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Yoghurt (LAB) as preventive method against COVID-19

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Introduction:

SARS-COV-2 explores every possible vulnerability in human body and uses it against the host. To treat this SARS-COV-2 induced COVID-19, we should consider and target the multiple factors this virus is targeting and identify the drugs for usage in a strategical way. This approach can save the patients from severe state of illness and damage associated with this disease.

COVID-19 has been associated with hyper inflammation [101-109] and delayed humoral immune responses [110-115]. Most of the complications with COVID-19 patients have been associated with early hypoxia, ARDS, pneumonia [116-122] and Acute Lung Injury [123-127]. Viral load has been found to be associated directly with incidence of lung injury/epithelial injury or remote organ injury in COVID-19 patients [128-133].

Conclusively, SARS-COV-2 is reported to be associated with severe immune dysregulation, delayed humoral responses and accelerated innate immune response mediated damages. As the pandemic is turning the world upside down, In order to address this disease we should first get an insight into the mechanism of action through which SARS-COV-2 is achieving the above said dysregulating or modulating effects on human immune system.

SARS-COV-2 dysregulates immune system by targeting innate immune system, adaptive immune system and different immune tolerance check points by dysregulating different miRNA's and the preexisting conditions or comorbidities of the patients.

This article targets the data available/ reported till date in the scientific community and tries to provide comprehensive review/insights into the beneficial usage of Probiotics (not all Probiotics) /Tyndallized Probiotics especially Yoghurt in preventing COVID-19 during very initial/early stages but not during the treatment of the disease.

Importance of Microbiota for Respiratory Viral Immunity:

Yoghurt consumption is good for enhancing the respiratory immune system [51,52]. Shi et.al conducted an analysis of 58 studies (9 randomized controlled trials; 49 animal studies) and reported that six of the eight clinical trials consisting of 726 patients show the importance of probiotics administration in reducing the risk of damage during respiratory tract viral infections (RTIs) [94].

Most commonly used probiotics were reported to be Lactobacillus followed by Bifidobacterium and Lactococcus [94]. Shi et.al concluded that in animal models, treatment with probiotics before viral challenge have beneficial effects against influenza virus infection by improving infection-induced survival (20/22 studies), mitigating symptoms (21/21 studies) and decreasing viral load (23/25 studies) [94]. Probiotics and commensal gut microbiota exerts their beneficial effects by strengthening the host immune system [94].

Bradley et.al reported that Microbiota can stimulate Interferon Signaling in Lung Stromal Cells that Protects from Influenza Virus Infection [99]. LAB (Lactic Acid Bacteria) can stimulate and induce the release of Interferon (IFN) [86,87,90,99] and IL-10 [88,92-95].

Probiotics can help in preventing and addressing viral exacerbations [62] and Lung Infection problems [61,65]. Eguchi et.al showed that respiratory syncytial virus (RSV) infection can be prevented with

probiotic lactic acid bacterium Lactobacillus gasseri SBT2055 [63]. In the experiment conducted by Eguchi et.al the expression level of the proinflammatory cytokines TNF-α, CCL2, IL-1β except IL-6 were reported to be reduced after 4 days in Probiotic treated mice [63].

Silvia et.al demonstrated that the administration of Lactobacillus casei CRL 431 or Lactococcus lactis NZ9000 were able to increase S. pneumoniae clearance rates in lung and blood [51], improved survival of infected mice and reduced lung injuries [60,3].

It has been demonstrated that gut-associated lymphoid tissue is stimulated by L. bulgaricus CRL 423 and S. thermophilus CRL 412, resulting in the enhanced production of cytokines and secretory IgA [4,5]. Perdigon et.al showed that LAB has the ability to stimulate the production of IgA [7]. Galdeano et.al showed that the Probiotic Bacterium Lactobacillus casei Induces the activation of the Gut Mucosal Immune System through Innate Immunity and adaptive immune system [57]. Probiotics play important role in stimulating adaptive immune system related IgA responses at the mucosal surfaces required by respiratory immune system for protection against respiratory viral infections [67,57,51].

Probiotic treatment could effectively inhibits LPS-induced autophagy in intestine epithelial cells [11]. Specific probiotic strains could decrease colonic LPS thus it's leakage into systemic blood, systemic inflammation and associated potential damage [12,13]. LAB can protect against inflammation in several cases [24,12,13,14,15,16,17,18]. Moludi et.al through their trial revealed that 12 weeks' probiotic supplementation (L. rhamnose) has a positive effect on endotoxemia and chronic inflammation in CAD (coronary artery disease) patients [14]. LAB is reported to be good for reducing the symptoms of upper respiratory tract during respiratory viral infections in overweight and obese adults [53]. Taken together LAB might be good for preventing co-morbid situations in people in some cases. LAB is good for addressing antibiotic associated side effects [22].

Microbiota might modulate Inflammasome:

Although intestinal flora are crucial in maintaining immune homeostasis of the intestine, the role of intestinal flora in immune responses at other mucosal surfaces remains less clear [95].

Wu et.al showed that TLR-7 ligands rescue the immune impairment in an antibiotic-treated mice during IAV infection [95]. This is in agreement with other studies by kelly et.al which reported that antibiotics dysregulate gut microbiota and downregulate TLR-7 expression at the other mucosal surfaces independent of the delivery Route i.e: either administered through oral or Intravenous ways [96]. Animal studies have also proved the adverse influence of antibiotics in viral Respiratory Tract Infections (RTIs) [97,98,99].

Conclusively, Wu et.al reported that good intestinal flora composition is critical in sustaining and regulating the toll-like receptor 7 (TLR-7) expression and signalling pathways during respiratory influenza virus infection [95].

Intact microbiota provides signalling leading to the expression of mRNA for TLR-7, MyD88, IRAK4, TRAF6, and NF-κB at steady state [95]. Significant changes in the composition of culturable commensal bacteria reduce the expression levels of components of the TLR-7 signaling pathway [95].

Ichinohe et.al also showed that commensal microbiota composition critically regulates the generation of virus specific CD4+ and CD8+ T cells and antibody responses following respiratory influenza virus infection [100].

Jeisy et.al showed that in the absence of effective TLR-7 signalling during damage induced by IAV infection, the M-MDSCs get accumulated to the infected site in Lungs rapidly, resulting in the suppression of Virus specific T cell (ex: CD8+ T cell) and other immune responses [101].

Yukong et.al observed that Influenza infection lead towards an increase in the proportions of Th1/Th2 and Th17/Treg cells in the infected group suggesting that influenza virus promotes inflammation mediated damage via Th1 and Th17 cells [102].

Yukong et.al observed that TLR-7 expression was upregulated in mice when infected with higher viral load of Influenza virus (IAV) infection than compared to normal uninfected control mice [102]. This upregulation of TLR-7 is reported to be associated with promoting inflammation and useful in controlling viral burden [102]. Although TLR-7 expression upregulation during inflammation further promotes inflammation, it is reported to be essential to sense and control the viral burden since TLR-7−/− mice is found to be subjected with faster viral growth and subsequent higher mortality rate [102]. Yukong et.al observed that increased viral load is associated with more damage due to monocyte and other inflammation mediated damage [102].

This is in agreement with other observations which states that TLR-7 reduction during acute phase of inflammatory response due to viral infection might lead to subsequent increase in viral load and subsequent damage induced by monocytes as seen in IAV [103,104,105,106].

Jeisy et.al showed that TLR-7−/− mice during IAV infection is associated with higher titers of viral burden in Lungs and subsequent higher mortality rate [101]. Jeisy et.al also reported that TLR-7 has important role during secondary stage of viral infection (IAV) through sensing the viral RNA and limiting viral growth through inflammation but not during earlier stages of the infection [101].

Wu et.al revealed the importance of intestinal flora in regulating immunity in the respiratory mucosa through the upregulation of the TLR-7 signaling pathway for the proper activation of inflammasomes [95]. Ichinohe et.al reported that local or distal injection of Toll-like receptor (TLR) ligands could rescue the immune impairment in the antibiotic-treated mice [100]. Intact microbiota provides signals leading to the expression of mRNA for pro-IL-1β and pro-IL-18 at steady state. During influenza virus infection, inflammasome activation helps in migration of dendritic cells (DCs) from the lung to the draining lymph node and T-cell priming [100]. Ichinohe et.al results revealed the importance of commensal microbiota in regulating immunity in the respiratory mucosa through the proper activation of Inflammasomes [100].

Gut Microbiota and Tregs relation:

It is now well established that resident microbes provide enormous advantages to the host, while dysbiosis can trigger acute and chronic inflammatory conditions [107]. One of the mechanisms by which these microbes regulate immunity is through controlling Tregs and Th-17 cells balance [107]. Taken together microbiota is essential for proper TLR-7 expression and signalling pathways along with proper activation of Inflammasomes [107].

Impaired Inflammasome in COVID-19:

Impaired Inflammasome activity observed in severe COVID-19 patients [108-112].

Microbiota dysregulations observed in COVID-19 patients and related Trials:

Gut microbial dysbiosis has been identified in COVID-19 patients, characterized by the enrichment of opportunistic pathogens and depletion of beneficial commensals [113,114,115]. Gut microbiota alterations are reported to be associated with disease severity. Zuo et.al reported that the severity of COVID-19 is positively correlated with the baseline abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi*, and inversely correlated with that of *Faecalibacterium prausnitzii* (an anti-inflammatory bacterium) [113]. Subjects with gut dysbiosis, such as elderly, immune-compromised patients and patients with other co-morbidities are reported to have more severe disease and poorer outcomes of COVID-19 [116].

However, not all probiotics are equivalent for efficacy [117]. A novel and more targeted approach to modulate gut microbiota as one of the therapeutic strategies for COVID-19 and its complications is much needed. In a recent study reported by d'Ettorre et al., among COVID-19 patients, oral

administration of a probiotic mixture significantly reduced the risk of developing respiratory failure, and a trend towards reduced rates of mortality [118].

It has been reported that Chinese University of Hong Kong team has developed an oral gut microbiota modulating formulation against COVID-19. In a pilot study, this formulation significantly improved clinical symptoms and reduced pro-inflammatory immune markers in COVID-19 patients [119].

Probiotics rescue from Antibiotic Abuse:

Viral infections predispose patients to secondary bacterial infections, which often result in a more severe clinical course [120]. Empirical antibiotics are sometimes used for the management of viral infection when secondary bacterial infection is a concern. However, Zuo et al. revealed that antibiotics use led to further loss of salutary symbionts and exacerbation of gut dysbiosis in COVID-19 patients [113] which is in confirmation with other authors [95,96]. Animal studies have also proved the adverse influence of antibiotics in viral RTIs [97,98,99]. These results suggest clinicians to avoid unnecessary antibiotics use in the treatment of viral RTIs.

Antibiotics are known for dysregulating gut microbiota [113] and gut microbiota is related to TLR-7 expression at mucosal surfaces [95] and reduction in TLR-7 is associated with higher mortality in COVID-19 patients[121]. Microbiota regulates the TLR-7 expression at mucosal surfaces which is helpful during viral infections [95,100,122].

Conclusively, early administration of LAB is beneficial to enhance viral immunity. LAB helps in enhancing Treg response, produce early interferon response, stimulate innate response and stimulate adaptive response by inducing IgA responses. Studies show that Lactobacillus protected against several respiratory virus in mice including IAV [123,122,124,125-128].

It has been revealed that intestinal flora is important in regulating immunity in the respiratory mucosa through the upregulation of the TLR7 signaling pathway for the proper activation of inflammasomes [95]. It has also been revealed that the commensal microbiota is important in regulating immunity the respiratory mucosa through the proper activation of inflammasomes [100].

Disadvantage of Probiotic Usage:

1. Although LAB is good for many conditions [19,20,21,24,25,26,28,29], it should be taken care that at-risk, Immunocompromised and immunosuppressed people in all ages (ex: HIV, Cancer, Gut diseases, ill ICU patients, critically sick infants,frail elderly subjects, postoperative, hospitalized patients and patients with immune compromised complexity etc…) should avoid taking LAB as it might harm them as a secondary infection [82,58,59,77,78,80,81,23,27].
2. People should get the advice/recommendation to consume LAB or not by consulting with their concerned family physician/doctor who might check the patient's previous health conditions and recommend based on them.

Alternative Solution:

Heat-Killed/(Tyndallized) Probiotics might be a solutions for this problem as observed in many other conditions. Chen et.al showed that pretreatment with a heat-killed E. faecalis probiotic can modulate the Monocyte Chemoattractant Protein-1 (MCP-1) and protect from/reduces the pathogenicity of two unrelated viruses influenza virus and enterovirus 71 (EV71) infections in mice [85].

Piqué et.al reported that their reviewed data indicate that heat-killed bacteria or their fractions or purified components have key probiotic effects, with advantages versus live probiotics (mainly their safety profile) [83,84].

Conclusion:

Conclusively, Probiotics might be helpful as a preventive measure [64,66,89,91] but not during the treatment of COVID-19 disease.

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