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# Theoretical benefits of yogurt-derived bioactive peptides and probiotics in COVID-19 patients – A narrative review and hypotheses

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## Review

## Theoretical benefits of yogurt-derived bioactive peptides and probiotics in COVID-19 patients – A narrative review and hypotheses

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## ABSTRACT

The world is currently facing a frightening coronavirus disease-2019 (COVID-19) epidemic. Severity of COVID-19 presentation is highly variable among infected individuals with increasingly recognized risk factors. Although observational studies suggested lower COVID-19 severity in populations consuming fermented foods, no controlled study investigated the role of diet. Yogurt, a fermented dairy product, exhibits interesting properties related to the presence of bioactive peptides and probiotics that may play a beneficial role in COVID-19 presentation and outcome. Peptides contained in yogurt are responsible for angiotensin-converting enzyme-inhibitory, bradykinin potentiating, antiviral, anti-inflammatory, antithrombotic, and antioxidant effects. The types and activity of these peptides vary widely depending on their amino acid sequence, on the probiotics used in yogurt production and on intestinal digestion. Additionally, probiotics used in yogurt exhibit direct angiotensin-converting enzyme-inhibitory, antiviral and immune boosting activities. Since COVID-19 pathogenesis involves angiotensin II accumulation and bradykinin deficiency, yogurt bioactive peptides appear as potentially beneficial. Therefore, epidemiological investigations and randomized controlled clinical trials to evaluate the exact role of yogurt consumption on COVID-19 manifestations and outcome should be encouraged.

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## 1. Introduction

Since December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread worldwide causing life-threatening manifestations and fatalities (Phan et al., 2020). In the beginning of 2021, the coronavirus disease-2019 (COVID-19) pandemic has been responsible for more than 82 million reported contaminations and 1.2 million deaths. In parallel, an

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extraordinary number of researches has been launched to investigate risk factors, clinical manifestations, preventative options and possible anti-COVID-19 therapies. SARS-CoV-2-infected patient presentations have been reported to include pneumonia (Gattinoni et al., 2020), venous thromboembolic events related to endothelial injury and hypercoagulability (Voicu et al., 2020), excessive inflammatory conditions with cytokine storm (Jamilloux et al., 2020), immune dysregulation (Giamarellos-Bourboulis et al., 2020), oxidative stress (Delgado-Roche and Mesta, 2020), hypertension (Ruocco et al., 2020) and new onset diabetes (Yang et al., 2010).

COVID-19 presentation highly varies between individuals suggesting the presence of underlying individual risk factors that affect the disease severity (Rahman and Sathi, 2020). Some have been extensively investigated factors such as age (Kang and Jung, 2020), gender (Jin et al., 2020) and various other demographic characteristics (Nepomuceno et al., 2020). Studies have reported a higher risk for severity in adults than children (Clark et al., 2020; Zimmermann and Curtis, 2020). Additionally, health conditions associated with increased COVID-19 severity have been reported to include obesity (Hamer et al., 2020), diabetes, prior morbidities at risk of immunodeficiency and chronic cardiovascular, kidney and respiratory diseases (Centers for Disease Control and Prevention, 2020).

Surprisingly, studies investigating dietary habits as risk factor for COVID-19 variability are scarce. The US Centers for Disease Control and Prevention (CDC) stated that dietary supplementation has no direct role in COVID-19 prevention or treatment, thus only recommending special diet due to possible modular effects of vitamins and minerals on the immune system (Centers for Disease Control and Prevention (CDC), 2020). Interestingly, differences in dietary habits have been hypothesized as playing a potential role in COVID-19 geographical (Jayawardena and Misra, 2020) and fatality rate variability (Bousquet et al., 2020). Cabbage and fermented milk consumption in certain countries such as Bulgaria, Greece, Romania and Turkey, have been associated with lower mortality rates (Bousquet et al., 2020; Fonseca et al., 2020). Such findings justified the hypothesis of probable protective effects of antioxidants and angiotensin-converting enzyme (ACE)-inhibitory peptides present in fermented foods that could affect COVID-19 presentation and outcome. More recently, a case-control study including 505 participants suggested that dietary intake of dough and yogurt is able to play a significant protective role by limiting COVID-19 incidence (Odds ratios 0.62, 95%-confidence [0.44–0.87] and 0.74 [0.56–0.98], respectively) (Mohseni et al., 2021).

Many nutrients contain bioactive peptides with ACE-inhibitory effects. Such peptides are effective alternatives to the pharmaceutical ACE inhibitors (Fan et al., 2019). Most fermented dairy products exhibit ACE-inhibitory activities with various potency according to the product type (Hernández-Ledesma et al., 2004). Yogurt being a fermented dairy product is uniquely rich in bioactive peptides with potent effective multi-functions useful to beneficially influence COVID-19 manifestations (Contreras et al., 2009; Donkor et al., 2007; Guerin-Danan et al., 1998). Multiple ACE-inhibitory peptides are present in probiotic yogurts with effective effects comparable to those of synthetic ACE-inhibitors (Donkor et al., 2007). Additionally, probiotics used in yogurt industry have beneficial immunomodulatory and antiviral effects with a possible role in the prevention and alleviation of COVID-19 infection. Since yogurt is more widely studied than any other dairy product, we aimed to review its properties that may beneficially alter COVID-19 pathogenesis, expression and outcome, reporting the characteristics, potency and stability of the different bioactive peptides involved.

The three main electronic databases (Pubmed, Embase and Google Scholar) were searched for the 1990/01–2020/12 period

using the following keywords (“Yogurt” OR “Probiotics”) AND (“COVID-19” OR “SARS-Cov-2” OR “Renin-angiotensin” OR “Kinin-kallikreine”). Our research was limited to the available English reports (abstracts or full texts). We selected all reports (original and review articles) focusing on the pathophysiological mechanisms and potential benefits in COVID-19 patients.

## 2. Reported health effects of yogurt

Yogurt, a dairy product produced by milk fermentation, contains lactic acid bacteria (LAB) which ferment lactose (producing lactic acid) and affects milk peptides and proteins (Algaron et al., 2004). Being a dairy product, yogurt is rich in variable minerals such as calcium, magnesium, potassium, and zinc, and vitamins such as vitamin B. Yogurt is also a good source of various other nutrients and energy. Interestingly, higher levels of proteins, vitamins and minerals have been reported in yogurt than milk, supporting its role in improving nutritional status and health of older adults and possibly healthy and active aging (El-Abbadi et al., 2014).

The fermentation process in yogurt includes complex reactions resulting in different fermentation by-products including enzymes. They activate inert milk proteins (e.g., albumins and casein) to bioactive peptides providing yogurt with functionalities that lack in non-fermented dairy products (Donkor et al., 2007). Multiple nutritional and health benefits of yogurt consumption have been attributed to these bioactive peptides including antihypertensive (Contreras et al., 2009; Hata et al., 1996), ACE-inhibitory (Donkor et al., 2007; Nielsen et al., 2009), immunomodulatory (Coste et al., 1992), anti-inflammatory (Guerin-Danan et al., 1998; Yoon et al., 2019), antioxidant (Gjorgievski et al., 2014; Lin and Yen, 1999), antithrombotic (Rojas-Ronquillo et al., 2012), platelet aggregation-inhibitory (Jolles et al., 1986) antimicrobial (López-Expósito et al., 2007), antiviral (Farnaud and Evans, 2003), anticancer (Rea et al., 2018), antidiabetic (Barengolts et al., 2019) and dietary nitrogen absorption regulatory effects (Gaudichon et al., 1994). Interestingly, yogurt has been reported to enhance resistance to upper respiratory tract infections (de Araujo et al., 2015; Fujita et al., 2013; Guillemard et al., 2010; Pu et al., 2017; Y. Wang et al., 2016), prevent common cold and influenza (Lehtoranta et al., 2014; Makino et al., 2010; Y. Yamamoto et al., 2019) and treat acute gastroenteritis and diarrhea (Dinleyici et al., 2012; Szajewska et al., 2013).

Many of these reported effects could appear of interest in COVID-19 patient management. However, each peptide from yogurt have multifunctional properties and activities depending on its amino acid sequence (Meisel and FitzGerald, 2003; Tagliazucchi et al., 2015). One supplemental issue is that health benefits have been reported based on different types of yogurt. Therefore, separating and identifying the useful peptides and studying the molecular mechanisms of their bioactivity and pharmacodynamics are crucial to consider potential clinical applications.

## 3. Yogurt bioactive ACE-inhibitory peptides

Various bioactive peptides derived from different yogurt types have been separated and sequenced (Table 1). Antihypertensive ACE-inhibitory peptides exhibit variable amino acid sequences including Val-Pro-Pro (VPP), Ile-Pro-Pro (IPP), Tyr-Pro, Lys-Val-Leu-Pro-Pro-Gln, Thr-Tyr-Lys-Glu-Glu, Tyr-Gln-Glu-Pro-Va1-Leu, Ser-Leu-Pro-Gln-Asn, Arg-Ile-Asn-Lys-Lys, Ala-Arg-His-Pro-His, Phe-Phe-Val-Ala-Pro (CEI5), Ala-Val-Pro-Tyr-Pro-Gln-Arg (CEIβ7) and Phe-Phe-Va1-A1a-Pro-Phe-Pro-G1u-Va1-Phe-G1y-Lys (CEI12) (Bousquet et al., 2020; Contreras et al., 2009; Donkor

**Table 1**  
The main milk-derived bioactive peptides and their reported activities.

Milk proteins	Bioactive peptide sequence	Enzymes and LAB involved in their production	Reported activities	Reference
β-casein	Val-Pro-Pro	<i>Lactobacillus helveticus</i> <i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i> <i>Streptococcus thermophilus</i>	ACE inhibition	(Donkor et al., 2007; Mohanty et al., 2016)
	Ile-Pro-Pro	<i>Lactobacillus helveticus</i>	ACE inhibition	(Seppo et al., 2003)
	Lys-Val-Leu-Pro-Val-Pro-(Glu)	<i>Lactobacillus helveticus</i>	ACE inhibition	(Mohanty et al., 2016)
	Asp-Lys-Ile-His-Pro-Phe, Tyr-Gln-Glu-Pro-Val-Leu	<i>Lactobacillus rhamnosus</i>	ACE inhibition	(Mohanty et al., 2016)
	Tyr-Gln-Glu-Pro-Val-Leu-Gly-Pro-Val-Arg-Gly-Pro-Phe-Pro-Ile-Ile-Val	Pepsin	ACE-inhibition Thrombin inhibition	(Rojas-Ronquillo et al., 2012)
	Leu-Asn-Val-Pro-Gly-Glu-Ile-Val-Glu	<i>Lactobacillus casei</i> Shirota	ACE inhibition	(Gobbetti et al., 2000)
	Asn-Ile-Pro-Pro-Leu-Thr-Gln-Thr-Pro-Val	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i>	ACE inhibition	(Gobbetti et al., 2000)
	Leu-Asn-Val-pro-Gly-Glu-IleVal-Glu	ND	ACE inhibition	(Gobbetti et al., 2000)
	Pro-Pro-Leu-Thr-Gln-Thr-Pro-Val	ND	ACE inhibition	(Gobbetti et al., 2000)
	Tyr-Gln-Glu-Pro-Val-Leu	<i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i> <i>Streptococcus thermophilus</i>	ACE inhibition	(Donkor et al., 2007)
	Phe-Phe-Va1-A1a-Pro-Phe-ProG1u-Va1-Phe-G1y-Lys (CEI12)	Trypsin and proline-specific endopeptidase	ACE inhibition Bradykinin potentiation	(Donkor et al., 2007)
	Phe-Phe-Val-Ala-Pro (CEI <sub>5</sub> )	Trypsin and proline-specific endopeptidase	ACE inhibition Bradykinin potentiation	(Donkor et al., 2007)
	Ala-Val-Pro-Tyr-Pro-Gln-Arg (CEIβ7)	Trypsin and proline-specific endopeptidase	ACE inhibition Bradykinin potentiation	(Donkor et al., 2007)
	Tyr-Pro-Phe-Pro-Gly-Pro-Ile	ND	Opioid agonist activity ACE inhibition Immunomodulation	(Nagpal et al., 2011)
	Tyr-Gln-Gln-Pro-Val-Leu-Gly-Pro-Val-Arg	ND	ACE inhibition Immunomodulation	(Nagpal et al., 2011)
Tyr-Pro-Phe-Pro, Ala-Val-Pro-Tyr-Pro-Gln Arg, Thr-Thr-Met-Pro-Leu-Trp	<i>Lactobacillus GG</i> Pepsin and trypsin	Opioid agonist activity ACE inhibition Immunomodulation	(Mohanty et al., 2016)	
k-casein	Ala-Arg-His-Pro-His	<i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i> <i>Streptococcus thermophilus</i>	ACE inhibition	(Donkor et al., 2007)
	Val-Ile-Gly-Ser-Pro-Pro-Glu-Ile-Asn	<i>Lactobacillus lactis</i> ssp. <i>cremoris</i>	ACE inhibition	(Gobbetti et al., 2000)
	Ser-Pro-Pro-Glu-Ile-Asn	<i>Lactobacillus lactis</i> ssp. <i>cremoris</i>	ACE inhibition	(Gobbetti et al., 2000)
	Ala-Arg-His-Pro-His-Pro-His-Leu-Ser-Phe-met	<i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i>	Anti-oxidative activity	(Mohanty et al., 2016)
	Met-Ala-Ile-Pro-Pro-Lys-Lys-Asn-Gln-Asp-Lys Ser-Arg-Tyr-Pro-Ser-Tyr-OH	ND ND	Antithrombotic activity Opioid antagonist activity	(Gobbetti et al., 2000) (Gobbetti et al., 2000)
αS1-casein	Thr-Thr-Met-Pro-Leu-Trp	ND	ACE inhibition Immunomodulation	(Gobbetti et al., 2000)
	Tyr-Lys-Val-Pro-Gln-Leu	ND	ACE inhibition	(Gobbetti et al., 2000)
	Arg-Tyr-Leu-Gly-Tyr-Leu	ND	Opioid agonist activity	(Gobbetti et al., 2000)
	Tyr-Leu-Gly-Tyr-Leu-Glu	ND	Opioid agonist activity	(Gobbetti et al., 2000)
	Val-Ala-Pro-Phe-Pro-Glu-Val-Phe	Pepsin	ACE inhibition Anti-oxidative activity	(Contreras et al., 2009)
	Arg-Tyr-Leu-Gly-Tyr	Pepsin	ACE inhibition Anti-oxidative activity	(Contreras et al., 2009)
αS2-casein	Tyr-Gln-Lys-Phe-Pro-Gln-Tyr	Pepsin	ACE inhibition Anti-oxidative activity	(Contreras et al., 2009)

ACE, angiotensin-converting enzyme, LAB, lactic acid bacteria, ND, not determined.

et al., 2007; Gobbetti et al., 2000; Maeno et al., 1996; Maruyama et al., 1985; Mohanty et al., 2016; Nagpal et al., 2011; Nakamura et al., 1995; Seppo et al., 2003; Tuomilehto et al., 2004; J. Wang et al., 2015; N. Yamamoto et al., 1999). All these bioactive peptides originate from the enzymatic degradation of casein during food processing and gastrointestinal digestion (Lebrun et al., 1995; Maruyama et al., 1985). They exhibit variable ACE-inhibitory potency with additional alternative antihypertensive mechanisms such as bradykinin-potentiating effects as suggested by the onset of hypotensive effects at concentrations lower than their effective ACE-inhibitory concentrations determined *in vitro* (Foltz et al., 2007).

Originally, the first ACE-inhibitory peptides were snake venom-derived bradykinin-potentiating peptides (BBPs) (Ondetti et al., 1971). Thereafter, such peptides were separated from bovine caseins and among plants and other food proteins (Yamamoto, 1997). Interestingly, amino acid sequences of snake venom-derived BBPs have been identified in the casein protein chains as inactive forms. They have been shown to typically contain 5 to 13 proline-rich peptides with a pyroglutamic acid residue at the N-terminus and a proline residue at the C-terminus. BBPs with lengths of more than seven amino acids show a high content of proline residues and a specific tripeptide sequence (Ile-Pro-Pro) at the C-terminus (Ilanzer et al., 2004). The presence of proline-rich peptides within



the sequenced casein-derived peptides supports the hypothesis stating that intestinal or peptic hydrolysis gives bradykinin potentiation characteristics to these peptides. Subsequently, enhanced yogurt proteolysis exposes the formed peptides to further modifications as the formation of N-terminal pyroglutamic acids (Pinto et al., 2020). Bovine casein-derived ACE-inhibitory peptides which share the common amino acid sequence at C-terminal (Pro-Pro or Ala-Pro) with snake venom-derived BBPs, exhibit almost equal effects on ACE and bradykinin (Maruyama et al., 1985).

Bioavailability, mechanisms and potency of ACE-inhibitory peptides are mainly determined by their size and sequence (Table 1). The amino acid sequence of the bioactive peptide controls its effects (Hernández-Ledesma et al., 2004). The abundance of proline residues, as observed in the most potent ACE-inhibitory peptides generated from casein fractions, enhances ACE-inhibitory effects of the bioactive peptides (Otte et al., 2007). Generally, potent ACE-inhibitory peptides are composed of hydrophobic, positively charged and aromatic or cyclic amino acid residues at the third, second, and first position from the C-terminus, respectively (Hernández-Ledesma et al., 2004). The presence of hydrophobic amino acids such as leucine, isoleucine, phenylalanine or proline at the C-terminal position of a peptide is predictive of its ACE-inhibitory activity (Tagliacozzi et al., 2015). The C-terminal tripeptide residues play an important role in determining its potency. The aromatic amino acids and imino acid proline have been shown to be the most effective C-terminal amino acids in binding to ACE, while other amino acids (e.g., dicarboxylic residues) exhibit weak binding characteristics (Cheung et al., 1980). Of note, bioactive peptides also vary in sequence and effects according to the LAB involved in yogurt fermentation (Hernández-Ledesma et al., 2004). The main LAB involved are *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (Dellaglio, 1988). Other LAB such as other *Lactobacillus*, *Streptococcus*, *Leuconostoc*, and *Bifidobacterium* are added to produce the particularities of each given yogurt. These probiotics may have direct antioxidant activities and even improve inflammatory conditions and regulate innate immunity.

The other main factor that controls the bioavailability and potency of ACE-inhibitor peptides is the intestinal and peptic digestion. ACE-inhibitory peptides may be hydrolysed by cellular peptidases prior to their transport across the intestinal epithelium (Quirós et al., 2008). The presence of proline residue in these peptides increases their resistance to enzymatic proteolysis (Tausin et al., 2002). Small peptides containing N-terminal Tyr and/or C-terminal Pro have shown improved stability against enterocyte peptidases, thus increasing their bioavailability (Fan et al., 2019). Also, digestion may modulate yogurt-related beneficial activity by promoting the formation of more active peptides (Hernández-Ledesma et al., 2004). *In vivo* peptide activation or deactivation is controlled by endogenous enzymatic proteolysis. Some peptides may be potent *in vivo* and weak *in vitro* and vice-versa (Yamamoto et al., 1999). Generation of ACE-inhibiting peptides from intestinal peptidase-mediated digestion of meals containing protein precursors has been investigated *in vitro* using simulated gastrointestinal fluids (Manso and Lopez-Fandino, 2003; Savoie et al., 2005), and *in vivo*. This was observed with the increase in plasma Ile-Pro-Pro and Leu-Pro-Pro peptides after lactotriptide-enriched yogurt ingestion (Lebrun et al., 1995). Probiotic strains involved in milk fermentation produce oligopeptides that may generate bioactive peptides following further digestion by pepsin and trypsin (Rokka et al., 1997). Finally, *in vivo* deactivation of ACE-inhibitory peptides obtained from casein occurs in case of intestinal breakdown, thus at risk of blood pressure lowering in such situations (FitzGerald et al., 2004).

#### 4. COVID-19 pathogenesis and relation to yogurt bioactive peptides

SARS-CoV-2 cell entry is due to its interaction mediated by the spike receptor binding domain with ACE2 protein at the host cell membrane (Walls et al., 2020). This interaction induces ACE2 down-regulation (Hoffmann et al., 2020; Silhol et al., 2020). ACE2 is a monocarboxypeptidase homologue of ACE that converts angiotensin II into angiotensin 1–7. Most studies support that ACE2 down-regulation contributes to COVID-19 manifestations through its critical counter-regulatory effects on the renin-angiotensin system which dysfunction results in the accumulation of angiotensin II and deficiency in angiotensin 1–7 (Gurwitz, 2020; Miesbach, 2020).

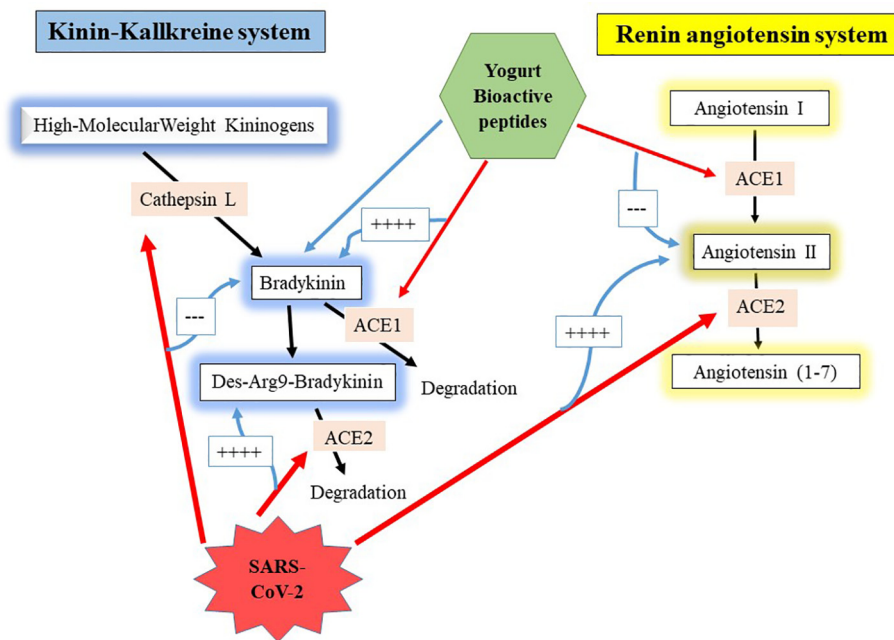
By contrast, ACE inhibition leads to a decrease in angiotensin II synthesis and angiotensin 1–7 breakdown (Deddish et al., 1998; Kuba et al., 2005). In heart failure patients, ACE inhibitors have been shown to reduce inflammatory cytokine production thus resulting in beneficial effects on the immune system (Gage et al., 2004). Using a population-based cohort study with multivariable propensity score-based regression, prior ACE inhibitors have been shown to substantially lower short-term mortality after sepsis (Hsu et al., 2020). Recently, a meta-analysis reported that prior ACE inhibitor use may have similarly reduced mortality in COVID-19 patients (Ghosal et al., 2020).

ACE2 plays a crucial role in affecting both renin-angiotensin and kinin-kallikrein systems, although this latter effect has been generally omitted (Sodhi et al., 2018; van de Veerdonk et al., 2020). We recently reviewed COVID-19-related effects on these systems, showing that snake-derived BPPs, if available and safe as a pharmaceutical drug, could act as an optimal therapy in COVID-19 patients due to its ACE-inhibitory and bradykinin-potentiating effects (Gouda and Mégarbane, 2020). As mentioned above, the reported potent ACE-inhibitory effects of yogurt-derived peptides together with their proposed bradykinin-potentiating effects may render these bioactive peptides effective to counteract COVID-19 pathogenesis and its deleterious health consequences (Fig. 1).

#### 5. Yogurt probiotics and possible benefits in COVID-19 patients

Aside from its role in producing bioactive peptides during food fermentation, the daily consumption of probiotics was suggested to be beneficial to human health by inhibiting allergy mechanisms, boosting the immune response and stimulating the antimicrobial and anti-viral defense (Bustamante et al., 2020). Debris of dead probiotic cells additionally plays a direct ACE inhibitor effect (Miremadi et al., 2014). All these benefits have been attributed to the ability of probiotics to regulate the gut bacterial ecosystem and subsequently modulate the immune system (Dargahi et al., 2019). For instance, probiotics interact with macrophages to facilitate the production of interleukin-12 which stimulates the production of interferon- $\gamma$ , a major antiviral cytokine (de Roock et al., 2011; Kitazawa et al., 1994; Kudva et al., 2011). Moreover, some probiotic strains including *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *Bulgaricus* and *Bifidobacterium bifidum* enhance interferon- $\alpha$  production by monocytes (Kitazawa et al., 1994). Interestingly, the reported immunomodulatory effects of probiotics are strain-specific (Wu et al., 2019).

Probiotics exhibit potent antimicrobial activity against viruses and bacteria causing respiratory tract infections (Kassaa, 2016). A meta-analysis of 52 published studies strongly supported the evidence that probiotics effectively contributed to prevent respiratory tract infections (Liu et al., 2018). Another meta-analysis of 23 randomized controlled trials supported that probiotics significantly



**Fig. 1.** Pathological consequences of SARS-CoV-2 effects on the renin-angiotensin and kinin-kallikrein systems and the presumed beneficial activities of yogurt-derived bioactive peptides on both systems. The red arrows refer to inhibition and the blue arrows refer to potentiation. ACE, angiotensin-converting enzyme.

**Table 2**  
Established antiviral activities of probiotics and bioactive peptides present in yogurt.

Investigated probiotics and bioactive peptides	Antiviral activity against	Methodology	References
Bioactive peptides produced by <i>Lactobacillus delbrueckii</i> WS4	SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-HKU1	<i>In silico</i>	(Chourasia et al., 2020)
Bioactive peptides derived from beta-lactoglobulin	SARS-CoV-2	<i>In silico</i>	(Çakır et al., 2021)
Bioactive peptides derived from <i>Lactobacillus plantarum</i> and <i>Bifidobacterium bifidum</i>	Enterovirus 71	<i>In vitro</i>	(Choi et al., 2010)
<i>Lactobacillus reuteri</i> Protectis	Coxsackievirus A, Enterovirus 71	<i>In vitro</i>	(Ang et al., 2016)
Probiotic metabolites of <i>Lactobacillus casei</i> and <i>Bifidobacterium adolescentis</i>	Rotavirus	<i>In vitro</i>	(Olaya Galán et al., 2016)
P18 peptide of <i>Bacillus subtilis</i>	Influenza virus	<i>In vitro and in vivo</i> (mice)	(Starosila et al., 2017)
<i>Lactobacillus gasseri</i> SBT2055	Respiratory sentential virus	<i>In vivo</i> (mice)	(Eguchi et al., 2019)

SARS-CoV-2, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle-East respiratory syndrome-related coronavirus; HCoV-HKU1, human coronavirus HKU1.

reduced the severity of respiratory tract infections in children (de Araujo et al., 2015). Probiotics have been demonstrated useful for preventing and treating influenza A H1N1 and respiratory syncytial viruses in experimental models (Eguchi et al., 2019; Kawase et al., 2010). Consumption of milk sources of probiotics significantly reduced the incidence of respiratory tract infections (Makino et al., 2010; Merenstein et al., 2010; Shida et al., 2017; Taipale et al., 2011).

SARS-CoV-2 may affect the intestinal and lung microbiota (Kopel et al., 2020; Xiao et al., 2020). Dysbiosis of beneficial bacteria and growth of opportunistic pathogens have been shown to correlate with the severity of COVID-19 (Tang et al., 2020; Zuo et al., 2020). COVID-19 patients may present intestinal microbial dysbiosis characterized by low numbers of various probiotic species such as *Bifidobacterium* and *Lactobacillus*, thus possibly requiring probiotic administration to restore the intestinal flora balance and decrease the risks related to SARS-CoV-2 infection (Xu et al., 2020).

Probiotics may help preventing and treating COVID-19 by preserving the gastrointestinal tract and lung microbiota since dysbiosis plays a major role in susceptibility to infections (Olimat et al., 2020). Diet containing probiotics may alleviate SARS-CoV-2 infection or at least the onset of complications by preserving the GI

microbiota including its structure, diversity and function (Gasmı et al., 2020). The use of fermented foods as dietary sources of probiotics to prevent or alleviate SARS-CoV-2 infection has been proposed (Olimat et al., 2020). Several trials to investigate probiotics-related efficacy to treat or prevent COVID-19 are currently ongoing (Infusino et al., 2020).

## 6. Direct antiviral effects of probiotics and bioactive peptides

Of SARS-CoV-2 proteins, the spike glycoprotein and 3-chymotrypsin-like cysteine protease (3CLpro) are the most critical proteins needed for viral cell entry and replication, respectively (Hall and Ji, 2020). The spike glycoprotein facilitates viral cell entry through the interaction of its receptor-binding domain (RBD) with human ACE2. The 3CLpro catalytically cleaves the coronavirus polyprotein at 11 conserved sites including a peptide bond between a glutamine at position P1 and a small amino acid (serine, alanine, or glycine) at position P1'. These two glycoproteins represent the major potential drug targets for coronavirus infections and were thus investigated *in silico* as possibly targeted by probiotics and bioactive peptides contained in yogurt (Table 2).

Recently, a study screened the possible inhibition of these two SARS-CoV-2 glycoproteins by 1420 bioactive peptides identified from the soy cheese peptidome produced using *Lactobacillus delbrueckii* WS4 for antiviral activity by employing the web tools, AVPPred, and meta-iAVP (Chourasia et al., 2020). Molecular docking analyses revealed that one of these peptides, the “KFVFPKQPNNML” demonstrated a strong affinity to Spike-RBD and 3CLpro of SARS-CoV-2. This peptide exhibited also the ability to interact with the Spike-RBD and 3CLpro of other  $\beta$ -coronaviruses including SARS-CoV, Middle-East respiratory syndrome-related coronavirus (MERS-CoV) and human coronavirus HKU1. Another computer-based study investigated two bioactive peptides derived from beta-lactoglobulin obtained by the treatment of goat milk whey fraction with trypsin (Ala-Leu-Pro-Met-His-Ile-Arg and Ile-Pro-Ala-Val-Phe-Lys) and showed their ability to inactivate both SARS-CoV-2 and ACE (Cakir et al., 2021).

Table 2 reviews additional yogurt bioactive peptides and probiotics tested *in vitro* and *in vivo* with direct antiviral activities including against viruses sharing some mechanistic similarities with SARS-CoV-2. Yogurt fermented with *Lactobacillus plantarum* and *Bifidobacterium bifidum* exhibited high anti-enterovirus 71 activity (Choi et al., 2010). *Lactobacillus reuteri* Protectis displayed a dose-dependent antiviral activity against Enterovirus 71 and Coxsackievirus type A strains 6 and 16 but not against Coxsackievirus type B strain 2 (Ang et al., 2016). Probiotic metabolites of *Lactobacillus casei*, and *Bifidobacterium adolescentis* were shown able to reduce protein liberation and calcium release in an intracellular model on MA104 cells, suggesting an effective antiviral activity against rotavirus infection (Olaya Galán et al., 2016). P18 peptide produced by the probiotic strain *Bacillus subtilis* showed complete inhibition of influenza virus *in vitro* and similar protective effect in mice to that of oseltamivir phosphate (Starosila et al., 2017). Finally, *Lactobacillus gasseri* SBT2055, a probiotic lactic acid bacterium, was shown able to prevent influenza A and respiratory syncytial virus infections in mice (Eguchi et al., 2019).

## 7. Conclusions and perspectives

Yogurt contains several bioactive peptides with reported benefits including antiviral, antioxidant, anti-inflammatory, antithrombotic and chest infection preventive effects. These peptides are effective through their ACE-inhibitory and possible bradykinin potentiating activities. These peptide activity and potency vary widely depending on their amino acid sequence, the probiotics used in yogurt fermentation, and the effect of intestinal digestion. As per our review, these effects are beneficial in COVID-19. We hypothesized that yogurt consumption may influence COVID-19 presentation and outcome. Further epidemiological studies evaluating the exact role of yogurt consumption on COVID-19 severity should be encouraged. Similarly, randomized controlled clinical studies evaluating the effects of special yogurt-enriched diet protocols on moderate-to-severe COVID-19 patients admitted to the hospital should be evaluated.

## 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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