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Raw Vegan Diet in the Context of SARS-CoV-2 Infection

Sirova veganska prehrana u kontekstu infekcije virusom SARS-CoV2

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Abstract. Most individuals infected with SARS-CoV-2 experience mild to moderate coronavirus disease 2019 (COVID-19), but the clinical presentation and general course varies widely and depends mainly on the patient's health status before the infection. Certain number of people, particularly those who had a severe COVID-19, experience multiorgan symptoms lasting weeks, months, or even years after infection and some exhibit an immunophenotype that supports chronic inflammation and may trigger autoimmunity and neuroinflammation. An unhealthy lifestyle and associated health conditions, particularly obesity, hypertension, type 2 diabetes, and hyperlipidemia, have been associated with the severity of COVID-19, but the data on the role of diet are still lacking. A raw vegan diet limits the intake of unhealthy food components such as saturated and unsaturated fats, sodium, and added sugars while being rich in fruits, vegetables, and whole grains, giving it some serious health benefits. The purpose of this review article is to give an overview of the factors associated with the severity and the outcome of COVID-19, to highlight all the important effects of raw vegan diet on individual health and to discuss them in the context of SARS-CoV-2 infection.

Keywords: COVID-19; Hypertension; Obesity; Raw Foods; SARS-CoV-2; Vegans

Sažetak. Većina osoba zaraženih virusom SARS-CoV-2 razvije blagu do umjerenu koronavirusnu bolest (COVID-19), ali klinička prezentacija i opći tijek bolesti uvelike se razlikuju i uglavnom ovise o zdravstvenom stanju pacijenta prije infekcije. Određeni broj ljudi, posebno onih koji su imali teški COVID-19, ima multiorganske simptome koji traju tjednima, a u nekim slučajevima i dulje od 12 mjeseci nakon infekcije, a neki pokazuju imunofenotip koji podržava kroničnu upalu i može dovesti do razvoja autoimunosti i neuroinflamacije. Nezdrav način života i s njim povezana zdravstvena stanja, posebice pretilost, hipertenzija, dijabetes tipa 2 i hiperlipidemija, povezani su s težim oblicima bolesti COVID-19, ali podatci o utjecaju prehrane na klinički tijek bolesti još uvijek nedostaju. Sirova veganska prehrana ograničava unos nepoželjnih sastojaka hrane kao što su zasićene i nezasićene masti, natrij i dodani šećeri, a istovremeno je bogata voćem, povrćem i cjelovitim žitaricama te stoga ima mnoge pozitivne učinke na zdravlje. Svrha ovog članka je dati pregled čimbenika povezanih s težinom i ishodom bolesti COVID-19, istaknuti sve važne učinke sirove veganske prehrane na zdravlje pojedinca i raspravljati o njima u kontekstu infekcije virusom SARS-CoV-2.

Ključne riječi: COVID-19; hipertenzija; pretilost; SARS-CoV-2; sirova hrana; vegani

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INTRODUCTION

Coronavirus disease (COVID-19) has quickly become a global health emergency, with more than 650 million people infected in 216 countries and more than 6.5 million confirmed deaths to date. The mortality rate is about 3% worldwide but varies between countries[1]. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that is spread in the population primarily by the direct contact or through the air. In many cases, the infection is asymptomatic. Symptomatic infections range from mild (sneezing, nasal congestion, fever, fatigue, cough, myalgias, headache, sore throat, diarrhea, and olfactory or taste abnormalities) to severe (shortness of breath, chest pain and hypoxemia) and may lead to respiratory failure, circulatory shock, and multiorgan failure in some individuals[2, 3]. COVID-19 survivors who had more severe form of the disease are also at greater risk of developing a long COVID-19 or post-COVID-19 syndrome (PCS) characterized by persistent symptoms lasting 3 months or longer after the acute COVID-19[4, 5].

> The clinical presentation of SARS-CoV-2 infection and the severity of COVID-19 depends largely on the underlying medical conditions before infection. Hypertension, obesity, and type 2 diabetes (T2D) are considered important factors in disease severity and are generally associated with unhealthy diets.

Whether the individual develops mild or severe COVID-19 depends mainly on underlying medical conditions and general health prior to the infection. Hypertension, obesity, and type 2 diabetes (T2D) are considered major factors in the disease severity[6–8] and are generally associated with poor diet. A precondition for good health is a diet that includes plenty of vegetables, fruits, and whole grains and limits the intake of processed foods[9]. All of these principles form the basis of the raw food diet, a type of diet that involves the consumption of foods that are uncooked or heated below 46°C[10]. Depending on the type of food consumed, the raw food diet can be divided into three basic subtypes. The raw vegan diet is the most common type of raw food diet (> 90% of practitioners) and excludes all animal products and byproducts. Somewhat more liberal is the raw lacto-ovo vegetarian diet, which includes plant-based foods along with raw eggs and unpasteurized and unhomogenized dairy products. Finally, the least restrictive is the raw omnivorous diet, which includes all raw animal products, including meat[10, 11]. Vegans consume less saturated fat, cholesterol, and added sugars and more vitamins C and E, fiber, folic acid, potassium, magnesium, and phytochemicals (plant compounds) such as carotenoids and flavonoids than other consumer subgroups, and therefore a raw vegan diet can be considered to promote good health[12, 13]. In addition, good bacteria, some of the nutrients, and food enzymes are not destroyed by thermal processing of foods, and at the same time, compounds that have potentially harmful effects, such as trans fatty acids (TFA) and advanced glycoxidation end products (AGE) cannot be formed[14–16]. Therefore, due to its constituents, the raw vegan diet has proven associations with strengthening of immune system, weight loss, improvement in blood pressure and lipid profile, lower risk of some cancers and cardiovascular disease, and has been shown to have antioxidant and anti-inflammatory effects[10, 11, 16–27]. In addition to the numerous beneficial effects of the raw vegan diet on human health, some deficiencies have been reported, including lower bone density, vitamin B12 deficiency, decreased high-density lipoprotein (HDL) cholesterol levels, amenorrhea and malnutrition in women, and increased risk of food poisoning[10, 11, 28–30]. However, most of these deficiencies could be prevented if the diet is well-balanced and wisely conducted[28, 31].

MAIN BODY

SARS-CoV-2 Infection – Factors Associated with Severe Clinical Course and Post-COVID-19 Conditions

The clinical presentation of SARS-CoV2-positive patients is highly variable, and the most common health conditions associated with a worse COVID-19 outcome are hypertension, obesity, metabolic syndrome (MS), dyslipidemia, cardiac dysfunction, hyperglycemia, and T2D[32–34]. All of these conditions are associated with endothelial injury and dysfunction, which, together with microvascular inflammation, play an important role in the severe clinical status of COVID-19[35, 36].

Although SARS-CoV-2 has direct effects on endothelial dysfunction[37], tissue damage is supported by elevated angiotensin II levels (ANG II) due to COVID-19 infection. Namely, ANG II is the major effector molecule of the renin-angiotensin-aldosterone system (RAAS). It damages endothelial cells and other tissues and therefore plays a key role in pathogenesis of hypertension and inflammation, causing hypercoagulability[38], atherosclerosis, and arteriosclerosis[39]. The level of ANG II is determined by angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin II, and by the activity of angiotensin-converting enzyme (ACE2), which lowers ANG II as it converts ANG II into harmless molecules that have vasodilatory effects. Since SARS-CoV-2 utilizes ACE2 for cells invasion and infection[40, 41] it decreases the levels of ACE2 due to the viral binding and endocytosis of a receptor-virus complex. Therefore, ANG II cannot be converted, leading to vasoconstriction, increased inflammation, and endothelial cell damage, increasing the risk of stroke, myocardial infarction, and respiratory failure. This is even more pronounced in people with hypertension, probably because of the already damaged endothelium, which provides the perfect background for the development of microvascular failure. In addition, it is possible that in people with hypertension, the availability of ACE2 to SARS-CoV-2 is increased because of an existing RAAS imbalance, resulting in a higher viral load that is associated with a worse acute disease course and outcome[42] and a greater likelihood of developing post-acute or post-COVID-19 symptoms. Therefore, it is not surprising that hypertension is the most common comorbidity in hospitalized COVID-19 patients[43].

In addition to hypertension, a strong association between the risk of hospitalization and obesity has also been found in COVID-19 patients, and more than 70% of COVID-19 patients requiring treatment in the ICU (intensive care unit) are obese[44]. There are many reasons why obesity favors COVID-19. Obesity, as a consequence of unhealthy dietary habits, may contribute to the dyshomeostasis of the intestinal microbiome[45] and consequently increase intestinal permeability, which facilitates the penetration of pathogens through the gastrointestinal epithelium[46]. In addition, the production of IL-17 and IL-23 in patients/persons with obesity is thought to cause a dysfunctional and inefficient immunologic response to viral infections[47], which may contribute to the higher morbidity and mortality in SARS-CoV-2 patients since patients with severe disease have elevated inflammatory markers (C-reactive protein; CRP) and inflammatory cytokines (interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α)), and decreased numbers of adaptive immune cells (CD3+ T cells, CD4+ T cells, CD8+ T cells, and B cells) and NK cells[48–52]. It is also possible that the adipose tissue serves as a reservoir for SARS-CoV-2 virus[44, 53]. The cytokine imbalance caused by chronic obesity leads to increased vascular permeability and leukocyte infiltration into tissues. This leads to cellular damage and impaired respiratory epithelial closure junctions, increasing the likelihood of severe respiratory failure in COVID-19 patients[53]. Obesity is also known to be a central pillar in the development of metabolic syndrome (MS), the prothrombotic and pro-inflammatory state that promotes the onset of severe COVID-19 symptoms. The pathogenesis of MS includes high levels of pro-inflammatory cytokines (TNF-α, IL -1, IL -6, PAI-1, leptin, IL -17, IL -23, and TGF-β) and adipokines, which together cause insulin resistance, arterial hypertension, and dyslipidemia[54], important risk factors for poor COVID-19 outcome.

Persons with obesity generally have higher vitamin D requirements because they ‘sequester’ vitamin D in fat cells, resulting in lower levels in the blood[55]. Since vitamin D is an important immunoregulatory substance that helps maintain the fine balance between pro-inflammatory and anti-inflammatory signals, it is not surprising that hypovitaminosis D is often associated with worse COVID-19 outcome[56]. Hypovitaminosis B12 is also associated with obesity[57], and contributes to an overall higher inflammatory state in the body, making it more susceptible to worse COVID-19 outcomes[58]. It is also discussed that low levels of B12 contribute to endothelial dysfunction and activation of platelet and coagulation cascades[59]. Moreover, vitamin B12 deficiency leads to an increased production of reactive oxygen species and subsequent oxidative stress[59], contributing to an unfavourable state during SARS-CoV-2 infection. In addition, early computer modelling and laboratory-based studies suggest that vitamin B12 can bind to at least one of the viral proteins, thereby slowing viral replication. A recent study showed that methylcobalamin the supplements had the potential to reduce COVID-19-related organ damage and symptoms[60]. A clinical trial conducted in Singapore showed that COVID-19 patients who received vitamin B12 (500 µg), vitamin D (1000 IU), and magnesium had lower COVID-19 symptom severity, and the supplements significantly reduced the need for oxygen and intensive medical support[60].

In a long-term analysis conducted in patients with a history of SARS-CoV-2 infection, lipid metabolism was found to be impaired and patients frequently had cardiovascular abnormalities[61]. Dyslipidemia increases the risk of serious COVID-19 outcomes, mainly because of increased production of lipoproteins and fibrinogen, which predispose patients to atherothrombotic events[62]. However, Wei and coworkers found that LDL and HDL levels were reduced in patients with COVID-19 in proportion to the severity of the disease[63]. One reason for these changes could be liver injury, which reduces LDL biosynthesis. Another reason is inflammation itself, which alters lipid metabolism, particularly through IL-6 reduction in cholesterol transport in the liver[64]. In addition, studies have shown that cholesterol can facilitate the interaction of the virus with ACE2, which promotes infection, but also may serve as a replication site for SARS-CoV-2 in the endothelium[63]. The virus may also cause direct endothelial damage that increases the risk for acute thrombotic events[63].

COVID-19 patients often exhibit dysregulation of glucose metabolism, and type 2 diabetes (T2D) is associated with increased morbidity and mortality in COVID-19 patients[65]. Indeed, hyperglycemia in T2D patients stimulates the formation of advanced glycation end products (AGEs), essential elements that generate oxidative stress and damage the vascular endothelium. In addition, hyperglycemia stimulates the synthesis of adhesion molecules that effectively contribute to leukocyte tissue damage and the occurrence of severe respiratory failure[66]. Therefore, pneumonia caused by SARS-CoV-2 tends to be more critical in T2D patients. Some authors believe that viruses use glucose for their viral replication, so hyperglycemia may even contribute to increased viral load and severity in COVID-19 patients[67]. In addition, it is important to mention the association of T2D with a chronic low-grade inflammatory pattern that contributes to higher morbidity and mortality in COVID-19 patients. As already known, hyperglycemia is strongly associated with the inhibition of lymphocyte function, reducing the functionality of innate and humoral immunity[68]. This immunodepression is associated with a higher susceptibility to the development and exacerbation of infections, including COVID-19[66, 67]. In addition, T2D is associated with impaired coagulation and fibrinolytic mechanisms that produce a prothrombotic state that, together with AGEs on the vascular endothelium, provokes hypercoagulability and endothelial damage, increasing COVID-19 morbidity and mortality from cardiovascular, cerebrovascular, and thromboembolic events[66].

Some people, particularly those who have had a severe acute illness, have symptoms that persist long after the acute infection and cannot be explained by any other diagnosis, i.e., they develop post-COVID-19 syndrome (PCS)[69]. PCS is manifested by a variety of symptoms such as dyspnea, cough, chest tightness, anosmia, fatigue, myalgia, arthralgia, hypertension, headache, cognitive difficulties, peripheral nerve dysfunction, psychological problems such as anxiety, mood swings, depression, post-traumatic stress disorder, sleep disturbances, and cardiovascular and metabolic complications[70]. The pathogenesis of PCS is not yet well understood, but it is suggested that tissue injury (pulmonary, vascular, or neuronal), the presence of viral particles, and especially the presence of chronic systemic inflammation may play an important role[70]. Systemic inflammation disrupts the integrity of the blood-brain barrier (BBB), allowing viruses and cytokines to enter the CNS, impairing the normal function of local immune cells such as microglia and astrocytes and leading to neuronal damage and a whole range of neurological and psychological symptoms[71]. Chronic inflammation also supports endothelium damage, associated with thrombotic events and multi organ damage[72]. Given all this, it is not surprising that PCS is more likely to occur in people who are at higher risk for developing more severe COVID-19, i.e., those with hypertension, obesity, MS, dyslipidemia, cardiac dysfunction, hyperglycemia, and T2D[73].

THE RAW VEGAN DIET: MAIN NUTRITIONAL BENEFITS AND RISKS

The raw vegan diet focuses mainly on eating foods that are typically low in calories and high in fiber, such as uncooked vegetables, fruits, grains, and legumes[10–13]. Therefore, people can eat more foods while drastically reducing calorie intake. This is one of the reasons why the raw food diet leads to weight loss and achieving the ideal body weight in most cases. Body mass index (BMI) has been shown to correlate negatively with the amount of raw food consumed and the duration of the raw vegan diet[11, 29, 74], although it has been shown that not only a long-term raw food diet but also a short-term raw food diet can lead to significant weight loss[75]. Uncooked foods also have a lower glycemic response, which contributes to weight loss in addition to low caloric intake[76]. In addition, the raw vegan diet also contributes to the prevention of T2D by reducing insulin response[77]. In most cases, weight loss resulting from following a raw food diet was associated with a reduction in high arterial blood pressure[18, 74, 75, 78, 79] (Figure 1). Hänninen et al.[75] showed that in participants who followed a raw vegan diet for 7 days, systolic blood pressure decreased significantly and was related to changes in body weight. Another study showed that in all 32 participants with hypertension who followed a raw vegan diet for 6 months, diastolic blood

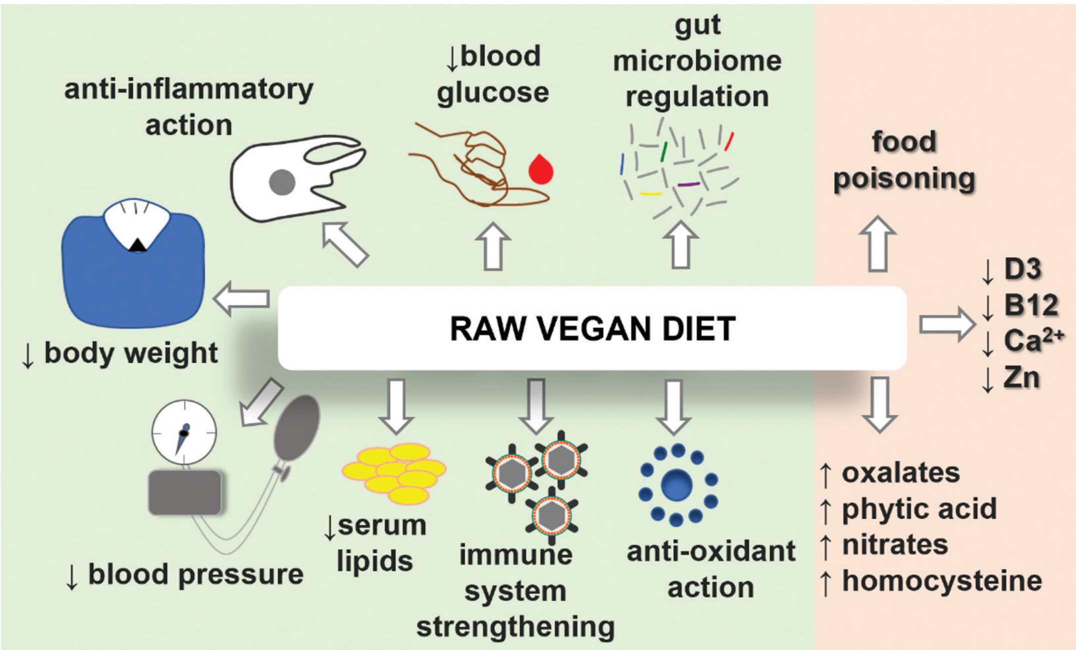

Figure 1. Positive and possible negative health effects of a raw vegan diet. A raw vegan diet has many positive health aspects (light green background), such as lowering blood pressure, body weight, blood glucose levels, and serum lipids, as well as having anti-inflammatory and antioxidant effects. There are also some disadvantages (light red background) of the raw vegan diet, such as food poisoning and, in the case of an unbalanced raw vegan diet, calcium, zinc, vitamin D3 and B12 deficiency.

pressure decreased significantly, although there was no correlation between the decrease in diastolic blood pressure and the decrease in body weight[74]. Interestingly, diastolic blood pressure returned to previous levels when participants switched to a cooked diet, although caloric and sodium intake remained unchanged[74]. A cross-sectional study of 2195 Americans aged 40-59 years showed that both raw and cooked vegetables had a beneficial effect on systolic and diastolic arterial blood pressure, with a much stronger association for raw vegetables compared with cooked vegetables[80]. A possible beneficial effect of the raw vegan diet on arterial blood pressure has also been reported in studies showing a negative correlation between consumption of raw vegetables and ischemic stroke, coronary heart disease, and mortality from ischemic heart disease[81, 82]. The beneficial effects of the raw food diet on the cardiovascular system are also supported by the effects of uncooked foods on the serum lipid profile (Figure 1). It has been shown that a 3-month raw vegan diet can result in significant decreases in phospholipids, total, and LDL cholesterol concentrations compared with individuals following a classic omnivorous diet[83, 84]. Individuals on a low-calorie, low-protein raw vegan diet for more than 2 years had lower plasma concentrations of total, LDL, and HDL cholesterol and triglycerides compared with gender-matched individuals on a Western diet[78]. In the study by Hänninen and colleagues[75], a diet based on uncooked vegetables reduced triglyceride and cholesterol concentrations after only 7 days, although this change was not significant compared with the group that ate cooked vegetables during the same period. In addition to lowering blood pressure and serum lipids, consumption of raw fruits and vegetables was also shown to reduce other cardiovascular disease risk factors, including waist circumference, heart rate, and glycosylated hemoglobin levels[85].

A raw vegan diet is a diet based on plants rich in natural antioxidants. Many studies have shown that raw vegan foods provide significantly more antioxidants than cooked foods and therefore have high anti-inflammatory potential (Figure 1). Based on nutritional records, vegans on average consume significantly more beta-carotene, vitamin E, vitamin C, and copper than omnivores[86]. In addition, eating unprocessed foods does not decrease the amount of vitamins, especially water-soluble ones such as vitamins C and B[86]. Therefore, it is not surprising that people who, on a long-term, eat raw vegan diet have better antioxidant status than omnivores[87]. One of the most important antioxidants abundant in raw foods are flavonoids, whose anti-inflammatory effects are due to their ability to inhibit enzymes such as prostaglandin synthase, lipoxygenase, and cyclooxygenase[88]. In addition, flavonoids have potent antiviral, antioxidant, anti-inflammatory, antiplatelet, and antithrombotic functions[88–90]. People on vegan and raw food diets also showed increased levels of lycopene, alpha- and beta-carotene, lutein, and vitamins with high antioxidant potential, including vitamin C and vitamin E[87]. Garcia and colleagues also showed that subjects on a long-term strict vegan and raw food diet have normal concentrations of vitamin A and high concentrations of beta-carotene and that the addition of fats and oils was the most important factor affecting plasma concentrations of vitamin A and carotenoids in raw food eaters[91]. Hänninen at al.[75] have shown that a diet rich in uncooked vegetables increases serum tocopherol and retinol levels after only one week. In light of the above, it is expected that a raw vegan diet will affect the immune system (Figure 1). This is one of the reasons why many studies on raw vegan diet are conducted in patients with impaired immune system function, especially in patients with rheumatoid arthritis (RA), where inflammation is one of the main underlying issues. Raw food has immunomodulatory and anti-inflammatory potential, and people who eat a raw vegan diet have lower levels of pro-inflammatory cytokines, CRP, and leptin[10, 85, 92]. A raw vegan diet also modulates immunity and inflammation by influencing the gut microbiome. Gas-liquid chromatography profiles of bacterial cell fatty acids from stool samples are significantly altered in people who practice an extreme raw vegan diet for one month compared with people who follow a classic Western diet[93]. In addition to the effects on physical health, the effects of raw diets on mental health should not be ignored, as the consumption of raw fruits and vegetables is associated with better mental health and a raw vegan diet may reduce anxiety and perceived stress level[94].

In addition to the numerous benefits that a raw vegan diet brings, it is important to point out that there are also some potential drawbacks (Figure 1). The raw vegan diet is often associated with low intake of fats and fat-soluble vitamins[10] and, if not well balanced, can lead to deficiencies in some micro- and macronutrients especially in children and adolescents According to the recommendations of the German Nutrition Society, vegans with a high proportion of raw foods in their diet would reach all recommended levels, except for vitamins D, B2, and B12 and the minerals calcium, zinc, and iodine[95, 96]. Most of these possible vitamin and mineral deficiencies could be compensated with a well-balanced raw vegan diet; i.e. mushrooms and cereal germ can provide enough vitamin D; oranges and green leafy vegetables are rich in calcium; consumption of Nori and/or Chlorella seaweeds in large quantities can provide adequate amounts of bioavailable vitamin B12; pine nuts, almonds, hazelnuts, broccoli, and carrots are rich in zinc; and lettuce, broccoli, and pineapple are rich in iodine[28]. Indeed, although it has been shown that a long-term raw vegan diet (>24 months) can cause cobalamin deficiency, and the cross-sectional study showed lower serum vitamin B12 concentrations in the vegans compared with the corresponding omnivorous controls, total vitamin B12 intake correlated significantly with serum vitamin B12 concentration[97]. People on a long-term well-balanced, raw vegan diet have been shown to have the same concentrations of vitamin B12 and folates[97] and no vitamin D deficiency[10] compared with the corresponding omnivorous control subjects. However, according to the European statements[98, 99] vegan diets should not be adopted by children[28, 100] without expert guidance, planning and supplementation since children are at higher risk for developing mineral and vitamin deficiencies due to increased needs during the growth[100]. Supplementation is sometimes necessary in adults as well, due to inadequate and/or excessive fiber supply and other components that limit bioavailability, such as phytate, which has a high affinity for chelating Zn^{2+}, Fe^{2+}, Mg^{2+}, Ca^{2+}, K^{+}, Mn^{2+} and other minerals[101] making them bio unavailable. High fiber consumption in raw vegans can also cause episodes of diarrhea and dehydration and increase the likelihood of bloating and flatulence or even bowel obstruction[102]. Compared to omnivores, vegans show higher homocysteine levels[94] which are associated with increased risk of heart disease, stroke and dementia[103, 104]. Higher oxalate levels in raw vegetarians may reduce the body's mineral absorption and contribute to kidney-related conditions and injuries[105]. Higher intake of nitrates[106] can increase risk for carcinoma[107], but also turn hemoglobin into methemoglobin causing weakness, tachycardia and dizziness. Due to higher plant food consumption raw vegans may be more exposed to pesticide residues than the general population[108]. Finally, cooking has critical effects on killing of food borne pathogens and therefore raw vegans are more likely to develop food poisoning[109].

A well-balanced raw vegan diet is associated with immune system enhancement, weight loss, improved blood pressure and lipid profile, lower risk of cardiovascular disease and has antioxidant and anti-inflammatory effects. Therefore, raw vegan diet has great potential in fighting infections and chronic diseases and could influence COVID-19 severity.

DISCUSSION AND CONCLUSIONS

Taking into account all the health benefits of a balanced and carefully implemented raw vegan diet, this diet could be a powerful tool to fight severe clinical course of the COVID-19 and also the effects of post-COVID-19 syndrome (Figure 2).

A raw vegan diet has a positive effect on blood pressure through several mechanisms closely related to the pathogenesis of SARS-CoV-2 infection[74–76, 78, 80] and may therefore reduce the possibility of developing more severe forms of COVID-19 and PCS. A raw food diet balances the RAAS[110] by regulating renal function, water

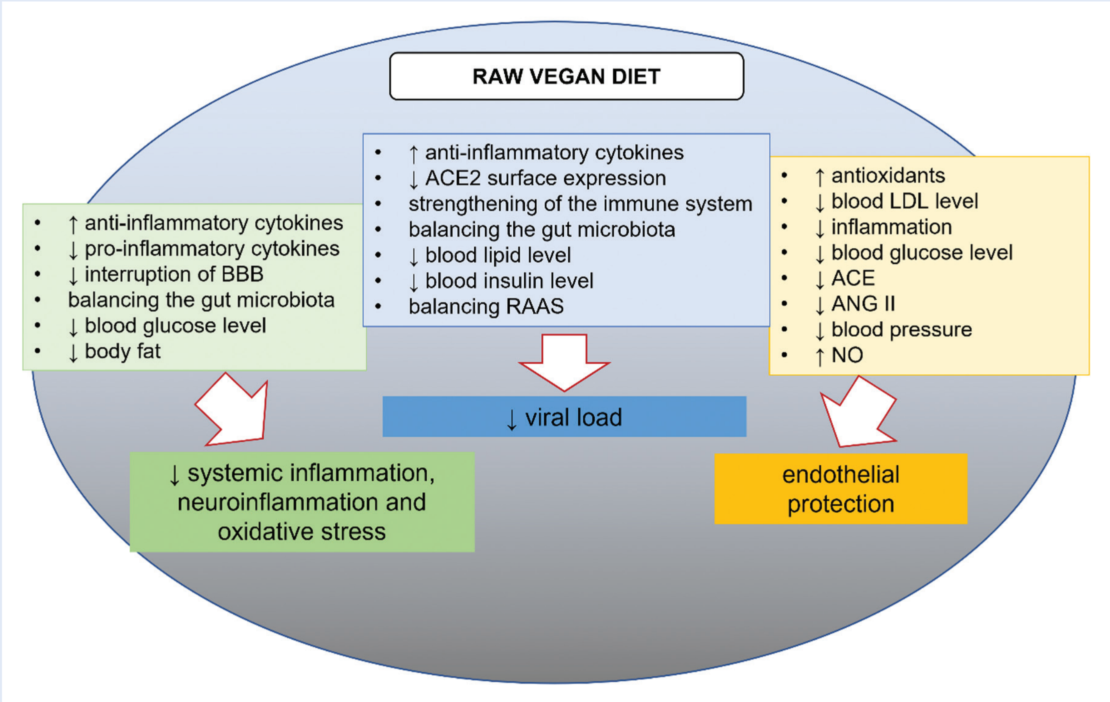

Figure 2. Positive health effects of raw vegan diet associated with pathogenesis of COVID-19 and post-COVID-19 symptoms. BBB, blood-brain barrier; RAAS, renin-aldosterone-angiotensin system; ACE, angiotensin converting enzyme; ACE2, angiotensin-converting enzyme 2; ANG II, angiotensin II.

homeostasis, and electrolyte balance, likely due to increased potassium intake[78, 79, 111]. A raw vegan diet has a positive effect on blood pressure through several mechanisms closely related to the pathogenesis of SARS-CoV-2 infection[74–76, 78, 80] and may therefore reduce the possibility of developing more severe forms of COVID-19 and PCS. A raw food diet balances the RAAS[110] by regulating renal function, water homeostasis, and electrolyte balance, likely due to increased potassium intake[79, 111]. In addition, the raw food diet inhibits angiotensin-converting enzyme activity (ACE)[112] which in turn leads to decreased production of ANG II and thus reduced vasoconstriction and tissue damage. Furthermore, although some studies have reported that inhibition of ACE could increase the overall expression of ACE2, it has been shown that inhibition of ACE leads to a decrease in membrane-bound ACE2[113], which is much more important in the context of SARS-CoV-2 infection because viruses can only use surface-expressed receptors for cell entry and invasion. Therefore, a decrease in membrane-bound ACE2 due to inhibition of ACE would decrease its availability to SARS-CoV-2 and reduce viral load and thus severity of infection[42]. In addition, COVID-19 patients have been shown to have an altered gut microbiota that is poor in *Lactobacillus* and *Bifidobacterium*[114], and this abnormality can be compensated for by a high-fiber diet, such as raw foods[93]. This could be another explanation for the beneficial effects of dietary fiber on arterial blood pressure. Namely, the major metabolites of the gut microbiota are the short-chain fatty acids acetates, which improve cardiovascular health and function and thus balance arterial blood pressure[115]. Another mechanism by which a raw vegan diet lowers blood pressure and could influence COVID-19 and PCS is by affecting endothelial function[116]. Raw vegan diet balances the production of endothelium NO and causes vasodilation, and the higher antioxidant content and anti-inflammatory effect of raw vegan diet protect the endothelium from injury and vasoconstrictor prevalence[117]. In addition, the raw food diet improves insulin sensitivity[118], which is important for normal vascular function. In contrast, in the state of insulin resistance, the insulin-stimulated NO pathway is selectively impaired, and compensatory hyperinsulinemia may activate the MAPK pathway, leading to increased vasoconstriction, pro-inflammation, increased sodium and water retention, and consequent elevation of blood pressure[119]. Consequently, normalization of blood glucose levels[76] decreases insulin secretion, and thus a raw vegan diet could decrease viral load, as insulin can promote SARS-CoV-2 cell entry[120] (Figure 2). Moreover, the reduction in insulin resistance achieved by the raw food diet favors better COVID-19 outcomes due to the inhibition of TNF-α and the general anti-inflammatory effect supported by the weight loss and the reduction in adipokine secretion due to the raw vegan diet[11, 78]. Indeed, in most patients with severe COVID-19 disease, the immune response is overstimulated, with activates pro-inflammatory monocytes and aberrant T cells producing large amounts of pro-inflammatory cytokines, particularly IL-6 and TNF-α, which trigger the cytokine storm[121, 122]. A high-fiber diet inversely correlates with the levels of potent pro-inflammatory cytokines such as IL-6, TNF-α, and IL-18 and therefore could contribute to the reduction of inflammation during and after COVID-19 infection[123]. Weight loss with a resulting reduction of a fat tissue supports lower values of inflammatory cytokines since studies have shown that adipocytes can synthesize proinflammatory cytokines, notably TNF-alpha, IL-1beta and IL-6[124]. Furthermore, flavonoids contribute anti-inflammation by inhibiting enzymes such as prostaglandin synthase, lipoxygenase, and cyclooxygenase[88]. In most cases weight loss is associated with a subsequent decrease in plasma concentrations of total, LDL and HDL cholesterol and triglycerides[83, 84], which has a beneficial effect on the cardiovascular system by reducing the predisposition to atherothrombotic events[78]. In addition, lowering serum cholesterol levels could reduce viral load by preventing the potential interaction of the virus with ACE2, its replication, and thus direct endothelial damage and acute thrombotic events[43]. Viral load could also be reduced by resveratrol, a polyphenol that is a naturally occurring highly powerful antioxidant which is very abundant in diets based on plant foods and has been shown to reduce the expression of ACE2[125]. Raw vegan food also has a positive effect on brain function. It improves cognitive function[126] by balancing arterial blood pressure, anti-inflammatory and antioxidant effects[127], and by regulating the microbiota[115]. Finally, it should not be ignored that the improvement of mental health through the consumption of raw fruits and vegetables[94] could help people to better cope with stress during COVID-19 pandemic.

Some potential negative effects of the raw food diet, such as vitamin D and B12 deficiency associated with severe COVID-19 disease and post-COVID-19 symptoms, may occur in people who eat an unbalanced raw vegan diet for a long period of time[97, 128], although it has been shown that s25(OH)D concentrations are not related to the type of diet, but rather to other factors, such as vitamin D supplementation, the degree of skin pigmentation, and the amount and intensity of sun exposure[129]. It has also been shown that individuals on a raw vegan diet are at risk of developing not only deficiencies in vitamin B12 and D, two important nutrients for proper nerve cell functioning, but also deficiencies in iron, magnesium, zinc, and calcium[130]. These nutrients are important for the functioning of the body and brain, especially for the prevention of sleep disorders and mental disorders that often occur after the COVID-19 infection. However, they can be prevented by a careful and well-balanced diet and therefore should not be considered a counterargument to a raw diet in the context of COVID-19[10, 28, 31, 97, 128], although this type of diet is not recommended for children, adolescences, as well as during pregnancy and lactation[28, 99, 100].

In conclusion, thanks to multiple mechanisms of action, the raw vegan diet has great immuno- and cardioprotective potential in combating chronic diseases and thus, could influence COVID-19 severity and conditions that follow COVID-19 recovery.

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