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The role of gum Arabic as an anti-inflammatory, antioxidant, and immune modulator in COVID-19: A review

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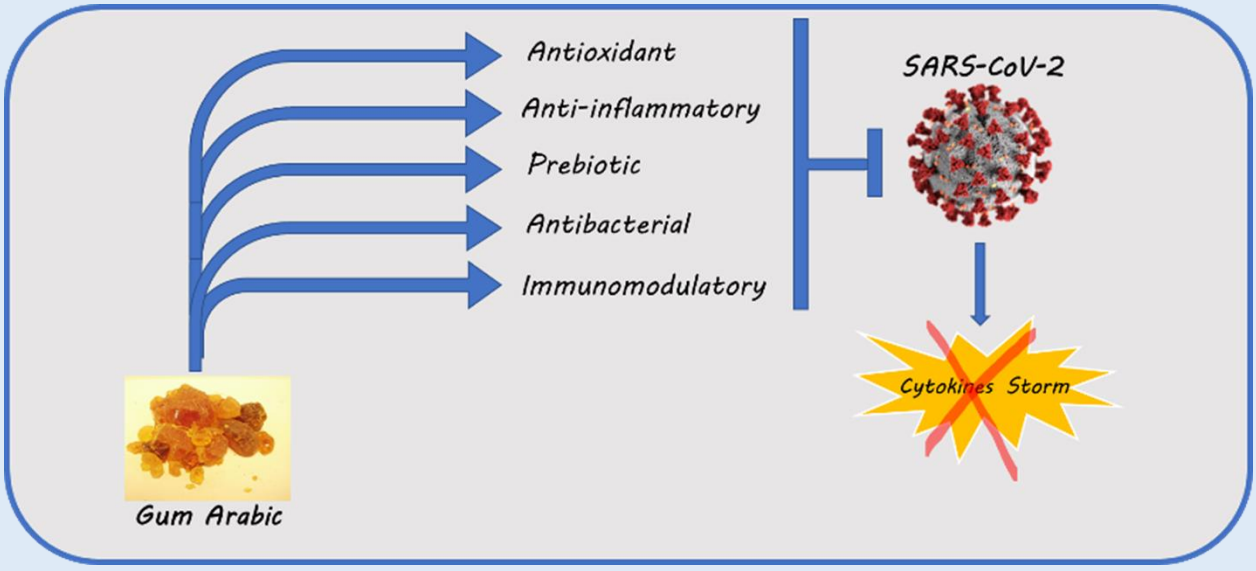
ABSTRACT

Background: Down-regulation of the lung inflammatory response seems to preserve pulmonary functions and improve survival in COVID-19. The key factor in overcoming the cytokine storm caused by COVID-19 by immunomodulation, rather than immunosuppression. Identifying the right mechanism to manipulate the immune regulatory networks in the lung—with minimal side effects—represents one of the many challenges in the treatment of COVID-19 disease. Immunomodulatory, anti-inflammatory, antioxidant, and gut-regulatory activities are the most significant properties of prebiotics. Therefore, it could be beneficial to consider them as an adjuvant dietary intervention among COVID-19 patients. Understanding the exact mechanism of prebiotic defense against infection and regulation of immune processes involved in COVID-19 are crucial for the development of novel therapeutic agents. Several studies considered Gum Arabic (GA) as a potent prebiotic with cytoprotective properties. This review aims to discuss and display the possibility of utilizing the beneficial effects of GA to modulate COVID-19 pathogenesis.

Keywords: COVID-19, Gum Arabic, Immunomodulation, dietary intervention, Gut microbiota, Anti-inflammatory, Antioxidant



INTRODUCTION In the first quarter of 2020, the World Health Organization (WHO) declared the pandemic COVID-19 outbreak. Several trials for COVID-19 treatment have been conducted. The world expects to experience many waves of COVID-19 outbreaks with the lifting of restrictions and lockdowns, and herd immunity is still far away to be achieved (1).

Mild COVID-19 affects healthy individuals leading to seasonal, slight to moderate cold flu-like symptoms affecting the upper respiratory tract. In contrast to the highly pathogenic virus, SARS-CoV-2 infects causes severe pneumonia, and acute respiratory distress syndrome (ARDS) (2). The main cause of death is ARDS and multiple organ failure is secondary to the cytokine storm (CS) (3). Inflammation is the key pathogenesis in COVID-19 patients (4) since the severity of ALI (Acute Lung Injury) was accompanied by an elevated expression of inflammation-related genes rather than increased viral titers (4). As a result, finding a way to block the CS using anti-inflammation therapy is critical for lowering COVID-19-related mortality (5).

The discovery of COVID-19 RNA in the stool of patients and the presence of diarrhea as one of the clinical symptoms proposed a link between the lung and the intestine (6). Gut microbiota was found to tune the immune system and balance the pro and anti-inflammatory response (7), can suppress viral infection and prevent immune over-reaction that can be destructive to lung and vital organ systems (8).

Gum Arabic (GA) is a natural exudate from *Acacia Senegal* and/or *Acacia seyal* trees (9-11). It is considered a safe additive dietary fiber since the 1970s, approved by FDA and JECFA (12). The chemical structure is composed mainly of polysaccharides with galactopyranosyl residues (11), which are rich in calcium, zinc, magnesium, and potassium salts (11). In addition to a small portion (about 10%), is a protein content corresponding to a complex Arabinogalactan-Protein (13).

Gum Arabic is widely used in physiological and pharmacological research as an experimental vehicle for drugs (13). GA exhibited strong anti-inflammatory, antioxidant, anti-microbial, and immunomodulatory effects in several studies in vivo and in vitro experiments

(Table -1) (14-32). We review the evidence showing that GA has the potential to support adjuvant efficacy in treating COVID-19-induced lung injury and acute respiratory distress syndrome secondary to COVID-19 infection, as well as provide a theoretical basis for GA application among COVID-19 patients as adjuvant and supportive therapy.

Table 1. Summarized Antioxidant, Anti-inflammatory and Immuno-Modulatory Effect of Gum Arabic on Vivo and Vitro Experimental Studies

Title	Biological Activities	Dose and Duration	Study Type	Experimental Models	Ref
Acacia Senegal gum exudate offers protection against cyclophosphamide-induced urinary bladder cytotoxicity (24)	GA revealed a significant recovery in the bladder by: • Increase response to Ach • 23% drop in bladder weight (edema) • Decrease NO content to control level. • Increase Glutathione (GSH) to control level. • Decrease Malondialdehyde (MDA) to control level. • Improvement of histological changes.	7.5 g/kg/day for 6 days	vivo	Male Swiss Albino Rats	21
Ameliorative Effect of Gum Acacia on Hookah Smoke-Induced Testicular Impairment in Mice (25)	• Increase Testosterone • Increase Estradiol • Increase luteinizing hormone • Decrease Androgen binding protein • Decrease Urine Cotinine • Glutathione • Total nitrite • Decrease Plasma inhibin B • Decrease Plasma of lactate dehydrogenase (LDH) • Decrease Alkaline phosphatase • No effect Lipopolysaccharide binding protein • Decrease Uric acid • Decrease 8-oxo-2'-deoxyguanosine • Decrease Cytochrome C • Decrease Malondialdehyde (MDA) • Decrease Nuclear factor-κB (NF-kB) • Decrease Nuclear factor erythroid 2–related factor 2 (Nrf2) • Decrease Interleukin- 6 (IL-6) • Decrease Interleukin-1β (IL-1β) • Decrease Transforming growth factor-β1(TGF- β1) • Decrease Tumor necrosis factor-α (TNFα). • Normal superoxide dismutase (SOD) expression in germ cells	15%, w/v, in the drinking water for 30 days	vivo	Male Mice	22
Antimicrobial and Immunomodulatory Effect of Gum Arabic on Human and Bovine Granulocytes Against Staphylococcus aureus and Escherichia coli (27)	• GA exhibiting a direct antibacterial effect on pathogenic S. aureus isolates. • Increase oxidative burst/ROS production of bovine and human granulocytes in a dose-dependent manner, • Increase NO and ROS production, • No effect was seen on neutrophil extracellular trap (NET),	5%,10%, 20% (w/v)	vitro & vivo	Bacteria, isolated primary blood-derived granulocytes	23

	Title	Biological Activities	Dose and Duration	Study Type	Experimental Models	Ref
	Antioxidant effect of Arabic gum against mercuric chloride-induced nephrotoxicity (28)	• GA reversal of (mercury) Hg-induced increase in creatinine, blood urea nitrogen, thiobarbituric acid reactive substances, and total nitrate/nitrite to control values, • Prevented Hg-induced degenerative changes of kidney tissues.	7.5 g/kg/day per oral administration) 5 days	vivo	Rats	24
	Effect of Gum Arabic on Oxidative Stress and Inflammation in Adenine–Induced Chronic Renal Failure in Rats (30)	• Decrease TNF-a concentration in urine and plasma. • Increase Anti-inflammatory cytokine IL-10 significantly increased in the GA-treated rats. • Decrease superoxide production to control levels. • Decrease DNA double-strand breaks. • Increase glutathione (GSH) concentration, • Increase superoxide dismutase (SOD) activity • Increase Total antioxidant activity (TAOA) in plasma.	(15%, w/v) 4 weeks	vivo	Rats	26
	Effect of Gum Arabic (Acacia Senegal) on C-reactive protein level among sickle cell anemia patients (19)	Decrease C-reactive protein (CRP),	30 g/day 12 weeks	vivo	Human (sickle cell anemia patients)	16
	Gum Arabic as novel antioxidant agent in sickle cell anemia, phase II trial (29)	• Increase TAC (total antioxidant capacity), • Decrease malondialdehyde (MDA) hydrogen • Decrease peroxide (H_2O_2)	30 g/day for 12 weeks	vivo	Human (sickle cell anemia patients)	25
	Gum Arabic (Acacia Senegal) Augmented Total Antioxidant Capacity and Reduced C-Reactive Protein among Hemodialysis Patients in Phase II Trial (31)	• Gum Arabic significantly augmented total antioxidant capacity level • Attenuated oxidative marker MDA • Decrease C-reactive protein • Increase hemoglobin level and RBC count	30g/day for 12 weeks	vivo	Human (end-stage renal diseases (ESRD) patients)	27
	Gum Arabic Ameliorates Impaired Coagulation and Cardiotoxicity Induced by Water-Pipe Smoke Exposure in Mice (17).	• GA significantly mitigated thrombosis in pial microvessels in vivo, and platelet aggregation in vitro. • Decrease Plasma concentrations of fibrinogen, • Decrease plasminogen activator inhibitor-1 • Decrease lipid peroxidation, • Decrease 8-isoprostane • Decrease malondialdehyde. • Increase glutathione, catalase and • Increase Total nitric oxide levels in heart homogenates. • Decrease nuclear factor erythroid-derived 2-like 2 (Nrf2) expressions by cardiac myocytes and endothelial cells, • Decrease DNA damage and cleaved caspase 3, • Decrease TNFα • Decrease IL-1β	(15%, w/v) for 30 days	vitro & vivo	Mice	14

	Title	Biological Activities	Dose and Duration	Study Type	Experimental Models	Ref
	Gum Arabic Fibers Decreased Inflammatory Markers and Disease Severity Score among Rheumatoid Arthritis Patients, Phase II Trial (32)	• Decrease Serum TNFα, • Decrease ESR • Decrease disease severity score DAS28	30g/dayGAfor 12weeks	vivo	Human (Rheumatoid Arthritis Patients)	28
	Gut Health-Promoting Benefits of a Dietary Supplement of Vitamins with Inulin and Acacia Fibers in Rats (33)	• Firmicutes • Actinobacteria phyla, Lactobacillus and Bifidobacterium spp) • Increase Calcium, • Increase Magnesium, • Increase Phosphorus • Increase Zinc concentrations in the femur. • GA has stronger prebiotic activity, which may lead to increasing mineral absorption.	4.5 g /100g (20% daily) for four weeks	vivo	Rats	29
	Increment of Lysosomal Biogenesis by Combined Extracts of Gum Arabic, Parsley, and Corn Silk: A Reparative Mechanism in Mice Renal Cells (34)	• Combined extract • Increase GSH in serum • Decrease MDA in renal tissues • Decrease BAX expression • Decrease cytosolic expression of cathepsin D • Increase expression of nuclear TFEB (indicates active transcription of the lysosomal genes and autophagy), • Increase active expression of LAMP-1 • No signs of cellular degeneration in renal histology. • (GA derived SCFAs act as mediators of intracellular GPR survival signals)	(3g/kg/day) for four weeks	vivo	Mice	30
	Role of L. plantarum KX519413 as Probiotic and Acacia Gum as Prebiotic in Gastrointestinal Tract Strengthening (35)	• GA reinforced immunoglobulin levels and had a modulatory effect on phagocytosis, • Decrease tumor necrosis factor α (TNF-α) levels • Decrease Bacterial procarcinogenic fecal enzyme activities • Decrease triglycerides • Decrease LDL • Increase Calcium • Increase Phosphorous • Increase Ig A • (The consumption of a combination of the prebiotic and probiotic as a synbiotic was shown to exert many health-improving properties, such as Reduced blood lipid levels, regulation of immune function, and reduction of the levels of carcinogen-releasing enzymes. The maintenance of healthy gut microbiota by prebiotics and probiotics can be considered a striking route for retaining human and animal health statuses and disease prevention)	(1% in distilled water) for 3 weeks	vivo	Male Mice	31

	Title	Biological Activities	Dose and Duration	Study Type	Experimental Models	Ref
	The Effect of Arabic Gum on Renal Function in Reversible Unilateral Ureteric Obstruction (36)	• Decrease Malondialdehyde • Decrease Superoxide dismutase • Decrease TNF-α • Decrease TGF-β1 • Decrease p53 in AG-1 • Attenuated the UUO-induced rise in oxidative stress markers and proinflammatory and profibrotic cytokines and the degree of renal tubular dilatation, indicating a protective effect in obstructive nephropathy.	15 g/kg/day for 16 days	vivo	Male Rats	32
	Waterpipe Smoke Exposure Triggers Lung Injury and Functional Decline in Mice: Protective Effect of Gum Arabic (18)	• Inhibited nuclear factor kappa-B (NF-κB) expression. • Augmented that of nuclear factor erythroid 2-related factor 2 (Nrf2). • Increase Cytoplasmic expression of glutathione in mice treated with GA and exposed to WPS. • Significant inhibition of the increase of TNF-α concentrations. • Augmentation of 8-isoprostane concentrations was significantly prevented by GA. • Abolished the increase of expression of NF-κB induced by WPS.	(15%, w/v) for 30 days		Mice	15

COVID-19 pathogenesis and the role of cytokine storm:

Cytokine storm (CS) is an exaggerated complex immune response to external stimuli (3). CS is characterized by uncontrolled and excessive release of pro-inflammatory cytokines (5). Innate immunity is considered as the first line of defense against viral infection (33, 34). Hence, interferon (IFN-I or IFN- α/ βis) represents the usual key immune defense reaction against viral infections and in the early stages of viral infection, IFN- I is the key player as an antiviral. The pro-inflammatory cytokine/chemokine response caused by rapid viral replication in lung epithelial and endothelial leads to the induction of apoptosis (35). The mechanism involves β and IFN γ through Fas–Fas ligand (FasL) or TRAIL–death receptor 5 (DR5) (36). In addition, unlike SARS patients, COVID-19 patients also presented with high levels of Th2 cell- secreted cytokines (such as IL-4 and IL-10), which delay the inflammatory response (3). The serum levels of IL-2 and IL-6 among COVID-19 patients are correlated with disease severity (37). The cytokine storm also plays a role in determining the prognosis of extra-pulmonary multiple-organ failure (38); explained by CS is the cause of damage to extra-pulmonary tissues and organs among some COVID-19 patients who did not develop respiratory failure (39).

Discrepancy in severe COVID-19, lymphocytes were activated as evidenced by high level of inflammatory cytokines, but patients have lymphocytopenia, (40). Rheumatologists believed that critical COVID-19 patients have shared the following: pathology with rheumatoid patients, unexpected deterioration within two weeks from infection, unexplained very low levels of lymphocytes, especially natural killer (NK) cells, as well as very high inflammatory markers, such as C reactive protein (CRP) and pro-inflammatory cytokines (IL-6, TNFα, IL-8) (5). In the same token, evidence of suppressed immunity among COVID-19 patients are

hypo-albuminemia, neutropenia and the diminished percentage of $CD8^+$ T cells (4).

Alteration of the immune response could be explained through lymphocytes directly attacked by the virus or indirectly damaged by a Cytokine storm (CS) (5). COVID-19 infects target cells by angiotensin-converting enzyme 2 (ACE2), the latter is not expressed on lymphocytes. Therefore, it is probable that CS is the cause of lymphocyte destruction. (5). In addition to leukopenia, the other abnormal laboratory findings include altered function of the liver and an extremely increase in ferritin levels (41). The latter is unclear-- whether it be an epiphenomenon with diagnostic value or if the ferritin is involved in the vicious cycle of escalating inflammation (41). A postmortem lung examination of a COVID-19 patient with severe ARDS, revealed edematous, diffuse alveolar damage, desquamation, and hyaline membrane formation (4).

Current modalities of treatment: The quick dissemination of scientific knowledge nowadays, leading to several therapeutic interventions, which have been tested in small sample size studies. A few studies continued in larger sample size studies and other studies failed to continue into large and multi trials to show therapeutic benefits or impact on survival (42, 43). Currently, management of COVID-19 is not completed yet, but supportive treatment is necessary and respiratory failure, due to ARDS, is the main cause of death (44).

The use of a corticosteroid as anti-inflammatory medications may delay viral eradication and raise the risk of secondary infection, especially in immunocompromised patients (5). Scientists thought of immunomodulatory agents to reduce systemic inflammation before it results in organ dysfunction (5). There were further recommendations to add anti-cytokinic biological agents, such as anti- IL-1 (anakinra) or anti-IL-6 (tocilizumab (TCZ)) (45). These drugs were previously recommended for rheumatoid, autoimmune inflammatory diseases and have high efficacy and therapeutic benefits (41). Nevertheless, these biological agents inhibit only specific inflammatory and may not be efficient in downregulation of the CS in COVID-19 since other cytokines maybe of substantial importance (5) and the same concept is applied to NSAID (46). However, researchers and scientists are trying to generate strong evidence based on clinical trials to treat and manage COVID-19.

Oxidative stress and COVID-19 pathogenesis: Since inflammation is a key pathogenesis in COVID-19 patients (4), finding a way to block the CS utilizing anti-inflammation therapy is critical to reducing mortality (5). Immunocompromised patients and patients with metabolic syndrome, like type-2 diabetes, cardiovascular disorders are considered as high risk for mortality (47) -- and in such patients dysbiosis is involved and could cause an increase in the mortality rate (6).

Researchers assumed that oxidative stress is a part of COVID-19 pathogenesis (4). Viral infections inhibit NRF2-mediated pathways and NF-κB signaling activation, causing reduction of antioxidant defense and exaggeration of inflammation and oxidative stress (48).

Modulation of gut microbiota as an immunomodulatory strategy against COVID-19 pathogenesis: Gut microbiota involving short chain fatty acids (SCFA) like the butyrate, acetate and propionate have a protective role in health, through regulating a group of host physiological functions, secreting both immunomodulatory signals and metabolites signals (6, 49). Furthermore, it maintains an optimal immune system to attack the virus. Several studies proposed that modification of gut microbiota could lessen inflammation (50-52).

Nevertheless, the question of how this microbiota is linked to the lungs has yet to be answered. A previous study found that neonatal gut microbiota colonization can modulate lung immunity, which plays an important role in the "gut-lung axis" (53). This axis is bidirectional, which means lung inflammations can affect the gut microbiota causing a disturbance of activation and levels of leucocytes, lead to lung damage. The re-introduction of probiotics helps in recovery of the lungs through SCFA, or host derived products, such as cytokines and chemokines at lung and gut (54). Also, the re-introduction of probiotic strains, such as *Bifidobacterium lactis* into apparent healthy elderly volunteers resulted in a significant rise in leukocytes and the tumoricidal activity of NK cells (55-57).

COVID-19 influences the gut microbiota (58) and many studies have shown that alterations of gut microbiota is associated with inflammatory bowel diseases (IBD) (59), type 2 diabetes mellitus (60), depression (61, 62), cardiovascular disease (63) (64), hypertension (65), lung cancer in humans (66-68) and pneumonia (57, 69).

Gum Arabic as prebiotic agent: Prebiotics are defined as dietary elements that can modulate the gut flora, resulting in improving the host's health and general wellbeing, with functional food effects (70, 71). In general, the term "Prebiotic" refers to food ingredients that are non-digestible and show beneficial effects on the host by stimulating the growth and/or activity of probiotics in the colon after fermentation" (72, 73). Gut microbiota metabolized polysaccharides and produce SCFAs, mainly butyrate, acetate and propionate (73).

Gum Arabic is a non-digestible dietary fiber and is mainly fermented by colonic intestinal bacteria (74-76). Dietary fibers are defined as carbohydrate polymers that are released after digestion and absorbed in the upper human intestine (77). Gum Arabic oral consumption increased the serum level of SCFAs, specifically Butyrate (19, 78, 79). Therefore, GA can be defined as prebiotic agent (80). Acacia exudates found to generate a significant increase in bifidobacteria and lactobacilli, compared to an equal dose of inulin; with less gastrointestinal complaints (29, 79, 80)

Role of Gum Arabic as an immunomodulatory, anti-inflammatory, and antioxidant agent in COVID-19: It has not yet been proven that Gum Arabic has a direct antiviral effect, although there are some Acacia species that exhibit antiviral activity against the hepatitis C virus (81). Nonetheless, GA exhibits an indirect effect through its anti-inflammation, anti-oxidation and immune-modulatory properties.

As mentioned above, viral load is not correlated with disease severity (82, 83), as the main pathogenesis is systemic inflammation and a cytokine storm (84), (82, 85) (40). Scientists suggested the addition of anti-inflammatory and storied to treatment regimens (5), (86).

In general, inflammation is associated with increased production of cytokines and chemokines, while GA causes an increase of anti-inflammatory cytokine IL10 (26) and a decrease in the pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8(22). GA significantly reduced TNF α among rheumatoid patients (28) and a shared pathogenesis between RA and COVID-19 has been established (5, 87).

Wapnir RA and his colleagues revealed that GA showed local anti-inflammatory effects by modifying nuclear factor-κB (NF-κB) on a small rat intestine (88). The anti-inflammatory effect of GA causes suppression of NF-κB activation not only in the small intestine in rats, but also in lung tissues in mice (15). The stimulation of NF-E2-related factor 2 (Nrf2) is important in protecting lungs from injury, though involvement of Nrf2 in COVID-19 is under study. However, areas with low prevalence of obesity (considering obesity a risk factor in COVID-19 severity) is associated with Nrf2 interacting nutrients intake; Hence, less severity of COVID-19, which attract

attention to the effect of Nrf2 as novel target therapy (89).

Gum Arabic has a strong antioxidant effect, which has been investigated in previous clinical trials among patients with sickle cell anemia. GA increased the TAC (total antioxidant capacity, associated with reduction in production of malondialdehyde (MDA), which enhances the antioxidant defense potentiality (25). This effect was detected by Ali NE et.al in hemodialysis patients when treated by 30g/day for 12 weeks (27).

Figure 1 summarized GA actions. Additional mechanisms that are of importance in COVID 19, GA through augmentation of Nrf2 expression in bronchial epithelial cells and alveolar cells which inhibits inflammation and oxidative stress (Figure 2).

In conclusion, the main pathogenesis of COVID-19 is due to inflammatory process and a cytokine storm. Thus, it is likely that GA consumption as prebiotic would be beneficial in supporting and controlling the inflammation and oxidation in coronavirus infected subjects as adjuvant therapy.

Figure 1. Potential pathway through which Gum Acacia (GA) influence gut-lung axis in COVID-19 pathogenesis

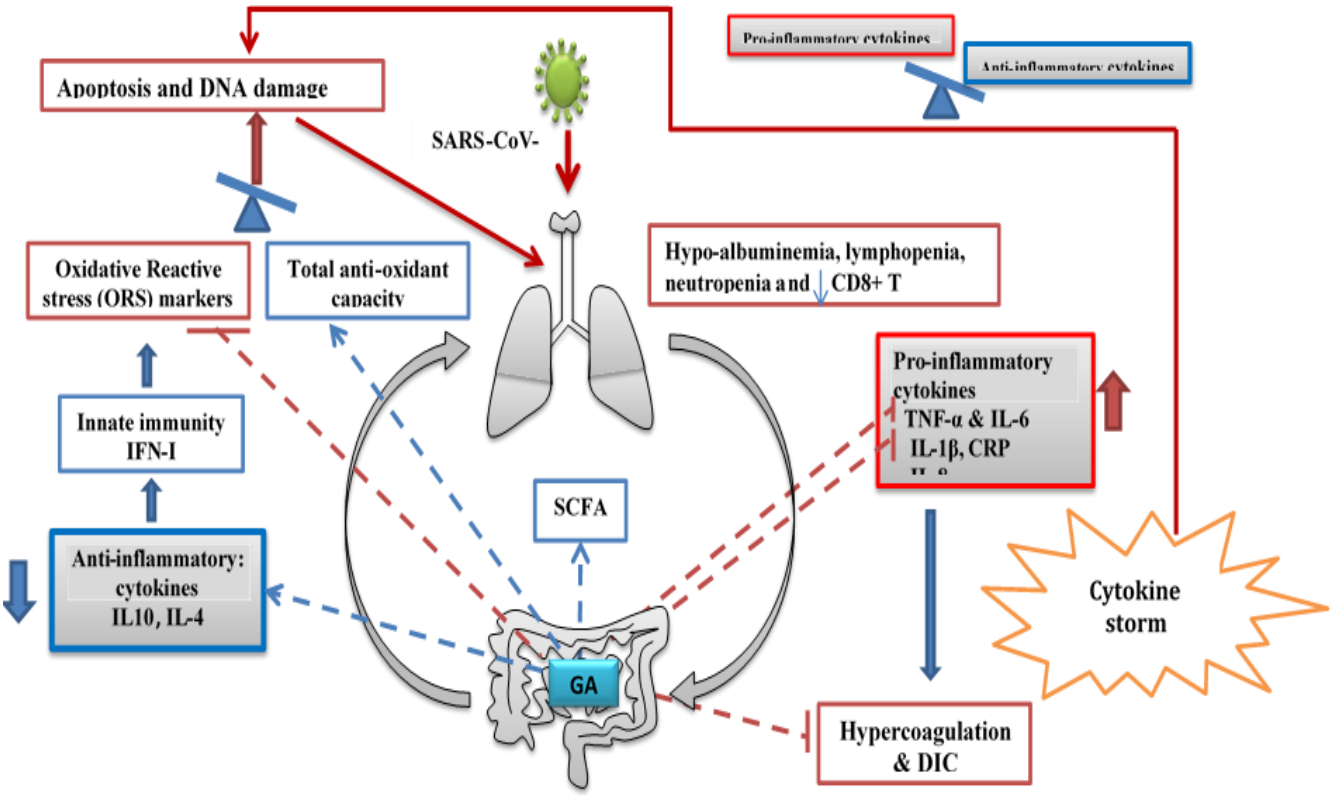


Figure 1. Potential pathway through which Gum Acacia (GA) influence gut-lung axis in COVID-19 pathogenesis**.** Short-chain fatty acids (SCFAs) are the main metabolites produced after GA fermentation in the large intestine. GA might influence gut-lung axis and lung function directly or indirectly. Indirectly through the health benefits of SCFAs and directly through the direct effect of GA on balancing the proinflammatory cytokines and the anti-inflammatory cytokines, hence reduce the cytokine storm (CS) in COVID-19. GA as strong prebiotic produces mainly butyrate. Through binding to G protein-coupled receptors (GPCRs) GA reduces the pro-inflammatory cytokines; tumor necrosing factor (TNF-α), interlukin-6 (IL-6), interlukin-8 (IL-8), and C-reactive protein (CRP), by which are considered as important cytokine storm (CS) markers in COVID-19. On the other hand, GA induces production of anti-inflammatory cytokines; interlukin-10 (IL-10) and interlukin-4 (IL-4). GA reduces the oxidative reactive stress (ORS) markers. GA influences intestinal mucosal immunity, and barrier integrity and function, systemically by leading to activation, and regulation of whole-body energy homeostasis. Peripherally GA systemically balances inflammation mainly by regulating the secretion of interleukins in COVID-19 disease.

COVID-19 and Gum Arabic in high-risk groups: Metabolic diseases are a worldwide public health issue associated with high morbidity and mortality (90). Obesity is considered the risk for factor for impaired metabolic function, T2D, dyslipidemia, hypertension, and cardiovascular disease (91)

Obesity is associated with dietary fiber intake and explained by increased systemic low grade inflammatory markers, due to excess adipose tissue. The imbalance between anti-and pro-inflammatory cytokines results in abnormal chemotaxis and macrophage differentiation, which compromises immune function (92). The innate response associated with obesity causing high release of pro-inflammatory elements correlates with COVID-19 severity (93). Several experimental studies confirmed the association between dietary fiber intake and obesity, body weight, cholesterol and blood glucose.

Gum Arabic decreased food intake and body weight, which were associated with the reduction of abdominal visceral adipose tissue (VAT). This effect occurred either by altering the satiety (94-96), gastric emptying (97) or altering glycaemic index (97-98).

In clinical trials, GA was consumed by diabetic patients for 12 weeks, which resulted in a significant reduction of fasting blood glucose levels and glycosylated hemoglobin (HbAc1) (99). This might be explained a study in which experimental mice GA inhibits absorption of glucose in the intestine by their action on membrane abundance of sodium-glucose transporter 1 (SGLT1) (100,101). Thus, GA may prevent and/or manage obesity, while reducing the impact of COVID-19 in high-risk patients.

Figure 2. Potential pathway through which Gum Acacia (GA) influences COVID-19 pathogenesis.

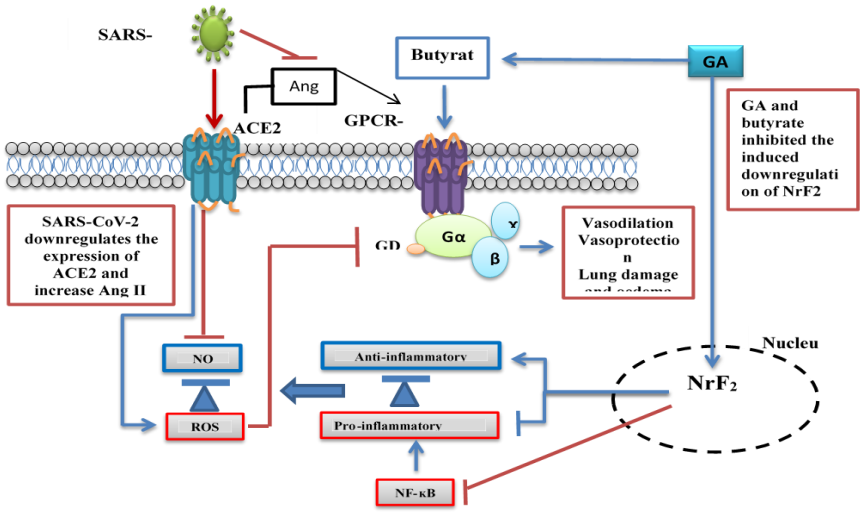


Figure 2. Potential pathway through which Gum Acacia (GA) influences COVID-19 pathogenesis. GA directly augments nuclear factor erythroid 2-related factor 2 (Nrf2) and increases the nuclear expression of Nrf2 of bronchial epithelial cells and alveolar cells. GA increase production of butyrate hence it inhibits the down-regulation of Nrf2 caused by SARS-CoV-2. SARS-CoV-2 infection down-regulates the expression of angiotensin converting enzyme 2 (ACE2) and increase angiotensin II (Ang II), thus leading to increased vasoconstriction, inflammation, fibrosis, lung damage and oedema. On the other hand, ACE2 inactivates (Ang I). Ang I interact with G protein coupled receptor (GPCR) Mas to produce a vasoprotective action to the lung; this mechanism is inhibited by over-activation of Ang II by SARS-CoV-2 infection. GA reduces oxidative stress markers and increase nitric oxide (NO) to imbalance the ORS/NO ratio and prevent inhibition of the vasoprotective action through effect of butyrate and direct augmentation of Nrf2 expression in bronchial epithelial cells and alveolar cells.

CONCLUSION: Gum Arabic is a potent prebiotic with potential effect to reduce the cytokine storm by balancing the pro-inflammatory and anti-inflammatory response in humans. The potential effect of GA as an antioxidant, anti-inflammatory and immunomodulatory of lung-gut axis balancing activity plays an important role in the adjuvant treatment of COVID-19 infections in human. There should be an increase in GA research to further clarify the actual physiological mechanism at a molecular level. This review may create an innovation in dietary interventions to boost immunity and counteract COVID-19 disease.

List of abbreviations: ACE2: angiotensin converting enzyme 2, ALI: Acute Lung Injury, ARDS: acute respiratory distress syndrome, CRP: C reactive protein, FasL: Fas–Fas ligand, GA: gum Arabic, IFN: interferon, MDA: malondialdehyde, NK: natural killer, Nrf2: NF-E2-related factor 2, SCFA: short chain fatty acids, SGLT1: sodium-glucose transporter 1, TAC: total anti-oxidant capacity, VAT: visceral adipose tissue, WHO: Organization.

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REFERENCES:

1. Wise J. Covid-19: Risk of second wave is very real, say researchers. BMJ. 2020;369:m2294. DOI: https://doi.org/10.1136/bmj.m2294
2. Ye Q, Wang B, Mao J. Cytokine storm in COVID-19 and treatment. Journal of Infection. 2020. DOI: https://doi.org/10.1016/j.jinf.2020.03.037
3. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the Cytokine Storm'in COVID-19. The Journal of infection. 2020. DOI: https://doi.org/10.1016/j.jinf.2020.03.037
4. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sciences. 2020:117583. DOI: https://doi.org/10.1016/j.lfs.2020.117583.
5. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clinical Immunology. 2020:108393. DOI: https://doi.org/10.1016/j.clim.2020.108393
6. Dhar D, Mohanty A. Gut microbiota and Covid-19- possible link and implications. Virus Res. 2020;285:198018. DOI: https://doi.org/10.1016/j.virusres.2020.198018.
7. Negi S, Pahari S, Bashir H, Agrewala JN. Gut microbiota regulates mincle mediated activation of lung dendritic cells to protect against Mycobacterium tuberculosis. Frontiers in immunology. 2019; 10:1142. DOI: https://doi.org/10.3389/fimmu.2019.01142.
8. Bingula R, Filaire M, Radosevic-Robin N, Bey M, Berthon J-Y, Bernalier-Donadille A, et al. Desired turbulence? Gut-lung axis, immunity, and lung cancer. Journal of oncology. 2017;2017. DOI: https://doi.org/10.1155/2017/5035371.
9. Pitkänen L, Heinonen M, Mikkonen KS. Safety considerations of plant polysaccharides for food use: a case study on phenolic-rich softwood galactoglucomannan extract. Food & function. 2018;9(4):1931-43. DOI: https://doi.org/10.1039/c7fo01425b.
10. Xu T, Gao C, Yang Y, Shen X, Huang M, Liu S, et al. Retention and release properties of cinnamon essential oil in

antimicrobial films based on chitosan and gum arabic. Food Hydrocolloids.2018;84:84-92. DOI: https://doi.org/10.1016/j.foodhyd.2018.06.003

11. Lopez-Torrez L, Nigen M, Williams P, Doco T, Sanchez C. Acacia senegal vs. Acacia seyal gums–Part 1: Composition and structure of hyperbranched plant exudates. Food Hydrocolloids. 2015;51:41-53. DOI: https://doi.org/10.1016/j.foodhyd.2015.04.019
12. Cox S, Sandall A, Smith L, Rossi M, Whelan K. Food additive emulsifiers: a review of their role in foods, legislation and classifications, presence in food supply, dietary exposure, and safety assessment. Nutrition Reviews. 2020. DOI: https://doi.org/10.1093/nutrit/nuaa038
13. Naushad M, Sharma G, Alothman ZA. Photodegradation of toxic dye using Gum Arabic-crosslinked-poly (acrylamide)/Ni (OH) 2/FeOOH nanocomposites hydrogel. Journal of Cleaner Production. 2019;241:118263. DOI: https://doi.org/10.1016/j.jclepro.2019.118263
14. Nemmar A, Al-Salam S, Beegam S, Yuvaraju P, Ali BH. Gum Arabic ameliorates impaired coagulation and cardiotoxicity induced by water-pipe smoke exposure in mice. Frontiers in physiology. 2019; 10:53. DOI: https://doi.org/10.3389/fphys.2019.00053
15. Nemmar A, Al-Salam S, Beegam S, Yuvaraju P, Ali BH. Waterpipe smoke exposure triggers lung injury and functional decline in mice: protective effect of gum Arabic. Oxidative medicine and cellular longevity. 2019;2019. DOI: https://doi.org/10.1155/2019/8526083
16. Kaddam LA, Kaddam AS. Effect of Gum Arabic (Acacia senegal) on C-reactive protein level among sickle cell anemia patients. BMC Research Notes. 2020;13(1):1-5. DOI: https://doi.org/10.1186/s13104-020-05016-2
17. Helmy A, El-Shazly M, Seleem A, Abdelmohsen U, Salem MA, Samir A, et al. The synergistic effect of biosynthesized silver nanoparticles from a combined extract of parsley, corn silk, and gum arabic: in vivo antioxidant, anti-inflammatory and antimicrobial activities. Materials Research Express. 2020;7(2):025002. DOI: https://doi.org/10.1088/2053-1591/ab6e2d
18. ALI KSE, SALIH TAA, DAFFALLA HM. In vitro Phytochemical, Larvicidal and Antimicrobial Activities of Gum Arabic Extract. Walailak Journal of Science and Technology (WJST). 2020;17(3):192-9. DOI: https://doi.org/10.48048/wjst.2020.5540
19. Matsumoto N, Riley S, Fraser D, Al-Assaf S, Ishimura E, Wolever T, et al. Butyrate modulates TGF-β1 generation and function: Potential renal benefit for Acacia (sen) SUPERGUM™ (gum arabic)? Kidney international. 2006;69(2):257-65. DOI: https://doi.org/10.1038/sj.ki.5000028
20. Ali BH, Ziada A, Blunden G. Biological effects of gum arabic: a review of some recent research. Food and chemical Toxicology. 2009;47(1):1-8. DOI: https://doi.org/10.1016/j.fct.2008.07.001
21. Al-Yahya AA, Al-Majed AA, Gado AM, Daba MH, Al-Shabanah OA, El-Azab AS, et al. Acacia Senegal gum exudate offers protection against cyclophosphamide-induced urinary bladder cytotoxicity. Oxidative medicine and cellular longevity. 2009;2. DOI: https://doi.org/10.4161/oxim.2.4.8878
22. Ali BH, Al-Salam S, Balushi KAA, Za'abi MA, Adham SA, Beegam S, et al. Ameliorative Effect of Gum Acacia on Hookah Smoke-Induced Testicular Impairment in Mice. Biomolecules. 2020;10(5):762. DOI: https://doi.org/10.3390/biom10050762
23. Baien SH, Seele J, Henneck T, Freibrodt C, Szura G, Moubasher H, et al. Antimicrobial and immunomodulatory effect of Gum arabic on human and bovine granulocytes against Staphylococcus aureus and Escherichia coli. Frontiers in Immunology. 2019;10. DOI: https://doi.org/10.3389/fimmu.2019.03119
24. Gado AM, Aldahmash BA. Antioxidant effect of Arabic gum against mercuric chloride-induced nephrotoxicity. Drug design, development and therapy. 2013;7:1245. DOI: https://doi.org/10.2147/dddt.s50928
25. Kaddam L, Fadl-Elmula I, Eisawi OA, Abdelrazig HA, Salih MA, Lang F, et al. Gum Arabic as novel antioxidant agent in sickle cell anemia, phase II trial. BMC hematology. 2017;17(1):4. DOI: https://doi.org/10.1186/s12878-017-0075-y
26. Ali BH, Al-Husseni I, Beegam S, Al-Shukaili A, Nemmar A, Schierling S, et al. Effect of gum Arabic on oxidative stress and inflammation in adenine–induced chronic renal failure in rats. PloS one. 2013;8(2). DOI: https://doi.org/10.1371/journal.pone.0055242
27. Ali NE, Kaddam LA, Alkarib SY, Kaballo BG, Khalid SA, Higawee A, et al. Gum Arabic (Acacia Senegal) Augmented Total Antioxidant Capacity and Reduced C-Reactive Protein among Haemodialysis Patients in Phase II Trial. International

Journal of Nephrology. 2020;2020. DOI: https://doi.org/10.1155/2020/7214673

28. Kamal E, Kaddam LA, Dahawi M, Osman M, Salih MA, Alagib A, et al. Gum Arabic Fibers Decreased Inflammatory Markers and Disease Severity Score among Rheumatoid Arthritis Patients, Phase II Trial. International journal of rheumatology. 2018;2018. DOI: https://doi.org/10.1155/2018/4197537
29. Massot-Cladera M, Azagra-Boronat I, Franch À, Castell M, Rodríguez-Lagunas MJ, Pérez-Cano FJ. Gut Health-Promoting Benefits of a Dietary Supplement of Vitamins with Inulin and Acacia Fibers in Rats. Nutrients. 2020;12(8):2196. DOI: https://doi.org/10.3390/nu12082196
30. Helmy A, El-Shazly M, Omar N, Rabeh M, Abdelmohsen UR, Tash R, et al. Increment of Lysosomal Biogenesis by Combined Extracts of Gum Arabic, Parsley, and Corn Silk: A Reparative Mechanism in Mice Renal Cells. Evidence-Based Complementary and Alternative Medicine. 2020;2020. DOI: https://doi.org/10.1155/2020/8631258
31. Chundakkattumalayil HC, Kumar S, Narayanan R, Thalakattil Raghavan K. Role of L. plantarum KX519413 as Probiotic and Acacia Gum as Prebiotic in Gastrointestinal Tract Strengthening. Microorganisms. 2019;7(12):659. DOI: https://doi.org/10.3390/microorganisms7120659
32. Hammad FT, Al Salam S, Nemmar A, Ali M, Lubbad L. The effect of Arabic gum on renal function in reversible unilateral ureteric obstruction. Biomolecules. 2019;9(1):25. DOI: https://doi.org/10.3390/biom9010025
33. Stambas J, Lu C, Tripp RA. Innate and adaptive immune responses in respiratory virus infection: implications for the clinic. Expert Review of Respiratory Medicine. 2020:1-7. DOI: https://doi.org/10.1080/17476348.2020.1807945
34. Rai KR, Chen B, Zhao Z, Chen Y, Hu J, Liu S, et al. Robust expression of p27Kip1 induced by viral infection is critical for antiviral innate immunity. Cellular Microbiology. 2020;22(11):e13242. DOI: https://doi.org/10.1111/cmi.13242
35. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-13. DOI: https://doi.org/10.1016/j.jinf.2020.03.037
36. Caulfield AJ, Lathem WW. Disruption of fas-fas ligand signaling, apoptosis, and innate immunity by bacterial pathogens. PLoS Pathog. 2014;10(8):e1004252. DOI: https://doi.org/10.1371/journal.ppat.1004252
37. Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect. 2020;50(4):382-3. DOI: https://doi.org/10.1016/j.medmal.2020.04.002
38. Castelli V, Cimini A, Ferri C. Cytokine Storm in COVID-19: "When You Come Out of the Storm, You Won't Be the Same Person Who Walked in". Front Immunol. 2020; 11:2132. DOI: https://doi.org/10.3389/fimmu.2020.02132
39. Pousa PA, Mendonca TSC, Oliveira EA, Simoes ESAC. Extrapulmonary manifestations of COVID-19 in children: a comprehensive review and pathophysiological considerations. J Pediatr (Rio J). 2020. DOI: https://doi.org/10.1016/j.jped.2020.08.007
40. Song J-W, Zhang C, Fan X, Meng F-P, Xu Z, Xia P, et al. Immunological and inflammatory profiles in mild and severe cases of COVID-19. Nature communications. 2020;11(1):1-10. DOI: https://doi.org/10.1038/s41467-020-17240-2
41. Shoenfeld Y. Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. Autoimmunity Reviews. 2020. DOI: https://doi.org/10.1016/j.autrev.2020.102538
42. Rochwerg B, Agarwal A, Zeng L, Leo YS, Appiah JA, Agoritsas T, et al. Remdesivir for severe covid-19: a clinical practice guideline. BMJ. 2020;370:m2924. DOI: https://doi.org/10.1136/bmj.m4542
43. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980. DOI: https://doi.org/10.1136/bmj.n967
44. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033-4. DOI: https://doi.org/ 10.1016/S0140-6736(20)30628-0
45. Ferro F, Elefante E, Puxeddu I, Baldini C, Bartoloni E, Barate C, et al. COVID-19: the new challenge for rheumatologists. First update. Clin Exp Rheumatol. 2020;38(3):373-82.
46. Capuano A, Scavone C, Racagni G, Scaglione F, NSAIDs in patients with viral infections, including Covid-19: Victims or perpetrators? Pharmacol Res. 2020; 157:104849. DOI: https://doi.org/10.1016/j.phrs.2020.104849
47. Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. Nutrients. 2020;12(5):1466. DOI: https://doi.org/10.3390/nu12051466

48. Laforge M, Elbim C, Frère C, Hémadi M, Massaad C, Nuss P, et al. Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nature Reviews Immunology. 2020;20(9):515-6. DOI: https://doi.org/10.1038/s41577-020-0407-1.
49. Rooks MG, Garrett WS. Gut microbiota, metabolites, and host immunity. Nature reviews immunology. 2016;16(6):341-52. DOI: https://doi.org/10.1038/nri.2016.42.
50. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009;58(8):1091-103. DOI: https://doi.org/ 10.1136/gut.2008.165886
51. Kang Y, Cai Y, Zhang X, Kong X, Su J. Altered gut microbiota in RA: implications for treatment. Zeitschrift für Rheumatologie. 2017;76(5):451-7. DOI: https://doi.org/10.1007/s00393-016-0237-5.
52. Khanna S, Jaiswal KS, Gupta B. Managing Rheumatoid Arthritis with Dietary Interventions. Frontiers in nutrition. 2017; 4:52. DOI: https://doi.org/10.3389/fnut.2017.00052
53. Tamburini S, Clemente JC. Neonatal gut microbiota induces lung immunity against pneumonia. Nature Reviews Gastroenterology & Hepatology. 2017;14(5):263-4. DOI: https://doi.org/ 10.1038/nrgastro.2017.34
54. Dumas A, Bernard L, Poquet Y, Lugo-Villarino G, Neyrolles O. The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases. Cellular microbiology. 2018;20(12):e12966. DOI: https://doi.org/ 10.1111/cmi.12966
55. Gill HS, Rutherfurd KJ, Cross ML, Gopal PK. Enhancement of immunity in the elderly by dietary supplementation with the probiotic Bifidobacterium lactis HN019. The American Journal of Clinical Nutrition. 2001;74(6):833-9. DOI: https://doi.org/10.1093/ajcn/74.6.833
56. Villanueva-Millán M, Perez-Matute P, Oteo J. Gut microbiota: a key player in health and disease. A review focused on obesity. Journal of physiology and biochemistry. 2015;71(3):509-25. DOI: https://doi.org/ 10.1007/s13105-015-0390-3
57. Zhang D, Li S, Wang N, Tan H-Y, Zhang Z, Feng Y. The crosstalk between gut microbiota and lungs in common lung diseases. Frontiers in Microbiology. 2020;11. DOI: https://doi.org/10.3389/fmicb.2020.00301
58. Groves HT, Higham SL, Moffatt MF, Cox MJ, Tregoning JS. Respiratory viral infection alters the gut microbiota by inducing inappetence. Mbio. 2020;11(1). DOI: https://doi.org/10.1128/mBio.03236-19
59. Caruso R, Lo BC, Núñez G. Host–microbiota interactions in inflammatory bowel disease. Nature Reviews Immunology. 2020:1-16. DOI: https://doi.org/10.4161/gmic.20228
60. Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine. 2020; 51:102590. DOI: https://doi.org/10.1016/j.ebiom.2019.11.051
61. Halverson T, Alagiakrishnan K. Gut microbes in neurocognitive and mental health disorders. Annals of Medicine. 2020(just-accepted):1-43. DOI: https://doi.org/10.1080/07853890.2020.1808239.
62. Meixedo ASP. Targeting gastrointestinal microbiota as new diagnostic and treatment options in Depression. 2020.
63. Luz PLd, Haas EA, Favarato D. Intestinal Microbiota and Cardiovascular Diseases. International Journal of Cardiovascular Sciences. 2020(AHEAD). DOI: https://doi.org/10.1093/cvr/cvz135.
64. Sanchez-Rodriguez E, Egea-Zorrilla A, Plaza-Díaz J, Aragón-Vela J, Muñoz-Quezada S, Tercedor-Sánchez L, et al. The Gut Microbiota and Its Implication in the Development of Atherosclerosis and Related Cardiovascular Diseases. Nutrients. 2020;12(3):605. DOI: https://doi.org/10.3390/nu12030605
65. Dannenberg L, Zikeli D, Benkhoff M, Ahlbrecht S, Kelm M, Levkau B, et al. Targeting the human microbiome and its metabolite TMAO in cardiovascular prevention and therapy. Pharmacology & Therapeutics. 2020:107584. DOI: https://doi.org 10.1016/j.pharmthera.2020.107584
66. Zheng Y, Fang Z, Xue Y, Zhang J, Zhu J, Gao R, et al. Specific gut microbiome signature predicts the early-stage lung cancer. Gut Microbes. 2020:1-13. DOI: https://doi.org 10.1080/19490976.2020.1737487
67. Ramírez-Labrada AG, Isla D, Artal A, Arias M, Rezusta A, Pardo J, et al. The Influence of Lung Microbiota on Lung Carcinogenesis, Immunity, and Immunotherapy. Trends in Cancer. 2020;6(2):86-97. DOI: https://doi.org 10.1016/j.trecan.2019.12.007
68. Zheng X, Sun X, Liu Q, Huang Y, Yuan Y. The Composition Alteration of Respiratory Microbiota in Lung Cancer. Cancer Investigation. 2020;38(3):158-68. DOI: https://doi.org 10.1080/07357907.2020.1732405

69. Dickson RP. The microbiome and critical illness. The Lancet Respiratory Medicine. 2016;4(1):59-72. DOI: https://doi.org/10.1016/S2213-2600(15)00427-0
70. Martirosyan D.M., Lampert T., Ekblad M. Classification and regulation of functional food proposed by the functional food center. Functional Food Science 2022; 2(2): 25-46. DOI: https://www.doi.org/10.31989/ ffs.v2i2.890.
71. Roberfroid M. Prebiotics: the concept revisited. The Journal of nutrition. 2007;137(3):830S-7S. DOI: https://doi.org/10.1093/jn/137.3.830s
72. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature reviews Gastroenterology & hepatology. 2017;14(8):491.
73. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut microbes. 2017;8(2):172-84. DOI: https://doi.org/10.1080/19490976.2017.1290756
74. Ahallil H, Abdullah A, Maskat MY, Sarbini SR, editors. Fermentation of gum Arabic by gut microbiota using in vitro colon model. AIP Conference Proceedings; 2019: AIP Publishing LLC.
75. Kishimoto A, Ushida K, Phillips GO, Ogasawara T, Sasaki Y. Identification of intestinal bacteria responsible for fermentation of gum Arabic in pig model. Current microbiology. 2006;53(3):173-7. DOI: https://doi.org/10.1007/s00284-005-0219-3
76. Phillips AO, Phillips GO. Biofunctional behaviour and health benefits of a specific gum Arabic. Food Hydrocolloids. 2011;25(2):165-9. DOI: https://doi.org/10.1016/j.foodhyd.2010.03.012
77. Capuano E. The behavior of dietary fiber in the gastrointestinal tract determines its physiological effect. Critical Reviews in Food Science and Nutrition. 2017;57(16):3543-64. DOI: https://doi.org/10.1080/10408398.2016.1180501
78. Kaddam L, Fdl-Elmula I, Saeed A. 17 Gum Arabic Beneficial Effects, Clinical Applications, and Future. IN: Gum Arabic: Structure, Properties, Application and Economics. Editor(s): Abdalbasit Adam Mariod, Academic Press, 2018, Pages 211-220, ISBN 9780128120026, 2018:211. DOI: https://doi.org/10.1016/b978-0-12-812002-6.00017-8
79. Calame W, Weseler AR, Viebke C, Flynn C, Siemensma AD. Gum Arabic establishes prebiotic functionality in healthy human volunteers in a dose-dependent manner. British Journal of Nutrition. 2008;100(6):1269-75. DOI: https://doi.org/10.1017/s0007114508981447
80. Slavin J. Fiber and prebiotics: mechanisms and health benefits. Nutrients. 2013;5(4):1417-35. DOI: https://doi.org/10.3390/nu5041417
81. Rehman S, Ashfaq UA, Riaz S, Javed T, Riazuddin S. Antiviral activity of Acacia nilotica against Hepatitis C Virus in liver infected cells. Virology journal. 2011;8(1):220. **DOI:** https://doi.org/10.1186/1743-422x-8-220
82. Del Valle DM, Kim-Schulze S, Huang H-H, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nature medicine. 2020:1-8. DOI: https://doi.org/10.1038/s41591-020-1051-9. Epub 2020 Aug 24.
83. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506. DOI: https://doi.org/10.1016/S0140-6736(20)30183-5
84. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nature Reviews Immunology. 2020:1-8. DOI: https://doi.org/10.1038/s41577-020-0331-4
85. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, et al. Covid-19 in immune-mediated inflammatory diseases—case series from New York. New England Journal of Medicine. 2020. DOI: https://doi.org/10.1056/nejmc2009567
86. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. The Lancet Infectious Diseases. 2020;20(4):400-2. DOI: https://doi.org/10.1016/s1473-3099(20)30132-8
87. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmunity reviews. 2020:102523. DOI: https://doi.org/10.1016/j.autrev.2020.102523
88. Wapnir RA, Sherry B, Codipilly CN, Goodwin LO, Vancurova I. Modulation of rat intestinal nuclear factor NF-κB by gum Arabic. Digestive diseases and sciences. 2008;53(1):80-7. DOI: https://doi.org/10.1007/s10620-007-9826-0
89. Cuadrado A, Pajares M, Benito C, Jiménez-Villegas J, Escoll M, Fernández-Ginés R, et al. Can activation of NRF2 be a strategy against COVID-19? Trends in Pharmacological Sciences. 2020. DOI:

https://doi.org/10.1016/j.tips.2020.07.003

90. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Annals of translational medicine. 2017;5(7). DOI: https://doi.org/10.1038/oby.2007.217
91. Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. Nature Reviews Endocrinology. 2020:1-2. DOI: https://doi.org/10.1038/s41574-020-0364-6
92. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. International journal of obesity. 2013;37(3):333-40. DOI: https://doi.org/10.1038/ijo.2012.62
93. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity. 2020. DOI: https://doi.org/10.1002/oby.23006
94. Dreher ML. Fiber and Healthy Dietary Patterns in Weight Regulation. Dietary Fiber in Health and Disease: Springer; 2018. p. 163-200. DOI: https://doi.org/10.1007/978-3-319-50557-2_9
95. Kennedy S. The development of a functional food breakfast and its effects on gluco-regulation, cognitive performance, mood and satiety in adolescents: Oxford Brookes University; 2016.
96. Rebello CJ, O'Neil CE, Greenway FL. Dietary fiber and satiety: the effects of oats on satiety. Nutrition Reviews. 2016;74(2):131-47. DOI: https://doi.org/10.1093/nutrit/nuv063
97. Müller M, Canfora EE, Blaak EE. Gastrointestinal transit time, glucose homeostasis and metabolic health: modulation by dietary fibers. Nutrients. 2018;10(3):275. DOI: https://doi.org/10.3390/nu10030275
98. Babiker AO, Kaddam LA. Risk factors of metabolic syndrome among adult Sudanese sickle cell anemia patients. BMC hematology. 2018;18(1):38. DOI: https://doi.org/10.1186/s12878-018-0110-7
99. Babiker R, Elmusharaf K, Keogh MB, Banaga AS, Saeed AM. Metabolic effect of gum Arabic (Acacia Senegal) in patients with type 2 diabetes mellitus (T2DM): randomized, placebo controlled double blind trial. Functional Foods in Health and Disease. 2017;7(3):222-34. DOI: https://doi.org/10.31989/ffhd.v7i3.325
100. Nasir O, Babiker S, Salim A-MM. Protective effect of gum Arabic supplementation for type 2 diabetes mellitus and its complications. Int J Multidiscip Curr Res. 2016; 4:288-94.
101. Jarrar AH, Stojanovska L, Apostolopoulos V, Feehan J, Bataineh MA, Ismail LC, Al Dhaheri AS. The effect of gum arabic (Acacia senegal) on cardiovascular risk factors and gastrointestinal symptoms in adults at risk of metabolic syndrome: A randomized clinical trial. Nutrients. 2021 Jan 9;13(1):194. DOI: https://doi.org/10.3390/nu13010194