerol	97, 98
18	*Garcinia mangostana*	α-Mangostin	99
19	*Psidium guajava*	Longifollen and quercetin	100
20	*Withania somnifera*	Withanolides	101

but not in humans. Another vaccine, in which virus like particles were grown in HEK293T cells and a measles virus vectored VPL vaccine, demonstrated a good neutralizing response with mild to moderate side effects[64].

Alternative treatment of chikungunya Infection

Chikungunya fever is a viral disease. It is not related with chicken or bird flu in any manner. Various allopathic medicines are available that claim to treat the disease, but they only provide symptomatic relief with numerous side effects. Some herbal drugs are also widely used as alternative to allopathic medicines for the management of the disease with high efficacy and safety. The details of such herbs are summarized in Table I.

CONCLUSION

Nowadays, chikungunya fever is considered as a serious public health threat. It is found worldwide, particularly in Africa and Asia including India. It is spread by the bite of infected mosquito especially *A. aegypti* and *A. albopictus.* The infection is seasonal and is at a peak during rainy season and becomes less intense during the dry season. There are highest chances of infection at day time as the primary vector of the disease bites during the day. The disease is diagnosed by using various techniques such as RT-PCR, RT-LAMP, serological tests like ELISA and by neutralizing techniques. No prophylactic treatment is available to prevent the disease. However, a range of supportive and symptomatic treatments are available for reducing the severity of the disease. Various vaccines have been tested on animal models, but till date only a few are in the stage of clinical trials. The herbal based treatment options are also in the stage of infancy. Hence, there is immense scope for developing effective prophylactic measures or treatment options in modern as well as alternative medicine systems.

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