A Wonder Drug Discovered for Chikungunya Treatment

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Various deadly diseases have infected the world population. One such alarming disease is chikungunya which spreads because of mosquito bite. Heavy rain and subsequent flooding are factors that contribute to mosquito breeding. Mosquitoes are transmitters of various disease causing germs and chikungunya virus is one such germ which causes chikungunya. Chikungunya virus is spread by the commonest mosquito in India known as *Aedes.* It transmits the virus from one person to another. The symptoms associated with chikungunya include fever, rashes, headache, weakness, severe joint pain, muscle pain and swelling. This severe pain and swelling sometimes last from months to years causing lifelong disability. Since the first outbreak of chikungunya in Africa in 1952, urbanisation, deforestation and global warming formed mosquito breeding grounds and globalisation of travel further spread the virus worldwide.

Recent report by "Centers of Disease Control and Prevention" confirms the presence of chikungunya virus in more than 100 countries across the world. Twenty eight out of twenty nine states in India have reported the presence of chikungunya virus where seasonal outbreaks lead to an increase in number of infected patients to more than 1 million annually.

The global spread of chikungunya and increase in chikungunya-infected patients led to significant research around the world but these endeavours couldn't deliver any drug or vaccine for chikungunya treatment. Therefore, the treatment given to the patients is directed towards recovery from the symptoms of fever, pain and weakness by giving anti-pyretics, analgesics and

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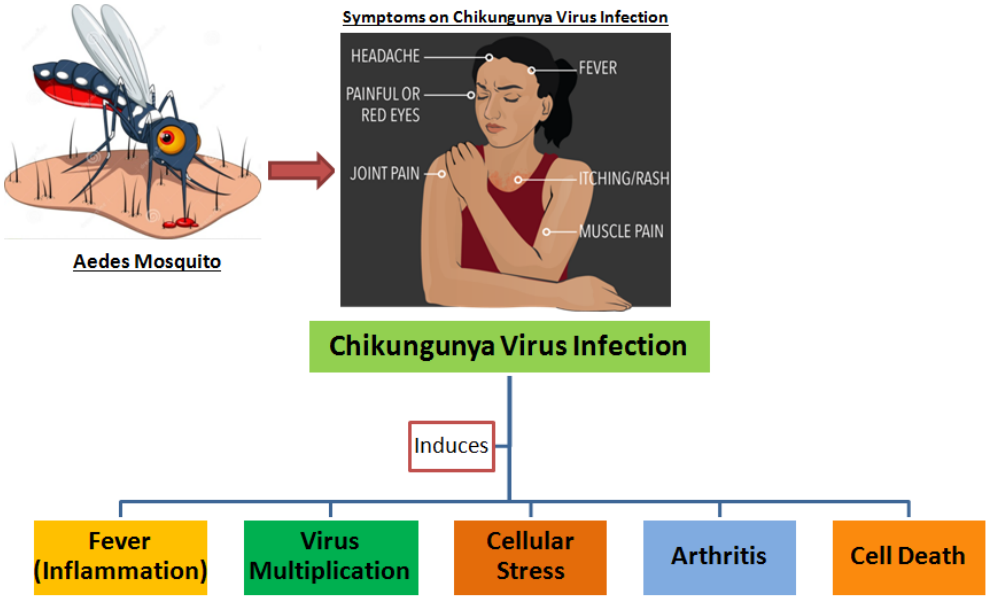
* Ms. Swati Gupta, Ph.D. Scholar from Defence Institute of Physiology and Allied Sciences -DRDO, Timarpur, Delhi, is pursuing her research on "Anti-Chikungunya Effects of andrographolide: Inhibition of Viral Replication and Mitigation of Associated inflammation." Her popular science story entitled "A Wonder Drug Discovered for Chikungunya Treatment" has been selected for AWSAR Award.



fluids, respectively. Considering the unavailability of a licensed drug or vaccine for chikungunya treatment, present study was designed to meet the global demand for an anti-chikungunya drug which could inhibit the multiplication of chikungunya virus and reduce the symptoms of fever, stress and arthritis.

A magical compound for chikungunya treatment: A team of scientists including Dr Lilly Ganju, Dr KP Mishra and research scholar Ms Swati Gupta at Defence Institute of Physiology and Allied Sciences (DIPAS), DRDO, Delhi, reported an extraordinary compound for chikungunya treatment in well-known journals including "*Asian Pacific Journal of Tropical Medicine*", "*Inflammopharmacology*" and "*Archives of Virology*". They searched the remedy of chikungunya taking help of Ayurveda and ancient folk remedies. They found a medicinal plant known as *Andrographis paniculata*, which has been used by folks as traditional medicine for the treatment of various infectious diseases. The common name of this plant is kalmegha or Bhunimba in Sanskrit, Kalmegh or Kiryat in Hindi, Chirayetah in Urdu and Creat or king of bitters in English. A major bioactive compound of this plant known as "Andrographolide" (Andro) was used in the study. Because of the bitter taste of andro, the plant is known as king of bitters. A 98% purified form of andro was purchased from a company named Sigma-Aldrich, USA and following tests were conducted to elucidate the effect of andro in the treatment of chikungunya.

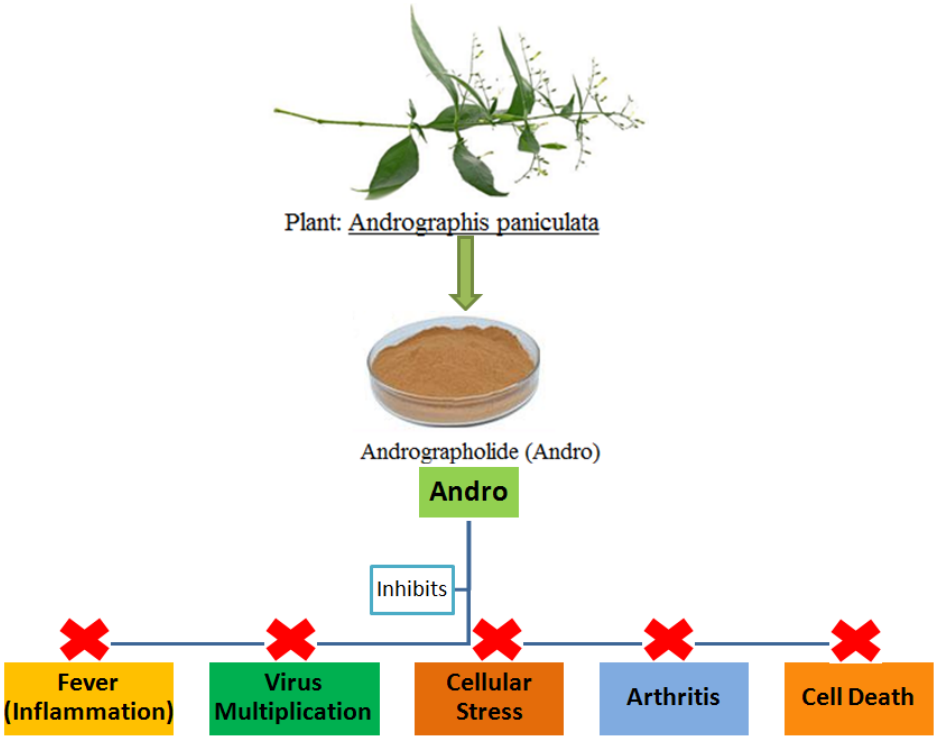
Andro as anti-pyretic (anti-inflammatory) agent: Chikungunya virus causes high fever and joint pain in infected patients. The reason behind this fever and pain is "fire" (inflammation) induced by chikungunya virus. Chikungunya infection induces release of various "fire inducing chemicals" (pro-inflammatory cytokines) which ignites "fire" inside the cell. To inhibit fever and

pain, it is essential to restrict the "fire" and release these "fire inducing chemicals". Therefore, the study was designed to elucidate the effect of andro on "fire" and "fire inducing chemicals". In the study, first a safe dose of andro was estimated to avoid its side-effects on cell. Considering this, various doses of andro (10, 5, 1 and 0.5 microgram/ml) were given to mouse cells. The study revealed that lowest dose of andro i.e. 0.5 microgram/ml did not cause any harm to the cells in comparison to the higher doses and hence the lowest dose was considered safe to use. Then, the safe dose was tested for its effect on "fire" and "fire inducing chemicals" in mouse cells. The results showed that andro treatment amazingly reduced the "fire" and "fire inducing chemicals" in the cells. Thus, the role of andro as anti-pyretic agent was confirmed.

Andro as anti-chikungunya virus agent: Virus enters inside the cell for increasing their number and also induces "fire" by releasing "fire inducing chemicals". For chikungunya treatment, it is essential to inhibit virus multiplication and release of "fire inducing chemicals". Therefore, the study was designed to investigate the effect of andro on chikungunya virus multiplication and virus induced "fire". Before studying the anti-viral effects of andro in humans, the safe dose of andro was confirmed. Considering this, various doses of andro (10, 5, 1 and 0.5 microgram/ml) were given to human cells. Surprisingly, again the lowest dose of andro, i.e. 0.5 microgram/ml, was found safe and effective in human cells. Now using this safe dose, the effect of andro on chikungunya virus-infected human cells was explored. Andro treatment substantially reduced virus multiplication and release of "fire inducing chemicals" in chikungunya infected cells. Along with human cells, andro treatment in chikungunya-infected mouse pups reduced the virus multiplication, virus induced "fire" and increased the number of virus killing immune cells thus eliminated the perpetrator virus from the animal. Thus, these experiments confirmed that andro is a potent anti-chikungunya virus agent.

Andro as anti-cellular stress agent: Viruses are dependent on host for their propagation. They hijack host "food" (proteins) for their multiplication and as a result generate stress inside the cell. To reduce stress and fulfill the continuous "food" demands, cell prepares more "food". But, sometimes these increased demands result in formation and accumulation of "under-cooked food" (unfolded proteins) which generate further stress to the cell. In order to survive and come out of the stress, cell tries different ways to reduce stress (unfolded protein response pathway) and when it fails to do so then it undergoes death (apoptosis). Virus being very smart, induces death of the cell for their propagation. Through cell death, virus gets released from one cell without coming in contact with the virus killing immune cells and gets the access to infect the new neighbouring cells.

Chikungunya virus, like any other virus, hijacks the host "food", induces cellular stress and also takes advantage of cell death in infecting the nearby cells. To treat chikungunya, it is essential to reduce chikungunya virus induced cell stress and cell death. Considering this, effect of andro on virus-induced cell stress and cell death was explored. On infecting the human cells with chikungunya virus, andro treatment was given subsequently. Interestingly, this charismatic compound efficiently mitigated the chikungunya virus-induced stress and also reduced the virus-induced cell death. Thus, the role of andro in inhibiting virus multiplication by reducing cell stress and cell death was validated.



Andro as anti-arthritic agent: Chikungunya virusinfected patients suffer from severe joint pain, muscle pain and swelling. To treat chikungunya, it is essential to treat these symptoms of arthritis. Therefore, the study was designed to elucidate the effect of andro on arthritis. In mouse, arthritis was induced by an injection of compound "complete freund's adjuvant" (CFA). Injection of CFA in mouse footpad induced various symptoms of arthritis which include joint swelling, disability in movement and aggression in animals due to pain. Following CFA injection, andro treatment was given subsequently. Interestingly, andro treatment reduced footpad swelling, far better than dexamethasone, a well-known drug for arthritis treatment. On further investigations, it was revealed that andro reduced the generation of chemicals involved in causing joint pain and swelling. Thus, the role of andro as potent anti-arthritic agent was confirmed.

The study, therefore, confirmed the role of this miraculous compound andro in treatment of chikungunya by reducing virus multiplication and associated symptoms like fever, stress and arthritis. Hence, andro can be a great hope for millions of patients infected with chikungunya virus who have been waiting for a remedy for the last 60 years. Considering the global demand for a remedy of chikungunya and hopes generated by the findings of the present study, further investigations using this wonder compound are the need of the hour for early development of an anti-chikungunya drug.