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Commentary

Artemisinin and its Derivatives as Repurposing Drug against COVID-19

Kanchan Kumari and Sandip K Mishra*

Cancer Biology Laboratory, Department of Cancer Biology, Institute of Life Sciences (Department of Biotechnology, Govt of India), Bhubaneswar, Odisha, India

***Corresponding Author:** Sandip K Mishra, Scientist-F, Cancer Biology Laboratory, Department of Cancer Biology, Institute of Life Sciences, Bhubaneswar, Odisha, India.

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The world is experiencing the outbreak of highly infectious RNA virus named COVID-19 or SARS-CoV-2 since December last year. As on 28 May 2020, World Health Organization (WHO) has reported 5,556,679 confirmed cases of COVID-19, including 351,866 deaths worldwide. Clinicians and scientists now know much about the characteristics of the virus and its effect on human health which is similar to SARC-CoV but with more serious outcomes [1]. Taking the help of its own spike (S) glycoprotein and host's receptor protein called angiotensin converting enzyme 2 (ACE-2) present on the cell membrane, the SARS-CoV-2 virus enters in the cells and releases its genome that integrates into the host genome. After hijacking the host cell regulated system it replicates in large number, infecting nearby cells and leading the infection to spread in different organs of the body [2]. The immune system of host might be one of the factors that can explain disease presentation leaving some people asymptomatic and others severely affected [3]. The immune response induced by COVID-19 infection leads to high levels of proinflammatory cytokines, neutrophils and reduced number of total lymphocytes affecting both innate and acquired immunity [4,5].

Hydroxychloroquine is one of the most promising drugs against COVID-19 [6] disease progression and management. Treatment with hydroxychloroquine show effective clearance of viral load in COVID-19 patients as reported in human trials [7,8]. Hydroxychloroquine is known as a potent anti-malarial drug also effective in disorders like Systemic lupus erythematosus (SLE), Cutaneous lupus erythematosus, Rheumatoid arthritis (RA) [9] and anti-SSA/Ro-antibody-associated congenital heart disorder. As an immunomodulatory, reports suggest that hydroxychloroquine alters T cell responses by inhibiting cytokines, INFα, TNFα and many more [10]. It inhibits Toll-like receptors 3, 7, 8 and 9 which results in reduced dendritic cell activation and reduced interferon production [11]. The inhibition of TLRs elucidates the function of hydroxychloroquine as a weak base leading to acidification of endosome [12]. Encouraging impact of hydroxychloroquine on glucose level [13] and in cardiac dysfunctions [14] explains its effectiveness against COVID-19, where diabetes [15] and cardiovascular disorders play critical role in disease onset and progression [16].

We have proved that the antimalarial drug, i.e. Artemisinin could work against Breast cancer metastasis [17]. Our hypothesis says that Artemisinin will work to fight COVID-19 infection. I would say that the way an anti-malarial drug i.e. hydroxychloroquine is showing great efficacy against COVID-19, Artemisinin is also going to be proven as an effective drug against COVID-19. New scientific discoveries come out of wild imagination but the imagination should be based on at least some reliable evidences, which may be direct or indirect. Artemisinin-based combination therapy [17] has been adopted by the World Health Organization as a first-line treatment for uncomplicated Plasmodium falciparum malaria. In endemic regions, it has proven more effective in treating the disease and even in reducing its transmission. Artemisinin is a chemical compound that reacts with iron to form free radicals, which can kill cells. Cancer cells require and uptake a large amount of iron to proliferate. They are more susceptible to the cytotoxic effect of artemisinin than normal cells.

Artemisinin and its derivatives represent the most important and influential class of drugs in the fight against malaria [18]. Since the discovery of Artemisinin in the early 1970s, the global community has made great strides in characterizing and understanding this remarkable phytochemical and its unique chemical and pharmacological properties. Today, even as Artemisinin continues to serve as the foundation for antimalarial therapy, numerous challenges have surfaced in the continued application and development of this family of drugs. These challenges include the emergence of delayed treatment responses to Artemisinin in malaria and efforts to apply Artemisinin for non-malarial indications. Here, we comment on the current understanding of the mechanism of action (MOA) of Artemisinin and in particular emphasize the importance of relating mechanistic studies to therapeutic outcomes, both in malarial and non-malarial contexts.

Here we propose Artemisinin and its derivatives (dihydroartemisinin (DHA), artemether, and artesunate) as promising drug candidates for treatment of COVID-19. *Artemisia annua* derived Artemisinin a well-known anti-malarial drug [19] that show higher chemotherapeutic index than chloroquine and is reported to be effective even in chloroquine-resistant human malarial strains [20]. As per a recent findings, Artesunate, a derivative of Artemisinin exhibits greater anti-inflammatory effect than hydroxychloroquine in RA patients [21]. WHO has recommended Artemisinin and its synthetic derivatives as a first line treatment in malaria [22]. Similar to hydroxychloroquine, Artemisinin and its derivatives effectively modulate immune system and provide direct benefit to host system, which is well evidenced by several groups of researchers [23-27]. Silva., *et al*. 2018 discusses the progress that have been made in delivery of Artemsinin and its derivatives for use for immunomodulatory purposes [28]. The substantial effect of Artemisinin and its derivatives on immune system can show promising results against immune related diseases [29]. Interestingly, encouraging immune suppressive results have been observed in combination therapy of Artemisinin and Hydroxychloroquine [30,31]. To our expectations, Artesunate shows strong anti-viral activities specially Hepatitis B virus and Hepatitis C virus as recently reported [32]. To address the availability of stable source of Artemisinin, efforts have been made for high-level semi-synthetic production of Artemisinin [33], which suggests the substantial efficacy of the drug and can be taken up in case of high demand.

In conclusion, immunomodulatory and anti-viral properties of Artemisinin and its derivatives may prove to be of great therapeutic importance against COVID-19 infection and disease progression.

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