Editorial Article **ISSN 2692-6261 | Volume 1**

Therapeutic Potential of Paclitaxel Against COVID-19: A Short Communication

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Received: 08 Nov 2020
Accepted: 30 Nov 2020
Published: 04 Dec 2020

Citation:

Pashmforosh M, Geographically Weighted Regression Modelling of the Spatial Association Between Malaria Cases and Environmental Factors in Cameroon. The New American Journal of Medicine. 2020; V1(4):1-3.

Abbreviations:

COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor-κB; IL-1β: Interleukin-1β; TNFα: Tumor necrosis factor α; TGFβ: Transforming growth factor β; IFN-γ: Interferon γ; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; ESCC: Esophageal squamous cell carcinoma; TLR-4: Toll-like receptor 4; BALF: Bronchoalveolar lavage fluid; HIV: Inhibition of human immunodeficiency virus; PLP2: Papain-like protease

1. Editorial

The coronavirus disease-2019(COVID-19) was reported in Wuhan, China, in late December 2019 and soon became the most serious global health challenge due to high rate of human-to-human transmission. The severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), is a single-stranded RNA virus and belongs to the large Coronaviridae family [1]. The pathogenesis of the COVID-19 still remains poorly understood. Cytokine storm, a hyper-inflammatory state, is considered as one of the most important causes of respiratory distress syndrome(ARDS) and death in patients with COVID-19. Clinical studies have reported that there is a strong association between the level of inflammatory cytokines and the severity of the COVID-19 [2]. The prognosis of the COVID-19 is good in most patients; however, in a small number of patients, it develops into ARDS and subsequently, death within a short time [1]. Given that there is no specific antiviral drug for treatment purpose, and no vaccine to prevent the disease, suppression of cytokine storm using FDA-approved drugs with multiple mechanisms of action may reduce the mortality of COVID-19.

Paclitaxel, an antineoplastic drug extracted from the Taxus brevifolia tree, is used to treat ovarian and breast cancer. It stabilizes microtubule polymer and prevents the disassembly of microtubules that leads to inhibition of cell division [3]. There are strong evidences indicating that paclitaxel at ultra-low non-toxic doses can inhibit inflammatory responses through different mechanisms. For instance, stabilization of endothelial microtubules, decreases neutrophil locomotion and leukocyte chemotaxis [4]. Furthermore, paclitaxel down-regulated the p38 MAPK (mitogen-activated protein kinase) signaling pathway, the nuclear factor-κB(NF-κB) and pro-inflammatory cytokines(Interleukin-1β(IL-1β), IL-6, IL-10, IL-5, IL-13, tumor necrosis factor α(TNFα), transforming growth factor β(TGFβ) and interferon γ(IFN-γ)) in various non-neoplastic conditions including endotoxin-induced acute lung injury, Schistosoma mansoni-induced pulmonary hypertension and sepsis-induced liver injury [5-8]. It is shown that SARS-CoV-2 induces cytokine production by activating the NF-κB/ MAPK signaling pathway [9]. Therefore, paclitaxel may be able to inhibit the cytokine storm through suppression of inflammatory cytokines production.

It is well established that IL-6, one of the critical cytokines in the pathogenesis of COVID-19, leads to proliferation, differentiation, recruitment, and survival of immune cells via activation of the Janus kinase(JAK) signal transducer and activator of transcription 3

(STAT) pathway [10]. Additionally, the increased expression of the activated form of STAT3 in the lung, up-regulates the pro-inflammatory cytokines and chemokines [11]. It is reported that paclitaxel could decrease the STAT3 and phospho STAT3(Ser727) level in human esophageal squamous cell carcinoma(ESCC) [12]. Therefore, blocking the JAK-STAT pathway by paclitexel is suggested as a therapeutic target for inhibition of the cytokine storm induced by SARS-CoV-2.

It is reported that the interaction between SARS-CoV-2 spike protein and toll-like receptor 4(TLR-4) induces pro-inflammatory cytokines expression, and regulates IL-6 secretion through activation of transcription factors like NF kB, AP-1, and MAPK pathway [13]. Inhibition of the TLR4-NF-κB pathway with paclitaxel has been indicated in lipopolysaccharide-induced kidney injury [8]. Moreover, a recent publication has shown that paclitaxel improved survival rates and decreased the levels of cytokines in bronchoalveolar lavage fluid(BALF) by inhibition of TLR4-NF-κB pathway through MUC1 in mice and human lung type II epithelial cell [14]. MUC1, a large transmembrane glycoprotein expressed in epithelial cells, has an important anti-inflammatory activity against pathogen-induced inflammation such as influenza A virus by suppression of TLR signaling, and production of the anti-inflammatory cytokines such as IL-10 [15]. It is possible that paclitaxel by inhibition of TLR4, decreases the levels of inflammatory cytokines in sever COVID-19 patients.

Moreover, the antiviral activity of paclitaxel, such as inhibition of human immunodeficiency virus(HIV)-1 protease, has been reported in some studies [16, 17]. In recent years, the induction of autophagy has been noticed as a new therapeutic target for viral diseases. Although little is known about the role of autophagy in the prevention and treatment of COVID-19. It is documented that the SARS-CoV-2 virus inhibits the autophagy system for increasing self-replication and escape from elimination, which makes an efficient viral dose density for viral pathogenicity [18, 19]. This virus hijacks autophagy through several mechanisms, including, overproduction of the membrane-associated papain-like protease(PLP2) that interacts with beclin-1(an autophagy-inducing peptide) and inhibits fusion of the autophagosome with the lysosome to increase the virus load in host cells[18]. It is shown that paclitaxel exerts an inductive effect of autophagy via various mechanisms such as the increased expression of beclin-1(an autophagy-inducing peptide) and LC3 (a marker of autophoagosome formation) [20]. Also, a previous study demonstrated that beclin-1 prevented the replication and reduced the titers of several positive-stranded RNA viruses including HIV-1, and improves clinical outcomes [21]. Therefore, paclitaxel may have an antiviral effect against SARS-COV-2 through autophagy-inducing activity.

According to these evidences, the authors suggest that paclitaxel may have therapeutic potential in COVID-19 through anti-inflammatory and possible antiviral activity; however, clinical trials are yet needed.

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