

## Nanotechnology in combatting Cytokine Storm in Covid-19 patients

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Cytokine storm involves an excessive production of inflammatory cytokines in the body. It has been characterised as one of the major causative mechanisms behind acute respiratory distress syndrome (ARDS). Cytokines are a collection of diverse proteins whose primary function lies in intercellular signalling and communication. The cytokines that largely contribute to initiating cytokine storms are interleukins, chemokines, interferons and colony-stimulating factors. In patients suffering from hyperinflammation and macrophage activation syndrome (MAS), large amounts of pro-inflammatory cytokines such as interferon- $\alpha$  (IFN $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), transforming growth factor beta (TGF $\beta$ ), etc., and chemokines (C-X-C motif chemokine ligand 10 (CXCL10), C-C motif chemokine ligand 2 (CCL2), etc.) are expressed. This causes an acute inflammatory response, resulting in the body's immune system attacking itself. This subsequently leads to ARDS and multi-organ failure, which is the main cause of death in cases of severe infections. Further, nanotechnology can be applied in a myriad of ways to neutralise cytokine storms, therefore minimising the onset of ARDS. One hypothesis that has been proposed to tackle cytokine storms in patients facing an acute case of COVID-19 is to use nano-formulations of dexamethasone. A dose of 6 mg of dexamethasone/day, administered orally for 10 days, showed a 35% decrease in deaths in patients who were being sustained on mechanical ventilation. It also resulted in a 20% reduction in deaths of non-ventilated patients. This indicates that dexamethasone is a promising drug in the treatment of COVID-19. Another nanotechnology-based solution that intervenes in the cytokine storm produced in COVID-19 patients is the use of a nanoparticle (NP) formulation of squalene-adenosine (SQAd) encapsulated in alpha-tocopherol. Adenosine, a naturally occurring compound in humans, is also used as a drug for multiple disorders and diseases. Squalene, an endogenous lipid that is produced by the human body as well, is used in conjugation with adenosine to improve blood circulation time and to lower the toxicity of pure adenosine. This formulation was ultimately used to encapsulate vitamin E (VitE) by the nanoprecipitation technique. Among the several in vivo studies that were conducted, SQAd/VitE NPs successfully reached the sites of acute inflammation and endothelial dysfunction in models of both local and systemic inflammation. Compared to the administration of free adenosine into patients, the SQAd/VitE NPs show greater precedence over the former method. Therefore, this formulation helps in combatting cytokine storms and also enhances the bioavailability of the drug, especially at the sites of inflammation.

*Keywords: Cytokine storm, COVID-19, Nanotechnology, Adenosine, Dexamethasone*

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