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Review Article

Reducing COVID-19 Risk through Dietary Supplementation of Plant Mannose Binding Lectins

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Abstract

One Sentence Summary: Increasing consumption of plant lectins (e.g., eating fruits and vegetables) may reduce COVID-19 risks.

Mannose binding lectins (MBL), a key molecule in our innate immune response, contributes to host defense against coronaviruses such as SARS-CoV. This article reviews the role of MBL in the innate immune response against coronavirus infections, highlights evidence of MBL's significance, and suggests dietary MBL supplementation through increased consumption of fruits and vegetables as an accessible and viable approach to minimizing COVID-19 infection risk.

Keywords:
SARS-CoV; SARS-CoV-2; Coronavirus; Mannose Binding Lectins; MBL; Lectins; Diet; Public Health

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1. Introduction

The global COVID-19 pandemic continues to spread. Public health measures in the USA have had limited efficacy with masks and social distancing the primary methods for reducing the infection rate. While a lot of research is focused on a vaccine which trains the adaptive immune system to provide an acquired immunity, the innate immune system should not be overlooked in its ability to help reduce the risk of COVID-19 infection. This article reviews the role of mannose binding lectins (MBL) in the innate immune system, knowledge about the epidemiology of COVID-19, and how supplementing MBLs increases resilience against COVID-19 infection. Several studies have shown that MBLs display anti-coronavirus properties of varying efficacy. Evidence supporting the positive effects of MBL with respect to COVID-19 infections includes (a) their ability to bind to coronaviruses thereby inhibiting infectivity and activating the complement system, (b) observed infection rates varying by race and ethnicity consistent with variations in mannose binding lectin levels, and (c) consumption of more plant lectins correlated with better outcomes and lower rates of infection. Supplementing MBL through diet to enhance innate immune response may therefore reduce infection rate, improve outcomes, and increase overall public health while vaccine development continues. MBLs are common and readily accessible from plants so it is recommended that people at risk of or infected by COVID-19 consider dietary supplementation of plant MBLs by increasing consumption of fruits and vegetables. Large scale population studies should be conducted to refine these generalized recommendations towards more effective dietary recommendations.

2. Discussion

2.1. Mannose Binding Lectins and Our Immune System

The innate immune system is our first line of defense against infection by invading pathogens.[1–3] Part of our innate immune system includes Mannose Binding Lectins (MBL), which are collectins in the C-type lectin superfamily dependent on calcium for binding.[3] The general role of MBL in the innate immune system is known.[1–3] MBLs are proteins produced by the liver and secreted into the serum where they can activate an immune response.[2] MBLs have carbohydrate recognition domains for prototypical pattern recognition allowing them to recognize and bind to infectious agents, including bacteria and viruses, thereby activating the complement system.[1,2] MBL binding and complement activation enhances phagocytosis by acting as an opsonin using the lectin pathway.[2,3] See Figure 1. Complement activation further serves as a bridge to our adaptive immune system for producing antigen specific antibodies, possibly resulting in acquired immunity.[2,4]

Multiple studies have shown that MBL deficiency increases susceptibility to infection, including influenza and SARS-CoV-1.[2,5,6] MBL deficiency is a condition affecting the immune system resulting in low levels of MBL in blood sera that occurs in up to 30% of the population, depending on ethnicity.[2,3] Innate MBL production is genetically determined where both over- or under-production can both be problematic for different reasons.[2,3] There are 3 coding region single-nucleotide polymorphisms (SNPs) for MBL at codons 52, 54 and 57 affecting MBL production.[2,3] The frequency of these SNPs varies among different ethnicities where the codon 54 variant is very common.[6]

2.2. COVID-19 and SARS-CoV-1

COVID-19 is caused by a coronavirus known as Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2). SARS-CoV-2 was previously known by its provisional name, 2019 novel coronavirus (2019-nCoV). Previous human coronavirus infections include Severe Acute Respiratory Syndrome CoronaVirus (SARS-CoV-1), which caused the SARS outbreak in Asia between 2002 and 2004, and Middle East Respiratory Syndrome CoronaVirus (MERS-CoV).

Coronaviruses are enveloped viruses with large single-stranded RNA genomes.[7] SARS-CoV-2 is genetically very similar to SARS-CoV-1 and both are in the coronavirus family, β-coronavirus genera lineage B.[8,9] Prior

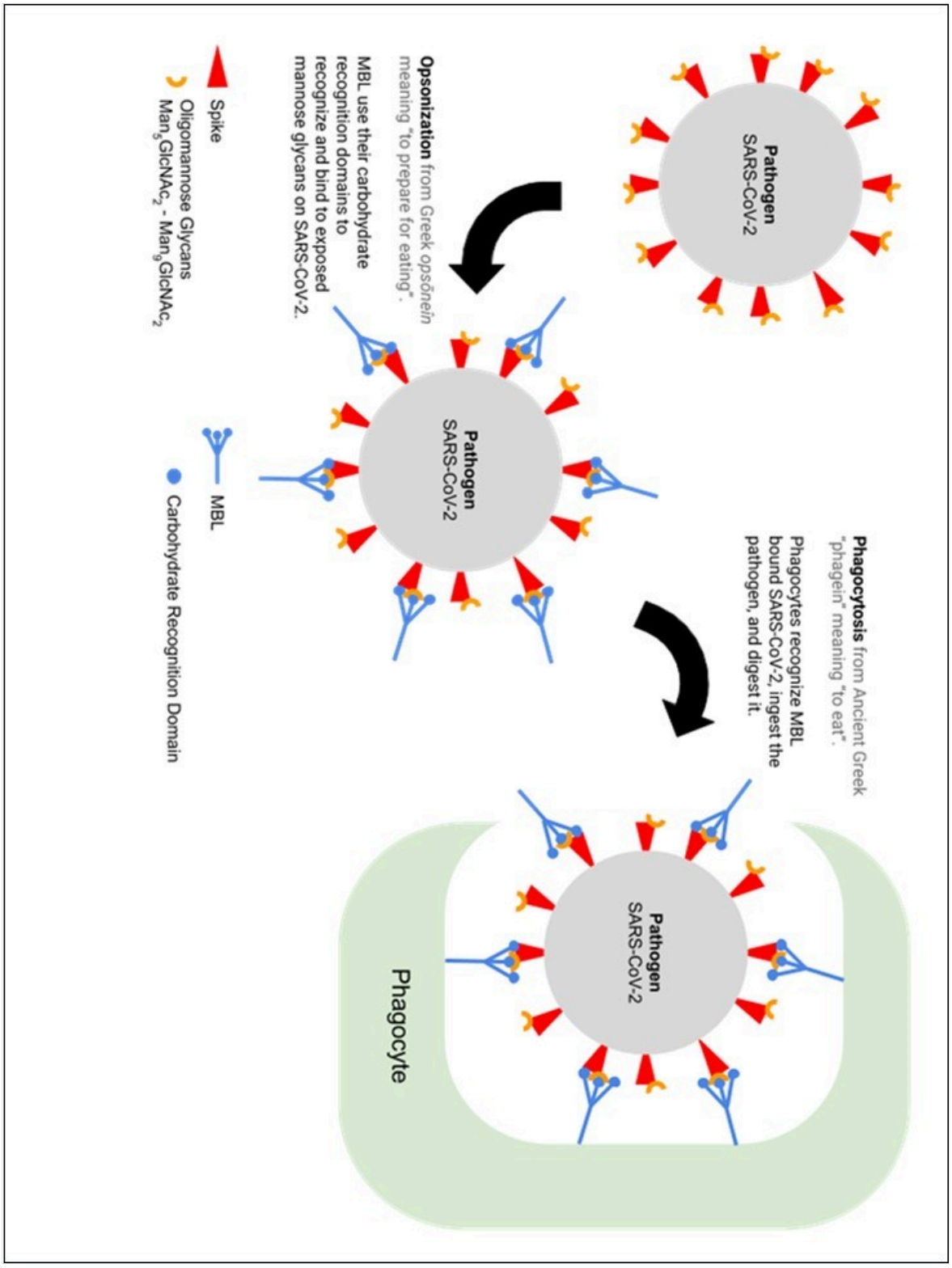

Figure 1. MBL binding and complement activation enhances phagocytosis by acting as an opsonin.

research has found SARS-CoV-2 maintains high homology, ~80% nucleotide identity, to SARS-CoV-1 across the entire genome.[8,10] Most SARS-CoV-2 proteins are also highly homologous (95%–100%) to proteins of SARS-CoV-1 virus.[11] The most abundant protein in coronaviruses, the nucleocapsid (N) protein, in SARS-CoV-2 has ~90% amino acid identity to the SARS-CoV-1 N protein.[10,11] The SARS-CoV-2 spike (S) protein has roughly 75% amino acid identity with SARS-CoV-1 with the spike receptor binding domain (RBD) is approximately 73% conserved.[10] The SARS-CoV-2 spike subunit S2, which fuses viral and host membranes, shares 99% identity with the SARS-CoV-1 S2.[11] Given these similarities, it's unsurprising

that both SARS-CoV-1 and SARS-CoV-2 S proteins contain a receptor binding domain for angiotensin-converting enzyme 2 (ACE2) which mediates entry of the coronavirus into host cells.[11,12]

S is the main target of antibodies during infection and a focus for vaccine design because it is virtually the only antigen present on the virus surface.[7,13,14] The SARS-CoV-2 S protein is extensively glycosylated with 22 N-linked glycan sequons per protomer so each trimer displays 66 N-linked glycosylation sites.[13,14] SARS-CoV-1 S possesses 23 N-linked glycosylation sequons per protomer with 20 of the 22 SARS-CoV-2 S glycosylation sequons conserved from SARS-CoV-1.[14] These S glycans are under selective pressure as they both facilitate immune system evasion by shielding specific epitopes from antibodies, yet also present opportunities for immune system recognition.[13,14] All 9 S2 glycans are conserved between SARS-CoV-2 S and SARS-CoV-1 S suggesting that immune system recognition and accessibility to antibodies will be comparable among these viruses.[14]

Site-specific glycosylation analysis suggests that the glycan shield of SARS-CoV-2, like other coronaviruses, exhibits numerous vulnerabilities.[13] Analysis of the glycans on SARS-CoV-1 S and SARS-CoV-2 S revealed they are more dispersed; resulting in less coverage than expected in an effective glycan shield.[13,15] Typically, viruses classified as "evasion strong" have significantly higher glycan shield densities correlated with an effective glycan shield; therefore, the lower glycan shield density of coronaviruses suggests susceptibility to host immune responses.[15]

SARS-CoV-1's less dense glycan shield reveals a broad spectrum of underprocessed oligomannose-type glycans with $Man_5GlcNAc_2$ to $Man_9GlcNAc_2$ glycans all present.[15] These underprocessed oligomannose-type glycans enable innate immune system recognition of coronaviruses by MBLs.[5,15] SARS-CoV-2, with similar genetics and proteins to SARS-CoV-1, also presents many oligomannose-type glycans from $Man_5GlcNAc_2$ to $Man_9GlcNAc_2$ suggesting similar characteristics and susceptibility to innate immune system recognition by MBLs.[13]

2.3. Mannose Binding Lectins vs Coronaviruses

MBLs exhibit significant activity against enveloped viruses, such as coronaviruses, as their glycosylated envelopes allow MBLs to interfere at two points of the viral life cycle: viral entry and viral shedding.[16] Prior research has shown that a number of plant lectins, especially plant MBLs, exhibit anti-coronavirus properties of varying efficacy against SARS-CoV-1.[17] (Based on their similarities and how the lectin pathway functions, the prior findings for SARS-CoV-1 are likely applicable to SARS-CoV-2.) Nearly two-thirds of the plant lectins previously tested, including almost all MBLs (exception: garlic), exhibited some anti-coronaviral properties with 20 of the 33 plant lectins tested active against SARS-CoV-1.[17] Of those 20 SARS-CoV-1 effective plant lectins, 14 were MBLs with the most potent being the MBL from leek, *Allium porrum*.[17] The broad spectrum of lectins capable of binding to SARS-CoV-1 is a likely result of its vulnerable glycan shield revealing a broad spectrum of oligomannose-type glycans. Therefore, it would be beneficial for host immune systems to have a broad spectrum of lectins available as lectins with different specificity interfere with different exposed glycans.[17]

As MBL and the innate immune defense are the first line host defense against pathogens, host lectin levels (specifically, MBL levels), and composition may contribute to both susceptibility and outcome (e.g., whether an infected host exhibits symptoms or remains asymptomatic). MBL deficient individuals are more susceptible to SARS.[6] Innate immune systems with insufficient levels of SARS-CoV-2 effective MBLs are overwhelmed resulting in infection and symptom expression. By contrast, hosts capable of maintaining sufficient levels of SARS-CoV-2 effective MBL could maintain a sufficient innate immune system response until the adaptive immune system responds to produce sufficient antibodies. Therefore, SARS-CoV-2 effective MBL levels could explain the wide variation in clinical results ranging from severe to asymptomatic individuals with SARS-CoV-2 antibodies.[18] In essence, individual outcomes depend on viral load vs host SARS-CoV-2 effective MBL levels.

2.3.1. Variations in MBL Levels by Race and Ethnicity

Presuming SARS-CoV-2 effective MBL levels are a significant factor is consistent with observations that those of certain racial and ethnic communities (including non-Hispanic Blacks, Hispanics, Latinos, and Asians) are at higher risk.[19,20] MBL deficiency is more common in people from Southeast Africa and South America.[21] Of the 3 SNPs resulting in MBL deficiency, those of sub-saharan African descent frequently had a codon 57 variant and those of South American descent frequently had a codon 54 variant.[21] A study of Hong Kong Chinese found that SARS patients more frequently had a codon 54 variant resulting in significantly

lower levels of MBL than control subjects.[6] While codon 54 and 57 variants and MBL deficiencies are quite frequent in those of Southeast African and South American descent, they are less frequent in Caucasians with estimates of only 10–15% of Caucasians having an MBL deficiency which likely contributes to lower susceptibility and lower rate of infection.[2,21,22]

The frequencies of these genetic differences and their resulting MBL deficiencies contribute towards why people of Southeast African and South American descent are more susceptible to SARS than Caucasians as observed in CDC data. Currently, as of June 30, 2020, the CDC reports "non-Hispanic Black persons" and "Hispanic or Latinos persons" are disproportionately affected at a rate several times that of non-Hispanic white persons.[20] As another example, the CDC also reports significantly higher infection rates in the "Non-Hispanic American Indian or Alaska Native" group which is also consistent with previous studies indicating lower MBL levels in the American Indian population.[20,23] The notable exception, Asians, who are more susceptible to infection are also the population group significantly more likely to wear masks resulting in their under-representation in the CDC data.[24–27]

2.3.2. Evidence That MBL Supplementation Is Effective

As plant lectins exhibit anti-coronavirus properties of varying efficacy, it's likely that plant MBL supplementation is a contributing factor towards COVID-19 risk and outcomes.[17] Plant lectins are common in food and dietary intake can be significant.[16,28] Many non-legume plant lectins, including MBL, maintain full biological activity after consumption as they are typically not inactivated by cooking, resist digestion, and enter the circulation intact.[16,28,29]

An example where an active lectin supplement may be demonstrating its anti-coronaviral properties is the Nictaba lectin from the tobacco plant (*Nicotiana tabacum*). Nictaba is a GlcNAc-specific agglutinin that is active against SARS-CoV-1, which exposes many glycans enabling interference with virus entry and virus release.[17] With the similarities between SARS-CoV-2 and SARS-CoV-1 in combination with Nictaba being the 4th most active lectin previously tested for SARS-CoV-1 (SI: >58.8), Nictaba may be potent against SARS-CoV-2.[17] Nictaba lectin, supplemented through the use of tobacco products, could explain the counter-intuitive observation that smokers have a significantly reduced risk of infection, which is highly unusual for a respiratory disease.[30–33] Though the risk of infection may be reduced by Nictaba, tobacco products cause other damage, including to the respiratory system, which demonstrably increases the severity of COVID-19.[34]

While tobacco products have clear disadvantages in increasing COVID-19 severity, their ability to reduce infection risk suggests plant lectin supplementation (e.g., consumption of fruits and vegetables) may be a viable approach to augmenting host MBL production and boosting innate immune system response to SARS-CoV-2. See Table 1. At a macro scale, existing differences in dietary MBL consumption is consistent with observed differences in outcomes between men and women. Women have been shown to eat more fruits and vegetables than men, which presumably confers additional protection and resistance to women.[35–37] This is consistent with observations that men are at higher risk for worse outcomes and death from COVID-19 than women.[38]

Fruit and vegetable consumption is also correlated with income where higher incomes are associated with higher levels of fruit and vegetable consumption.[37] This is consistent with observations that higher rates of infection are correlated with lower household incomes.[39] By contrast, "food deserts" have limited access to healthy foods such as fruits and vegetables. Food deserts are often correlated with lower incomes and race as African American and Latino communities are more likely to be in food deserts.[40] With reduced dietary consumption of fruits and vegetables in food deserts and increased susceptibility from MBL deficiencies, African American and Latino communities are more likely to have higher risk and susceptibility to COVID-19 which is consistent with CDC data.[20]

2.4. Dietary Supplementation and target MBL Levels

With MBL levels a critical factor in COVID-19 infection risk and outcomes, it is important to determine the appropriate amount of MBL supplementation appropriate for mitigating COVID-19 risk. Further research here is recommended as MBL blood concentrations vary widely from undetectable to as high as 10 µg/ml, and MBL deficiency criteria is not standardized with prior studies using thresholds ranging from 0.1 µg/ml to 1 µg/ml.[2] A prior study found that the median serum level of MBL in Hong Kong Chinese SARS-CoV-1 patients was significantly lower (0.733 µg/ml) than that in control subjects (1.369 µg/ml); an average

Table 1. Of the 20 plant lectins that previously tested active against SARS-CoV-1, 9 are from plant species commonly eaten or used, and of those, 6 are mannose binding lectins. None of these lectins were toxic below 50 µg/ml concentrations with even the most toxic lectin from Taro (Colocasia esculenta), an edible plant frequently consumed by several cultures.

List of Commonly Available Lectins Previously Tested Against SARS-CoV-1

		SARS-CoV-1 Results				
Type	**Lectin**	**EC50 (µg/ml)**	**CC50 (µg/ml)**	**SI**	**Plant Species**	**Common Name**
Mannose	APA	0.45 ± 0.08	>100	>222.2	Allium porrum	Leek
(GlcNAc)n	UDA	1.3 ± 0.1	>100	>76.9	Urtica dioica	Stinging nettle
Mannose	Morniga M II	1.6 ± 0.5	>100	>62.5	Morus Nigra	Black mulberry tree
GlcNAc	Nictaba	1.7 ± 0.3	>100	>58.8	Nicotiana tabacum	Tabacco plant
Gal	Morniga G II	50 ± 13	>100	>2	Morus Nigra	Black mulberry tree
Mannose	AUA	18 ± 4	>100	>5.5	Allium ursinum	Ramsons (Wild Garlic)
Mannose	Col O	>60	63 ± 3	na	Colocasia esculenta	Taro
Mannose	ASA, ASA I	>100	>100	na	Allium sativum	Garlic

GlcNAc: N-acetyl glucosamine,
Gal: galactose,
na: no activity

difference of 0.636 µg/ml.[6] For the average adult, this translates to a difference of 3,180 µg, which represents an estimate for the average adult MBL deficiency between control and SARS-CoV-1 patients.

To illustrate the viability of dietary MBL supplementation, we posit an extreme example of compensating for MBL deficiency using leek (*Allium porrum*), as it has the highest selectivity index (SI: >222) for SARS-CoV-1 with an EC_{50} of 0.45 µg/ml.[17] At a leek lectin concentration of 10,000 µg/kg, an average adult can supplement at the EC_{50} level with ~1/5 kg of leek yielding ~2,000 µg of *Allium porrum* (APA) MBL lectins compensating for ⅔ of the average adult MBL deficiency from a single source.[17,41] As many plant lectins display anti-coronaviral properties of varying efficacy ($na \leq SI \leq >222$), a varied diet high in fruits and vegetables incorporating a broad spectrum of plant lectins, especially MBLs, should yield additive benefits for each SARS-CoV-2 effective lectin.[17]

4. Recommendations

While research continues for a vaccine to SARS-CoV-2, we can take precautionary steps to strengthen our innate immune response thereby reducing infection risk and improving outcomes. Many plant lectins, especially mannose binding lectins, interfere with the viral life cycle of coronaviruses and facilitate recognition by the innate immune system. While mannose binding lectins are common in legumes and alliums (e.g., leeks, onions, shallots, wild garlic, chives, etc…), plant lectins exhibit a broad range of specificities with varying levels of affinity.[41] Therefore, dietary supplementation of SARS-CoV-2 effective plant MBL through a general increase in consumption of fruits and vegetables should reduce infection rate and improve COVID-19 outcomes. It is also important to maintain sufficient calcium levels as MBL is dependent on calcium for binding. Policy and other measures encouraging fruit and vegetable consumption by increasing their accessibility and availability to at risk populations are also recommended.

Further studies and experimentation should be considered to understand in more detail the impact of various MBL genotypes and MBL deficiencies with respect to COVID-19. Results from these studies may be used to identify higher risk individuals, enable better prediction of outcomes, and improve treatment methodologies. As many plant lectins exhibit anti-coronaviral properties, large scale population studies of diet and infection with respect to COVID-19 infection and outcomes should be conducted to identify foods most likely to contain lectins effective against SARS-CoV-2. Results from these studies would enable refinement of dietary recommendations for at risk groups and facilitate further study of specific SARS-CoV-2 effective lectins. Together, future studies in these directions could inform public policy decisions towards improving overall public health.

Author Contributions

All authors have read and agreed to the published version of the manuscript. Authorship must be limited to those who have contributed substantially to the work reported. Kevin Lau is responsible for research, conception, analysis and writing of this article.

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Competing Interests

The authors have declared that no competing interests exist.

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