Letter to Editor:
Possible Benefits of Paclitaxel Therapy for COVID-19

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Dear Editor

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 the 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 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 the treatment of the disease, suppression of cytokine storms using FDA-approved drugs with multiple mechanisms of action may reduce the COVID-19-related mortality.

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 leading to inhibition of cell division [3]. It has been reported that paclitaxel at ultra-low non-toxic doses (15 mg/m^2) can inhibit inflammatory responses through different mechanisms. For instance, stabilization of endothelial microtubules decreases neutrophil locomotion and leukocyte chemotaxis [4, 5]. Furthermore, paclitaxel down-regulated the p38 mitogen-activated protein kinase (MAPK) 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 [6-9]. SARS-CoV-2 induces cytokine production by activating the NF-κB/ MAPK signaling pathway [10]. Therefore, paclitaxel may be able to inhibit the cytokine storm through the 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 (STAT) pathway [11]. Additionally, the increased expression of the activated form of signal transducer and activator of transcription 3 (STAT3) in the lung up-regulates the pro-inflammatory cytokines and chemokines [12].

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It is reported that paclitaxel could decrease the STAT3 and phospho STAT3 (Ser727) levels in human esophageal squamous cell carcinoma (ESCC) [13]. Therefore, blocking the JAK-STAT pathway by paclitaxel is suggested as a therapeutic target for the 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 the expression of pro-inflammatory cytokines, and regulates IL-6 secretion through the activation of transcription factors, like NF-κB, AP-1, and MAPK pathway [14]. Inhibition of the TLR4-NF-κB pathway with paclitaxel has been indicated in lipopolysaccharide-induced kidney injury [9]. 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 the TLR4-NF-κB pathway through MUC1 in mouse and human lung type II epithelial cell [15]. MUC1, a large transmembrane glycoprotein expressed in epithelial cells, has an important anti-inflammatory activity against influenza virus-induced inflammation by suppression of TLR signaling and production of anti-inflammatory cytokines, such as IL-10 [16]. It is possible that paclitaxel by inhibition of TLR4 decreases the levels of inflammatory cytokines in severe 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 [17, 18]. 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 inhibits the autophagy system from increased self-replication and escape from elimination, which makes an efficient viral dose density for viral pathogenicity [19, 20]. This virus hijacks autophagy through several mechanisms, including, the overproduction of the membrane-associated papain-like protease (PLP2) that interacts with beclin-1 (an autophagy-inducing peptide) and inhibits the fusion of the autophagosome with the lysosome to increase the virus load in host cells. Paclitaxel exerts an inductive effect on autophagy via various mechanisms, such as the increased expression of beclin-1 (an autophagy-inducing peptide) and LC3 (a marker of autophagosome formation) [21]. 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 improved clinical outcomes [22]. Therefore, paclitaxel may have an antiviral effect against SARS-COV-2 through autophagy-inducing activity.

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

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceived of the presented idea: Saeedeh Shariati and Marzieh Pashmforosh; Collected the data: Hamideh Aghaei Nezhad and Mojtaba Haghighat; Wrote the manuscript with support from: Saeedeh Shariati, Marzieh Pashmforosh and Hamideh Aghaei Nezhad; Read and approved the final manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

References

[1] Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020. [DOI:10.1016/S0140-6736(20)30920-X]

[2] Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine & Growth Factor Reviews. 2020. [DOI:10.1016/j.cytogfr.2020.05.002] [PMID] [PMCID]

[3] Kavallaris M. Microtubules and resistance to tubulin-binding agents. Nature Reviews Cancer. 2010; 10(3):194-204. [DOI:10.1038/nrc2803] [PMID]

[4] Roberts RL, Nath J, Friedman MM, Gallin JI. Effects of taxol on human neutrophils. Journal of Immunology. 1982; 129(5):2134-41. [PMID]

[5] Lin H, Chen Y, Shi A, Pandya KJ, Yu R, Yuan Y, et al. Phase 3 randomized low-dose paclitaxel chemoradiotherapy study for locally advanced non-small cell lung cancer. Frontiers in Oncology. 2016; 6:260. [DOI:10.3389/fonc.2016.00260] [PMID] [PMCID]

[6] Kassa B, Mickael C, Kumar R, Sanders L, Koyanagi D, Hernandez-Saavedra D, et al. Paclitaxel blocks Th2-mediated TGF-β activation in Schistosoma mansoni-induced pulmonary hypertension. Pulmonary Circulation. 2018; 9(1):2045894018820813. [DOI:10.1177/2045894018820813] [PMID] [PMCID]

[7] Sevko A, Michels T, Vrohlings M, Umansky L, Beckhove P, Kato M, et al. Antitumor effect of paclitaxel is mediated by inhibition of myeloid-derived suppressor cells and chronic inflammation in the spontaneous melanoma model. The Journal of Immunology. 2013; 190(5):2464-71. [DOI:10.4049/jimmunol.1202781] [PMID] [PMCID]

[8] Mirzapoiazova T, Kolosova IA, Moreno L, Sammani S, Garcia JG, Verin AD. Suppression of endotoxin-induced inflammation by taxol. European Respiratory Journal. 2007; 30(3):429-35. [DOI:10.1183/09031936.00154206] [PMID]

[9] Zhang D, Li Y, Liu Y, Xiang X, Dong Z. Paclitaxel ameliorates lipopolysaccharide-induced kidney injury by binding myeloid differentiation protein-2 to block toll-like receptor 4-mediated nuclear factor-κB activation and cytokine production. Journal of Pharmacology and Experimental Therapeutics. 2013; 345(1):69-75. [DOI:10.1124/jpet.112.202481] [PMID] [PMCID]

[10] Ma Q, Pan W, Li R, Liu B, Li C, Xie Y, et al. Liu Shen capsule shows antiviral and anti-inflammatory abilities against novel coronavirus SARS-CoV-2 via suppression of NF-κB signaling pathway. Pharmacological Research. 2020:104850. [DOI:10.1016/j.phrs.2020.104850] [PMID] [PMCID]

[11] Arnaldez FI, O'Day SJ, Drake CG, Fox BA, Fu B, Urba WJ, et al. The Society for Immunotherapy of Cancer perspective on regulation of interleukin-6 signaling in COVID-19-related systemic inflammatory response. Journal for Immunotherapy of Cancer. 2020; 8(1):e000930. [DOI:10.1136/jitc-2020-000930] [PMID] [PMCID]

[12] Li Y, Du H, Qin Y, Roberts J, Cummings OW, Yan C. Activation of the signal transducers and activators of the transcription 3 pathway in alveolar epithelial cells induces inflammation and adenocarcinomas in mouse lung. Cancer research. 2007;67(18):8494-503. [DOI:10.1158/0008-5472.CAN-07-0647] [PMID]

[13] Zhang X, Wu X, Zhang F, Mo S, Lu Y, Wei W, et al. Paclitaxel induces apoptosis of esophageal squamous cell carcinoma cells by downregulating STAT3 phosphorylation at Ser727. Oncology reports. 2017; 37(4):2237-44. [DOI:10.3892/or.2017.5503] [PMID]

[14] Astuti I. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020. [DOI:10.1016/j.dsx.2020.04.020] [PMID] [PMCID]

[15] Wang Y-M, Ji R, Chen W-W, Huang S-W, Zheng Y-J, Yang Z-T, et al. Paclitaxel alleviated sepsis-induced acute lung injury by activating MUC1 and suppressing TLR-4/NF-κB pathway. Drug Design, Development and Therapy. 2019; 13:3391. [DOI:10.2147/DDDT.S222296] [PMID] [PMCID]

[16] McAuley J, Corcilius L, Tan H, Payne R, McGuckin M, Brown L. The cell surface mucin MUC1 limits the severity of influenza A virus infection. Mucosal immunology. 2017; 10(6):1581-93. [DOI:10.1038/mi.2017.16] [PMID]

[17] Ryang J, Yan Y, Song Y, Liu F, Ng TB. Anti-HIV, antitumor and immunomodulatory activities of paclitaxel from fermentation broth using molecular imprinting technique. AMB Express. 2019; 9(1):194. [DOI:10.1186/s13568-019-0915-1] [PMID] [PMCID]

[18] Krawczyk E, Luczak M, Majewska A. [Antiviral and cytotoxic activities of new derivatives of natural sesquiterpenes and taxol (Polish)]. Medycyna Doswiadczalna i Mikrobiologia. 2005; 57(1):93-9. [PMID]

[19] Carmona-Gutierrez D, Bauer MA, Zimmermann A, Kainz K, Hofer SJ, Kroemer G, et al. Digesting the crisis: Autophagy and coronaviruses. Microbial Cell. 2020; 7(5):119. [DOI:10.15698/mic2020.05.715] [PMID] [PMCID]

[20] Panda PK, Fahrner A, Vats S, Seranova E, Sharma V, Chipara M, et al. Chemical screening approaches enabling drug discovery of autophagy modulators for biomedical applications in human diseases. Frontiers in Cell and Developmental Biology. 2019; 7:38. [DOI:10.3389/fcell.2019.00038] [PMID] [PMCID]

[21] Zhang Q, Si S, Schoen S, Chen J, Jin X-B, Wu G. Suppression of autophagy enhances preferential toxicity of paclitaxel to folliculin-deficient renal cancer cells. Journal of Experimental & Clinical Cancer Research. 2013; 32(1):99. [DOI:10.1186/1756-9966-32-99] [PMID] [PMCID]

[22] Shoji-Kawata S, Sumpter R, Leveno M, Campbell GR, Zou Z, Kinch L, et al. Identification of a candidate therapeutic autophagy-inducing peptide. Nature. 2013; 494(7436):201-6. [DOI:10.1038/nature11866] [PMID] [PMCID]

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