International Journal of Current Medical and Biological Sciences Volume 1, Issue 2:58-68:2021
Review

Foods That Improving the Immune System against Covid-19 and Its Infectiousness

Covid-19 ve Bulaşıcılığına Karşı Bağışıklık Sistemini İyileştiren Gıdalar

Eyyüp Karaogul[1]*, İbrahim Hayoğlu[1], Akif Cicek[1], Mustafa Beğenç Taşcanov[2], Zülkif Tanrıverdi[2], Sümeyra Cicek[3], Berika Hayoğlu[4]

[1] Harran University Faculty of Engineering, Food Engineering Department, Sanliurfa/Türkiye
[2] Harran University Department of Cardiology, Sanliurfa/Türkiye
[3]Igdır University Faculty of Engineering, Bioengineering and Sciences Deparment Igdır/Türkiye
[4]Acıbadem University, Faculty of Health Sciences, Department of Nutrition and Dietetics, İstanbul/Türkiye

***Corresponding Author:**
Assoc.Prof. Eyyüp KARAOĞUL
Harran University Faculty of Engineering, Food Engineering Department, Sanliurfa/Türkiye

ORCID: 0000-0001-8162-6838

E-mail: e.karaogul@harran.edu.tr
Received: 21.12. 2021
Published: 24.12.2021

Abstract

Background: The main aim of this study is to comment nutrients that can potentially increase immunity to coronavirus (COVID-19) and lower the risk of getting sick.

Methods: Severe acute respiratory syndrome associated with coronavirus [SARS-CoV] and SARSCoV-2 pathogenic to human enter their target cells such as lung, intestine, kidney and blood vessels via angiotensin converting enzyme 2 (ACE2) indicated by epithelial (Fang et al., 2020, Wan et al., 2020). Moreover, in COVID-19 patients, the level of Protein C in the cell was decreased after infection. (Panigada et al.). These conditions can cause a cross-linked fibrin clot. In this case, it may be possible to lower the risk of COVID-19 by inhibition of ACE2 and higher immunity of protein C. Levels of ACE2 and Protein C are important in this respect. While ACE2 and Protein C levels can control any nutrient, the risk can be significantly reduced. Thus, the effects of ACE2 and Protein C were evaluated from the literature.

Results: The level of Angiotensin converting enzyme 2 is significantly effective for protection from coronavirus disease (COVID-19). In this case, foods that provide ACE2 inhibition were evaluated in this study. In Table 1 shows a list of foods that inhibit angiotensin converting enzyme 2 (ACE2).

Conclusion: Foods that can strengthen immunity against coronavirus (COVID-19) and reduce the risk of disease are of great importance in this period. In addition, it may be important to slow down the factors that cause coronavirus. ACE2 and Protein C levels are important in this regard. If any nutrient can control ACE2 and Protein C levels, the risk can be significantly reduced. It was noticed that the immunity against COVID-19 could be improved with Cuttlefish, Sardinelle (Sardinella aurita), Rohu (Labeo rohita), Grass carp, European Carp (Cyprinus carpio L.), Cirrhinus mrigala, Salmon (Salmo salar), Katsuo-bushi, Acetes indicus, Common Oat (Avena sativa), Goat milk protein, Kacang goat meat, Milk protein, Yoghurt beverages with quinoa, Lupin and Other legumes, Whey protein, Mungbean, Walnut protein, Peanut protein, Corn germ protein, Sunflower (Helianthus annuus L.) protein, Antioxidants and fish oil, Wheat germ protein, Rice bran protein, Sesame (Sesamum indicum L.), Egg yolk and Cucurbita ficifolia, Egg protein, Egg white protein, Fucus spiralis, Cannabis sativa L., Sweet sorghum grain protein, and Onion seeds.

Key words: COVID-19, nutrients food, immunity, ACE

Introduction

COVID-19, which emerged in the city of Wuhan, China, is a rapidly spreading disease transmitted from person to person by droplet infection. The coronavirus epidemic, which started as an epidemic at first, later turned into an endemic and was later declared a pandemic by the World Health Organization. It is of great importance to comply with the hygiene rules and to have an adequate and balanced diet, both during the pandemic process and the mutation period after it (1, 2).

Health risks still remain important in our country, where the mutation process is experienced after the second and third stages of the coronavirus epidemic (Covid-19). While it was previously stated that only the elderly and individuals with health problems were at risk, today it has become more contagious due to mutated viruses, and accordingly, it is seen that young people and children are also caught in the epidemic and undesirable results leading to death are encountered (3).

Although there is no drug that can prevent or treat the transmission of coronavirus so far, it is not yet clear that the vaccine will bring a complete solution (4). Therefore, one of the greatest measures that can be taken today is to keep our immune system strong and not to get sick as much as possible. For this, it is necessary to have a healthy and balanced diet as well as regular sleep and physical activity (5).

Especially in nutrition, it should be preferred to consume more foods containing elements that increase body resistance and strengthen the immune system. In terms of a balanced diet, it is of great importance that the foods consumed are rich in protein, fiber, vitamins, minerals and especially antioxidants (6).

Regular nutrition is very important during and after the infection in the body. Especially when infections turn into a febrile illness, they damage the body, creating a need for more energy and nutrients. Therefore, a healthy diet is very important both during and after the COVID-19 illness. While no food has been able to prevent COVID-19 so far, it is important to have a healthy and balanced diet and a strong immune system (7).

Angiotensin converting enzyme 2 or ACE2 for short; It is a kind of enzyme found in the lungs, arteries, heart, kidneys and intestines, which is attached to the outer surface of the cells (cell membrane) (8).

The transmembrane protein ACE2 serves as the main entry point for cells and causes various types of coronavirus to infiltrate into cells. The S1 protein is located at the ends of SARS-CoV and SARS-CoV2. When this protein binds to the enzymatic portion of ACE2 on the cell membrane, both virus and enzyme enter the cell by endocytosis. This event led to the idea that it could help curb the coronavirus by reducing the amount of ACE2 in cells (8).

It has been realized that ACE2 and protein C can be controlled and thus the risk can be reduced with some nutrients, and some of these nutrients are given in Table 4.

In this paper, it has aimed to reveal the approaches between the relationships of nutrient and COVID-19 virus as well as ACE-II enzyme.

Protein

Proteins are linear polymers composed of 20 different L-alpha-amino acids (9). The different chemical properties of the side chains of amino acids determine the three-dimensional structure of proteins and therefore affect protein function (10).

Proteins are nitrogen-containing substances made up of amino acids. They serve as the main structural component of other tissues in the body, including muscles. In addition to being used to produce hormones, enzymes, and hemoglobin, proteins can also be used as a source of energy (11).

In order for proteins to be used by the body, they must be catalyzed into their simplest form, amino acids. 20 amino acids are required for human growth and metabolism. Twelve of these amino acids are non-essential amino acids that can be synthesized by our body. The other eight amino acids are essential amino acids that cannot be synthesized in our body and must be consumed in our diet (11) (Table 1).

Table 1. Bases amino acids found in the human body (12)

Essential amino acids	**Non-essential amino acids**
Phenylalanine	Glycine
Valine	Alanine
Tryptophan	Sistine
İsolosin	Tyrosine
Methionine	Aspartic Acid
Lysine	Glutamic acid
Losin	Serine
Hemi-Essential amino acids	Aspargin
Histidine	Glutamine
Arginine	Prolin

Protein C

Protein C (PC) is an important anticoagulant and antithrombotic for the human coagulation system. Protein C exerts its anticoagulant effect by inactivating FVa and FVIIIa together with protein S (PS). Protein C is found in human blood at a concentration of 4 µg/mL. In its deficiency, the risk of thrombosis in the veins is high. When these blood clots (thrombocytes) break off from the vein surface and mix with the blood stream, it can cause stroke, heart attack. A blood clot can be life-threatening if not detected and treated early (13).

Protein C (PC) is an important natural inhibitor of the human blood coagulation system. Protein C is a vitamin K-dependent glycoprotein with a molecular weight of 62,000 Daltons. Protein C is a special protein with both anticoagulant and antithrombotic functions in blood coagulation steps. Human Protein C is synthesized in the liver as a single-chain protein precursor and remains in the blood as an inactive zymogen until it is proteolytically degraded and

activated. Protein C is activated only where and when it is needed (14).

For protein C to be activated, thrombin must associate with the thrombomodulin (TM) receptor located on the endothelial cell surface. The thrombin-thrombomodulin complex formed on the endothelial cell surface binds to the inactive Protein C. Protein C becomes active as a result of thrombin-Protein C interaction. Activated protein C then complexes with protein S, a vitamin K-dependent cofactor (13) (Figure 1).

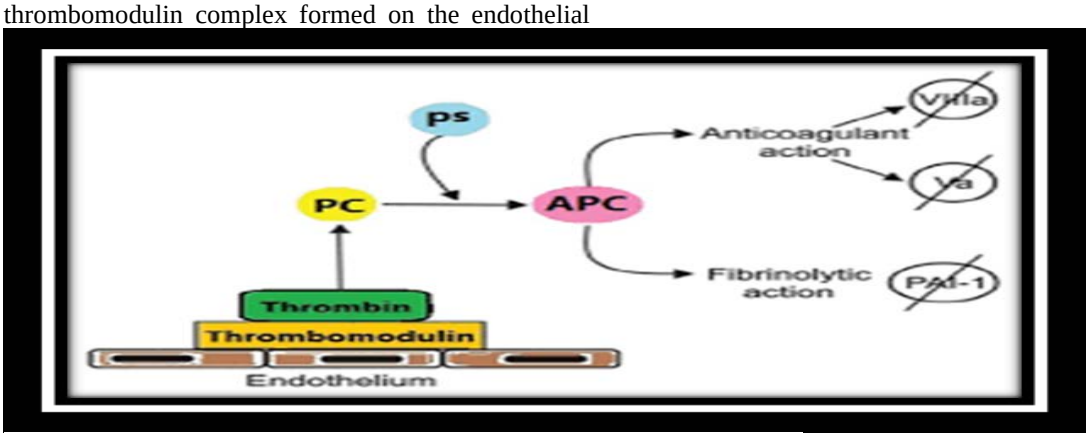

Figure 1. Model of thrombin-thrombomodulin activation of protein C (15)

Protein C is a serine protease that requires Vitamin K for its normal biosynthesis. It is a member of a vitamin K-dependent family that also includes coagulation protein factors VII, IX, X, S and Z proteins and prothrombin (16, 17) (Table 2).

Table 2. Vitamin K-dependent proteins (16)

Protein	Molecular weight (Da)	Number of polypeptide chains	Number of Gla zones	Carbohydrate content (%)	Plasma concentration (µg/mL)
Factor II	72000	1	10	8	80-90
Factor VII	50000	1	10	9-10	0.47
Factor IX	57000	1	12	17	4
Factor X	59000	2	11	15	6.4
Protein C	62000	2	9	29	4
Protein S	71000	1	11	7-8	25-35

Protein C was isolated from bovine plasma by Johan Stenflo in 1976 and was named "Protein C" because it was the third protein purified by DEAE-Sepharose. However, the function of Protein C in the physiological regulation of coagulation remained elusive for the next several years. Human plasma Protein C was purified by Kisiel in 1979 (16, 18).

Human Protein C circulates in the plasma as a zymogen and is converted to activated Protein C (APC) by specific cleavage by thrombin-bound thrombomodulin on the membranes of endothelial cells and plays a critical role in regulating the functioning of thrombin (16, 19).

Synthesis and Structural Properties of Protein C

Protein C, like all Vitamin K-dependent proteins that play a role in coagulation steps, is synthesized in the liver. This protein is synthesized as a long single-chain protein precursor consisting of 461 amino acids and is present in the blood as a two-chain inactive zymogen until it is proteolytically degraded and activated (13). The cDNA for human Protein C (hPC) encodes a protein consisting of 461 amino acids. The primary sequence of protein C is either directly detected or inferred from cDNA sequencing. Protein C is a glycoprotein with a molecular weight of 62000 Da (20). Protein C contains 23% carbohydrates and consists of 2 chains, one light (21 kDa) and the other heavy chain (41 kDa) linked by disulfide bonds (21). The structure of APC includes the interaction of the protease with the Ca2+ dependent cofactor Protein S on the membrane surface and the endothelial cell Protein C receptor (EPCR). Glutamic acid is carboxylated by reacting in the liver due to Vitamin K. This region interacts with the negatively charged phospholipid in the presence of calcium ions, and this is a prerequisite for the anticoagulant effect of APC. As protein S cofactor, it functions to regulate the anticoagulant function of APC (22) (Figure 2).

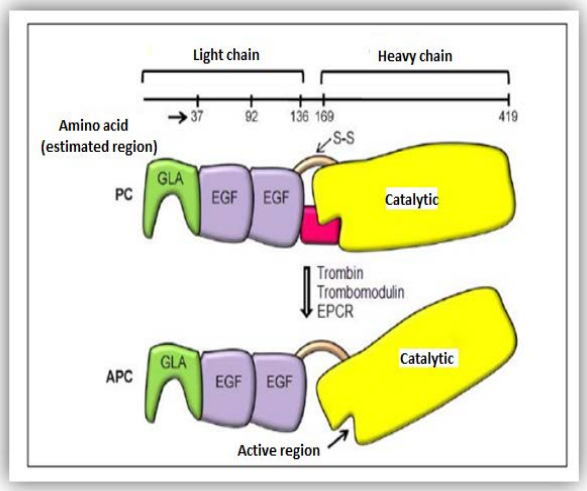

Figure 2. Protein C structure (16)

Protein C Activation

Protein C circulates in the blood as a zymogen (inactive) and is activated only where and when it is needed. For protein C to be physiologically functional, it must be converted to an active serine protease. Human Protein C activation occurs by enzymatic removal of a small activation peptide from the amino acid end of the heavy chain (21) (Figure 3).

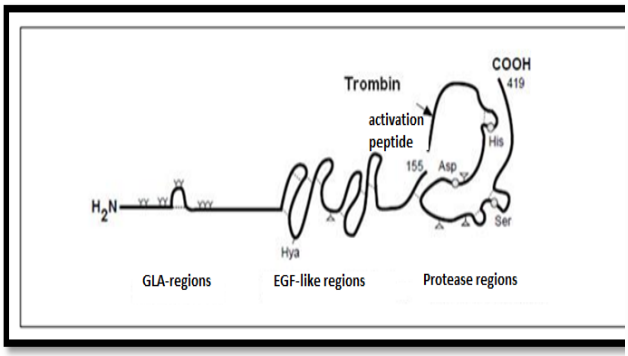

Figure 3. Human Protein C structure. Symbols: Y=Gla-sites, Hya=erytho-β-hydroxyaspartic acid, O=catalytic sites, Δ= N-linked glycosylation/glycosylation sites (16)

The Physiological Role of Protein C

All Vitamin K-dependent proteins have so far been stated to have a coagulation-related activity. In contrast, Protein C is a coagulation inhibitor and plays a critical role in regulating the functioning of thrombin (18). Many mechanisms that inhibit the spread of the coagulation process have been described on the endothelial cell surface. The anticoagulant Protein C cascade, one of the anticoagulant mechanisms, regulates blood coagulation by inactivation of Factors VIIIa and Va and increased fibrinolytic activity (23) (Figure 4).

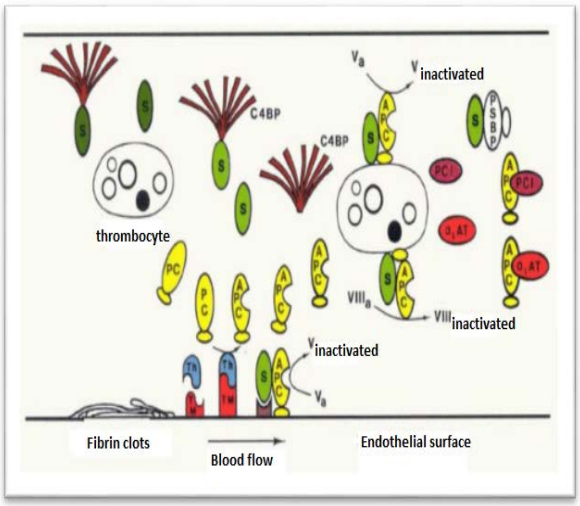

Figure 4. Formation and function of Activated Protein C (16)

Protein C Deficiency

Protein C with a half-life of 6 hours is a trace protein found in human blood at a concentration of 4 □g/mL. Serious problems occur when the amount of Protein C in the blood drops. Patients with protein C deficiency are at risk of deep vein thrombosis (DVT) and other coagulation complications as a result of tissue oxygen deprivation; some can be life threatening (13, 16) (Figure 5).

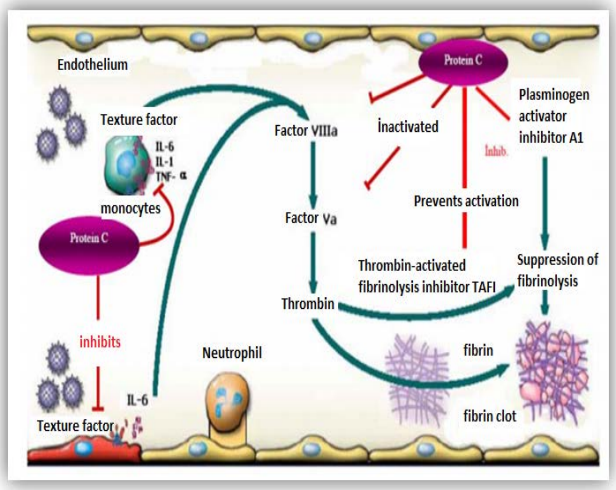

Figure 5. Protein C and the inflammation cascade (16)

PROTEIN S

The spike protein (S protein) is a diverse type I transmembrane protein with up to 1,160 amino acids for avian infectious bronchitis virus (IBV) and up to 1,400 amino acids for feline coronavirus. In addition, this protein is highly glycosylated due to the presence of 21 to 35 N-glycosylation sites. Spike proteins bind to trimers on the virion surface to have a distinctive "corona" or crown-like appearance. The ectodomains of all CoV spike proteins share the same function in two domains, an N-terminal domain called S1 responsible for receptor binding, and a C-terminal S2 domain responsible for fusion: the diversity of CoV into disordered spike proteins (S proteins) that

transform into various forms in receptor interactions. and their response to various environmental triggers of virus-cell membrane fusion (24).

Structure of Protein S

The coronavirus spike protein (S Protein) is a class I fusion protein (25, 26). The formation of an α-helix-helix structure of these fusion proteins is characteristic of the class, including the α-helix secondary structure and regions of C-terminal fragments predicted to form helices. While the S2 subunit is the most conserved of the protein, the S1 subunit can sequentially cleave between strains of even a single coronavirus. S1 consists of two subunits, the N-terminal domain (NTD) and the C-terminal domain (CTD). It acts as binding both (NTD) and (CTD) receptor binding domains (RBDs), various proteins and sugars (25) (Figure 6).

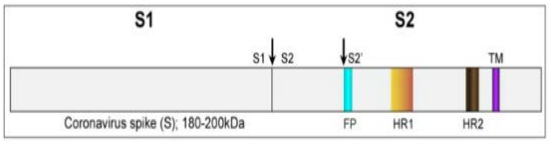

Figure 6. Severe acute respiratory syndrome (SARS)-CoV spike protein schematic (25)

Spike protein (S protein) plays a very important role in viral infection and pathogenesis. S1 binds by recognizing the receptors, and subsequent conformational changes in S2 facilitate fusion between the viral envelope and the host cell membrane. Models describing the S-mediated membrane fusion event have expanded from knowledge of S protein structures and their functions (24, 26).

Spike Glycoprotein (S) The spike glycoprotein (S), formerly called "E2", forms large, petal-shaped spikes on the virion surface. The S protein can be divided from its N-terminal end outside the envelope to its C-terminal end inside the envelope, into three structural regions: These consist of a large outer region, a transmembrane region, and a short carboxyterminal cytoplasmic region, which can be subdivided into two sub-regions, S1 and S2, respectively. The S1 subregion contains the N-terminal portion of the molecule and forms the spherical portion of the spikes. It is responsible for binding to specific receptors on the surface of appropriate cells (24) (Figure 7).

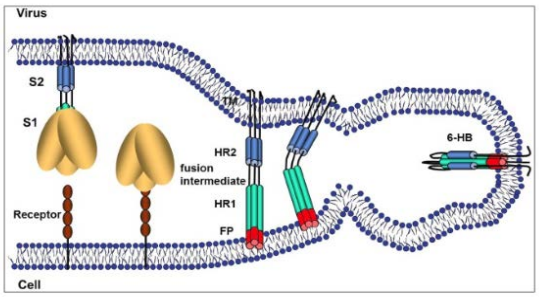

Figure 7. Schematic illustration of CoV S protein-mediated membrane fusion (25)

The S glycoprotein has adapted to species-specific differences in the host cell receptor (ACE2). The S protein binds to the specific receptor on the host cell, fusing the viral envelope with the host cell membrane; it also induces cell-cell fusion. Expression of the S protein alone can induce fusion of receptor-bearing cells (25) (Figure 8).

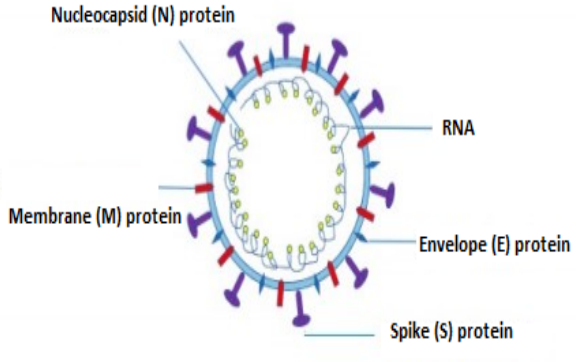

Figure 8. Schematic structure of the coronavirus(27)

The S glycoprotein is the primary factor in virus recognition by the immune system of the infected host. It is the chief inducer of neutralizing antibodies produced during infection. In conclusion, the S protein is considered as a multifunctional protein that plays an important role in cell tropism, host selection, neutralizing antibody formation, and the pathogenesis and biology of CoV infections (25) (Table 3).

Table 3. S protein-based vaccines against SARS-CoV (28)

Category	Advantages	Disadvantages
Vaccines*		
Full-length S protein	Promotes protective immunity as well as neutralizes antibody and T-cell responses	May cause unhelpful immune responses (64,65)
DNA-based	Promotes immunoglobulin G, neutralizing antibody and T cell responses and/or protective immunity	May have low efficacy in humans; repeated doses may cause toxicity (59,131)
Viral vector-based	Promotes neutralizing antibody responses, protective immunity and/or T-cell responses	May cause ADE effect, possibly due to pre-existing immunity (60,61,65)
Recombinant S protein-based	Promotes high neutralizing antibody responses and protective immunity	Basically, humoral responses; needs repeated doses and adjuvants (62)
RBD	Extremely potent neutralizing antibody promotes T-cell responses and protective immunity	Not identified (70-73)

DNA-based	Neutralizing antibody promotes T-cell responses and/or protective immunity	May cause low responses that cannot neutralize mutants (132-134)
Viral vector-based	Promotes neutralizing antibody responses, protective immunity and/or T-cell responses	Possible genomic integration of external DNA; viral vector instability (75,135)
Recombinant RBD protein-based	It is more reliable and effective than other RBD vaccines; promotes neutralizing antibody and T cell responses, protective immunity and cross protection	Requirement to repeat doses and adjuvants (26,70-72)

ACE-II ENZYME

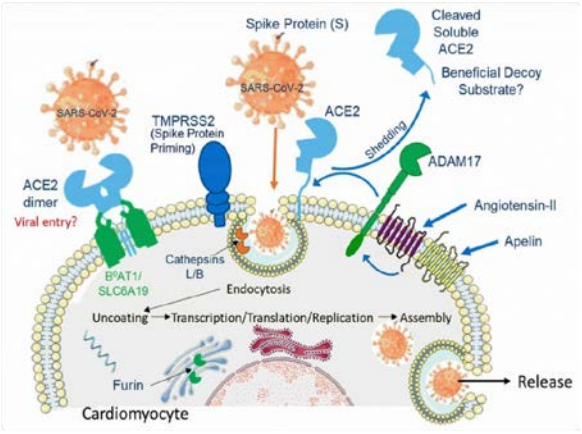

Figure 9. Schematic diagram of key proteins predicted to be expressed by human cardiomyocytes from RNASeq data (29)

Angiotensin converting enzyme 2 or ACE2 for short; It is an enzyme attached to the outer surface (cell membrane) of cells in the lungs, arteries, heart, kidneys, and intestines (30). ACE2 accelerates the hydrolysis of angiotensin II hormone, which is a vasoconstrictor, to angiotensin (1-7), thereby reducing blood pressure. In addition, ACE2 acts as the entry point into cells for some coronaviruses. The human version of the enzyme is called hACE2 (31) (Figure 9).

ACE2 counteracts the activity of angiotensin converting enzyme (ACE) by decreasing the amount of angiotensin-II and increasing. In this way, it has become a promising drug target in the treatment of cardiovascular diseases (32). Angiotensin converting enzyme 2 is a zinc-containing metalloenzyme found on the surface of endothelial cells and other cells.

ACE2 is a single-pass type I membrane protein with an enzymatically active domain on the surface of cells in lung and other organ tissues (30). The extracellular domain of ACE2 is cleaved from its transmembrane domain by another enzyme known as ceddase. Subsequently, the soluble protein obtained is released into the blood stream and excreted through the urine (33) (Figure 10).

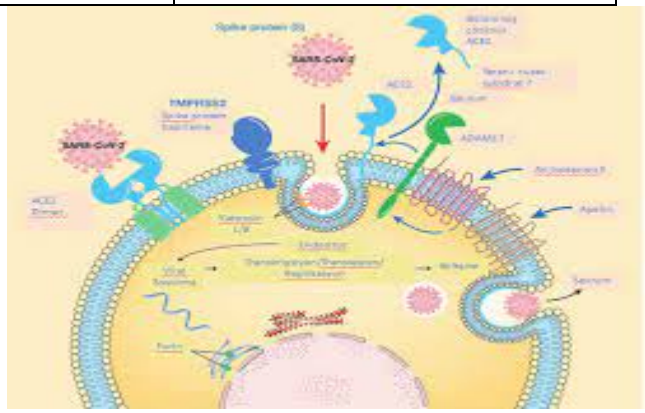

Figure 10. Life cycle of SARS-CoV-2 (34)

Position in the Body

ACE2 is known to be found in many organs. The most common sites of ACE2 binding are the cell membrane of alveolar epithelial cells of the lung, enterocytes of the small intestine, arterial and venous endothelial cells, and arterial smooth muscle cells in many organs. ACE2 mRNA is also found in the cerebral cortex, striatum, hypothalamus, and brain stem (35).

The main task of ACE2 is to act as a counterbalance to ACE. The ACE enzyme cleaves the hormone angiotensin I to the vasoconstrictor angiotensin II. ACE2 in turn cleaves the carboxyl-terminal amino acid phenylalanine from angiotensin II and hydrolyzes it to the vasodilator angiotensin (1-7). In addition, ACE2 can cleave many other peptides (36).

Entry Point to Human Body for Coronavirus

The transmembrane protein ACE2 serves as the main entry point for cells and causes various strains of coronavirus to infiltrate into the cell. To explain in more detail, when the S1 protein, located at the ends of SARS-CoV and SARS-CoV2, attaches to the enzymatic domain of ACE2 on the cell membrane, both the virus and the enzyme are taken into the cell by endocytosis (37). In addition, with this entry process, the production of the S protein in the virus begins to be carried out by the serine protease in the cell. This inhibition is considered a potential therapeutic and is currently being studied (38).

This led to the idea that coronavirus could be prevented by reducing the amount of ACE2 in cells. As an antithesis to this, it has been stated that ACE2 has a protective effect against viral lung injury by increasing the production of vasodilator angiotensin 1-7 (39).

A systematic review and meta-analysis published July 11, 2012 found that “the use of ACE inhibitors resulted in a 34% reduction in pneumonia risk compared to controls. Additionally, in patients at high

risk of pneumonia, particularly those with stroke and heart failure, use of ACE inhibitors It has also been shown that the risk of pneumonia is reduced by treating it (40).

WHAT IS ACE-II INHIBITOR

ACE is defined as an important enzyme in the renin-angiotensin system (RAS), which plays an important role in the regulation of blood pressure (41). RAS, which plays a role in the regulation of fluid balance and blood pressure in the body, is a proteolytic system and is one of the important metabolic pathways that are effective in the control of the cardiovascular system. In RAS, angiotensinogen protein synthesized from the liver is converted to angiotensin-I by the action of the renin enzyme secreted by the kidney. Angiotensin-I is converted to angiotensin-II, which has vasoconstrictor properties, by ACE produced in the lungs (42). The presence of angiotensin II causes an increase in blood pressure and stimulates the secretion of aldosterone. As a result, inhibition of angiotensin II formation with ACE-inhibitors prevents vasoconstriction and lowers blood pressure (43).

Therefore, ACE inhibition activity appears to be a useful method in the treatment of hypertension (44). Hypertension, a common condition worldwide, is a controllable risk factor associated with cardiovascular disease. The use of food protein-derived natural ACE inhibitor peptides in the treatment of hypertension is considered a safer alternative since they do not have side effects (45).

With this; It is reported that bioactive peptides of natural origin generally show activity at higher concentrations than their synthetic counterparts, and functional foods containing these peptides are recommended to be used for disease prevention rather than disease treatment (46).

According to ACE-II enymes, the nurtition sources that ımproving the ımmune system against Covid-19 were illustrated in Table 4.

Table 4. The nutrition food as caused inhibition of angiotensin-converting enzyme 2

Nutrition Sources	Nutrition Sources
Cuttlefish (47, 48)	Mungbean (71)
Sardinelle (*Sardinella aurita*) (49-51)	Walnut protein (72, 73)
Rohu (*Labeo rohita*) (52)	Peanut protein (74)
Grass carp (53)	Corn germ protein (75)
European Carp (*Cyprinus carpio* L.) (54)	Sunflower (*Helianthus annuus* L.) protein (76)
Cirrhinus mrigala (55)	Antioxidants and fish oil (77)
Salmon (*Salmo salar*) (56)	Wheat germ protein (78)
Katsuo-bushi (57)	Rice bran protein (79)
Acetes indicus (58)	Sesame (*Sesamum indicum* L.) (80)
Common Oat (*Avena sativa*) (59)	Egg yolk and Cucurbita ficifolia (81)
Goat milk protein (60)	Egg protein (82)
Kacang goat meat (61)	Egg white protein (83)
Milk protein (62)	Fucus spiralis (84)
Yoghurt beverages with quinoa (63)	Cannabis sativa L. (85)
Lupin and Other legumes (64)	Sweet sorghum grain protein (86)
Whey protein (65-70)	Onion seeds (87)

Nutritions

In addition to these nutrients, it is important to increase the body's resistance and improve the immune system.

The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) recommend eating a variety of seasonal fresh local foods in our daily diet, consuming less processed foods and striking a balance between different food groups.

According to the proposal of these organizations; 50% of our daily diet is energizing foods (whole wheat bread and cereal groups, potatoes, rice, etc.), 35% is protective foods (foods containing vitamins, minerals and antioxidants such as vegetables and fruits) and 15% is protein. rich foods (fish, chicken, meat, eggs, milk, etc.).

Legumes are another source of protein with sufficient strength and high nutritional value. Green, red lentils, chickpeas, bean varieties, kidney beans, etc. are among the foods that can be consumed every day.

In addition to ensuring adequate water consumption, it will be very beneficial to use olive oil in daily nutrition.

In addition, products such as probiotic-fortified yogurt and kefir can be consumed especially during this period, as they support the immune system.

It is important to consume vegetables such as carrots, broccoli, zucchini, cabbage, cauliflower, parsley, as well as fruits such as oranges, tangerines, and apples, which are rich in vitamins A, B, C, D, E, zinc and antioxidants that strengthen the immune system. Especially since citrus fruits are rich in vitamin C, which supports the immune system, the consumption of these fruits should be emphasized, and if possible, fresh lemon should be squeezed into meals and salads.

Vitamin A helps in the formation of teeth, bones, soft tissues and mucus in a healthy way and in maintaining eye health. The antioxidant beta carotene is a fat-soluble bioactive provitamin and is converted into vitamin A, which is essential for a strong immune system. It is known to reduce susceptibility to infection and is critical as it improves immunity.

B group vitamins are water soluble vitamins. It is necessary for glucose metabolism. It helps prevent complications in the nervous system, brain, muscles, heart, stomach and intestines.

Vitamin C (ascorbic acid) is one of the essential vitamins that cannot be synthesized by humans, so it must be taken from the outside, is a natural antioxidant. Vitamin C helps improve the immune system and increases the production of white blood cells that fight infections. It has been observed that vitamin C limits the transformation of upper respiratory tract infections into lower respiratory tract infections. The most common source; citrus fruits (grapefruit, oranges, lemons, tangerines and limes).

Vitamin D provides the synthesis of antimicrobial peptides in the body and has a positive effect on antioxidant genes. It is synthesized in our body under the influence of sunlight. It is a fat-soluble vitamin and its absorption in the body increases when consumed with fat. During the COVID 19 pandemic, vitamin D supplementation is important in case of reduced contact with the sun due to quarantine and protection measures. 600 IU/day is recommended for vitamin D supplementation.

Vitamin E is also effective in strengthening the immune system. Good sources of vitamin E; green leafy vegetables, legumes and oily seeds such as hazelnuts and walnuts. 3 servings of seasonal vegetables, 15-20 hazelnuts (30 gr) or 5-6 walnuts (30 gr) and legumes (lentils, dried beans, chickpeas) 2-3 times a week should be consumed daily.

Zinc is a trace element that acts as a regulator of the immune system. It has been shown that zinc deficiency increases the risk of pneumonia, while high zinc levels decrease it. It is reported that zinc is a potential protective microcomponent against pneumonia caused by COVID 19, and a dose of 75 mg/day shortens the duration of pneumonia.

Naringenin, a naturally occurring flavonoid in foods, is commonly found in the skins of citrus fruits such as tangerines, citrus fruits, lemons and bergamot, tomatoes and figs. Antioxidant naringenin is effective against DNA-repairing, anti-cancer, bacteria and viruses, and has protective effects on heart health.

Grape seeds, blueberries, black elderberries, blackcurrants, persimmons, carob are the main sources of antioxidants and proanthocyanidins.

Attention is drawn to the importance of using citrus peels among components such as potential COVID 19 suppressive green tea and olive leaf tea.

Green tea; It is a source of antioxidants that help fight infection (Effective Ingredients: polyphenols, catechins (EGCG, EGC), caffeine, strictinin)

Ginger: Helps reduce sore throat and other inflammatory diseases (Active Ingredients: zingerone, shogaols, gingerols).

Cinnamon; Antioxidant, Neurodegenerative, antibacterial, blood sugar regulator, cholesterol lowering, heart protective (Active Ingredients: cinnamaldehyde, polyphenols, coumarin)

Clove: Antioxidant, antibacterial, protects the lungs, antique

Conclusion

Foods that can strongly increase immunity against coronavirus (COVID-19) and minimize the risk of getting sick are gaining great importance in this period. It is also important to slow down the factors that cause this disease. ACE2 and Protein C levels are potentially important. If ACE2 and Protein C levels in any food are kept under control, the risk of disease can be strongly avoided. It has been noticed that immunity against COVID-19 can be improved with Cuttlefish, Sardinelle (Sardinella aurita), Rohu (Labeo rohita), Grass carp, European Carp (Cyprinus carpio L.), Cirrhinus mrigala, Salmon (Salmo salar), Katsuo. -bushi, Acetes indicus, Common Oats (Avena sativa), Goat milk protein, Kacang goat meat, Milk protein, Yogurt drinks with quinoa, Lupine and other legumes, Whey protein, Mung bean, Walnut protein, Peanut protein, Corn germ protein, Sunflower (Helianthus annuus L.) protein, Antioxidants and fish oil, Wheat germ protein, Rice bran protein, Sesame (Sesamum indicum L.), Egg yolk and Cucurbita ficifolia, Egg protein, Egg white protein, Fucus spiralis, Cannabis sativa L., Sweet sorghum grain protein and Onion seeds.

Ethical Approval: No
Author Contributions:
Concept: E.K: M.B.T; İ.H
Literature Review: A.C; Z.T;
Design: İ.H; S.C; A.C;
Data acquisition: M.B.T; Z.T;
Analysis and interpretation: A.C; İ.H
Writing manuscript: E.K; M.B.T; İ.H; B.H
Critical revision of manuscript: M.B.T; Z.T; B.H
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: Authors declared no financial

References

1. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in nutritional status impact immune cell metabolism and function. Frontiers in immunology. 2018;9:1055.
2. Muslu M, Ersü DÖ. Yeni Koronavirüs (SARS-CoV-2/COVID-19) Pandemisi Sırasında Beslenme Tedavisi ve Önemi. Beslenme ve Diyet Dergisi. 2020;48(1):73-82.
3. WHO. Coronavirus disease (COVID-19). . Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
4. Sarıtaş A, Çalışkan T, Öztop MB. SARS-CoV-2 (Covid-19) Hastalığında Nutrisyon.
5. Galanakis CM. The food systems in the era of the coronavirus (COVID-19) pandemic crisis. Foods. 2020;9(4):523.
6. Muscogiuri G, Barrea L, Savastano S, Colao A. Nutritional recommendations for CoVID-19 quarantine. European journal of clinical nutrition. 2020;74(6):850-1.
7. FAO. Maintaining a healthy diet during the COVID-19 pandemic Food and Agriculture Organization of The United Nations. Available from: https://doi.org/10.4060/ca8380en.

8. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circulation research. 2020;126(10):1456-74.
9. Cox MM, Nelson DL. Lehninger principles of biochemistry: Wh Freeman New York; 2008.
10. Lodish H, Berk A, Kaiser CA, Kaiser C, Krieger M, Scott MP, et al. Molecular cell biology: Macmillan; 2008.
11. Hoffman JR, Falvo MJ. Protein–which is best? Journal of sports science & medicine. 2004;3(3):118.
12. Meister A. Biochemistry of the amino acids: Elsevier; 2012.
13. Wu H, Bruley DF. Chelator, metal ion and buffer studies for protein C separation. Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology. 2002;132(1):213-20.
14. Radosevich M, Zhou F-L, Huart J-J, Burnouf T. Chromatographic purification and properties of a therapeutic human protein C concentrate. Journal of chromatography B. 2003;790(1-2):199-207.
15. Dittman WA, Majerus PW. Structure and function of thrombomodulin: a natural anticoagulant. 1990.
16. Demirci B. Protein C Saflaştırılması İçin Moleküler Baskılanmış Adsorbentler. 2013.
17. Castellino FJ. Human protein C and activated protein C: components of the human anticoagulation system. Trends in cardiovascular medicine. 1995;5(2):55-62.
18. Goldenberg N, MANCO-JOHNSON MJ. Protein C deficiency. Haemophilia. 2008;14(6):1214-21.
19. Josic D, Hoffer L, Buchacher A. Preparation of vitamin K-dependent proteins, such as clotting factors II, VII, IX and X and clotting inhibitor Protein C. Journal of Chromatography B. 2003;790(1-2):183-97.
20. Zambaux M, Bonneaux F, Gref R, Dellacherie E, Vigneron C. Preparation and characterization of protein C-loaded PLA nanoparticles. Journal of controlled release. 1999;60(2-3):179-88.
21. Kisiel W. Human plasma protein C: isolation, characterization, and mechanism of activation by α-thrombin. The Journal of clinical investigation. 1979;64(3):761-9.
22. Rezaie AR. Exosite-dependent regulation of the protein C anticoagulant pathway. Trends in cardiovascular medicine. 2003;13(1):8-15.
23. Esmon CT. Protein S and protein C: biochemistry, physiology, and clinical manifestation of deficiencies. Trends in cardiovascular medicine. 1992;2(6):214-9.
24. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012;4(6):1011-33.
25. Heald-Sargent T, Gallagher T. Ready, set, fuse! The coronavirus spike protein and acquisition of fusion competence. Viruses. 2012;4(4):557-80.
26. Bosch BJ, Van der Zee R, De Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. Journal of virology. 2003;77(16):8801-11.
27. Zhou Y, Yang Y, Huang J, Jiang S, Du L. Advances in MERS-CoV vaccines and therapeutics based on the receptor-binding domain. Viruses. 2019;11(1):60.
28. Du L, He Y, Zhou Y, Liu S, Zheng B-J, Jiang S. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Nature Reviews Microbiology. 2009;7(3):226-36.
29. Robinson EL, Alkass K, Bergmann O, Maguire JJ, Roderick HL, Davenport AP. Genes encoding ACE2, TMPRSS2 and related proteins mediating SARS-CoV-2 viral entry are upregulated with age in human cardiomyocytes. Journal of molecular and cellular cardiology. 2020;147:88-91.
30. Hamming I, Timens W, Bulthuis M, Lely A, Navis Gv, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2004;203(2):631-7.
31. Kasmi Y, Khataby K, Souiri A, Ennaji MM. Coronaviridae: 100,000 years of emergence and reemergence. Emerging and reemerging viral pathogens: Elsevier; 2020. p. 127-49.
32. Mascolo A, Urbanek K, De Angelis A, Sessa M, Scavone C, Berrino L, et al. Angiotensin II and angiotensin 1–7: which is their role in atrial fibrillation? Heart failure reviews. 2020;25(2):367-80.
33. Lambert DW, Yarski M, Warner FJ, Thornhill P, Parkin ET, Smith AI, et al. Tumor necrosis factor-α convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). Journal of Biological Chemistry. 2005;280(34):30113-9.
34. Tunçok Y, İncir C. BÖLÜM 7 COVID-19 İÇİN AŞI VE İLAÇ ÇALIŞMALARI.
35. Kabbani N, Olds JL. Does COVID19 infect the brain? If so, smokers might be at a higher risk. Molecular pharmacology. 2020;97(5):351-3.
36. Kuba K, Imai Y, Penninger JM. Multiple functions of angiotensin-converting enzyme 2 and its relevance in cardiovascular diseases. Circulation Journal. 2013;77(2):301-8.
37. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, et al. SARS coronavirus entry into host cells through a novel clathrin-and caveolae-independent endocytic pathway. Cell research. 2008;18(2):290-301.
38. Akhmerov A, Marbán E. COVID-19 and the heart. Circulation research. 2020;126(10):1443-55.
39. Imai Y, Kuba K, Penninger JM. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Experimental physiology. 2008;93(5):543-8.
40. Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. Bmj. 2012;345.

41. Korhonen H, Pihlanto A. Bioactive peptides: production and functionality. International dairy journal. 2006;16(9):945-60.
42. Marques C, Manuela Amorim M, Odila Pereira J, Estevez Pintado M, Moura D, Calhau C, et al. Bioactive peptides-Are there more antihypertensive Mechanisms beyond ACE inhibition? Current pharmaceutical design. 2012;18(30):4706-13.
43. Villegas JM, Picariello G, Mamone G, Espeche Turbay MB, Savoy G, Hebert EM. Milk-derived angiotensin-I-converting enzymeinhibitory peptides generated by Lactobacillus delbrueckii subsp. lactis CRL 581. 2014.
44. Stuknytė M, Cattaneo S, Masotti F, De Noni I. Occurrence and fate of ACE-inhibitor peptides in cheeses and in their digestates following in vitro static gastrointestinal digestion. Food chemistry. 2015;168:27-33.
45. Rasika D, Ueda T, Jayakody L, Suriyagoda L, Silva K, Ando S, et al. ACE-inhibitory activity of milk fermented with Saccharomyces cerevisiae K7 and Lactococcus lactis subsp. lactis NBRC 12007. Journal of the National Science Foundation of Sri Lanka. 2015;43(2).
46. Hayes M, Tiwari BK. Bioactive carbohydrates and peptides in foods: An overview of sources, downstream processing steps and associated bioactivities. International journal of molecular sciences. 2015;16(9):22485-508.
47. Amado IR, Vazquez JA, Gonzalez P, Esteban-Fernandez D, Carrera M, Pineiro C. Identification of the major ACE-inhibitory peptides produced by enzymatic hydrolysis of a protein concentrate from cuttlefish wastewater. Marine drugs. 2014;12(3):1390-405.
48. Balti R, Bougatef A, Sila A, Guillochon D, Dhulster P, Nedjar-Arroume N. Nine novel angiotensin I-converting enzyme (ACE) inhibitory peptides from cuttlefish (Sepia officinalis) muscle protein hydrolysates and antihypertensive effect of the potent active peptide in spontaneously hypertensive rats. Food Chem. 2015;170:519-25.
49. Bougatef A, Nedjar-Arroume N, Ravallec-Ple R, Leroy Y, Guillochon D, Barkia A, et al. Angiotensin I-converting enzyme (ACE) inhibitory activities of sardinelle (Sardinella aurita) by-products protein hydrolysates obtained by treatment with microbial and visceral fish serine proteases. Food Chem. 2008;111(2):350-6.
50. Jemil I, Mora L, Nasri R, Abdelhedi O, Aristoy MC, Hajji M, et al. A peptidomic approach for the identification of antioxidant and ACE-inhibitory peptides in sardinelle protein hydrolysates fermented by Bacillus subtilis A26 and Bacillus amyloliquefaciens An6. Food research international. 2016;89(Pt 1):347-58.
51. Martinez-Alvarez O, Batista I, Ramos C, Montero P. Enhancement of ACE and prolyl oligopeptidase inhibitory potency of protein hydrolysates from sardine and tuna by-products by simulated gastrointestinal digestion. Food & function. 2016;7(4):2066-73.
52. Chalamaiah M, Jyothirmayi T, Diwan PV, Dinesh Kumar B. Antiproliferative, ACE-inhibitory and functional properties of protein hydrolysates from rohu (Labeo rohita) roe (egg) prepared by gastrointestinal proteases. Journal of food science and technology. 2015;52(12):8300-7.
53. Chen J, Wang Y, Zhong Q, Wu Y, Xia W. Purification and characterization of a novel angiotensin-I converting enzyme (ACE) inhibitory peptide derived from enzymatic hydrolysate of grass carp protein. Peptides. 2012;33(1):52-8.
54. Darewicz M, Borawska-Dziadkiewicz J, Vegarud GE, Minkiewicz P. European Carp (Cyprinus carpio L.) Protein-Derived Ex Vivo Digests and In Vitro Hydrolysates Differ in the ACE I Inhibitory Activity and Composition of Released ACE Inhibitory Peptides. Protein and peptide letters. 2017;24(2):156-64.
55. Elavarasan K, Shamasundar BA, Badii F, Howell N. Angiotensin I-converting enzyme (ACE) inhibitory activity and structural properties of oven- and freeze-dried protein hydrolysate from fresh water fish (Cirrhinus mrigala). Food Chem. 2016;206:210-6.
56. Darewicz M, Borawska J, Vegarud GE, Minkiewicz P, Iwaniak A. Angiotensin I-converting enzyme (ACE) inhibitory activity and ACE inhibitory peptides of salmon (Salmo salar) protein hydrolysates obtained by human and porcine gastrointestinal enzymes. International journal of molecular sciences. 2014;15(8):14077-101.
57. Fujita H, Yoshikawa M. LKPNM: a prodrug-type ACE-inhibitory peptide derived from fish protein. Immunopharmacology. 1999;44(1-2):123-7.
58. Dhanabalan V, Xavier M, Kannuchamy N, Asha KK, Singh CB, Balange A. Effect of processing conditions on degree of hydrolysis, ACE inhibition, and antioxidant activities of protein hydrolysate from Acetes indicus. Environmental science and pollution research international. 2017;24(26):21222-32.
59. Bleakley S, Hayes M, N OS, Gallagher E, Lafarga T. Predicted Release and Analysis of Novel ACE-I, Renin, and DPP-IV Inhibitory Peptides from Common Oat (Avena sativa) Protein Hydrolysates Using in Silico Analysis. Foods. 2017;6(12).
60. Espejo-Carpio FJ, Perez-Galvez R, Guadix EM, Guadix A. Optimisation of the hydrolysis of goat milk protein for the production of ACE-inhibitory peptides. The Journal of dairy research. 2013;80(2):214-22.
61. Mirdhayati I, Hermanianto J, Wijaya CH, Sajuthi D, Arihara K. Angiotensin converting enzyme (ACE) inhibitory and antihypertensive activities of protein hydrolysate from meat of Kacang goat (Capra aegagrus hircus). Journal of the science of food and agriculture. 2016;96(10):3536-42.
62. Cui P, Yang X, Liang Q, Huang S, Lu F, Owusu J, et al. Ultrasound-assisted preparation of ACE inhibitory peptide from milk protein and establishment of its in-situ real-time infrared monitoring model. Ultrason Sonochem. 2020;62:104859.
63. Obaroakpo JU, Liu L, Zhang S, Lu J, Pang X, Lv J. alpha-Glucosidase and ACE dual inhibitory protein hydrolysates and peptide fractions of sprouted quinoa

yoghurt beverages inoculated with Lactobacillus casei. Food Chem. 2019;299:124985.
64. Boschin G, Scigliuolo GM, Resta D, Arnoldi A. ACE-inhibitory activity of enzymatic protein hydrolysates from lupin and other legumes. Food Chem. 2014;145:34-40.
65. Chatterjee A, Kanawjia SK, Khetra Y, Saini P. Discordance between in silico & in vitro analyses of ACE inhibitory & antioxidative peptides from mixed milk tryptic whey protein hydrolysate. Journal of food science and technology. 2015;52(9):5621-30.
66. FitzGerald RJ, Meisel H. Lactokinins: whey protein-derived ACE inhibitory peptides. Die Nahrung. 1999;43(3):165-7.
67. Guo Y, Jiang X, Xiong B, Zhang T, Zeng X, Wu Z, et al. Production and transepithelial transportation of angiotensin-I-converting enzyme (ACE)-inhibitory peptides from whey protein hydrolyzed by immobilized Lactobacillus helveticus proteinase. Journal of dairy science. 2019;102(2):961-75.
68. Martin M, Hagemann D, Nguyen TT, Schwarz L, Khedr S, Moskopp ML, et al. Plasma concentrations and ACE-inhibitory effects of tryptophan-containing peptides from whey protein hydrolysate in healthy volunteers. European journal of nutrition. 2020;59(3):1135-47.
69. Vermeirssen V, Van Camp J, Augustijns P, Verstraete W. Angiotensin-I Converting Enzyme (ACE) inhibitory peptides derived from pea and whey protein. Mededelingen. 2002;67(4):27-30.
70. Vermeirssen V, van der Bent A, Van Camp J, van Amerongen A, Verstraete W. A quantitative in silico analysis calculates the angiotensin I converting enzyme (ACE) inhibitory activity in pea and whey protein digests. Biochimie. 2004;86(3):231-9.
71. Gupta N, Srivastava N, Bhagyawant SS. Vicilin-A major storage protein of mungbean exhibits antioxidative potential, antiproliferative effects and ACE inhibitory activity. Plos One. 2018;13(2):e0191265.
72. Liu M, Du M, Zhang Y, Xu W, Wang C, Wang K, et al. Purification and identification of an ACE inhibitory peptide from walnut protein. J Agric Food Chem. 2013;61(17):4097-100.
73. Wang C, Tu M, Wu D, Chen H, Chen C, Wang Z, et al. Identification of an ACE-Inhibitory Peptide from Walnut Protein and Its Evaluation of the Inhibitory Mechanism. International journal of molecular sciences. 2018;19(4).
74. Shi A, Liu H, Liu L, Hu H, Wang Q, Adhikari B. Isolation, purification and molecular mechanism of a peanut protein-derived ACE-inhibitory peptide. Plos One. 2014;9(10):e111188.
75. Musa A, Gasmalla MAA, Ma H, Sarpong F, Wali A, Awad FN, et al. Effect of a multi-frequency counter-current S-type ultrasound pretreatment on the defatted corn germ protein: enzymatic hydrolysis, ACE inhibitory activity and structural characterization. Food & function. 2019;10(9):6020-9.
76. Megias C, del Mar Yust M, Pedroche J, Lquari H, Giron-Calle J, Alaiz M, et al. Purification of an ACE inhibitory peptide after hydrolysis of sunflower (Helianthus annuus L.) protein isolates. J Agric Food Chem. 2004;52(7):1928-32.
77. McCarty MF. A central role for protein kinase C overactivity in diabetic glomerulosclerosis: implications for prevention with antioxidants, fish oil, and ACE inhibitors. Medical hypotheses. 1998;50(2):155-65.
78. Qu W, Ma H, Jia J, He R, Luo L, Pan Z. Enzymolysis kinetics and activities of ACE inhibitory peptides from wheat germ protein prepared with SFP ultrasound-assisted processing. Ultrason Sonochem. 2012;19(5):1021-6.
79. Uraipong C, Zhao J. Rice bran protein hydrolysates exhibit strong in vitro alpha-amylase, beta-glucosidase and ACE-inhibition activities. Journal of the science of food and agriculture. 2016;96(4):1101-10.
80. Wang R, Lu X, Sun Q, Gao J, Ma L, Huang J. Novel ACE Inhibitory Peptides Derived from Simulated Gastrointestinal Digestion in Vitro of Sesame (Sesamum indicum L.) Protein and Molecular Docking Study. International journal of molecular sciences. 2020;21(3).
81. Eckert E, Zambrowicz A, Pokora M, Setner B, Dabrowska A, Szoltysik M, et al. Egg-yolk protein by-product as a source of ACE-inhibitory peptides obtained with using unconventional proteinase from Asian pumpkin (Cucurbita ficifolia). J Proteomics. 2014;110:107-16.
82. Wang Y, Landheer S, van Gilst WH, van Amerongen A, Hammes HP, Henning RH, et al. Attenuation of renovascular damage in Zucker diabetic fatty rat by NWT-03, an egg protein hydrolysate with ACE- and DPP4-inhibitory Activity. Plos One. 2012;7(10):e46781.
83. Yu Z, Liu B, Zhao W, Yin Y, Liu J, Chen F. Primary and secondary structure of novel ACE-inhibitory peptides from egg white protein. Food Chem. 2012;133(2):315-22.
84. Paiva L, Lima E, Neto AI, Baptista J. Angiotensin I-Converting Enzyme (ACE) Inhibitory Activity, Antioxidant Properties, Phenolic Content and Amino Acid Profiles of Fucus spiralis L. Protein Hydrolysate Fractions. Marine drugs. 2017;15(10).
85. Teh SS, Bekhit AEA, Carne A, Birch J. Antioxidant and ACE-inhibitory activities of hemp (Cannabis sativa L.) protein hydrolysates produced by the proteases AFP, HT, Pro-G, actinidin and zingibain. Food Chem. 2016;203:199-206.
86. Wu Q, Du J, Jia J, Kuang C. Production of ACE inhibitory peptides from sweet sorghum grain protein using alcalase: Hydrolysis kinetic, purification and molecular docking study. Food Chem. 2016;199:140-9.
87. Tassin S, Broekaert WF, Marion D, Acland DP, Ptak M, Vovelle F, et al. Solution structure of Ace-AMP1, a potent antimicrobial protein extracted from onion seeds. Structural analogies with plant nonspecific lipid transfer proteins. Biochemistry-Us. 1998;37(11):3623-37.