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Table 1. How astaxanthin is related to the clinical characteristics of COVID-19

COVID-19 clinical characteristics	Relation to astaxanthin	Reference
Elevated production of pro-inflammatory cytokines (IL2, IL-1β, IL-8, etc.)	Inverse correlation	(2, 6, 12)
Increased production of IL6 & TNF-α	Inverse correlation	(2, 6, 12)
Increased production of CRP	Inverse correlation	(2, 23, 12)
NF-kB/MAPK signaling pathway activated	Inverse correlation	(12, 13, 57)
Activate JAK/STAT-3 signaling pathway	Inverse correlation	(6, 12, 74)
Increase TLR4 signaling	Inverse correlation	(50, 77)
Dysregulate CRS	Regulate CRS	(12, 13)
Imbalance RAS signaling pathway induce ROS, inflammation	Inverse correlation, inhibit inflammation	(23, 42, 46, 51)
Induce oxidative stress	Inverse correlation	(12, 13, 46, 51)
Increase VEGF	Inverse correlation	(6, 74)
Decrease lymphocytes, NK cells	Inverse correlation	(6, 14)
Increased risk of sepsis	Inverse correlation	(3, 12)
Increase risk of ALI/ARDS	Inverse correlation	(12, 59)
Increase risk of heart failure	Inverse correlation	(8, 42, 50)
Increase risk of CNS injury	Inverse correlation	(75, 77, 80, 82)

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Table 2. Animal studies investigating effect of astaxanthin on inflammatory/oxidative stress

Clinical Characteristics	ASX dose / study model	Outcome of the study	Reference
Production of pro-inflammatory cytokine, such as IL-6 & TNF-α leading to CRS	100 mg/kg, i.p. / LPS challenged mice	- Significant decrease in serum level of IL-6, TNF-α - Increased survival rate	(12)
Sepsis, Lung Injury	100 mg/kg, i.p. / LPS challenged mice	- ASX protects LPS induced lung injury - Repressed alveolar wall swelling - Attenuated the decline in number of pulmonary alveoli	(12)
Oxidative stress induced Lung fibrosis	100 mg/kg/ mice	- ASX was reported to exert protection of alveolar epithelial cells type II - Inhibited ROS generation and dose- dependent apoptosis, - Inhibited cytochrome c (Cyt c) release - Activation of caspase 9, caspase-3, Nrf-2 and other cytoprotective genes.	(51)

Risk of ARDS	100 mg/kg, i.p. / LPS challenged mice	- ASX reduces the risk of ARDS - Reduced cytokine level, such as IL-6, CRP, COX-2 & TNF-α, etc.	(12), (13)
Acute Lung Injury	100 mg/kg, i.p. / LPS challenged mice	- ASX attenuated LPS induced ALI - Suppressed the inflammatory cytokines, such as IL6 & TNF-α - Inhibited the activity of MAPK/NF-kB signaling pathway.	(12)
Risk of chronic lung injury due to inflammatory cytokines	10μM/ human gingival keratinocyte line NDUSD-1	- Inhibited NF-kB/p65 - Decreased production of IL-6 - Decreased TNF-α significantly in 1-12h and IL-1β was below detection level.	(9)
Risk of diabetic	0.05%/ diabetic rat	- Reduced ROS - Decreased plasma CRP, IL-6, MCP-1 - Enhanced antithrombin-III.	(62)
RAS induced ROS/oxidative stress	NA/ mice	- Decreased oxidative stress - Lowered systolic blood pressure - Improved endothelial function	(42, 47)

Risk of CVD	Astaxanthin 5% in olive oil (50 mg/kg/ daily rally), Stroke prone spontaneously hypertensive rats	- Significant reduction in blood pressure - Delayed incidence of stroke	(76)
Risk of thrombosis	5, 10 & 30 mg/kg/day, hyperlipidemic rat	- Reduced blood coagulation - Reduced platelet aggregation - Promoted fibrinolytic activity	(93)

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Table 3. Clinical studies involving human investigating the safety, bioavailability and effects of astaxanthin

Study	Study population & study design	Dosage	Duration of supplementation	Effects of astaxanthin
Spiller *et al.* (87)	Double-blind, placebo-controlled human clinical trial, healthy volunteers	12 mg/day	8 weeks	- Significant reduction in CRP level - No adverse effect
Park *et al.* (14)	Double-blind, placebo-controlled human clinical trial, healthy young women	2 mg/day & 8 mg/day	8 weeks	- Significant decrease in CRP level - Reduced oxidative stress - Decreased plasma 8-hydroxy-2'-deoxyguanosine - Increased total T and B cell population - Enhanced NK cell cytotoxic activities - Stimulated lymphocyte proliferation

				- Decreased DNA damage significantly - Stimulated immune system
Baralic *et al*. (88)	40 elite soccer players, placebo controlled. Randomized	4 mg/day	90 days	- Increased immunoglobulin - Decreased pro-oxidant/antioxidant balance - Controlled CRP - Attenuated muscle damage
Iwamoto *et al*. (89)	Volunteers, open labelled	Different doses: 1.8, 3.6, 14.4, 21.6 mg/day	2 weeks	- Reduction of LDL oxidation
Mercke Odeberg *et al*. (90)	Healthy man volunteers, open	40 mg	8 weeks	- Enhanced bioavailability with

	labelled parallel			lipid-based formulation
Spiller *et al*. (91)	Healthy adults, randomized double blind, placebo controlled	6 mg/day (3 x 2 mg tablets/day)	8 weeks	- Demonstrated safety assessed by measures of blood pressure and biochemistry
Miyawaki *et al*. (92)	Healthy males, single blind, placebo controlled	6 mg/day	10 days	- Improved blood rheology

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