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## Enhancement of immune tolerance of COVID-19 patients might be achieved with alginate supplemented therapy

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### ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a devastating pandemic virus that has neither an effective cure nor vaccine so far. Once inside the body, blood viremia increases significantly in conjunction with uncontrolled awry immune response that induces severe unbalanced cytokine storm. This cytokine storm is initiated although the number of T lymphocyte is severely reduced alongside damaged lymphoid tissue and systemic body inflammation. It will be a demanding need to find a natural polymer that has both anti-inflammatory and immune-enhancing effects that can induce the immune system to fight off the virus in a balanced manner. Alginate is a natural polysaccharide extracted from brown Algae and has been used extensively as an immune activator in different *in vivo* model animals and *in vitro* cell culture systems. Based on our recent experiment and other findings cited in the literature, we propose the introduction of alginate in the therapeutic regime of COVID-19 patients.

**Keywords:** Alginate, COVID-19, T lymphocyte, cytokine storm

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### INTRODUCTION

The recent declaration of WHO of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a pandemic was imposed by the widespread of the virus in almost every country in the world. SARS-CoV-2 is a positive single-stranded RNA virus that was naturally mutated to infect human from its intermediate hosts (bats and pangolins) (Letko et al., 2020; Zhang, 2020). Major concerns of SARS-CoV-2 in relation to other viruses are that firstly, SARS-CoV-2 infection appears before first symptom onset hit, secondly, up to 56% of patients experience no fever or other related symptoms and require no hospitalization finally a strict quarantine measure is the only solution to decrease viral spread (Ho, 2020). SARS-CoV-2 exhibit several structural and non-structural proteins that antagonize host antiviral immune response (antagonize interferons INFs), evade host immune system and promote its replication (Channappanavar et al., 2017; Zmmer, 2020).

Symptoms of SARS-CoV-2 infection include dyspnea, severe respiratory distress, hypoxemia, lymphopenia, exaggerated cytokine release known as cytokine storm (awry and excessive uncontrolled inflammatory cytokine production) and micro blood clotting in lungs and several body organs. These symptoms indicate that immune system homeostasis plays an important and significant role during viral pathogenesis and pneumonia development (Jiang et al., 2020; Li et al., 2020; Zheng et al., 2020). Several coronavirus disease (COVID-19) patients experience an exaggerated and uncontrolled release of cytokines although suffering lymphopenia. Analysis of T lymphocytes in those patients indicated that these T cells show high levels of exhaustion (high expression levels of Tim-3 and PD-1 markers) and show signs of reduced diversity (Ho, 2020; Zheng et al., 2020). This in part could explain the uncontrolled release of cytokines and the initiation of cytokine storm niche in lungs first and whole body lastly.

A rapid reduction in T cell lymphocytes (CD4<sup>+</sup> and CD8<sup>+</sup>) was observed in SARS-CoV-2 patients shortly after contracting the virus. Although reduced in number, yet they exhibited elevated levels of CD69, CD38 and CD44 which are markers of T cell hyper-activation. This loss in T cell density was compensated during the recovery phase of patients and this was not due to new cells production from thymus but due to lymphocyte recirculation between body tissues and peripheral blood. This indicates that SARS-CoV-2 infection could interfere with lymphocyte production in lymphoid organs with unknown mechanism. Consistent with this, reports from COVID-19 patients in China revealed that severely infected patients suffer from lymphoid tissues destruction (spleen atrophy, lymph node atrophy and necrotic foci all over the body) (Wen Zhang et al., 2019). Since immune cells and lymphoid tissues exhibit no ACE2 surface markers, it was postulated that T cell depletion as a direct consequence of inflammation and cytokine storm initiated by a viral infection (Wen Zhang & Yan, 2019).

Viral induced inflammation was accompanied with significantly elevated levels of inflammatory cytokines such as IL-6, IL-7, IL-10, TNF- $\alpha$ , granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1) and macrophage inflammatory protein 1 alpha (MIP1A) was confirmed in those patients (Ho, 2020; Lin et al., 2020).

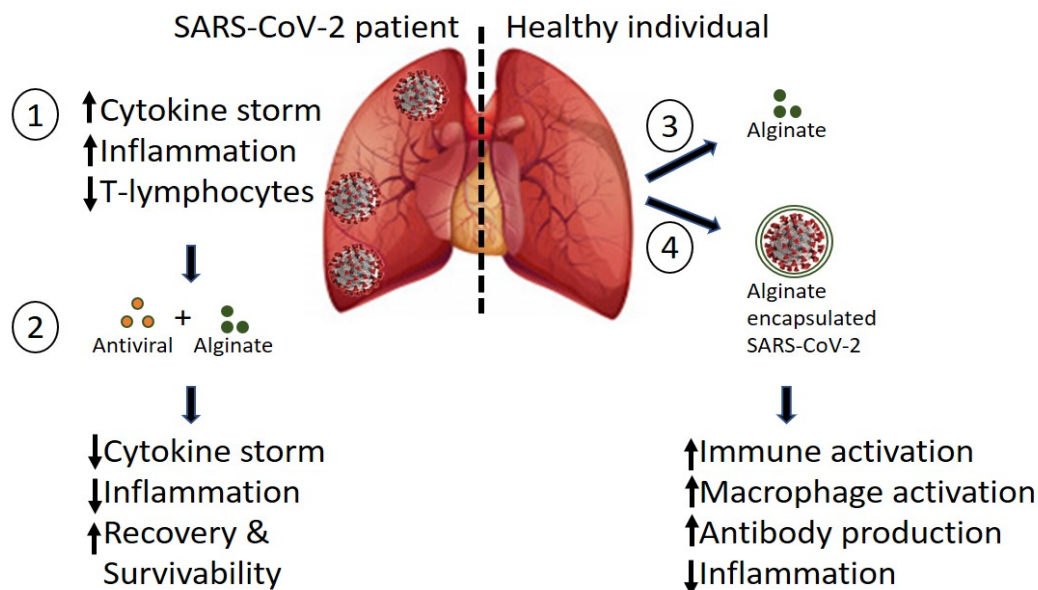
The proposed therapeutic regime in different countries was based on the use of anti-viral drugs along with anti-inflammatory drugs. Chloroquine and hydroxy-chloroquine were used as anti-inflammatory drugs in different countries before its withdrawal due to associated heart complications (Choudhary et al., 2020; Molina et al., 2020). In addition, UK recently approved the use of dexamethasone as an efficient anti-inflammatory drug for COVID-19 patients alongside with Lopinavir as anti-viral therapy. Furthermore, another therapeutic regime was proposed for COVID-19 patients that rely on using Intravenous immunoglobulin (IVIg) and anti-coagulant (low molecular weight heparin) for better recovery from COVID-19 severe and lethal symptoms (Lin et al., 2020).

It is obvious from the presented evidence above that SARS-CoV-2 complications are based on a weakened immune system and local & systemic inflammation in the body. Hence it is evitable and necessary to look for natural candidate therapies that activate the immune system and reduce inflammation burden in the body. Based on our recent unpublished experiment in a mouse model of osteoarthritis (OA), we have shown that a naturally occurring polysaccharide namely alginate was able to boost immunity and reduce inflammation significantly than the untreated group.

Marine algae are considered as a source of bioactive agents such as alginate, that have a variety of biological characteristics. Alginate is an important naturally occurring polysaccharide that can be found in several marine brown algae such as *Macrocystis pyrifera*, *Laminaria hyperborean* and *Ascophyllum nodosum* (Kurt Ingar Draget, 2005; Szekalska et al., 2016). Based on alginate source, alginate co-polymer can be consists of either  $\alpha$ -L-guluronic (G- block polymer) or  $\beta$ -D-mannuronic (M-Blocks polymer) residues or as a mixture of the two blocks (MG) with superior biological characteristics such as solubility, no biological toxicity, gelation and as a scaffold matrix for living cells (Andersen et al., 2015; Wawrzynska et al., 2018).

Alginate extraction is a simple multi-step process that includes the digestion of raw source with diluted mineral acid followed by purification and transformation into salt derivative (sodium or calcium) Expansion in the annual industrial production of alginate is expected to exceed 30000 metric tons with special emphasis on alginate quality refining for mammalian compatibility for pharmaceutical and biomedical applications (Kurt, 2005; Paredes-Juarez et al., 2014).

Physicochemical properties of alginates introduce them as potential candidates for several biomedical applications. They possess mucoadhesive properties, the feasibility of chemical and physical modifications, biocompatibility, no immunogenicity and non-toxicity.



**Figure 1.** Hypothetical diagram of alginate application to treat Covid-19 patients. 1- Covid-19 patients suffer from dysregulated immune response accompanied by cytokine storm and lymphopenia (decrease in T-lymphocytes). 2- Here we postulate that adding alginate supplement to the anti-viral medications can enhance patient immunity, reduce inflammation and increase recovery and survivability of patients. Alginate supplement can either be administrated to health individual to boost their immune system through macrophage activation (3) or can be used as encapsulation to inactivated SARS-CoV-2 during vaccination routine to enhance body response and specific antibody production (4).

Alginates have been used successfully as an anti-oxidant and anti-inflammatory drug to treat diabetic conditions, hypertension, viral infection (Szekalska et al., 2016) and in wound healing application (Thomas, 2000). In our recent unpublished study on a rat model of osteoarthritis (OA), we have shown that a naturally occurring polysaccharide namely alginate was able to decrease lipid peroxidation, Aggrecanase (ADAMTS4) and concentration of  $\beta$ -glucouronidase in sera of rats. At the same time, increase antioxidant activity significantly than the untreated group.

In addition, alginate is the only natural marine polysaccharide that possesses a carboxyl group in each sugar ring which is of great importance when incorporating alginate gels with drug cargos (Xing et al., 2020). Alginate oligosaccharides effectively inhibit oxidative stress, modulate the immune response and fight inflammation by free radical scavengers, induce cytokine release and control expression of transcription factor Nuclear Factor Kappa B (NF- $\kappa$ B). NF- $\kappa$ B is an important regulator of both innate and adaptive immunity (Ge et al., 2018; Xing et al., 2020). Anti-inflammatory activity of

alginate oligosaccharide rely on inhibition of nitric oxide (NO) production, prostaglandin E2 (PE2) and cyclooxygenase 2 (COX-2) in RAW264.7 macrophages (Xing et al., 2020). Studies on sulphated alginate derivatives have shown that it has a potent antioxidant, anti-inflammatory and immune regulatory role on human macrophages. The polymer was superior in superoxide radical's scavenger, regulate IL-6, CXXL8 and TNF- $\alpha$  (Kerschenmeyer et al., 2017). Furthermore, another study indicated that sodium alginate successfully induces the activation of macrophage like-cells invitro through NF- $\kappa$ B pathway activation. This was followed by controlled production of proinflammatory cytokines such as IL-1 $\beta$ , IL-6, IL-12 and TNF- $\alpha$  (Yang et al., 2009). Finally, alginate enriched mannuronate (M-alginate) was found to be a potent inducer for cytokine production than guluronate alginate (Lee et al., 2012) especially induce monocyte and macrophage cytokine production for the treatment of inflammatory diseases and immune-deficient diseases (Ge et al., 2018; Kerschenmeyer et al., 2017; Kurt Ingar Draget, 2005; Yang & Jones, 2009).

Administration of chitosan/alginate nanoparticle encapsulated bee venom (CH/AL-BV) via the nasal route to pigs after being vaccinated against porcine reproduction and respiratory syndrome virus (PRRSV), could improve their immune response and viral clearance against the virus. This effect was attributed to the high production of CD4<sup>+</sup> T lymphocytes, T helper cells and T memory cells (Lee et al., 2018). Similar results were obtained during PR8 influenza virus immunization in mice (Mosafer et al., 2019).

Alginate gels are nano-porous and have been used extensively in dressing applications, wound healing and tissue engineering (Andersen et al., 2015; Lee & Mooney, 2012) owing to their capability of slow and controlled induction of proinflammatory cytokines (IL-8 and TNF- $\alpha$ ) that help maintaining tissue immune homeostasis (Ge et al., 2018; Wiegand et al., 2009). Alginate gels incorporated with slow-release low molecular weight heparin were found to induce neovasculature in traumatic tissues by the induction of vascular endothelial growth factor (VEGF) release (Lee et al., 2003) and prevent blood clotting and sepsis (Li et al., 2020).

### Recommendation

Here we hypothetically propose that alginate and alginate derivatives could be used successfully as a therapeutic supplement to moderate and severe infected COVID-19 patients to reduce body inflammation and boost their immune system to reduce blood viremia, decrease lipid peroxidation and increase antioxidant activity. Also, regular daily intake of alginate for healthy individuals could enhance their immune system and may provide additional protection against SARS-CoV-2 infection. Finally, we recommend the use of alginate gels as encapsulation compartment during SARS-CoV-2 vaccination trials to induce a potent immune response and SARS-CoV-2 antibody production.

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### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

### Conflict of Interest

The authors declare no conflict of interest.

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