REVIEW PAPER

UDK: 616.98:578.834
578.834

DOI: 10.5937/hralsh2001025M

Virome/SARS-CoV-2 cross-talk: Free space for natural products

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Received 14 November 2020
Accepted 18 December 2020

Abstract

One of the most striking marks of infection caused by the SARS-CoV-2 is the distinguishing heterogeneity of the clinical presentations in a population that varies from asymptomatic to severe forms. Pandemic proportion brings into the foreground the number of people with severe forms of the disease, putting aside the fact that a large portion of the population is an asymptomatic, making them silent carriers of the virus. Additional confusion is made by inconsistent data about the presence of the virus in the nasopharyngeal region and the manifestation of the disease symptoms. Different tissue distribution of virus in the body starting from guts, liver, muscles, kidney etc. without any signs of tissue destruction, opens up the possibility that individuals with negative results of PCR test in the nasopharyngeal swab may also be latent carriers of the infection. Overall clinical presentation of the disease is influenced by the initial protection gained through the accumulated "experience" collected from previous encountering of corona family and noncorona viruses, resulting in overlapping of the humoral and cellular immunity. Apart from this, unjustifiably neglected but very significant form of host defense against infection is disease tolerance based on cohabitation with pathogen. It is important to note that consequences of the disease tolerance in terms of pathological and epidemiological aspects are quite different then classical antiviral immune response. This work will elaborate the impact of virome on the course of infection at all stages taking into account both immune resistance, as an ability of the host immune system to eliminate pathogen, and disease tolerance, as a form of host defense with neutral to positive impact to pathogen load. Also, in accordance with the above mentioned, the potential of naturally occurring compounds to profile the course of infection and to support currently available protocols for COVID-19 treatment was discussed.

Key words*: SARS-CoV-2; Disease tolerance; Virome; Immune resistance; Naturally occurring compounds.*

INTRODUCTION

Evidence suggests that about one in five people infected with COVID-19 will experience no symptoms with significantly reduced potential to transmit the virus in comparison to symptomatic one. At the first look paradoxical, some of the studies showed that viral load detected in asymptomatic patients can be similar to that in symptomatic ones, which also theoretically suggests the potential transmission from asymptomatic patients to the rest of population [1]. There is no consensus in science if asymptomatic infections are indeed a 'silent driver' of the pandemic [2]. As part of a large population study in Switzerland, scientists demonstrated viral spread among people living together [3]. Bi *et al*. recently reported that the risk of an asymptomatic person passing the virus to others in their home is about one-quarter of the risks of transmission from a symptomatic person in similar setting [3]. A remarkably lower virus transmission potential of asymptomatic individuals compared to symptomatic ones has been widely confirmed [4, 5]. In parallel, Dr. Ayres *et al*. found that the potential of latent carriers of the pathogen to disseminate infection rapidly decreases through the time counting from the moment of host exposure to the intruder, although the presence and the number of

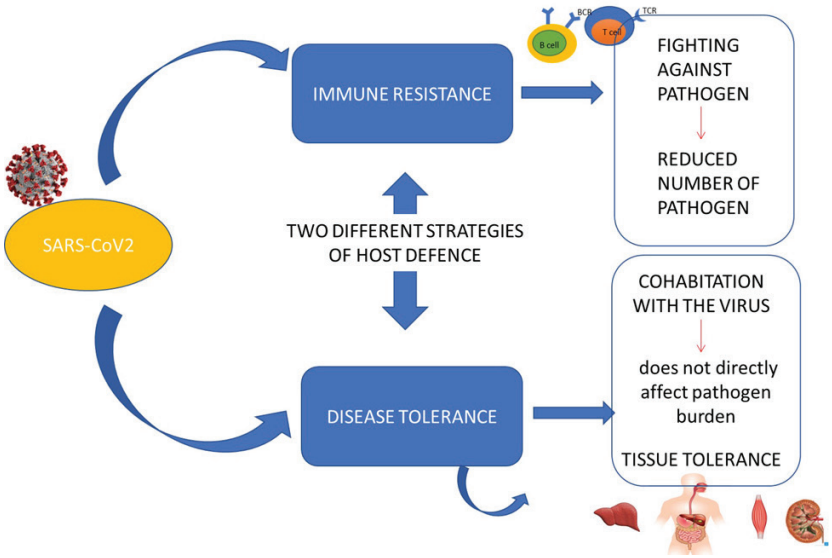
pathogens are similar to those observed in symptomatic individuals [5, 6]. At the first month of pandemic, the rate of asymptomatic infections was estimated as 81% [7]. Lately, numerous meta-analyses evaluated the contribution of asymptomatic individuals in COVID-19 infected population, revealing a remarkable lower range compared to previous reports, approximately from – 15 to 40% [4, 8]. The analysis defined asymptomatic people as those who showed none of the key COVID-19 symptoms during the entire follow-up period. An aspect that has not been taken into consideration and largely relativizes these statistics is the fact that the absence of viral particles in the nasopharyngeal region doesn't mean that the new coronavirus is not present in other tissues, particularly in the gut. There are multiple indications for this. Although it is underlined that SARS-CoV-2 primarily causes lung infection, it was recently reported that SARS-CoV-2 RNA was found in the feces of infected patients [9]. The question arise from this is how many healthy individuals, qualified as negative on PCR test to SARS-CoV-2 are also latent carriers of the virus, whose particles are not detectable in nasopharyngeal area? More importantly, this initiated thoughts about the role of immunity, as well as disease tolerance developed in the past to other members of the coronavirus family and even non-coronaviruses in protection against SARS-CoV-2. How the protection developed upon the introduction of other corona family members contributed to massive asymptomatic or mild clinical presentation of the COVID-19 in the human population? Dr. Patrick *et al*. 15 years ago reported that most sera evaluated for the SARS-CoV-1 antibodies cross-reacted with homologous peptide sequences on HCoV-OC43 nucleocapsid protein, establishing that these cases were indeed producing cross-reacting antibodies [10]. Therefore, it becomes clear that the immune response against SARS-CoV-1 in patients had evolved through repeated infections by different CoVs throughout their lives. This report is further accomplished with the new data confirming a similar overlapping of SARS-CoV-2 cellular immune response with other CoVs and even non-corona viruses, with T cell repertoire recognizing peptides from HCMV, HHV-5 and influenza A virus [11, 12]. T cell mediated fortification collected from the experienced viral infections presented a significant platform for individual protection to COVID-19 infection. Altogether, the host defense against the new virus is orchestrated by whole life experience and the memory of it stored at the virome-host network.

HOST VIROME INVOLVEMENT IN PROTECTION AGAINST SARS-COV-2

Although we usually characterize viruses as pathogens, it has become outward that healthy individuals are also colonized with a vast number of viruses composing the "virome" [13]. Apart from human virome is defined as the total collection of bacterial and eukaryotic viruses in the body, the term virome is often equalized with the gut viral community. The recent investigation of the gut virome population opens a new frame of understanding of the virus commune, shifting it from exclusively pathogenic to intrinsic components of the healthy human gut microbiome with an important role in homeostasis maintenance and host defense. This is a brilliant example of the duality principle in living nature, where any of the elements is not exclusively harmful or beneficial, but flexibly defined within the specific context of interactions. It is obvious that contact between pathogen and host is not exclusively related to risks of disease development, but so importantly connected with health maintenance, with the aim to establish the state of bidirectional comfort. Viral inhabitants of the gut are overall underestimated participants of the microbiota community. While the complex interactions of bacterial and plant viruses in human health maintenance are frequently studied, the presence of mammalian viruses and their relations with other constituents of microbiome as well as input on human health mainly remains unclear [14]. Acute, persistent, and latent viral infections make eukaryotic viruses integrated members of the commensal microorganisms. Norovirus is widespread and it is found in asymptomatic infected humans [15, 16]. Mouse norovirus (MNV) is also found in mice housed in conventional and specific pathogen-free animal facilities [17, 18]. MNV infects immune cells in gut-associated lymphoid tissues and epithelial cells including tuft cells, whereas MNV-infected immunocompetent mice are typically asymptomatic [19]. On the list of eukaryotic viruses detected in human guts as a part of viroma in fecal samples from children were *Adenoviridae*, *Anelloviridae*, *Astroviridae*, and *Picobirnaviridae*, and family members, and species such as enteroviruses, rotaviruses and sapoviruses [13]. Importantly, viruses whose presence is usually connected with disease development such as herpesviruses, polyomaviruses, anelloviruses, adenoviruses, papillomaviruses, polyomaviruses, hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV) are also present in the intestinal viromes of some individuals, indicating that the gastrointestinal tract contains viruses known as pathogenic but disassociated from the disease expression (14). While the presence of these pathogenic viruses remain "dormant" in the host, they have become a part of the healthy individual virome specified as "pathobionts" [20, 21]. On the list of pathobionts, even replicative active coronavirus family members (SARS and MERS) were detected in the gut without causing macroscopic or histological changes [22, 23].

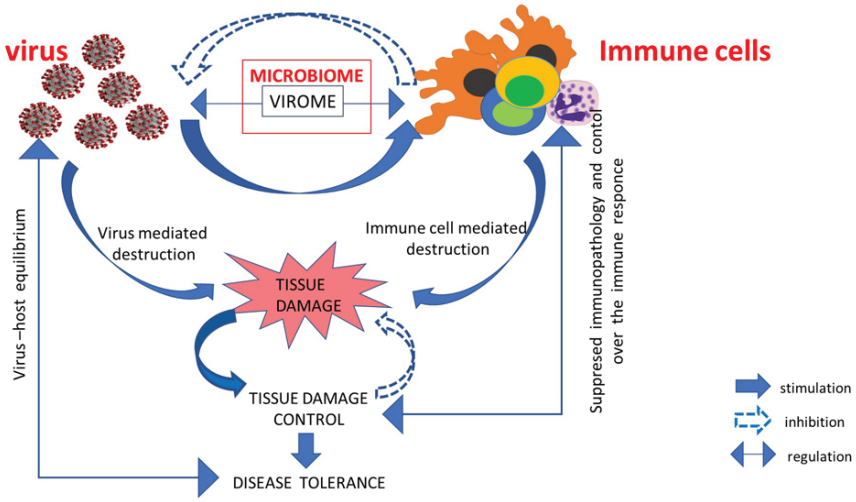
DISEASE TOLERANCE IN COVID-19

There are two possible defense mechanisms performed by the host upon pathogen introduction enabling infected asymptomatic individuals to establish the control up to infection resistance and tolerance (**Scheme 1**) [24]. Traditionally, the defense response in animals against microbes has been equalized to the eradication of microbes through the activation of microbial killing pathways by the immune system, referred as "resistance mechanisms." While the "resistance to infection" is intensively explored through the centuries, starting from Edward Jenner's groundbreaking input to immunization and the final execution of smallpox, Pasteur's germ theory, Robert Koch four criteria, rounded by description of cellular and molecular mechanisms of host defense by Elie Metchnikoff and Paul Ehrlich, the "disease tolerance" is still underestimated in humans [25]. The phenomenon of disease tolerance presents an inherent component of host defense against infections. This approach is based on the tissue damage restriction in the presence and independently from the pathogen load. This can be considered as the opposite of the resistance to infection, the most commonly investigated route used by the host to restore the balance through the reduction of the number of pathogens (**Scheme 1**). Clarification of the distinction between these two defensive mechanisms is of essential importance for understanding the differences in pathological as well as epidemiological consequences of both. Upon pathogen introduction in the host, the buildout of an active immune response will implicate essentially different mechanisms than the development of tissue tolerance, which will be reflected in remarkable differences in disease pathology, host cellular behavior and overall epidemiological signature. It is also important to split the concept of "disease tolerance" from "immune tolerance" [26, 27]. However, distinction between these two processes doesn't exclude their interplay and cooperative contribution of immune tolerance to disease tolerance establishment.



Scheme 1. Two strategies of host deffence against infection. While the immune resistance mechanisms are based on pathogen eradication, disease tollerance presents a nonagressive form of host protection, promoting a host health in parallel with neutral to positive impact on pathogen fitness.

Phenomenon of disease tolerance was first documented in plants in the second half of 19th century by Nathan Augustus Cobb, an American plant pathologist who observed the ability of certain strains to growth regardless of the presence of a fungal infection, describing it as "rust-enduring" not "rust-resistant" wheat [28]. Even though this type of host defense against invaders was discovered and explored in the last century, it was not recognized as important in animals until last decade. Accordingly, disease tolerance can be counted as a completely new field in biology of infection in animals and humans. It was showed that "decision" to fight or tolerate the pathogen following malaria infection can be defined by a genetic variation [29]. Soon after, it was found that the main principle of tissue protection from protozoan-induced hemolysis in mice is provided by the heme-catabolizing enzyme heme oxygenase-1 [29]. The hypothesis that disease tolerance is an ancient form of host protection and health maintenance has been further empowered with the discovery of Dr. Ayres and Dr. Schneider who demonstrated that the simple organisms such as fruit fly *Drosophila melanogaster* can also use disease tolerance as a host defense mechanism in the context of gram-positive and gram-negative bacterial infection [30, 31]. All together, these studies have provided insights into disease tolerance as an alternative and/or complementary form of host defense. Upon pathogen introduction, in interplay with host microbiota, innate, and soon after, adapted immunity are stimulated to restrict pathogen load. In parallel, pathogens alone and/or trapped into the immune system network, promote stress and tissue damage. This enforces activation of tissue damage control mechanisms, implicating a wide range of evolutionary conserved responses to stress and damage. Accurate tissue damage control mechanisms are a leading force of disease tolerance establishment, manifested by functional recovery of parenchyma tissues and vital homeostatic parameters (**Scheme 2**). On the other



Scheme 2. Central role of tissue damage control in immune resistance and disease tolerance orchestration. Intruder alone and/or trapped into the immune system network, promotes stress and tissue damage. This lead to the activation activation of tissue damage control mechanisms. Correct tissue damage control resulted in functional recovery of parenchyma tissues and vital homeostatic parameters. Simultaneously, tissue damage control program buffers immunopathological consequences of triggered antiviral immune response. Optionaly, tissue damage control can lead to virus-host equilibrium and disease tolerance.

hand, tissue damage control programs should enable immune mediated resistance mechanisms to function under limmited immunopathology, leading to successful pathogen clearance and abrogation of disease transmission [26]. In summary, damage control mechanisms play a central role in the host defense profile, orchestrating immune resistance and disease tolerance (**Scheme 2**). In this network, microbiome and more strictly, virome could be a template for host positioning to the upcoming infection. There are clear indications that in the long term period after infection resolution, the virus becomes a member of the viral commune, with less or more replicative potential. It is speculated that its hidden presence within certain organs (e.g., liver, muscles, kidney) apart from the gut where it can be detected, can influence long term immunity. Gaebler *et al*. found continued evolution of the humoral response to SARS-CoV-2 in asymptomatic or mild disease cases between 1.3 and 6.2 months after the infection in a manner consistent with the antigen persistence [32]. Detection in the feces as well as analysis of intestinal biopsies confirmed the presence of whole viral particles in half of the tested individuals [10]. Additionally, there are data confirming good prognostic relevance of the presence of SARS-CoV-2 in guts for disease outcome [33]. This further means that months after the infection in moderate, as well as asymptomatic forms, SARS-CoV-2 became a member of healthy individual virome commune influencing not only dynamics of additional flow in host- virus cohabitation, but through this, affecting the further host contacts with other viruses, both within and out the coronavirus family.

In a certain paradoxical way, the tissue tolerance to SARS-CoV-2 was detected across a wide variety of organs of patients with fatal outcomes of COVID-19 infection, but not as a consequence of the viral load in different tissues [10]. Severe inflammation was restricted to the lungs and reticuloendothelial system, and even there it was not in strict association between inflamed area and the presence of viral RNA or proteins. In different organs such as gastrointestinal tract, heart and muscles, and less often the liver and kidney, frequent presence of SARS-CoV-2 was detected without even minor signs of injury related to it. The authors describe this phenomenon as tissue tolerance toward the SARS-CoV-2. Additionally, tissue inflammation and organ damage in COVID-19 showed an unexpected pattern of inconsistent correlation with the distribution of the viral particles. Lack of strict link between inflammation and virus presence, indicates the possibility that immune cells activated by the viral particles can shift from the viral epitope to self-antigens with a certain homology, leading to autonomies immune attack toward self-tissue.

SILENT CARRIERS OF SARS-COV-2 AND POTENTIAL RISKS FROM THE VACCINATION

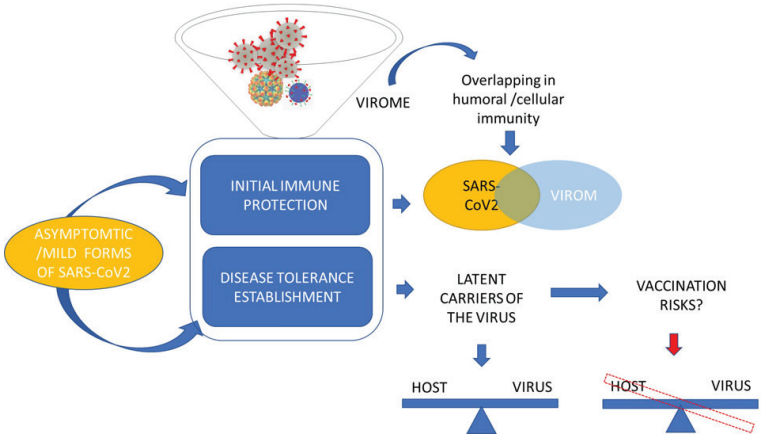
Finally, there are many elements bringing into connection COVID-19 and the infection with *Mycobacterium tuberculosis*. This analogy can be very helpful for better understanding the pathology of the disease as well as the potential risks related to immunotherapeutic approaches in the treatment of COVID-19, preferentially referring to silent carriers of SARS-CoV-2. The contribution of asymptomatic individuals carrying SARS-CoV-2 in the total population under pandemic is remarkable, and our ability to detect them is limited, according to the tissue tolerance platform and random distribution of the virus in tissues. Hypothetically, this group could be extended to the people recovered from the COVID-19 in whose SARS-CoV-2 is retained in guts, and possibly other tissues, in a disease-tolerant manner and in equilibrium with the host under certain control by the host immunity. As it is mentioned above, there are indicators of viral particles persisting out of the respiratory tract after the infection.

At the end of the last century disease induced by *Mycobacterium tuberculosis* was the leading cause of death from infectious diseases [34]. It is estimated that over 2 million of people die from tuberculosis yearly and about 8 million people deal with the disease. Individuals who have been exposed to the bacillus but may have controlled it in the form of a latent infection, may number in hundreds of millions [34].

Taylor *et al*. showed that a plasmid DNA vaccine (Hsp60/lep) that has been previously shown to be highly effective against intravenous or intraperitoneal inoculation with virulent *M. tuberculosis* H37Rv failed to protect mice in an aerosol infection model or in a model of latent tuberculosis in the lungs. Moreover, when the vaccine was given in an immunotherapeutic model, the immunized mice developed classical Koch reactions characterized by multifocal discrete regions of cellular necrosis throughout the lung granulomas [35]. Similar and equally severe reactions were seen in mice inoculated with a vaccine with DNA coding for the Ag85 antigen of *M. tuberculosis*. This previously unanticipated safety problem indicates that DNA vaccines should be used with caution in individuals who may have already been exposed to *M. tuberculosis* [35].

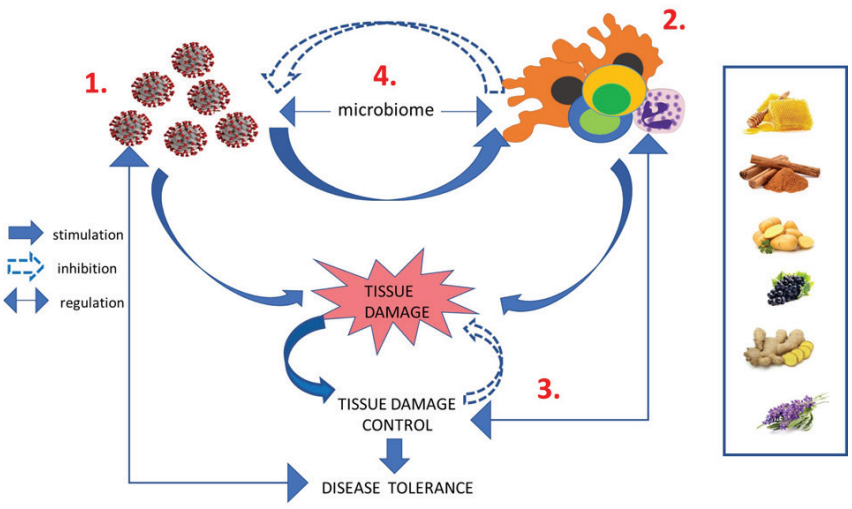
Applying this template on COVID-19 infection, it is reasonable to speculate that a similar approach based on DNA vaccination to protect individuals and support the establishment of collective immunity, could hypothetically lead to development of severe symptoms of the disease, when inoculated into hidden silent carriers of SARS-CoV-2.

In summary, after almost a year of intensive research and collected experience with the patients, there are serious weaknesses in understanding of disease pathology and host defense against COVID-19 infection. A much deeper analysis than a simple reduction to immune resistance and B and T cell-mediated immunity is needed, taking into account the virome-derived initial protection and the development of disease tolerance as a less known, but not less important template of host protection against invaders (**Scheme 3**). From this standpoint, rapidly developed decisions about massive vaccination including the type of vaccines, should be reconsidered (**Scheme 3**).



Scheme 3. Microbiome as a template for the host positioning to the upcoming infection. Apart from classical immune response to infection, disease tolerance, developed through cohabitation between invader and the host, might be important aspect of SARS Cov-2 infection in terms of pathology as well as epidemiology, leading to reevaluation of certain type vaccine usage in latent carriers.

There are several checkpoints defining the flow of the infection (**Scheme 4**). Apart from the intrinsic factors, numerous naturally occurring compounds (NOC) we are exposed to through the diet and beverage, influence each of them, shaping host and pathogen interplay. Most of NOC are active on few checkpoints in parallel, reducing the pathogen viability, promoting establishment of tissue damage control, favoring disease tolerance and/or optimal immune response (**Scheme 4**).



Scheme 4. Naturally occurring compounds on each check point of host defense against infection. Biologically active compounds uptake through food, beverage or supplementation shape the immune response and interfere with conventional therapeutic approaches.

NATURALLY OCCURRING COMPOUNDS IN DEFENSE SERVICE OF COVID-19

At the moment even though vaccination started in some countries we still don't have specific therapy for the management of COVID-19. Thus, a lot of effort is put on the encountering preventive and therapeutic strategies for eradication of this disease. Since the discovery of new drugs is an exhausting and long-lasting process, repurposing and repositioning of currently available drugs is the fastest approach. However, modern medicine is still limited in the treatment of viral infection due to the high viral mutation rate, development of resistance, high amount of side effects and costs of existing therapies [36]. Nowadays only few antiviral drugs on the market are effective enough and one of the possible alternative sources of potentially new drugs is definitely nature. In general, naturally occurring compounds apart from their healing potential serve as matrices for derivatization or inspiration for synthetic drugs made according to their structure when their quantity or delivery is limited. Since 1981 till the mid of 2019, around 40% of approved drugs are isolated naturally occurring compounds or their derivatives [37]. In general, antiviral drugs can be classified into those inhibiting the interaction of the virus with the host cell membrane or receptor, viral uncoating inside the cell, nucleic acid synthesis as the next step in viral life cycle, integration into host cell DNA, proteases, and release of new viruses from the host cell in final instance [38]. Together with these therapeutic approaches directed to different steps of viral infection, other strategies are also settled, targeting cellular receptors or host enzymatic machinery utilized by the virus or modulation of host immune response to viral infection related. Since the pandemic was proclaimed in March this year all the effort is put into the service of COVID-19 eradication. If we switch to SARS-CoV-2 virus, few major proteins, viral and human, enable its inoculation and replication inside the host cells. The penetration of SARS-CoV-2 virus into the host cells happens as a result of the binding of SARS-CoV-2 spike protein (S) to host receptors and on S protein priming by the host cell proteases. Type II transmembrane serine protease (TMPRSS2) cleaves S spike glycoproteins activating the glycoprotein for host cell entry [39]. TMPRSS2 is critical for spreading of other viruses, like influenza A viruses and coronaviruses etc. [40- 42]. Hoffman *et al*. demonstrated that similarly to other coronaviruses, SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor for entring into the host cell and the serine protease TMPRSS2 for S protein priming [43, 44]. ACE2 is an analogue of the angiotensin converting enzyme type I (ACE) important for regulation of blood pressure. SARS-CoV-2 encodes two proteases, the papain-like protease (PLpro) and 3-chymotrypsin-like main protease (3CLpro or Mpro), that are in charge for the proteolytic cleavage of virus polypeptide into nonstructural proteins important for viral replication [45]. The nonstructural proteins further assemble the viral replicase complex, triggering replication and transcription of the viral genome. All proteins mentioned above served as a target for searching the libraries of naturally occurring compounds as potential drugs [46]. Additional support comes from the previous studies on other corona viruses such as SARS-CoV-1 [47]. Important tool in these initial studies is performing a virtual screening of natural compounds libraries using *in silico* molecular docking that gives insights into potential drug candidates. Plenty of *in silico* studies using the molecular targets mentioned above were carried out in the last year. Since many of them are already elaborated elsewhere, only few of them will be presented in this review. One of the first studies was done on traditional Chinese herbs that identified 11 natural products capable of inhibiting ACE2. The bioactive compounds selected in this study were baicalin, scutellarin, hesperetin, nicotianamine, glycyrrhizin, naringin, naringenin, hesperidin, neohesperidin, and nobiletin [48-51]. Further studies highlighted different groups of alkaloids, terpenes, flavonoides, limonoids, lignans, terpenoids, tannins, phenolic acids and fatty acids as compounds of interest. Few hundreds of plants are rich in potential ACE inhibitors and some of them are present in food or spices that are frequently used like cinnamon (*Cinnamomum zeylanicum Blume or Cinnamomum verum J. Presl*.), pepper (*Capsicum* spp.), olive (*Olea europaea* L.), curcumin (*Curcuma longa*), garlic, green tea etc. A second molecular target widely studied is TMPRSS2. Its role in other viral infections like influenza and SARS- CoV-1 is known and inhibitors were found among flavonoids (baicalein and baicalin), terpenes and peptides. Rahman *et al*. segregated 12 metabolites (iridoids, diterpenes and lignans) using *in silico* studies based on TMPRSS2 blockade [52]. The potential TMPRSS2 inhibitors can be extracted not only from plants but also other sources like marine corals, algae, and mushrooms. The third molecular target that attracts attention is 3CLpro, a specific viral enzyme. Gurung *et al*. revealed that terpenoids bonducellpin D and caesalmin B and the flavonoid 5,7-dimethoxyfavanone-40-O-b-d-glucopyranoside showed affinity toward all 3 coronaviruses, SARS-CoV-1, SARS-CoV-2 and MERS-CoV [53]. They are present in some herbs used in Chinese traditional medicine and also in European mistletoe (*Viscum album*). Some other authors indicated potential inhibitors of 3Cpro of SARS-CoV-2 between kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin, oleuropein, catechin, curcumin, and epigallocatechin that can be extracted from lavender (*Lavan-*

dula angustifolia), basil (*Ocimum basilicum*), mandarin (*Citrus reshni*), cinnamon (*Cinnamomum zeylanicum*), chamomile (*Matricaria recutita*), ginger (*Zingiber officinale*), licorice (*Glycyrrhiza uralensis*, *Glycyrrhiza glabra*, and *Glycyrrhiza*), black pepper (*Piper nigrum*), cannabis (*Cannabis sativa*), cloves (*Syzygium aromaticum*), oregano (*Origanum vulgare*), rosemary (*Rosmarinus officinalis*) [46, 47, 49, 53, 54]. It is important to note that the compounds able to block more than one target inside the SARS-CoV-2, might be multiply beneficial. In addition, the fact that some herbal compounds showed activity against other viruses put them into the foreground. For example glycorhizzin was efficient against Human Immunodeficiency Virus Type 1 (HIV-1), Herpes Simplex Virus Type 1(HSV-1), Hepatitis C virus, Varicella-Zoster virus and SARS-Coronavirus. Rhein and chrysophanic acid from *Aloe vera* (*Aloe barbadensis*) and Rhubarb (*Rheum palmatum*) are efficient against poliovirus influenza [55]. It is obvious that naturally occurring compounds are able to interact with the virome mediating the host-pathogen relation in terms of immune resistance as well as disease tolerance as a two forms of host response to intruder. Apart from the fact that human virome includes commensal, pathogenic and novel bacteriophages, eukaryotic viruses involved in acute or persistent infection, endogenous retroviruses and under investigated forms that settle whole organism, it is usually equalised with gut viral family as a part of gut microbiome. Consumption of food and oral admission of pathogens both influence the establishment of host pathogen equilibrium mainly leading to disease tolerance. Trillion of microbes in the human body are actively involved in optimal health maintenance and profiling the host response to infection. Everything that helps maintain the balance in the gut might positively regulate immune response and defense from the disease.

In this term, it is important to mention that a multicenter randomized clinical trial evaluating the efficacy of resistant potato starch, carbohydrate, in reducing the need for hospitalization for COVID-19 positive patients has recently started (NCT04342689) [56]. This study will include 1500 non-hospitalized COVID-19 positive patients. The rationale for this study is that fiber ferment serves as a prebiotic protecting the gut microbiota at a multiple level. Directly, resistant starch feeds the microbiome, decreases ileal and cecal pH promoting the growth of beneficial microorganisms [57, 58]. Protecting the mucus layer, resistant starch prevented the damage of the epithelium and also presented a great support in healing of leaky gut and protecting gut barrier integrity. In addition, it decreases the IL-6 level, one of the mostly abundant inflammatory mediators in COVID-19 patients, by elevating butyrate levels [59]. Butyrate reduces overall inflammation, in particular in lungs, and reduces ACE2 receptor expression, suppressing the entry of viruses. It also induces antimicrobial activity of intestinal macrophages. Beside direct influence on the gut, it influences the function of resident antigen-presenting cells in lungs, weakening the inflammatory reactions [60].

On the other hand, naturally occurring compounds apart from direct antiviral activity have other biological effects that might be important for prevention and also for suppression of the disease. For example, known antioxidative features of naturally occurring compounds will be important in both aspects of restriction of viral reproduction and protection of host cells from virus-mediated damage A huge body of evidence accumulated over the past decade indicates that patients infected with RNA viruses including human influenza virus, Hepatitis C virus (HCV), human immunodeficiency virus (HIV) are under chronic oxidative stress. Reactive oxygen species are important signaling molecules and mediators of essential processes inside the hosts like apoptosis, impaired immune defense and stimulated viral replication [36]. Second important aspect that might be relevant for defense from COVID-19 infection is the immunomodulatory properties of numerous naturally occurring compounds. Apart from their direct effect on the immune system of patients, targeting the viral proteins will have repercussions on disease outcome. Dysregulated inflammatory response is known as a hallmark of COVID-19, and considerable morbidity and mortality is associated with obsessional immune responses and further tissue damage [61]. It is found that SCoV2-PLpro is able to trigger an evasion mechanism against host antiviral immune responses through interferon production due to blocking of IRF3 phosphorylation and nuclear translocation [62]. The other important target that might be influenced by SCoV2-PLpro is NF-kB signaling pathway [63]. Since the viral proteases have the potential to inhibit host innate immune responses and inflammatory response it is reasonable to expect that targeting them with naturally occurring compounds will be a dual therapeutic strategy. The family of naturally occurring compounds provides a source of biologically active molecules that are able to affect COVID-19 infection in all stages, from the initial to the late, and from mild to severe presentations, enforcing different strategies.

NATURALLY OCCURRING COMPOUNDS IN CLINICAL TRIALS

Even though *in silico*, *in vitro* and *in vivo* studies provided a lot of evidence about the potential of naturally occurring compounds against COVID-19 infection, definitive proofs will come from patients. Till today more than 4000 clinical trials focused on COVID-19 were reg-

istered in the US National Library of Medicine Clinical Trials website. Searching the database with COVID-19, phytochemicals, polyphenols, phytotherapy as keywords showed that many of them are intended to explore naturally occurring compounds or extracts as a supplement to therapy or prophylaxis against COVID-19 [56]. Due to the scope of this paper, only a few studies will be presented herein. Few of them are dedicated to Chinese traditional medicine and usually include a mixture of plants and recipes with a lot of empirical data about their efficacy in treatment of viral infections. Prospective, double-blind, randomized trial on 140 COVID-19 patients, evaluating of the effect of dietary supplement of quebracho and chestnut tannins in combination with Vit B12 on cytokines level, and intestinal microbiota composition will be done in Argentina (ClinicalTrials.gov Identifier: NCT04403646). Randomized double-blind placebo-controlled proof-of-concept trial of resveratrol for the outpatient treatment of mild coronavirus disease (COVID-19) will be enrolled on 200 patients with an aim to evaluate the influence of the treatment on the rate of hospitalization (ClinicalTrials.gov Identifier: NCT04400890). Interventional clinical trial on 100 participants is currently ongoing evaluating the efficacy of *Caesalpinia spinosa* extract (P2Et) on reducing the length of hospital stay of patients. The authors suggest that this supplementation will improve the general condition of patients, reduce the inflammatory mediators and the viral load. Interventional study in phase 4 evaluating multiplied therapy zinc, quercetin, bromelain and vitamin C on the clinical outcomes of patients showed that therapy might be useful in prevention of severe presentation of disease [64]. Quercetin is a polyphenolic compound found in onion, red grapes, honey and citrus fruits. It possesses antioxidant, antiviral and anti-inflammatory properties, but also it might inhibit platelet aggregation and capillary permeability [65]. On the other hand, since bromelain, protein-digesting enzyme mixture from the pineapple plant, stimulates natural killer cells and T helper cells, it might be useful as anti-inflammatory agent (ClinicalTrials.gov Identifier: NCT04410510) [66] . Based on the known potential of quercetin to inhibit the production of proinflammatory cytokines and enzymes (cyclooxygenase and lipoxygenase) included in metabolism of arachidonic acid, one more study is dealing with the efficacy of quercetin (Quercetin Phytosome) on the survival time, symptoms and inflammatory parameters of 200 participants (ClinicalTrials.gov Identifier: NCT04578158) [67, 68]. Interventional clinical trial on 524 participants evaluating preventive effect of epigallocatechin-3-gallate (EGCG), a biologically active polyphenol on health care workers that is the most exposed group (ClinicalTrials.gov Identifier: NCT04446065). In another interventional study on 200 patients, safety and effectiveness of dietary supplement of plant polyphenol in conjunction with vitamin D3 will be studied (ClinicalTrials.gov Identifier: NCT04400890). Six registered studies are planned to investigate the potential of honey constituents on COVID-19 infection and health status of patients. From ancient times it is well known that honey and propolis have anti-inflammatory, antibiotic, antifungal, antiviral, antioxidant, anti-cancer, immunomodulatory, hepatoprotective effects and antiviral properties [69-73]. They have been used as supplements for many immune related diseases. The composition of honey varies depending on the plant sources and region where it is collected. A multicenter, placebo-controlled, randomized clinical trial was performed in 4 clinical centers in Pakistan. 313 patients with moderate and severe pathology were included in the study. Patients received honey and *Nigella sativa* seeds in addition to standard therapy [74]. The applied treatment significantly improved clinical signs, viral clearance and survival COVID-19 patients (ClinicalTrials.gov Identifier: NCT04347382). Propolis is composed from 50% resins, 30% waxes, 10% essential oils, 5% pollen, and 5% other compounds like polyphenols and flavonoids [69]. Since it was shown that propolis components have inhibitory effects on the ACE2, TMPRSS2 and PAK1 signaling pathways, a pilot randomized study evaluating the Brazilian green propolis extract on oxygen therapy dependency time or hospitalization time on 120 participants started (ClinicalTrials.gov Identifier: NCT04480593). The initial results of these studies are still awaited. We anticipate that results of some of the mentioned trials will demonstrate the safety and the efficacy of naturally occurring compounds as an adjunctive treatment for COVID-19 infection.

CONCLUSION

COVID-19 infection is characterized by an extremely heterogeneous clinical presentation of the disease, from non-manifestation to severe forms. Today, it is known that the microbiome in a broader sense, or more strictly virome, can serve as a template for the host positioning to the upcoming infection. Recent data confirms that in the long time period upon resolution of infection, virus becomes the integrative part of viral commune, less or more replicative, continuously shaping host response to future exposure to other infections. Apart from classical immune response to infection it is now clear that disease tolerance, developed through cohabitation between invader and the host, might be important aspect of SARS-CoV-2 infection starting from the individual level, in terms of disease pathology, to collective, in terms of epidemiology. This further implicated reevaluation of certain type

vaccine usage in latent carriers. In addition to intrinsic factors such as microbiome, naturally occurring components that we consume through food, beverage or supplementation have a significant role in profiling the immune response and interferes with conventional therapeutic approaches.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Ministry of Education, Science and Technological Development of the Republic of Serbia [451-03-68/2020-14/200007]. We thank Dr. Violetta Andriolo, medical editor at Amboss, Berlin, for critical reading of the manuscript and helpful discussion.

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Virom/SARS-CoV2 interakcija: Upražnjeno mesto za prirodne komponente

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Kratak sadržaj

Jedna od najupečatljivijih oznaka infekcije uzrokovane SARS-CoV-2 je heterogenost kliničke slike u populaciji koja varira od asimptomatske do teške forme. Pandemijska srazmera čini da brojnost ljudi sa teškom formom bolesti dolazi do izražaja, potiskujući činjenicu da je veliki deo populacije asimptomatski nosioc virusa. Dodatnu konfuziju unose nekonzistentni podaci o prisustvu virusa u brisu nazofaringealne regije i ispoljavanja bolesti. Različita distribucija virusa u telu, počevši od creva, preko jetre, mišića, bubrega itd., a bez znakova tkivnog oštećenja, otvara mogućnost da osobe sa negativnim rezultatima PCR testa u nazofaringealnom brisu mogu biti latentni nosioci infekcije. U osnovi različite kliničke slike bolesti može biti inicijalna protekcija prema SARS-CoV-2 infekciji stečena akumuliranim „iskustvom" u susretu sa drugim pripadnicima porodice korona ali i nekorona virusa, koja je ishodovala formiranjem humoralnog i celularnog imuniteta sa preklapajućim repertoarom. Osim toga, neopravdano zapostavljeni, ali vrlo značajan oblik odbrane domaćina od infekcije je tolerancija na bolest koja se temelji na suživotu s patogenom. Važno je napomenuti da su posledice tolerancije na bolest u smislu patoloških i epidemioloških aspekata prilično različite od klasičnog imunskog odgovora. Ovaj rad će diskutovati uticaj viroma na tok infekcije u svim fazama uzimajući u obzir oba- klasični imunski odgovor sa ciljem eliminacije patogena i sticanje tolerancije na bolest, kao oblik odbrane domaćina od infekcije u suživotu sa patogenom koji može da varira od neutralnog do sibmiotskog. Takođe, u skladu s gore spomenutim, razmatraće se o potencijal komponenata iz prirode da oblikuju tok infekcije i pruže podršku aktuelnim terapeutskim pristupima u lečenju COVID-19.

Ključne reči: *SARS-CoV-2; Tolerancija na bolest; Virom; Imunski odgovor; Prirodne komponente.*