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Food policy, nutrition and nutraceuticals in the prevention and management of COVID-19: Advice for healthcare professionals

Yasemin Ipek Ayseli [a], Nazli Aytekin [b], Derya Buyukkayhan [c], Ismail Aslan [d], Mehmet Turan Ayseli [e,f,*]

[a] Osman Gazi Family Health Center, 33330, Mezitli, Mersin, Turkey
[b] School of Applied Sciences, London South Bank University, London, SE1 0AA, UK
[c] Faculty of Medicine, Department of Pediatrics, Division of Neonatology, University of Health Sciences Turkey, 34668, Üsküdar, İstanbul, Turkey
[d] Vocational High School, University of Health Sciences Turkey, 34668, Üsküdar, İstanbul, Turkey
[e] Department of Food Engineering, Faculty of Chemical and Metallurgical Engineering, Yıldız Technical University, 34210, Esenler, Istanbul, Turkey
[f] Genetris Danısmanlık, Mersin University Technopark, 33343, Yenisehir, Mersin, Turkey

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ABSTRACT

Background: The 2019 novel coronavirus (2019-nCoV) represents an ongoing major global health crisis with a potentially unprecedented death toll and socio-economic impact in the modern era. Measures taken to reduce the rate of transmission are too unprecedented, but are deemed necessary. The extensive strain on public health services has meant that individual agency is increasingly called for. To support this, there is a need to review policy and procedure governing the food and commerce industries in particular. Additionally, it is necessary to convey a more comprehensive and nuanced understanding of relevant diet and lifestyle factors to both health-care practitioners and the general public.

Scope and approach: To our knowledge, a review of possible additional measures for healthcare proffesionals, which includes the possible nutritional management COVID-19 pandemic does not yet exist.

Key Findings and Conclusions: This review identifies i) changing trends in consumer awareness and purchasing patterns in response to COVID-19, and their potential future implications for the food and food-commerce in-dustry ii) problematic elements of policy relevant to the outbreak of COVID-19, including the handling of wild-life and food-commerce, ii) newly emergent technologies in food science which represent viable and cost-effective means to reduce the risk of transmission of coronavirus, such as anti-microbial packaging, iii) impor-tant nutritional considerations with regard to coronavirus disease prevention and management, including nutrition in early infancy, and the role of select micronutrients (vitamins and minerals), phytochemicals and probiotics in conferring protection against both viral infection and pathogenicity.

1. Introduction

In the last twenty years, several viral outbreaks such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV; 2002–2003), H1N1 influenza (2009), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (2012), Polio (2014), European Food Safety Authorization (EFSA)(2020), Zika (2016) and SARS-CoV-2 (2019–2020) have taken place (Dey, Rahman, Siddiqi, & Howlader, 2020).

In late December 2019, the new viral pneumonia outbreak was first detected in Wuhan, the largest metropolitan area in China's Hubei province (Ibrahim, Abdelmalek, Elshahat, & Elfiky, 2020). At present,

the 2019-nCoV outbreak, more commonly referred to as Coronavirus disease 2019 (COVID-19) remains a global cause for concern (Dey et al., 2020).

In addition to the effect of global recession, extensive public health measures taken to contain or reduce the rate of viral transmission have altered the pattern of consumer behavior. One of the most discernible shifts in consumer purchasing behavior has been in the food and nutrition (esp. Nutraceuticals) industry, which has seen an increased consumption of nutraceuticals, functional foods and a trend toward healthier meal-types and home-cooked food (Aday & Aday, 2020). This shift represents a change in the dominant health paradigm; a move from

a curative to a preventative model. Similarly, there has been increased concern about food safety policy, which is reflected in the sheer scale of measures now implemented in this regard (Aday & Aday, 2020).

Whilst food and food commerce lies at the heart of many microbial outbreaks, including COVID-19, most of the measures taken to contain the spread of the virus do not relate to the point of provision of food to the consumer. Furthermore, although the economic impact of COVID-19 on public health sectors is widely acknowledged, nutritional advice, which represents the primary modifiable risk factor for disease prevention and management, is relatively underemphasised. In this connection, there is a need for comprehensive reviews focused on the potential application of food science and nutrition in the prevention, management and treatment of viral outbreaks. This is especially true in relation to coronavirus, which was in fact first identified in the 1970's (Mcintosh et al., 1970). This short-fall is an obstacle to the global public health measures taken against COVID-19, and is a limiting factor for input by health care professionals and thus, individual agency (Yuce and Kocabay, 2020).

2. Impacts of COVID-19 on food policy and consumption

2.1. Traditional Chinese medicine (TCM), wet markets and wildlife food consumption

Wet markets are found world-wide and form an essential component of agriculture, farming and food commerce industries. A typical representation of a wet market is an open-air site market for meat, seafood and bushmeat, as well as live (domestic and wild) animals for purposes of consumption. In recent times, wet markets have been identified as a major origin for viral outbreaks which are transmitted from animals to human beings e.g. SARS in 2003, H1N1 "swine flu" virus in 2009 and SARS-CoV-2 in 2019–2020 (Xu et al., 2020).

The first incidence of SARS was identified to have arisen from a wet market located in the southern Guangdong Province in 2003. Similarly, the COVID-2019 pandemic is thought to have arisen from the Huanan seafood market in 2019–2020 (Aday & Aday, 2020). Specifically, COVID-19 is believed to have been transmitted through wild animals, including horseshoe bats, pangolins and the civet. The route of possible transmission to humans identified are both direct, through their consumption as food produce, and indirect, through farming and marketing practises (Xu et al., 2020).

In response to such findings, the Chinese government, through the Standing Committee of the National People's Congress, has announced a string of strict limitations on the farming and consumption of 'bushmeats' to reduce the risk of further outbreaks. The first such change was introduced 26 January 2020 and ordered all business operations including agricultural produce markets, supermarkets, food and beverage sellers and online sales platforms shall strictly prohibit trade of wild animals in any form (Vyawahare, 2020). On 24 February 2020, the Chinese government additionally a nationwide ban on the commercial breeding and trade in (almost) all terrestrial wild animal species, not just protected species. Subsequently, China's wildlife-farming industry, valued at $74 billion prior to the outbreak of coronavirus, and projected to grow to $123 in 2023 (Humane Society International, 2020) is now at a total standstill. Whilst these measures are welcomed, they do not address the breeding and trade of wild-life for use as pets, ornamental items and traditional medicine.

The primary driving forces behind wild-life trade in China are wholesale demand for food (e.g. snake, turtle and bat for soup) and medicine (e.g. tiger bone and bear bile). Recent population based surveys indicate that the COVID-19 epidemic has had little impact on consumer demand for wild-life products, with only 46% of the Chinese population being reported not to consume such produce (Zhang & Yin, 2014). Interestingly, this figure gives an inflated sense of a public concern however, since it is estimated that 29% have already suffered a food-borne viral infection, and up to 13% may simply lack access to

these markets (Zhang & Yin, 2014).Whilst much of the focus on wild-life trade is centered on China, due to its relatively large population, economic power and its socio-political significance, wilde-life products are likewise in high demand across Asia and Africa. There is a sustained demand for bat (soup) in Thailand for example (Suwannarong & Schuler, 2016). These findings indicate that the current measures have not been successful in promoting the necessary socio-cultural shift; a shift in perception of risk associated with food products at the level of the general population. There is a pressing need to introduce public health measures which employ the health belief model to address public perception and consumer demand to prevent the emergence, or growth, of a 'black-market' for these meats.

Interestingly, whilst consumer preference for wild-life produce has not changed much, the consumption of fresh seafood is in decline (Blancheton et al., 2007). This is attributable to concern over the environment however, and is not attributable to the COVID-19 outbreak. Nevertheless, since fish presents a relatively reduced risk of infectious diseases, land-based fish farming represents a viable future dietary and economic alternative to wild-life meat (Blancheton et al., 2007).

2.2. Takeaway food consumption

Despite the level of scrutiny there have not as yet been any reports of direct transmission through food stuffs however, and the risk of transmission from meat is reported by public health bodies as being minimal. It was recently announced by the European Food Safety Authority (EFSA) and The European Centre for Disease Prevention and Control (ECDC) that transmission of SARS-CoV and MERS-CoV through food consumption was not found to occur. In other words, the virus is commonly passed on through directly contact of infected people whose could not cover his/her mouth and nose when coughing and sneezing, thoroughly foods or food stuff (European Food Safety Authorization (EFSA), 2020). Food products can however become contaminated through air-borne respiratory droplets from infected persons, or from hand-to-food contact. These modes of transmission carry significant implications for the global food-supply chain, particularly at the point of processing, preparation, packaging and service or delivery.

Packaging type, including material, has a significant impact on risk reduction however. It has been recently shown that the SARS substrain in particular has relatively long viability outside of living hosts on materials made with propylene, cardboard, stainless steel and copper (Tekin et al., 2020). The median half life estimate of COVID-19 at room temperature is around 16, 13, 9 and 2 h for propylene, steel, paper and aluminum respectively (Grant et al., 2020). Findings in relation to packaging type have not yet led to any change in food policy or practises in the food industry, including food outlets, which have been restricted to take-out and/or delivery in most countries, particularly during 'lockdown' conditions.

Most sectors of industry within the food supply chain remain (ed) open and functioning during the COVID-19 crisis, having been able to implement the necessary precautionary measures from a public health perspective. The food science industry has too made some significant strides in this time, including the development of viable antimicrobial (including viral) packaging technologies, which inhibit microbial growth (Contreras, Toselli, & Strumia, 2017, pp. 36–58). Such advances in technology have not yet been adopted by the food industry despite their potential utility in preventing spread of disease.

2.3. Packaged and unpackaged food consumption

As stated above, one important area of oversight appears to be packaging, which in relevant to food packaging and transport. In this connection, whilst data in this regard is still limited, emerging evidence strongly suggests that packaged foods present significantly less risk to consumers, than freshly prepared or unpackaged foods (European Food Safety Authorization (EFSA), 2020). As a result, food security concerns

have arisen because of the people on lockdown restrictions. To prevent the tranmission of 2019-nCoV among producer, a series of measures are taken for unpackaged foods includes fresh fruits, vegetables and bread in different countries (Aday & Aday, 2020). On the 20 Maruta & He, 2020, The bread and other unpackaged foods buying regulations has been changed by Agriculture and Forest Ministry of Turkey. Consumers can not longer touch unpackaged foods with bre hands.

Across the globe, the demand for whole foods, including unpackaged foods such as fruits and vegetables, as well as uncooked meats and fish are widely reported to have risen, in line with a corresponding shift toward home-cooked food. In contrast, some EU consumers showed opposite reaction against COVID-19 pandemic. According to the recent research study of Mintel, 23% of French consumers preferred online shopping during COVID-19 outbreak and similarly this purchasing approach has spread to many EU countries (Mintel, 2020).

2.4. Uncooked meat products consumption

Amongst these food groups, the supply of meat has been of greatest concern, since it represents a potential prior living host. This concern is presently heightened amidst recent reports from the German Federal Institute for Risk Management (BfR) which indicate that workers in the meat-sector are at much greater risk of contracting coronavirus than those in other sectors of the food industry. It is not however reflected at the level of the consumer, who is typically reported to stockpile meats in anticipation of a shortage, as well as demonstrating a preference for meat over fish, and beef as opposed to other meats, such as pork and chicken (Rude, 2020). which have experimentally been shown to be relatively resistant to infection with COVID19 (McNamara, Richt, & Glickman, 2020).

As stated by the European Food Safety Authority, 2019-nCoV cannot multiply in or on food; to do this, they need a living animal or human host. In contrast, it has been recently reported the transmission of 2019-nCoV in salmon. The news resulted in halted the exportation of salmon from EU countries to China (Aday & Aday, 2020). It seems that the n-CoV appears to have effected meat sector more than other food categories as noted BfR on 19th June. However, if meat and meat products are heated to at least 70 °C for at least a few minutes before consumption, the risk of foodborne infection can be reduced (BfR, 2020).

3. Nutraceuticals and functional food use during pandemic: A focus on 'self-protection'

Due to the imminent danger presented by the rapidly spreading COVID-19, viable prophylactic and therapeutic measures which can be developed and applied at the level of the general public are being sought after. This urgent requirement for a solution are reflected on the individual level by an unprecedented rise in consumer sales of supplementary nutrients, nutraceutical products and functional foods which were considered to be effective against influenza and SARS virus, have been on the front burner during this pandemic. This, despite a consistent and continuing counter-narrative in the media about the inefficacy of existing options.

In such a climate, it is of particular importance that health-care professionals exposed to more dangerous environments than the general population seek other solutions not only to protect them from infection but also to mitigate the impact of the effects of viral load in case of being infected (Yuce and Kocabay, 2020). Therefore, the daily consumption of supplementary foods and nutraceuticals become popular among health care professionals and individuals with high infection risk (Furlong, 2020). Put in dollar terms, dietary supplements in the US achieved a sales revenue of $ 345 million during the full 2019. By comparison, dietary supplement sales reached $ 435 million during the six-week period of the outbreak that ended on April 5, 2020 (Grebow, 2020).

Such findings are consistent with Google and Tastewise research which demonstrated there is rising trend for vitamin C, D, zinc, elderberry, rosemary, echinacea, melatonin, phosphatidylserine, collagen, and mushrooms. This finding is of note also because of the well-known increase in prevalence of internet searches for 'food' and 'immune system', which rose 670% globally in the first 2 weeks of March. Although, consumers are seeking to use any functional food that is used self-medicating their moods (Furlong, 2020).

As data from in vitro studies accumulates, several viable mechanistic targets for combatting COVID-19 are evident. These include those targeting specific elements of the SARS-CoV-2 genome, including the spike protein (S), the RNA-dependent RNA polymerase, the membrane protein (M), the envelope protein (E), the NTPase/helicase, required for virus budding and SARS-CoV main protease (3CL protease) are gaining popularity to prevent the enterence of CoV into the cells of the human body (Lu & Shi, 2020). In this connection, Table 1. (see appendix) presents a list of mechanisms of action by which the select micronutrients and phytochemicals discussed herein have been shown to be effective in the prevention of viral infection and pathogenicity.

3.1. Breastfeeding approach

Whilst it was initially thought that children were not as susceptible to infection with virulent strains COVID-19, SARS-CoV-2 infection in neonates, infants and children have been reported. The prognosis for COVID-19 infection in child patients is a relatively positive one however. Child patients typically present only mild symptoms; child COVID-19 patients tend to be asymptomatic, when compared to older age groups (Lu & Shi, 2020). It has however been reported that the risk of developing critical complications from COVID-19 infection is higher in children under the age of 3 (Xu et al., 2020).

The first report of COVID-19 infection in children came from the USA and comprised of a sample of infants and children aged between 2 months and 15 years (Xu et al., 2020). Following this, this first incidence of child mortality resulting from COVID-19 came from Iran's North Khorasan province, on March 24, 2020 (Dursun, 2020). This received signficant attention from global media and heightened interest in the relatively cost-effective and realistic solutions being suggested in the field of paediatric nutrition.

In this connection, breastfeeding represents an important prophylactic agent against a host of communicable and non-communicable diseases, and also has well-established therapeutic effects (e.g. because it contains mother's antibodies). This message has been clearly communicated by the media and breastfeeding has subsequently been reported to be significantly more popular amongst mothers than in previous years (Chen et al., 2020; Lu & Shi, 2020).

Whilst vertical transmission in utero is still doubtful (Wei et al., 2020), a small number of cases in which newborns were found to be infected with SARS-CoV-2 have been reported (Fox et al., 2020). According a recent systematic review conducted by the World Health Organization (WHO), of the 46 mother-infant dyads in which the mother was found to test positive for COVID-19 using Real Time-PCR, only 13 infants tested positive for the virus. It is conjectured that viral-transmission to these infants may have been via air-borne respiratory droplets, since only 1 of these children had a mother whose breast milk tested positive for viral particles detected in her breastmilk of a total of 3 (Wei et al., 2020).

More than 20 reports have been published on this topic to date, however the findings have been inconsistent. Some of these inconsistencies are explained by differences in the methods of assessment used, primarily sampling and testing. Antibody testing has indicated differences in levels of expression in the reproductive tissues of pregnant women, which in fact reflects the degree of viral infiltration; the risk of transmission. Data is largely limited to case-studies at present, which further suggest the existence of multiple confounding factors, including prior infection with a beta-coronavirus. In one such case study, a woman who contracted in the second trimester produced samples of cord blood

Table 1
The most preferred phytochemicals, micronutrients and active(s) from natural sources on the treatment or preventive of COVID-19 (Modified from Annunziata et al., 2020; Iddir et al., 2020).

Active(s)*	Study Description	Study Design	Study population characteristics	Daily dose provided/Treatment	Delivery medium/ Length of study (Phase)	Main Results	Reference
Propolis	Effect of propolis on the treatment of COVID-19	–	–	1 ml (250 mg)/10 kg (body weight)	Propolis extract	Natural PAK1 blocker	Maruta and He (2020).
Fiber	Effect of fiber on the treatment of influenza infection	Prospective human cohort study	n = 219,123 men and 168,999 women, aged 50–71 y 9 y follow-up	10 g/d increase in dietary fiber	Dietary fiber	Consumption of dietary fiber correlated with lowered mortality from infectious and respiratory diseases	Park, Subar, Hollenbeck, and Schatzkin (2011).
Melatonin	Melatonin as a potential adjuvant treatment for COVID-19	–	–	–	–	Natural PAK1 blocker; Melatonin may play a role of adjuvant medication in the regulation of immune system, inflammation and oxidation stress, and provide support for patients with ALI/ARDS and related complications	R. Zhang and Yin (2014); Maruta and He (2020).
Quercetin	Effect of quercetin on Prophylaxis and treatment of COVID-19.	A Double-blind, Randomized, Controlled Study	50 participants (18 Years and adult, older adult)	500 mg and 1000 mg for group-1 and group-2.	Dietary Supplement: Quercetin Prophylaxis/12 weeks (Phase 1)	Immune system modulatory	www.clinical trials.gov
Polyphenols from Broussonetia papyrifera	–	Evaluation of the inhibitory activities of polyphenols against MERS- and SARS-CoV proteases	–	Compounds were individually tested at concentrations ranging from 0 to 200 μM	–	All the tested compounds had a dose-dependent inhibitory activity on SARS-CoV protease with an IC50 ranging from 30.2 to 233.3 μM	Annunziata et al. (2020)
Forsythoside A from Forsythia suspense	–	CEK cells infected with IBV	–	Forsythoside A 0.16 mM, 0.32 mM, and 0.64 mM	–	(i) dose-dependent viral load reduction, (ii) IBV nucleocapsid protein expression reduction and (iii) dose-dependent inhibition of IBV infection	Annunziata et al. (2020)
(−)-catechin gallate and (−)-gallocatechin gallate	–	Quantum dots-conjugated oligonucleotide system used for the inhibitor screening of SARS-CoV nucleocapsid proteins	–	–	–	Marked anti-SARS-CoV nucleocapsid protein activity. In particular, (i) dose-dependently ability to attenuate the binding activity at concentrations≥0.005 μg/ml, (ii) more than 40% inhibition activity at 0.05 μg/ml and (iii) IC50 at the same concentration	Annunziata et al. (2020)
Elderberry	The treatment of influenza	Non-randomized, double-blind trial	100 participants at the age of 20–65 (female)	15 cc 4 times daily for 5 days	Dietary Supplement/ Phase 4		www.clinical trials.gov
Crude polyphenolic extract from Sambucus nigra	–	Vero cells infected with IBV	–	Crude polyphenolic extract 0.004 g/ml	polyphenolic extract	viral replication inhibition, (ii) dose-dependent reduction of virus titers by four to six orders of magnitude at 1.0 and 0.1 MOI,respectively, (iii) inhibition of infection process at an early stage and (iv) altered virus structures and membrane vesicles	www.clinical trials.gov
Probiotic mixture	Study to evaluate the effect of a probiotic in COVID-19	A double blind, randomized, controlled study	40 participants (18 Years and adult, older adult)	Oral daily capsule containing probiotic strains with maltodextrin as excipient, administrated for 30 days (1 pill od containing 1 × 10E9 cfu of the probiotic)	Dietary Supplement: Probiotic	–	www.clinical trials.gov
Selenium	Evaluation of response to influenza vaccine	Human randomized, double-blinded RCT	119 participants (50–64 Years)		50, 100, or 200 mg Se/day, meals with Se-enriched onions	SEPS1 mRNA (marker of inflammation) increased (p < 0.05) after one week of vaccine administration, being dependent	Goldson et al. (2011).

(*continued on next page*)

Table 1 (*continued*)

Active(s)*	Study Description	Study Design	Study population characteristics	Daily dose provided/Treatment	Delivery medium/ Length of study (Phase)	Main Results	Reference
					(50 mg se/day), unenriched onions and placebo/12 weeks	on the dose of Se per each intervention arm.	
Zinc	Assessment of zinc supplementation on cold symptoms.	Human randomized, double-blinded RCT	100 patients (placebo group = 50)	–	13.3 mg of zinc gluconate	A faster decrease of the cold symptoms like fewer days with coughing, hoarseness, headache, nasal congestion and sore throat	Mossad, Macknin, Medendorp, and Mason (1996).
Vitamin A	Effects of vitamin A supplementation on acute lower respiratory tract infections (LRTI)	Meta-analysis of RCTs	10 studies (n = 33.179 children)	–	–	There was no effect of vitamin A supplementation on acute LRTI incidence or prevalence of symptoms	Chen, Zhuo, Yuan, Wang, and Wu (2008)
Vitamin E	Assessment of vitamin E supplementation and community acquired pneumonia.	Human RCT	7469 participants at the age of 50–69 (male)	–	Vitamin E supplement	Lower incidence of pneumonia in individuals receiving vitamin E supplements (RR: 0.28; CI: 0.11–0.69).	Hemilä (2016)
Vitamin D	Vitamin D testing and treatment for adults with COVID-19	A double blind, randomized, controlled study	100 participants (18 Years and adult, older adult)	The dosage for the first two weeks will be 10,000 IU/day b.i.d. (age 18–69 years) or 15,000 IU/day t.i.d. (age 70+) After two weeks of taking vitamin D, if vitamin D levels are still below 30 ng/ml, continue the dosage for 3 more weeks. If vitamin D levels are 30–49 ng/ml, continue at a dosage of 5000 IU/day. If vitamin D levels are 50+ ng/ml, stop supplementation.	Dietary Supplement: Oral vitamin D3 capsules/PahseI	–	www.clinical trials.gov
	Assessment of vitamin D supplementation on respiratory tract infection (RTI).	Meta-analysis of RCTs	11 placebo-controlled studies (RTCs) (n = 5660 patients).		Vitamin D supplement	Vitamin D had protective e_ects against RTI (OR: 0.64; CI, 0.49–0.84). This was more pronounced by individual daily dosing compared to bolus doses (OR = 0.51 vs. OR = 0.86, p = 0.01).	Bergman, Lindh, Björkhem-Bergman, and Lindh (2013).
Vitamin C	The treatment of influenzae and common cold	A Double-blind, Randomized, Controlled Study	221 participants at the age of 1–6	Vitamin C (25mg/5 ml) given at dose of 5 ml to children 1–2 years old, 7.5 ml to children 3–4 years old and 10 ml to children 5–6 years old	Drug/Dietary Supplement for 12 weeks/Completed	–	www.clinical trials.gov
	Assessment of vitamin C supplementation on cold symptoms (RTI).	Meta-analysis of RCTs	9 randomized controlled trials (n = 5500) in children (3 months–18 years of age).	–	Vitamin C supplement	Daily supplementation in vitamin C with extra doses reduced the time of having a common cold	Ran et al. (2018).

*Phytochemicals, micronutrients or probiotic strain; **CEK:**Chicken embryo kidney; **IBV**: Infectious bronchitis virus; **SARS-CoV:**SARS-related coronavirus; **IC50:** Half-maximum inhibitory concentration; **MERS-CoV:** Middle East Respiratory Syndrome coronavirus; **MOI:** Multiplicity of infection. **ALI:** Acute lung injury; **ARDS:** Acute respiratory distress Syndrome; **PAK1**: RAC/CDC42-ac.

and placenta which tested negative for SARS-CoV-2 antibodies at the point of delivery, despite testing positive in her serum sample. In another however, a woman who had previously also been infected with SARS (SARS-CoV-1) tested positive for COVID-19 across all the tissues sampled, and also in her breast milk. Whilst it is difficult to generalise from such small samples, the available data does however suggest that the detection of antibodies in the milk at the point of delivery might give strong indication of the risk of transmission. Furthermore, to improve validity, breast milk should not collected for up to several weeks after the end of the infective period, since collection during this period can reduce the detection of viral RNA (Fox et al., 2020).

It is well-known that breastmilk transmits antibodies from the mother and that this confers enhanced immunity against likely microbial exposures to the newlyborn infant. It has recently been shown that secretory immunoglobulin A (sIgA) which constitutes 90% of the immunoglobulins content in breastmilk, plays an important role in the immune response against COVID-19 (Powell et al., 2020; Yurttas, Calik, Yalcin, & Kaner, 2020). The importance so sIgA has also been demonstrated in other viral infections, such as infection with the rotavirus; the human immuno-deficiency virus (HIV), the norovirus, the herpes simplex viruses, echoviruses 6 and 9, and polioviruses 1, 2 and 3 (Yurttas et al., 2020). Finally there is data to suggest that the risk of viral infection with COVID-19 in infants changes according to the duration of breastfeeding episodes. Short episodes appear to represent a negative independent risk factor for infection and it is in this connection that WHO have issued guidelines for breastfeeding at home and in a hospital setting (Popofsky et al., 2020).

Given the available data, it is clear why mothers are advised that young infants should be exclusively breastfed, by major global non-profit public health organizations like WHO and the United Nations Children's Fund (UNICEF) (Pandolfi et al., 2019; Yurttas et al., 2020).

3.2. Probiotics

Probiotics refer to those types of bacteria, such as bifidobacteria, and to a lesser extent yeast, which have been found to be beneficial to human health; to act synergistically with human physiology. Probiotics have been shown to contribute toward a gastrointestinal (GI) microbiome associated with a 'healthy' immune system. More specifically, they are able to modulate host immune responses to produce outcomes associated with a reduced risk of a wide range of communicable and noncommunicable disease states through various mechanisms of interaction (Akour, 2020). More importantly perhaps, the maintenance of these bacterial colonies at the level of the GI tract, and the skin, has been shown to prevent the manifestation of certain diseases by maintenance of the structural and functional integrity of the epithelium; our physical barriers against infection (Wieërs et al., 2020). In this connection, a significant reduction in the risk of viral infection, including respiratory viruses, has also been observed (Saad, Delattre, Urdaci, Schmitter, & Bressollier, 2013). Most of the data to support the role of the gut microbiome in conferring protection against viral infection comes from experiments on animals; there is a call for population based longitudinal research on humans, and for clinical trials. It has been recently shown that a new peptide (P18) that is produced by *B. subtilis,* have inhibition effect against influenza virus in vitro. Interestingly, the antiviral effect of P18 in mice was comparable to that of oseltamivir phosphate (Tamiflu®) (Akour, 2020). Another study in mice, intranasal inoculation of *L. reuteri* or *L. plantarum* have been shown protective effects against pneumonia virus lethal infection (Gabryszewski et al., 2011). Recent randomized placebo-controlled trials have demonstrated that the consumption of the heat-killed L. *lactis* JCM 5805 may confer additional anti-viral properties through numerous mechanisms including the modulation of viral genetic expression (Kanauchi, Andoh, AbuBakar, & Yamamoto, 2018). These results were in agreement with those reported by Wei Xu et al. (2020), who stated that the aforementioned probiotics were used in the treatment of a COVID-19 patient, commonly as an

adjuvant to pharmaceutical therapies. It has been recently observed that an alteration of the physiological homeostasis of intestinal microbiota, also known as dysbiosis, is correlated with some diseases. Dysbiosis associated with a loss of species diversity were correlated with very diverse diseases from antibiotic-associated diarrhea to type 2 diabetes or common infectious diseases, among others (Le Chatelier et al., 2013). A recent meta-analysis has shown that probiotics may be associated with less antibiotics use in infants and children in the context of reducing the risk of symptoms of the common cold (King et al., 2019). Again, further investigations in the form of clinical trials are needed to determine validated protocols tailored for specific populations, and studies which determine the relationships between different strains and disease states (Biogaia, 2020).

The potential benefit of a healthy GI, and skin, microbiome appears to be understood by the health-conscious stratum of the general public. In this connection, growing trends in the consumption of kefir, boza, probiotic drinks/yoghurt and pickles such as kimchi, sauerkraut have been seen, and may be contributed to an increasing awareness of the relevant benefits to immune system functioning. There is some debate with regard to the relative efficacy of specific bacterial strains and their viability in different populations, and under different internal and external environmental conditions. Additionally, no published studies so far evaluated the use of probiotics for the management of COVID19, so their role is not yet established (Akour, 2020).

3.3. Phytochemicals

3.3.1. Curcumin (diferuloylmethane)

Curcuminoids are a class of polyphenolic compounds produced by plants of the family *Curcuma longa*, and are responsible for their yellow colour. Curcumin is the major curcuminoid synthesized by turmeric, a variety of ginger (*zingiberaceae*). Curcumin has been determined to have the greatest anti-inflammatory, (Fadus, Lau, Bikhchandani, & Lynch, 2017), anti-oxidant (Zahedipour et al., 2020), and anti-microbial action (Manoharan et al., 2020) amongst the phenolic compounds produced by turmeric, and is credited for the use of turmeric in traditional medicine (e.g. Ayurveda).

Several review papers detailing preliminary evidence of the therapeutic utility of curcumin in combatting coronavirus, including the SARS-CoV-2 substrain, through a range of direct and indirect mechanisms, have been published this year. In terms of direct anti-viral activity, a newly emergent analysis using molecular docking has reported that curcumin is able to directly inhibit SARS-CoV-2 entry into target cells after binding to the viral nucleocapsid and nsp 10 proteins, for which it has a high affinity (Suravajhala et al., 2020). Further investigation in vitro and in vivo is required to validate this finding however.

In addition to modulating cellular signalling in response to infection with coronavirus, curcumin has also been found to reduce risk of disease manifestation through a number of indirect mechanisms, including inhibition of i) the entry of coronavirus into target cells, ii) viral replication, iii) viral protease (Zahedipour et al., 2020). It is further speculated that curcumin may influence the pathogenicity of coronavirus through a number of other, well established mechanisms of action. For example, curcumin may reduce lung tissue damage resultant from coronavirus infection by modulating levels of inflammation, through its anti-cytokinetic activity. Amongst the many mechanisms identified, inhibition of interleukin 1 (IL-1), IL-8 and tumor necrosis factor alpha (TNF-alpha), secondary to the inhibition of transcription factors nuclear factor kappa B (NFkB) and activator protein-1 (AP-1), has been demonstrated to limit damage to lung tissue in response to respiratory viral infection (Avasarala et al., 2013). Dietary intake of curcumin or turmeric alone appears to be ineffective in achieving the discussed therapeutic outcomes however. Whilst the available data is conflicting, the bioavailability and efficacy of curcumin under physiologic conditions, both from turmeric and as an isolate, has been widely contested (Lopresti, 2018). In response, several proprietary nutraceutical

formulations of curcumin have been manufactured.

These include curcumin-lecithin-piperine complexes, curcumin-phosphatidylserine complexes and formulas which include sesquiterpenoids (also found in turmeric), such as Biocurcumax™ (Jamwal, 2018). These formulations have been experimentally shown to have a far more potent effect than either turmeric or curcumin isolate; these formulations overcome losses of potential activity due to problems with bioavailability, uptake, solubility and cellular metabolism, through the addition of carrier molecules and other synergistic compounds.

In addition to representing a relatively cost-effective and non-invasive mode of therapy, both turmeric and curcumin have been shown to be safe; non mutagenic, nongenotoxic, non-toxic (including reproductive toxicity) at large doses sustained over extended periods (e. g. 6 g/day for 7 weeks) (Soleimani, Sahebkar, & Hosseinzadeh, 2018).

3.3.2. Elderberry (Sambucus nigra)

The dark blue to purple berries of the Elderberry plant have been used for hundreds of years in Europe in the production of traditional medicines and foods. Nowadays, *Sambucus nigra* L., widely known as black elderberries which exhibits antimicrobial, antioxidant, antiinflammatory effect in vitro and in vivo (Chen et al., 2014). Previous studies demonstrated that the phenolic compounds of elderberries can inhibit the penetration of influenza virions in vitro (Annunziata et al., 2020; Yasmin et al., 2020). This herbal extract, which is generally used among the moher under the observation of doctors, is sold with Vitamin C as syrup or effervescent tablet. Previous research studies clearly demonstrated that elderberry plant has both antiviral properties against some subtypes of the flu virus. Additionally, more research is needed to examine the role of elderberry benefits for n-CoV-2.

3.3.3. Bee propolis

PAK1 (RAC/CDC42-activated kinase 1) is called as the major "pathogenic" kinase that give rise to many diseases including cancer, malaria, pandemic viral infections, mainly influenza, HIV and COVID-19. Previous studies demostrated that bee propolis is dominated by caffeic acid (CA) and its ester (caffeic acid phenethyl ester = CAPE) that may provide to inhibit PAK1. Furthermore, the cell-permeability of CA and its esters are rather poor by the reason of their COOH moiety that may enhance by 1,2,3-triazolyl esters (called 15A and 15C). As a result, the standardized extract of propolis is widely used stimulating the immune system and blocking coronavirus-induced fibrosis of lungs among the healthcare-professionals as natural PAK1 blocker. The recommended daily dosage of standardized propolis extract is 1 ml (250 mg)/10 kg (body weight) for COVID-19 patients (Maruta & He, 2020) and 10–40 drop drops (60–240 mg active propolis ingredient) for children (1–10 years) at high risk of COVID-19 (Yuksel & Akyol, 2016).

3.3.4. Resveratrol (3,5,4′-trihydroxy-trans-stilbene)

Resveratrol belongs to a class of naturally occurring polyphenolic compounds called stillbenoids. Whilst commonly associated with red grapes' skin, and red wine therefore, it has been detected in over 70 different plant species to date, including berries of the Vaccinium family, such as blueberries, cranberries and bilberries. It is also known to be present in high quantities in peanuts and in cocoa beans (Burns, Yokota, Ashihara, Lean, & Crozier, 2002).

Amongst the polyphenols, resveratrol has been relatively well studied. The biological activity of resveratrol is known to be extensive, and its activity more potent than other stillbenoids. In addition to being a powerful anti-oxidant, resveratrol is able to exert significant angiogenic, anti-inflammatory, anti-carcinogenic and anti-microbial (including antiviral) effects (Salehi et al., 2018).

All of these properties are relevant to some/all possible stages of a viral infection, from infection to disease progression, and the potential therapeutic viability of resveratrol in the treatment and prevention of RNA viruses and in respiratory disease viruses in particular, has been amply reviewed (Wahedi, Ahmad, & Abbasi, 2020).

The therapeutic efficacy of resveratrol has been demonstrated in vitro in relation to the novel coronaviruses MERS-CoV (Lin et al., 2017) and SARS-CoV-2 (Wahedi et al., 2020).

Treatment with resveratrol post infective phase (for 48 h) resulted in a significant inhibition of i) MERS-CoV induced cellular apoptosis mediated by caspase-3 cleavage, and ii) viral replication, corresponding to a reduced expression of viral nucleocapsid protein. Furthermore, consecutive administration of relatively low doses of resveratrol was observed to inhibit MERS-CoV infection completely (Lin et al., 2017).

Although via a more indirect pathway, like curcumin, resveratrol has recently been shown to disrupt the action of the viral spike protein (S-protein) used by SARS-CoV-2 to enter target cells. Using molecular dynamic stimulation, Wahedi et al. (2020) have revealed resveratrol to form a highly stable complex with the human angiotensin converting enzyme-2 (human ACE-2) receptor, which is required by COVID-19 to enter target cells using S-protein (Wahedi et al., 2020).

As with curcumin, it appears necessary to consume supplemental resveratrol to guarantee a therapeutic effect. The bioavailability of resveratrol has been reported to be negligible irrespective of dose, or dose duration. This has been attributed to a low level of uptake at the level of the GI tract, its low solubility/high affinity for binding lipids, and the rapid metabolism (into glucuronides and sulfate metabolites) and elimination of resveratrol at the level of the kidneys and liver (Wenzel & Somoza, 2005).

Numerous dietary factors have also been suggested to impact bioavailability, although findings have been inconsistent. For example, numerous studies report an increased uptake of supplemental resveratrol, based on greater circulating levels, when consumed with food whilst others report a delayed but not significantly altered overall uptake (Burkon & Somoza, 2008).

More qualitative investigations have indicated the macronutrient composition as a key determinant of uptake, and have reported that a high-fat content/the adherence to a high-fat diet leads to a reduced uptake of supplemental resveratrol, as evidenced by reduced plasma concentrations (Ramírez-Garza et al., 2018). Again, this finding is not supported by similar studies elsewhere, which instead measure conjugated resveratrol (Vitaglione et al., 2005).

These inconsistencies are likely explained by variables as yet unidentified, as well as differences in methods of sampling (e.g. free vs. conjugated or protein bound resveratrol) and analysis. Importantly, manufactured resveratrol formulations, including micronized trans-resveratrol (Howells et al., 2011), resveratrol. magnesium-dihydroxide complexes (Aguiar et al., 2018) and combinations with carrier molecules, such as piperine (Johnson et al., 2011) have been demonstrated to offer far superior availability, as evidenced by functional assays and clinical outcomes. Such preparations also reduce the risk of adverse cytotoxic effects associated with the excess consumption of resveratrol.

3.3.5. Melatonin (N-acetyl-5-methoxytryptamine)

Melatonin is a neurohormone that is primarily produced in the pineal gland of the central nervous system (CNS). The primary function of melatonin is to synchronize all physiological systems into a 'circadian rhythm'. Melatonin has also been shown to regulate Rapid Eye Movement (REM) sleep; dream activity, and seasonal adaptation (Mazzucchelli et al., 1996).

Interestingly, whilst the maintenance of circadian rhythm is its most distinguished function in human physiology, melatonin is identified to have first evolved as an antioxidant produced by photosynthetic prokaryotic organisms (Tan & Reiter, 2020). Melatonin continues to function as a potent anti-oxidant in human systems (Reiter, 1996). It is also shown to regulate the expression, metabolism and function of other anti-oxidants and anti-oxidant enzymes (e.g. glutathione peroxidase and superoxide dismutase), as well as immune processes which generate oxidative stress, in both CNS and non-CNS tissues (Rodriguez et al., 2004). In this connection, melatonin is now being understood to have wide-ranging involvement in both innate and adaptive immunity. First

and foremost, melatonin is involved in the global regulation of the immune system, which is centrally mediated; the immune system is responsive to the circadian rhythm, which is manifest as melatonin signalling along the immune-pineal axis (Esquifino, Pandi-Perumal, & Cardinali, 2004).

Melatonin production has also been found to take place in the skin (Slominski, Tobin, Zmijewski, Wortsman, & Paus, 2008) and in the GI tract (Cheng, Tsang, Ku, Wong, & Ng, 2004 the immune system as major physical (and chemical) barriers toward the external environment. Tissues of the respiratory tract, which make-up the other major physical barrier of the immune system, do not produce melatonin, but are responsive to it. Within this network of receptor-mediated interactions, melatonin can promote immunity across a range of different pathways. Importantly, acute inflammation, such as in viral infection, is associated with a shift from CNS to peripheral melatonin production (Markus et al., 2018).

The structural and functional integration between melatonin and the immune system has generated a lot of scientific interest in terms of its potential therapeutic application in both CDs and noncommunicable, disease (NCD). Numerous direct and indirect mechanisms have been the subject of enquiry with regard to respiratory virus diseases, including COVID-19, and some have already produced positive results. Amongst these, melatonin supplementation has been demonstrated to function synergistically with other pharmaceutical agents that have well-established efficacy against SARS-CoV-2. Data from a novel inter-actome model of chemical-to-protein and protein-to-protein interactions, derived from the identification of differentially expressed genes from patient blood samples, has produced important findings. Melatonin was shown to be more effective than hydroxychloroquine/chloroquine treatment in modulating the downstream effects of these shifts, particularly the interaction between host matrix metallopeptidase-9 and viral ACE-2, which is known to precipitate SARS-CoV-2 infiltration into cells (Hazra, Chaudhuri, Tiwary, & Chakrabarti, 2020). It is in this connection that an algorithm for high dose melatonin supplementation as an adjunctive therapeutic agent to hydroxychloroquine/chloroquine treatment in COVID-19 patients has been suggested (Grunewald, Shaban, Mackin, Fehr, & Perlman, 2020). Data elsewhere indicates that melatonin may also prevent viral infiltration via a different mechanism. Molecular docking analysis has revealed melatonin to significantly inhibit intracellular calmodulin, which is necessary to 'anchor' ACE-2 on to cell surfaces (Feitosa et al., 2020). More importantly perhaps, melatonin has been found to be the most potent inhibitor of the SARS-CoV-2 main Protease (MPro), also referred to as chymotrypsin-like protease, amongst the database of (74) proteins currently identified to inhibit MPro. It has been recently shown that MPro inhibition represents a major therapeutic target because it is an enzyme central to viral replication and because it is a protein conserved in coronaviruses; it is dissimilar to human proteins (Zhang & Yin, 2014). Melatonin has also been put forward as an adjuvant treatment to reduce the risk of complications in COVID-19 patients. The immunomodulatory, anti-inflammatory and anti-oxidant effects of melatonin are indicated to attenuate the pathogenesis of certain cardiovascular, respiratory and immune system diseases, as well as complications linked to the co-existence of metabolic syndrome, that are associated with more severe cases of infection (El-Missiry & El-Missiry, 2020).

The viability of melatonin as a preventative agent for these complications in COVID-19 is principally underpinned by its demonstrated efficacy in other models of viral infection. For example, melatonin has been shown to attenuate the pathogenesis of lung disease tissue induced by the respiratory syncytial virus. This effect is linked to the inhibition of inflammatory processes in respiratory tissues, and in immune cells involved in the acute phase, which are linked to the over-production of pro-inflammatory cytokines, such as TNF-alpha, secondary metabolites and immune products, such as H_2O_2, and nitrous oxide, that generate a persistent state of oxidative stress (Huang, Cao, Liu, Shi, & Wei, 2010).

Melatonin is also being suggested as a therapeutic option to prevent the less common complications of COVID-19, such as those which affect the CNS (Romero et al., 2020).

The principle dietary precursor for melatonin synthesis is the amino acid ʟ-tryptophan. When tryptophan concentrations in the amino acid pool of the plasma are relatively increased, the passage of tryptophan across the blood-brain barrier is enhanced and the conversion of tryptophan into melatonin via the serotonin-*N*-acetylserotonin-melatonin can be significant (Hajak et al., 1991). Although, melatonin is not considered to be a nutraceutical in the traditional sense; it is found in bread, sour cherry, tomato, walnut, cocoa powder, black olive, kefir, red wine, beer, black and green tea (Kocadağlı, Yılmaz, & Gökmen, 2014) and it has been recently suggested that consumption of food containing or promoting the synthesis of melatonin at dinner (Muscogiuri, Barrea, Savastano, & Colao, 2020). Melatonin is also treated as a food supplement in countries which permit its use, such as in the United States. More importantly, supplemental melatonin is illegal in many countries, including in the UK, due to its classification as a hormone.

The risk-to-benefit profile engendered by specific environmental factors may however warrant the use of melatonin in specific populations (Zhang et al., 2020). There is evidence to support a case being made for its use in COVID-19 patients who represent older persons and/or those with symptoms indicating the infiltration of neural tissues. Importantly, both these factors are associated with significantly reduced endogenous melatonin production (Sack, Lewy, Erb, Vollmer, & Singer, 1986). Long-term melatonin supplementation in older person is further indicated from in *vivo* evidence of a significant reduction in age-related chronic, systemic inflammation. This type of inflammation is self-propagating, a powerful accelerant of cellular senescence, and represents an independent risk factor for both NCDs and CDs, including viral infections (Sack et al., 1986).

3.3.6. Quercetin

Quercetin is a phenolic compound belonging to the flavonoid class; it is a flavonol. Quercetin has been identified in wide range of different plant species. Existing data indicates quercetin is most abundant in certain medicinal plants, such as aloe vera, soft fruits, such as strawberries, and in cruciferous vegetables, such as cauliflower, and dark green leafy vegetables, such as kale (Sultana & Anwar, 2008).

Flavonoids are commonly understood to function as an anti-oxidant within biological systems, and quercetin has particularly well-established efficacy in the prevention of hydrogen peroxide (H_2O_2) induced cellular damage (Chow, Shen, Huan, Lin, & Chen, 2005).

Over time, quercetin has been widely reviewed to exhibit a range of additional properties, including functionality as an anti-inflammatory, anti-carcinogenic (anti-proliferative and pro-apoptotic) and anti-microbial agent (Karak, 2019).

Data relating to the anti-viral activity of quercetin is in short-fall and does not include a comprehensive assessment of potentially undesirable effects in other systems. With regard to the potential therapeutic utility of quercetin as an anti-oxidant in coronavirus disease; in the modulation of oxidative damage induced by the host immune response to infection, several factors must be considered. Whilst elevated levels of H_2O_2 have been linked to increased viral replication, tissue damage and disease progression in COVID-19 patients (Qin et al., 2020), low levels of H_2O_2 are generally found to be beneficial in combatting viral infections, including COVID-19, according to the mitohormetic concept of immune response (Gebicki & Wieczorkowska, 2020). Furthermore, the anti-oxidant activity of quercetin is only demonstrable in conjunction with the presence of sufficient concentrations of reduced glutathione peroxidase, without which it functions instead as a pro-oxidant (Markus, Fernandes, Kinker, da Silveira Cruz-Machado, & Marçola, 2018; Yuce & Kocabay, 2020)

Quercetin has been conjectured to have potential applications in the early stages of viral infection based on certain mechanisms of action identified in *vitro* in relation to other respiratory viruses. Much of this

conjecture comes from healthcare professional and is not supported by scientific data. One example relates to prior findings of therapeutic action of quercetin against a range of influenza A viruses, as it has been demonstrated to inhibit viral infiltration into target cells by binding to the HA2 subunit of the viral glycoprotein hemagglutinin surface protein (Wu et al., 2016). Whilst some have conjectured the therapeutic utility of quercetin in COVID-19 based on this finding, there is no data to support this. Furthermore, coronaviruses express a variant of this protein which has a different structure: the hemagglutinin-esterase glycoprotein, shared instead with influenza C viruses (Zeng, Langereis, Van Vliet, Huizinga, & De Groot, 2008).

There is however evidence from an emergent in *vitro* investigation to support the role of specific quercetin derivatives in the inhibition of SARS-CoV-2 main protease (MPro), required for viral protein assimilation, and toll-like receptors (TLRs), which trigger host inflammatory responses. In particular, rutin, or quercetin-3-rutinoside, a quercetin derivative, has been recently shown to form a stable interaction with SARS-CoV-2 MPro and TLRs 2, 6 and 7, resulting in their inhibition (Hu et al., 2020). Further investigation is required to validate the safety and efficacy of rutin, with a view of the dose-response relationship, in *vivo*.

Whilst epidemiological data is strongly indicative of the role of dietary quercetin in disease prevention, its bioavailability from natural sources is contested. The available data suggests that these inconsistencies primarily result from the fact that quercetin from natural sources takes many different forms (all of which are bound to a sugar moiety; as glycosides), corresponding to varying levels and rates of uptake, as well as the use of assays which lack sensitivity to all forms. Comprehensive analyses have revealed quercetin contained within food (in glycosidic form) to have a long half-life (12 h) in circulation and accumulable in plasma, due to a relatively low rate of elimination (Hollman et al., 1997).

Since the dose-response relationship between the different forms of quercetin and their effects on disease processes have not yet been determined, supplemental formulations which offer enhanced and reproducible levels of uptake have typically been used to investigate its biological properties.

At supraphysiological concentrations (associated with supplemental intake), quercetin and other flavanols have been identified to function as endocrine disruptors. In this connection, quercetin has been demonstrated to act as a potent progesterone antagonist. This presents potential complications, particularly for women with reproductive capacity, since progesterone is required to oppose estrogen and casts a clear shadow over the ad-hoc use of supplemental quercetin. This is evidenced by studies which have identified high-dose supplemental quercetin as an independent risk factor for endometrial cancer (Nordeen, Bona, Jones, Lambert, & Jackson, 2013).

Importantly, supraphysiological concentrations of quercetin are not associated with an increased risk of breast cancer, which is also understood to be caused by unopposed estrogen. This is because progesterone has differential effects on tissues, and its antagonism appears to have a greater negative impact on mucosal tissues. In this connection, progesterone and related compounds are known to have immunomodulatory effects that influence the outcome of microbial infections across a diverse range of mucosal sites, including those which line the respiratory tract and lungs (Hall & Klein, 2017). At present, our understanding of these effects are incomplete, and appear both complex and paradoxical.

In regard to infection with respiratory viruses, progesterone has been shown in *vivo* to promote certain positive outcomes, which include improved antibody responses, and are associated with a significant reduction in lung tissue damage (Mauvais-Jarvis, Klein, & Levin, 2020). In addition to reduced tissue damage, an increased rate of repair of lung tissue has been observed in *vivo* in the post infective phase, and is accounted for by the stimulation of epidermal growth factor amphiregulin (AERG) (Hall et al., 2016). Thus, progesterone is reported to limit the severity and progression of viral respiratory infections (e.g. to viral pneumonia), as well as improved recovery.

On the other hand, progesterone has been found in vitro to downregulate important innate immune responses to viral infection (e.g. natural killer cell activation) (Baley & Schacter, 1985) as well as inhibiting certain cellular anti-viral response pathways (e.g. NFkB signalling pathways) (McKay & Cidlowski, 1999). Interestingly, in *vivo* studies report progesterone to greatly increase the risk of re-infection upon second exposure (to the same strain), despite improving antibody responses (Hall and Klein., 2017). Overall, despite some inconsistencies in the data, progesterone appears to have important beneficial effects in viral infections, which are compromised by supplemental quercetin. Since dietary quercetin has good bioavailability, and since further research is needed to determine the therapeutic protocols, dose-response relationships and clinical outcomes of supplemental quercetin, it is likely wise to err on the side of caution and avoid supplemental intake of quercetin without professional guidance, especially in sexually reproductive women.

3.4. Vitamins and minerals

Essential vitamins and minerals directly or indirectly impact on all internal physiological systems. Therefore, a comprehensive understanding of the potential therapeutic advantage of modulating micronutrient status for the prevention or treatment of COVID-19 is difficult to achieve. On the other hand, U.S. vitamin sales growth today is leveling off somewhat but is still significantly high. While sales skyrocketed during the six weeks ending April 5, 2020, up 44% from that same time period in 2019, by contrast in the six weeks ending May 17, 2020, vitamin sales growth was lower, at 16% higher year-over-year.

This section examines a few select vitamins and minerals based on the relative attention they have received with regard to possible therapeutic applications in the transmission and treatment of viral infections, and the corresponding abundance of supporting data.

Additionally, all of the nutrients discussed are associated with reported widespread deficiency in those sub-groups of the general population that have been highlighted as being at greater risk of COVID-19. These comprise of persons who are clinically underweight (body mass index; BMI >18.9 kg/m^2) or overweight (BMI >24.9), the children and elderly, pregnant and lactating women, those with pre-existing medical conditions (particularly if immunosuppressed), those using drugs (prescription or otherwise) which interfere with nutrient uptake and metabolism, and those who adhere to dietary regimes which eliminate major food groups, especially vegans. In the case of vitamin D, those at high risk also include those who tend toward the avoidance of exposure to sunlight. Common causes for this avoidance outside of preference, include individual or group lifestyle choices (e.g. night shift workers, those who adopt specific styles of religious, or non-religious, attire), as well as residential (e.g. institutionalized persons) or geographic factors i. e. people who live higher up in the northern hemisphere. Those with photosensitivity also typically avoid sunlight.

Whilst improved dietary intake measures need to first always be considered, there is a strong call for some degree of supplemental intake, particularly in the sub-groups previously identified. In addition to having greater requirements, it is now well established that the current Western diet features a relatively diminished micronutrient profile, of industrially produced, or technologically processed foods, which may ultimately and paradoxically propagate the pursual of a diet sparse in micronutrient density (Aytekin, Godfri, & Cunliffe, 2019).

3.4.1. Vitamin D and C

Of all of the nutrients discussed herein, the prevalence of vitamin D, or cholecalciferol, deficiency is widely reviewed as being the most-widespread within modern industrialized countries (Sack, Lewy, Erb, Vollmer, & Singer, 1986). Current guidelines are under review by many governments worldwide, and differences in requirements as well as the need for additional supplementation across different sub-populations has been the topic of much scientific investigation of late.

Vitamin D has had a lot of attention in recent years, and is now well established as a key player in immune system function. As with the other nutrients discussed, vitamin D deficiency is also significantly linked to risk of viral infection, severity and to the functioning of the immune system more broadly (Khalili, Nasiripour, & Etminiani-Esfahani, 2010) and likely to increase during 'lock-down', since a great deal of vitamin D is synthesized by skin cells in response to direct sunlight (Grant et al., 2020).

In terms of the treatment of viral infections, it is interesting to note that vitamin D status is most consistently linked to viruses (and bacterial infections) associated with the respiratory system (Lu & Shi, 2020). In this connection, vitamin D has been demonstrated to inhibit replication and release of rhinoviruses, have direct anti-viral activity, associated with respiratory infections, and increase the antiviral function of bronchial epithelial cells (Telcian et al., 2017). Whilst the previous study refers to a non-enveloped virus, it is of note that vitamin D has been shown to have a relatively more significant inhibitory anti-viral effects against enveloped viruses (rhabdoviruses) such as the corona virus, which have enhanced cell surface adhesion capabilities that enable them to infect target cells more effectively (Beard, Bearden, & Striker, 2011). Their envelope also provides them with an additional protective outer-barrier (Lu & Shi, 2020).

In terms of dosing, 2000 I.U./day have been shown to be clearly beneficial in both the prevention and treatment of viral infections, and are not associated with any significant risk (Khalili et al., 2010). Being fat-soluble, vitamin D is naturally most abundant in organ meats, particularly in liver and kidney meat. Dairy, particularly full-fat varieties also represent an important source of intake, as are eggs. Vitamin D in its biologically active form is basically non-occurring in vegetables and so fortified foods represent the only viable non-supplemental.

Vitamin C is the vitamin most readily associated with viral infections at the level of the general public. Vitamin C is the major water-soluble anti-oxidant in mammalian systems, within which it functions in synergy with vitamin E, the principal fat-soluble anti-oxidant (Seabra et al., 2006). Pathogenic activity directly results in damage to the body's tissue and host responses to invasion propagate this damage, particularly in the acute phase in which non-specific immune responses predominate (Franz, Rammelt, Scharnweber, & Simon, 2011). Whilst maintaining oxidative capacity is important in combatting invasion by pathogens, there is data to support the role of vitamin C in both prevention and management of viral infections in humans at doses around 1000 mg–2000 mg/day. Vitamin C has consistently been demonstrated to significantly shorten the duration of viral infection (Hemilä & Suonsyrjä, 2017). The inconsistency in reports may arise from differences in assessment of continued infection, as there is evidence to support a marked reduction in symptoms (e.g. 85%), particularly more severe symptoms, even when compared to control groups using traditional cold & flu medication (Hemilä, 2017).

Vitamin C has been indicated to function in the prevention and treatment of viral infections through a number of predominantly indirect mechanisms. In terms of prevention, it is important to note that vitamin C is involved in the structure and functioning of the nasal and gastric mucosa (e.g. in controlling the secretion of mucus). Vitamin C is also essential to maintaining the integrity of the outer and inner epithelium. Together, these two contributions represent an important role in vital bio-physical and chemical barriers against viral infections, particularly those that are air-borne and associated with respiratory pathologies (Calder, Carr, Gombart, & Eggersdorfer, 2020). Vitamin C has also been shown to inhibit the development of virally induced pneumonia, a possible and possibly fatal secondary pathological complication of COVID-19 (Cai et al., 2015).

The antiviral action of vitamin C appears to be primarily attributable to its role in positively regulating the production of antiviral cytokines; alpha and beta interferons. When administered in the early stages of an influenza infection, this action has been demonstrated in vitro to significantly reduced viral infiltration into lung tissue, corresponding to a reduced inflammatory response in this tissue type (Boretti & Banik, 2020). Vitamin C deficiency has correspondingly been demonstrated to result in an increased lung pathology in influenza infected animals (Li, Maeda, & Beck, 2006).

Whilst the dose of 1000 mg/day is considerably higher than the guideline recommendations, it represents half of the tolerable upper limit, which is 2000 mg/day (Krinsky et al., 2000). Issues with tolerance at higher doses relate to dose-dependent gastrointestinal disturbances, and has been observed to be tolerated at much higher doses when administered intravenously. In recent times, there has been a slow but increasing trend toward the intravenous administration of high-dose vitamin C for various aims, including the treatment of viral infection. Such studies have to date reported significant reductions in duration and symptomology (Mikirova & Hunninghake, 2014). Although limited, there is emerging evidence to suggest that it may be effective in the treatment of a COVID-19 infection (Erol, 2020).

Vitamin C can be found in highest concentrations in organ meat, particularly kidneys. It can also be obtained in sizeable concentrations from dark green leafy vegetables and from fruits, particularly citrus fruits.

3.4.2. Vitamin A

Retinol, the most biologically active form of vitamin A, is in fact understood to share much functionality with vitamin C in terms of the immune system; retinol and vitamin C have common and synergistic immunological functions (Calder et al., 2020). An important example relevant to the transmission of COVID-19, is the role these vitamins play in the maintenance of the secretion, structure and function of the nasal and gastric epithelium and mucosa (Sirisinha, 2015) the two most fundamental physical barriers against infection. Interestingly, and unlike vitamin C, retinol may also provide protection against viral infection indirectly by altering the composition of the gut microbiome to promote the relative dominance of *Lactobacillus spp.,* which in turn has been found to inhibit passage of the virus into the bloodstream at the level of the gut (Lee & Ko, 2016).

The importance of vitamin A in the prevention and treatment of infection, viral or otherwise, is often overlooked. This likely arises from the risk of retinol toxicity, which typically manifests when high doses; doses greater than the tolerable upper limit (TUL), which is > 10,000 I·U, or 3000 mcg of retinol, or retinol esters (Food and Nutrition Board, 2001), are administered over a period of several months to non-deficient adults (Hathcock et al., 1990). Children require much less, and those with compromised liver function (e.g. due to hepatitis, or consumption of drugs whose metabolism 'taxes' detoxification pathways) are more easily affected. There is also a risk of teratogenicity if higher doses are taken during pregnancy.

This information at first presents an ethical minefield to the physician, and a psychological barrier to the individual, when potentially seeking to utilize retinol as an anti-viral agent. This is because, although many of the immunological functions of retinol are observed at doses below the TUL, its most potent action, which is the complete inhibition of viral replication, has only been observed at doses ranging from 20,000 to 25,000 I·U, or 6000–7500 mcg (Soye et al., 2013).

Supplementations is however strongly encouraged under two circumstances; if the person is deficient in vitamin A, *or* if the person has a severe viral infection (and does not demonstrate risk factors for this treatment).

Clinical deficiency requires biochemical testing and should be

tailored according to changing biomarkers. In addition to being more prevalent than one might expect, a diminished retinol status has consistently been identified as an independent risk factor for viral infection and is associated with increased severity of symptoms, duration and response to treatment (Ross, 2007). Supplementation protocols for virally infected people may typically involve 20,000–25,000 I·U for 7–14 days. There is no report of any toxic effects resulting from this protocol in the extant literature to date.

The richest natural sources of retinol include organ and other fatty meats, particularly liver and kidney meat (Williams, 2007). Eggs and dairy are also an important source. Vegetables and grains do not contain retinol, they contain carotenoids, which may (or may not) be subject to endogenous conversion to retinol. The conversion rate is very low, subject to a myriad of changes in the internal environment, including infection, and is relatively inefficient in certain common genotypes (Nocker, Burr, & Camper, 2007). Fortified products therefore represent the major source of intake for vegans.

3.4.3. Selenium

Along with zinc, this trace mineral is increasingly being recognised as a key nutrient in host defence systems. The importance of selenium in the functioning of the immune system is principally defined in terms of its anti-oxidant activity, particularly as a cofactor for the glutathione peroxidase (GP) enzyme system complex. The antioxidant activity of GP is relatively unparalleled by many accounts, and maintaining status and functionality is associated with a protective advantage against non-virally infected cells and reduced activation of viral cells following oxidative stress (e.g. from inflammation) in HIV models (Sappey et al., 1994). GPx and selenium also have an important role to play in protecting healthy tissue from the deleterious effects of inflammation caused by illness; by inflammation associated with a host immune response. In this connection, GPx has been shown to significantly reduce levels of cytoxicity and inflammation in lung tissue, which is resultant from infection with viruses, such as influenza, that target the respiratory system (Yatmaz et al., 2013).

It must be noted however that viruses code for their own GPx and increased expression of GPx, but not selenium, have been reported enhance viral replication, and so the cytopathological effects (Diamond, Jun, & Mansur, 2001). (Free) selenium has been demonstrated to have a significant positive impact the pathogenicity of viral infections through some rather unexpected modes of action. Most interestingly, emerging data suggests that selenium may act to modify patterns of genetic expression within viruses. In this connection, animal studies have demonstrated that deficiency causes genetic changes within specific viruses, which promote virulence in benign viral strains, and bring about enhanced virulence in already virulent strains (Beck, Levander, & Handy, 2003). This may have important applications in treatment of a virus like COVID-19, which has multiple substrains; is able to express different patterns of genetic variation.

Whilst relatively less work has been carried out to examine the potential antiviral benefits resulting from supplemental intake in non-deficient persons, recent animal studies indicate that supplementation can enhance antiviral defence systems in numerous ways, including increased production of interleukins and interferons; communication molecules which enable the identification and destruction of virally infected cells by promoting antigen presentation and activating signalling pathways for humoral intervention (Shojadoost et al., 2019). These functions represent a viable solution to the transmission of new strains of viruses, which typically take much longer to identify, and build a resistance to.

Current data indicates that a higher level of intake (typically 200 mcg/day) is required to achieve these beneficial effects in humans. Selenium can be found in high quantities in marine foods. Important non-animal sources include nuts and seeds, particularly brazil nuts and sesame seeds. Caution is required with supplementation since requirements vary. Prolonged intake at high levels is associated with risk of toxicity.

4. Conclusion and future aspects

Taking into account the consumer requirements during ongoing viral outbreak, the aim of this review was to accelerate the development of new innovations for different sectors including food, agriculture, nutraceuticals, packaging and personal care products. As the recent emerging issues such as COVID-19 pandemic showed, even the most developed contries and their manufacturers can become helpless against viral transmission. In this situation, food and packaging companies are not able to fully guarantee that their products are free from undesirable virus contagion. There is no doubt, viral contagions like and transmissions of 2019 novel coronavirus (SARS-CoV-2) from different sources created a wide safety scares on the market. Considering the unsanitary conditions of wet markets alongside with wildlife-animals in far east contries, the wet markets must be regulated again on the advise of the countries facing virus outbreak.

In order to avoid health risks, (1) most of the countries must regulate their legislations to reduce the risk of contagion until the product reaches the end consumer; (2) Developing new antiviral packaging materials or using packaging for fresh consumed foods are urgently needed; (3) The nutritional status of people unaffected, pre-disposed or infected with SARS-CoV-2 must be carefully investigated; (4) nutraceutical manufacturers must follow new direction to develop anti-SARSCoV-2 agents. This is extremely important to protect children, infant and babies agianst new viral infections that might happen in upcoming years.

Considering that individual we live in the world of viruses, not viruses in our wold; the importance of paying more attention to our eating habits is clearly understood during a crisis of this nature and magnitude. Furthermore, the requirement (medical equipments, pharmaceuticals, foods, disinfectants etc.) of individuals infected with virus should be carefully registered in the "specific governmental system" to ensure the continuity of health system. More importantly, the immunest-system status of healthcare-professionals (doctor, nurse, midwife, pharmacist, hospital workers and others) and their numbers must follow as far as possible to protect them from tranmission of virus.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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