Food and COVID-19

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2020 will undoubtedly be remembered as the year of the SARS-CoV-2 pandemia that has caused so far more than 22 million reported illnesses and about 780,000 deaths worldwilde. In an effort to counteract the pandemic, great challenges have been required to the entire scientific community from medical to engineering, to sociological and economic fields. In the last months, issues regarding nutrition and foods very often gained media attention although only rarely the information provided to consumers resulted to be useful or clearly presented. Scientist suggestions to consume more vitamins or vegetables according to their presumed antiviral activities, are very common, generally on the basis of the conclusions of controversial clinical trials or weak experimental studies that are thus confusing and misleading. In our study, with the aim of clarifying these relevant issues, we critically reviewed more than 100 studies in the mare magnum of the most recent literature comprising both clinical and in silico reports on food or functional ingredients as promising therapeutic approaches for COVID-19.

In conclusion, it is expected that the COVID-19 pandemic may be the first of many other global health crises that could be further exacerbated by progressively weakened health status and nutritional quality level will be important to fight and prevent the next pandemia coming from viruses, bacteria or other sources.

Keywords: Food ; COVID-19 ; SARS-CoV-2 ; micronutrient ; Clinical trial ; immune system ; food component ; in silico study ; protein interaction ; nutraceutic

1. Introduction

Foods are complex systems containing macro- and micronutrients, as well as plant secondary metabolites, that can take part in biochemical processes and help to achieve or maintain a state of wellbeing [1][2][3]. During the first phases of the new pandemic, the potential contribution of foods to addressing the coronavirus disease 2019 (COVID-19) has become a highly debated topic, fuelled by misleading fake news that are not supported by scientific results [4].

Coronaviruses (CoVs) are positive-sense single-stranded RNA viruses (Group IV of the Baltimore classification). CoVs are part of the Coronaviridae family and fall into the Orthocoronavirinae subfamily, which includes four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus [5][6]. Until 2019, six coronaviruses capable of infecting humans were known. Two of these, both from the Betacoronavirus group, caused major epidemics characterized by fatal respiratory disease: SARS-CoV, responsible for severe acute respiratory syndrome (SARS) in 2002 in the province of Guangdong in China; and MERS-CoV, responsible for Middle-East respiratory syndrome (MERS) in 2012 in the Kingdom of Saudi Arabia [7]. On 31st December 2019, a new CoV, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [8], was responsible for the outbreak of the COVID-19 pandemic in China [9]. The previous SARS and MERS outbreaks involved 29 and 27 countries, respectively, and, given that over 170 countries have been affected by the COVID-19 pandemic after only 3 months, the severity of thisinfection is evident [10][11][12]. The most common symptoms and signs of SARS-CoV-2 infection are respiratory symptoms, fever, dry cough, fatigue, and dyspnoea [13][14], whereas the clinical manifestations of infection range from asymptomatic to severe pneumonia. It is noteworthy that pneumonia, a lower respiratory tract infection, has occupied the first position in the communicable disease rank and the fourth position in the top ten causes of death globally in 2016 [15].

Although the design and production of a vaccine and its safe use represent the best solution to control the pandemic, during our writing, no pharmaceutical treatments or vaccines are available for COVID-19 [16]. However, unlike bacterial infections, viral diseases are often not treated with drugs because of latency, viral resistance, high mutation rates, and several frequent adverse side effects of treatment [17][18][19]. Therefore, eradicating viral diseases is rather challenging, and many viruses remain without preventive vaccines or effective antiviral treatments. In the early phase of the pandemic, only a few therapeutic protocols are available to reduce symptoms such as fever, pain, and impaired breath functionality, or to reduce diffuse microclots in the lungs [20].

In our review, two ways to tackle COVID-19 with food or food components are discussed, namely the untargeted approach through immune enhancement, which is currently being investigated in clinical trials, and the targeted approach through the interaction of food molecules with host or virus proteins, that is being investigated by in silico studies (Figure 1).

Figure 1. Scheme of current lines of research discussed in the present paper regarding food, food components, or diets used against coronavirus disease 2019 (COVID-19). The untargeted approach is based on immune system enhancement through food components and is being investigated in ongoing clinical trials, and the targeted approach is focused on the interaction between specific compounds and host or virus proteins and is being investigated by in silico studies.

2. Food as an Immune System Enhancer in Current Clinical Trials

The intake of some foods or food supplements can be extremely important for the strengthening of the immune system [21][22] and preventing the onset of pathologies such as respiratory infections. This aspect may represent a new frontier in the field of functional foods and an important resource for elderly people, as well as for immunosuppressed individuals or high-risk communities such as those in hospitals or retirement homes. An appropriate intake of micronutrients is necessary at every stage of growth, and particularly in some physiological conditions (older age, severe nutritional deficiencies, and stressful situations). Vitamins and minerals take part in many human biological and biochemical processes and are involved in immune system fortification (reinforcement of epithelial barriers, activation of immune cells, and enhancement of cytokines and antibody production) [23] and the wellness state. The role of some micronutrients as supporting agents in the prevention and treatment of respiratory tract viral infection has been largely demonstrated [24][25].

In the case of COVID-19, many clinical trials investigating the effect of food components on COVID-19 prevention/treatment are currently in progress. Clinical trials related to food, used for the prevention/treatment of COVID-19 as of 24 May 2020 are discussed in this review.

Sixteen clinical trials related to the supplementation of a single micronutrient or a micronutrients combination. Seven trials involves the co-therapeutic use of vitamin C, whereas five studies concern the administration of vitamin D. It is noteworthy that in several of the described clinical trials, zinc is a component of the micronutrient mixture. The role of zinc in improving the immune system in several diseases, including respiratory infections, has been previously demonstrated. In other seven clinical trials, the supplementation of other foods, food components, or diets has been proposed.

3. Food Compounds in Preliminary in Silico Studies

It may be of great relevance that some food components have adequate effects to be worth assessing with a targeted approach as potential candidates for treatment.

To better understand the potential roles of foods and their components in the fight against SARS-CoV-2, a brief description of the potential molecular targets already identified in the infection cycle [26] is needed. Considering the genomic similarities between SARS-CoV-2 and both MERS-CoV (50%) and SARS-CoV (79%) [27][28], some common features can be outlined in order to identify possible key factors for both drug discovery and food implications. It is well established that during the adsorption stage, the spike S-protein domain on the virus envelope is involved in binding with the human host angiotensin-converting enzyme (ACE2) to attack respiratory cells [29] in a very similar manner to that of the previous SARS-CoV. However, the much higher infectivity of this virus compared with that of the previous SARS-CoV and MERS-CoV infections could be explained by the recent finding of a region potentially involved in sialic-acid binding, which regulates host-cell infection [30]. Once SARS-CoV-2 is able to enter the cell and use the host translational machinery, the replication stage starts by expressing 16 nonstructural proteins (NSPs). Although not all of these proteins are well characterized yet, some of them may represent a potential target. In particular, viral papain-like protease (PLpro) and main protease (Mpro or 3CLpro) (the COVID-19 virus Mpro is in the Protein Data Bank (PDB) with accession number 6LU7) enzymes that are responsible for the cleavage of several critical viral proteins are considered the Achille's heels of SARS-CoV-2, showing little structural variation compared with their SARS-CoV counterparts [31]. The NSPs assemble into the replicase–transcriptase complex (RTC) and create a suitable environment for viral RNA synthesis. This process follows the translation and assembly of viral replicase complexes. SARS-CoV-2 then releases RNA into the host cell. Genomic RNA is translated into viral replicase polyproteins pp1a and pp1ab, which are then cleaved into small products by viral proteinases. Using a discontinuous transcription process, the polymerase produces a series of subgenomic mRNAs that are finally translated into key viral proteins. Viral proteins and genomic RNA are subsequently assembled into virions in the endoplasmic reticulum and Golgi apparatus, and then transported via vesicles and released from the cell.

Once molecular targets have been identified, studies to characterize potential drug candidates can be conducted in silico [28]. If the selected active compounds have good absorption, distribution, metabolism, excretion and toxicity (ADMET) properties and respect "Lipinski's Rule of 5" (a series of four rules that suggest if a molecule can be properly orally administrated, if more than one rule is not respected the molecule is not suitable for oral administration), then in vitro and in vivo analyses are required in order to define their efficacy, safety, and toxicological profile. Finally, clinical trials will be necessary to investigate the potential therapeutic efficacy and tolerability of the selected molecules [32]. An important advantage of these approaches is the rapid assessment of efficiency and toxicity in cell lines or animal studies in order to optimize the final choice. This advantage is essential, considering the rapid infection spread and the virus' lethality.

In the case of COVID-19, many in silico studies searching the activity of food components on SARS-CoV-2 proteins are currently in progress. The main recent in silico studies regarding the affinity of naturally-occurring compounds from food for either viral targets and/or host targets to counteract SARS-CoV-2 as of 4th July 2020 are discussed in our review.

Many studies have been focused on the activity of compounds isolated from food sources, such as glycyrrhizin, glabridin, glycyrrhetinic acid, and many polyphenols, such as caffeic acid, resveratrol, kaempferol, curcumin, demetoxicurcumin, quercetin, catechin, epicatechin gallate, hesperetin, hesperidin, δ-viniferin and myricitrin. Moreover, other studies have been focused on mixtures of compounds derived from food matrices, such as garlic and cinnamon, that were separated and then individually studied in silico.

4. Conclusion

The potential contribution of food to consumers' health and wellbeing has so far been only partially exploited by food science. We expect that the pandemic health emergency and the urgent need to strengthen prevention and control strategies will contribute to the mobilization of research efforts in innovative topics including nutraceutical activities, food/drug interactions, improved bioavailability, and novel formulations of natural food components. Food-based approaches generally offer the advantage of reduced adverse side effects with respect to conventional pharmacology approaches.

A promising approach that involves food chemistry could be the formulation of food-based immune enhancers for COVID-19 patients to allow the proper intake of macro- and micronutrients and, at the same time, to help reduce infection severity. In this context, the ongoing clinical trials discussed will give useful indications of the efficacy of the proposed protocols (compounds, dose, administration, etc.) and direct research toward new strategies.

The other strategic approach reported herein involves the discovery of lead compounds from food matrices through in silico studies.Selected compounds can then be developed in drug-design studies, evaluated further in vitro and in vivo studies, and lastly tested in clinical trials.

In conclusion, we had focused the attention on the possible role of food in the war against the new COVID-19 disease in order to highline this alternative research strategy waiting for the results of the described ongoing studies.

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