Exp Biomed Res 2022; 5(4): 427-439
Doi: 10.30714/j-ebr.2022.162

Experimental Biomedical Research **Review article**

Correlation between COVID-19 and cancer comorbidity: COVID-19 biomarkers in cancer patients

Melisa Ozkan [1], Amrita Tiwari[2]

[1]*Department of Bioengineering, Yildiz Technical University, İstanbul, Türkiye*
[2]*Department of Biotechnology, Old Dominion University, Virginia, USA*

ABSTRACT

Due to the COVID-19 pandemic, many cancer patients around the globe exhibit difficulties to maintain the treatment they needed. However today, it is well known that the mortality rate of cancer patients is higher when they get COVID-19 infection. For these patients with both COVID-19 and cancer, biomarkers can help prognosis. For some biomarkers, gender differences can be observed which affects the disease severity. Additionally, the review focuses on ACE2 as a biomarker for cancer patients, the receptor SARS-COV-2 uses to enter the host cell. Additionally, the usage of flavonoids can be an alternative treatment method due to their various promising therapeutic properties such as anti-inflammatory, antioxidant, antiproliferative, anti-inflammatory, and anticancer activity. When used for cancer therapy, Flavonoids can play a key role in different mechanisms such as inactivation of carcinogens, cell cycle arrest, antiproliferation, and angiogenesis inhibition. Due to the ability of both ACE2 inhibition and anticancer property, flavonoids can be used as a new treatment strategy for cancer patients with COVID-19. Therefore, it is crucial to understand the relation between COVID-19 and cancer to design new specific treatments.

Key words: COVID-19, cancer, biomarkers, ACE2, SARS-COV-2, treatments.

✉ *Melisa Ozkan,*
Department of Bioengineering, Yildiz Technical University, İstanbul, Türkiye
E-mail: melisaozk1@gmail.com
Received: 2022-07-04 / Revisisons: 2022-08-13
Accepted: 2022-09-04 / Published online: 2022-09-15

Introduction

As for cancer patients with COVID-19, the symptoms are mostly the same in the general population. Therefore, if a cancer patient tests positive for COVID-19, the way of treatment would depend on the cancer type, stage of treatment, and severity of COVID-19. Due to insufficient data, it is not possible to say that all cancer patients are at a much higher risk of getting COVID-19 infection. However, it is clear, that when cancer patients are exposed to the virus their mortality rate is much higher. Cancer patients already exhibit weakened immune systems due to cancer treatments like chemotherapy, radiotherapy, stem cell transplantation, or CAR-T cell therapy which makes them have worsened conditions [1].

The review covers four different aspects of COVID-19 and cancer. The first part focuses on cancer patients with test positive for COVID-19 and how the cancer experiments had to stop their studies because of the pandemic and what kind of effects this shut down will have in the future by giving examples of the number of colon cancers compared to before the lockdown. The interruptions in cancer screening programs

during the COVID-19 pandemic will inevitably lead to additional cancer cases in the future and even increased deaths from undiagnosed cancer.

The second part focuses on biomarkers with a high comorbidity rate for cancer patients with test positive for COVID-19. According to the National Cancer Institute, a biomarker is a biological molecule that could be found in blood, body fluids, or tissues. Biomarkers are a sign of a normal-abnormal process or a disease, like cancer or COVID-19. Different substances like proteins, antibodies, nucleic acids, etc. could be counted as a biomarker [2].

For patients with both COVID-19 and cancer, biomarkers like CRP, IL-6, and others are reliable values and can help prognosis. CRP and IL-6 levels are directly associated with the severity of COVID-19 in cancer patients [3].

Also, the gender difference in biomarker levels is explained. By information gathered from the second heading, the third part focuses on the gender differences in developing these biomarkers, especially why males have higher levels of most of the COVID-19 biomarkers than females. Additionally, it is acknowledged that males and females differ in their both innate and adaptive immune responses to foreign and self-antigens. Studies show a difference in their innate and adaptive immune responses between men and women, possibly associated with sex-specific inflammatory responses caused by genes on the X chromosome. The X chromosome contains a high density of immune-related genes which means, women generally produce stronger innate and adaptive immune responses than men which gives females a biological advantage. This difference in immune responses between men and women is contributed by sex chromosome genes and sex hormones like estrogen, testosterone, and androgens. Estrogen is known to be an immune activator, unlike testosterone which is immune suppressive. Furthermore, the Androgen receptor inhibits antibody production [4].

Further studies are needed to be done on that topic however, these reasons can be summarized as genetics, epigenetics, and hormones. Also, studies suggest that ACE2 protein is a possible biomarker for COVID19 infection and there is a gender difference in ACE expression as well [5].

Lastly, the final part is about the ACE2 receptor which males have higher levels just like the case in the biomarkers. ACE2 is a transmembrane glycoprotein with an enzymatic domain located on the outer surface of human cells. ACE is responsible for converting angiotensin I into angiotensin II. ACE2 gene can be found on the X chromosome. To decrease the ACE2 activity to treat COVID-19, especially for cancer patients, some papers suggest using ACE inhibitors or blocker drugs and some of them suggest using flavonoids instead of drugs. Brief information about flavonoids and their use in health is also given as a separate title in that part. Flavonoids can be found in plants naturally. They have phenolic structures and properties like antioxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic. Therefore, flavonoids are known to have beneficial effects on human health which makes them useful in different areas like nutraceuticals, pharmaceuticals, and cosmetic applications [6].

Correlation between Covid-19 and cancer

Undiagnosed cancer during Covid-19 pandemic

As this virus spreads around the world thousands of cancer laboratories and clinical trials across the globe had to close. Cancer research became nonessential, and it was not the priority during these difficult circumstances. However, shutting down an experimental lab could have serious consequences in the future and the researchers believe that it will take approximately two years

to get back to the pre-lockdown form for cancer science [7].

To increase the hospital's capacity to fight the COVID-19 pandemic, many cancer centers had to postpone their nonessential cancer services. National Cancer Institute predicts that during the COVID-19 lockdown, there will be nearly 10,000 additional deaths over the next decade, only because of underdiagnosed and undertreated breast and colorectal cancers. During the lockdown period, many cancer patients experienced delays in diagnosis or keep continuing the cancer treatment they needed [8].

In a recent study in France, data on patient hospital stays in public or private hospitals were collected to examine for the year 2020. The study contained pre-lockdown, lockdown, and post-lockdown periods to find out the effects of the pandemic on colorectal cancer. The statistics of the report showed that there is a risk for an increased rate of undiagnosed colorectal cancers in the future. As shown in Figure 1, in 2020 there is a decrease, approximately 20%, in the number of colonoscopies and colorectal resections which are crucial services for early diagnosis of cancer. Another study in the United Kingdom shows that only a 3-month of delay in colorectal cancer resection could be responsible for 5,000 related deaths [9].

In the year 2020, 18,650 cancer patients with COVID-19 got involved in fifty-two different studies from different countries for a pooled analysis. According to the study, a total of 4243 deaths were documented and the statistics show that the mortality rate, for patients who have both cancer and COVID-19, was 25.6% [10].

COVID-19 biomarkers in cancer patients

Another study examined 69 COVID-19 patients with the severe condition and showed considerably higher levels of ferritin compared with the other patients who do not have a severe state [11].

Some of the most important biomarkers shown in Figure 2 are explained below:

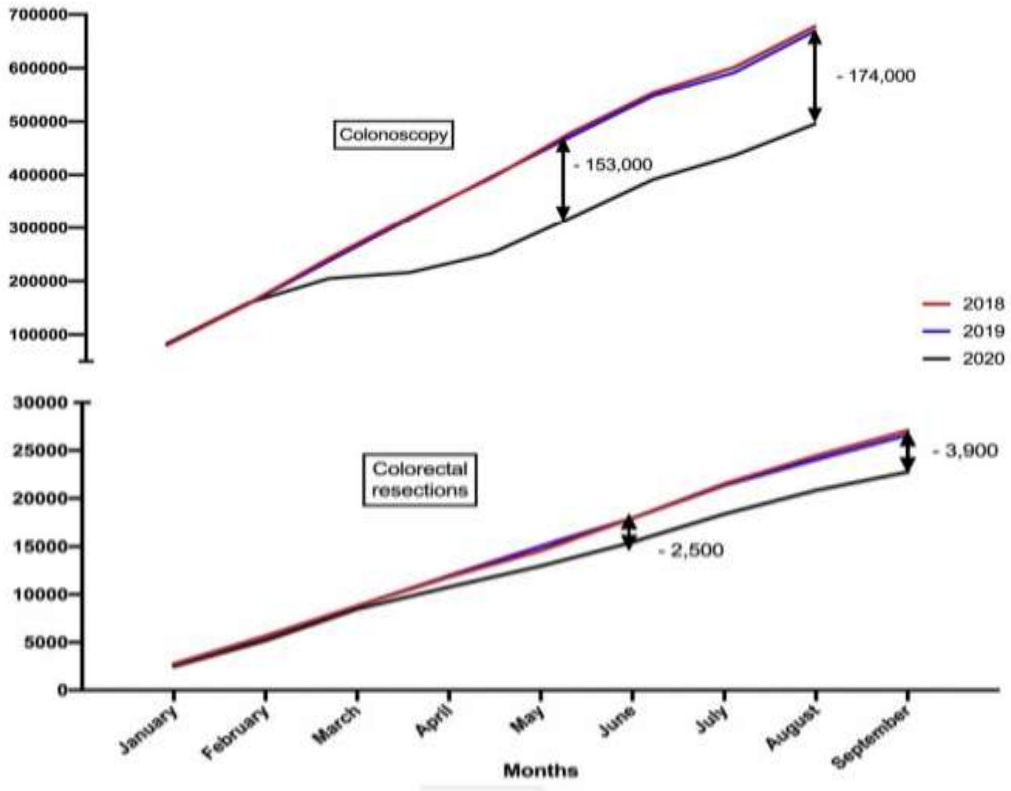

Figure 1. Number of colonoscopy and colorectal resection procedures for cancer diagnosis by months [9].

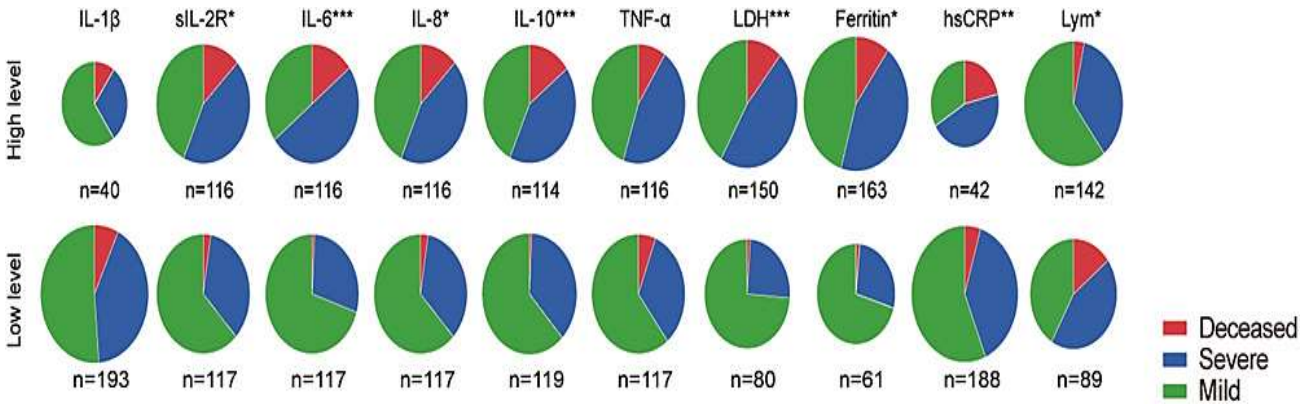

Figure 2. Ratios of COVID-19 severities based on biomarkers [12].

C-reactive protein (CRP) is a kind of acute protein, and the level of CRP quickly increases in infections. CRP levels can be used to show the severity of the COVID-19 infection. CRP release from the liver is controlled by Interleukin-6 (IL-6) which is a cytokine that plays a crucial role in fever and acute immune response. Just like CRP, IL-6 is a reliable prognostic value in severe COVID-19 infection [13]. Human Epididymis Protein 4 (HE4) is a biological marker for detecting ovarian cancer and a reliable recently found COVID-19 marker.

Ferritin is a kind of protein that stores or releases iron in the body, and it can be found in various tissues, some organs like the liver, spleen, and bone marrow. Ferritin is also a serum biomarker and an acute-phase protein that shows higher serum concentration in various inflammatory diseases like novel COVID-19 infection [14]. When ferritin level increases, it can cause a cytokine storm which is related to the severity of COVID-19 infection [15].

These exaggerated levels of biomarkers further lead COVID-19 patients to an acute respiratory distressed syndrome, multiple organ failure, and death [12]. Also, the levels of HE4 and IL6 together could be responsible for smell and taste disorders which is one of the outcomes of COVID-19 infection [16]. In 2020 from 13 February to 3 March, at a hospital in Wuhan, 252 COVID-19 patients enrolled in a study to examine their levels of serum biomarkers in COVID-19 infection and cancer. Out of all patients included in the study, 130 of them were males and 122 of them were females. The study also aimed to determine whether gender was a potential factor contributing to the elevation of HE4 in patients. For mild COVID-19 patients, levels of HE4 increased, unlike the normal subjects. HE4 levels gradually increased parallel with the disease severity, not related to the patient's gender. Additionally, the levels of cancer biomarkers like CEA, CA125, CA153, and CYFRA21-1 gradually increased in COVID-19-infected patients. Data gathered from the study is given in Table 1 [17].

Gender difference in biomarker levels

Gender is one of the important factors for inflammation reaction in COVID-19 patients. Males and females had different innate immune responses, which could be related to the innate immune responses of gender-related hormones [12]. From 26 January 2020 to 3 March 2020, a total of 548 patients with COVID-19 were enrolled in a study in Wuhan. Among all the patients, 314 of them were counted as severe cases, and 90 of them died during the period, 279 of them were males and 269 of them were females. According to the results of the study, the mortality rate because of the COVID-19

Table 1. Inflammatory and serum cancer biomarkers and their association with the severity of COVID-19 infection [17].

Category	Reference	All Patients	Mild	Severe	Critical
IL-2	0.1-4 pg/ML	6 (37.9)	9 (53.4)	2.8 (0.7)	2.9 (0.9)
IL-4	0.1-3.2 pg/ML	3 (5.7)	2.6 (1)	2.3 (0.8)	8.4 (20)
IL-6	0.1-2.9 pg/ML	99.6 (307.9)	64.6 (137.7)	150.7(449.2)	57.4 (105.6)
IL-10	0.1-5 pg/ML	4.2 (2)	3.9 (1.8)	4.3 (1.7)	5.6 (3.6)
TNF-α	0.1-23 pg/ML	5.4 (6.1)	5.6 (6.6)	5.5 (6.1)	3.2 (2)
HE4	46.5 (14.7) pmol/L	121 (117)	73.6 (38.3)	145.7 (118.4)	284.0 (201.6)
CYFRA21-1	1.9 (0.8) µg/L	2.8 (2.1)	2.2 (0.9)	3.3 (2.9)	3.9 (2.4)
CEA	2.1 (1.2) µg/L	5.1 (8.9)	3.4 (2.2)	5.3 (6.3)	12.8 (24.7)
CA125	10.5 (4.6) µg/L	28.9 (35.3)	18.1 (13.6)	33.1 (40.4)	72.3 (56.1)
CA153	10.1(4.4) µg/L	16.6 (12.5)	14.4 (8.9)	17.7 (13.9)	24.6 (18.9)

infection for males was 22.2% while for females was 10.4% which is lower compared to males. Therefore, it is possible to hypothesize that gender-specific differences affect inflammation reaction, which leads to gender bias in the severity and mortality of COVID-19. As we know from previous studies, males have a higher mortality rate in severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) which is a similar case for COVID-19. The result of the study shows that males produced more IL-10 than females did, which was positively related to androgen concentration in males [18]. Males had higher levels of proinflammatory cytokines (like TNF-alpha). With or without comorbidity, patients in the male groups had higher levels of ferritin and CRP compared with female groups regardless of their age. Under the stimulation of PBMC (peripheral blood mononuclear cell) in vitro, females had higher numbers of increasing T cells in peripheral blood compared to males. Meanwhile, females had higher antibody responses, higher basal immunoglobulin levels, and B cell numbers compared with males [12].

Male COVID-19 patients were likely to develop weakened immune defense and exaggerated production of IL-10, CRP, LDH, TNF-α, and ferritin. Therefore, this state further leads them to

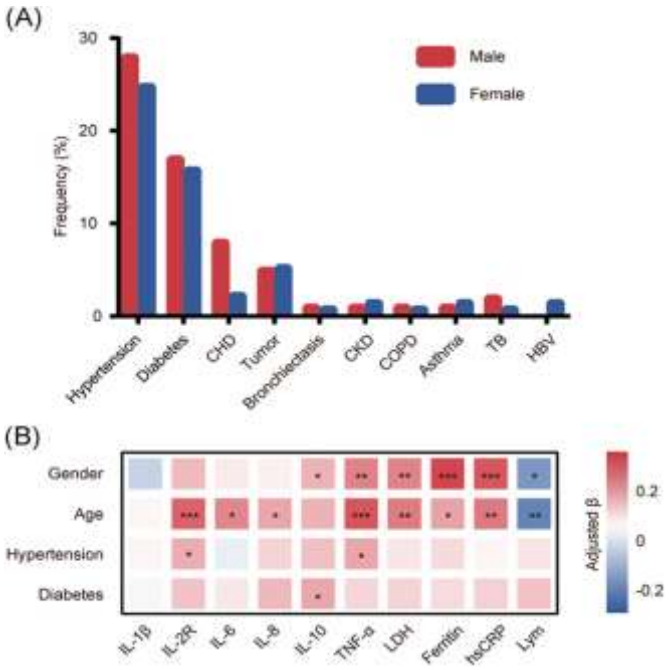

Figure 3. COVID-19 biomarkers and their relation with age, gender, and comorbidities [12].

cytokine storm, multiple organ failure, and death. Severe COVID-19 male patients showed a higher CRP level compared with females, not related to the patient's age and co-morbidities. It is acknowledged that C-reactive protein (CRP) greater than 15 mg/L provides a marker of disease severity and levels greater than 200 mg/L is related to five times the odds of death in infected patients. Also, compared with female COVID-19 patients, males had considerably

higher levels of tumor necrosis factor-alpha (TNF-alpha) and IL-2 [12] (Figure 3,4).

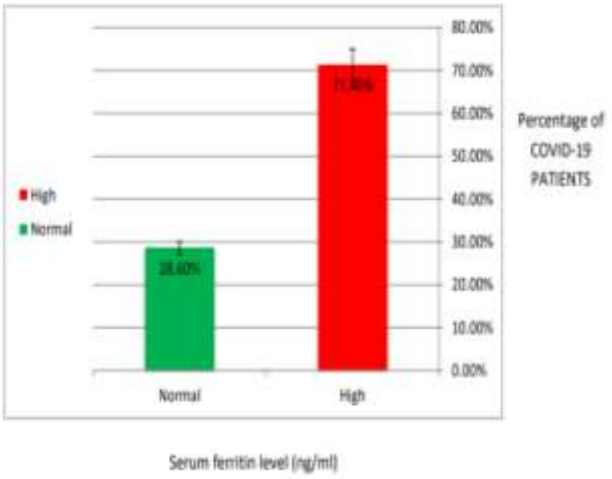

Figure 4. serum ferritin levels of non-hospitalized COVID-19 patients compared with normal ferritin values [15].

In the year 2020, from August 12 to December 30, a total of 210 non-hospitalized COVID-19 patients in Egypt were included in a study to find out their percentage of serum ferritin levels by using the ELISA technique [15].

There is an immunological difference between females and males and because of that, some researchers proposed considering sex as a factor in the COVID-19 clinical trials [19]. Today, it is well known that males and females differ when it comes to immunological innate and adaptive responses to foreign and self-antigens. Previous studies show that for SARS- and MERS-CoV infections, the progression of the disease is highly affected by the host immune response [20].

A novel report clearly shows that when compared to COVID-19-infected female patients, male patients have higher innate cytokines, lower T cell response, and a higher mortality rate [21]. Experiments in female mice show that treatment with an estrogen receptor antagonist increased mortality after SARS-CoV infection, which indicates that for immune response, hormones play a crucial role in infection [22]. In a recent study in China, 1558 male and 1499 female patients were examined to point out the gender differences in COVID-19 infections. The concentration of C-reactive protein (CRP) in male and female patients in the first week after symptoms was similar.

However, from the second week to the seventh week, the level of CRP in male patients was considerably higher while lymphocyte levels were lower. Also, the number of inflammatory cytokines, interleukin-6 (IL-6), and neutrophils was higher in male patients as well [19].

Factors affecting gender difference in covid-19 biomarkers

SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) to gain entry to the host. The S spike of the coronavirus attaches to the cellular ACE2 a receptor that is located on the respiratory epithelial cells. Plasma ACE2 levels in men are higher than in females, biologically. This gender difference could be the reason why men COVID-19 patients are at higher risk of getting infected or having outcomes [5].

As previously reported from epidemiological studies, the density of the ACE2 receptor in bronchial cells is higher in men compared with women, which is associated with higher infection ratios in males. Plasma ACE2 has also been reported at a much higher level in as well. Also, the gene encoding ACE2 protein is X-linked and is expressed at a particularly high level in the testes, which could explain the gender differential in infection and even deaths because of it. A few recent studies showed that epigenetics explains the difference between the COVID-19 symptoms and severity for infected patients [23].

Differential effects of sex hormones may also explain the sex difference in COVID-19 patients.

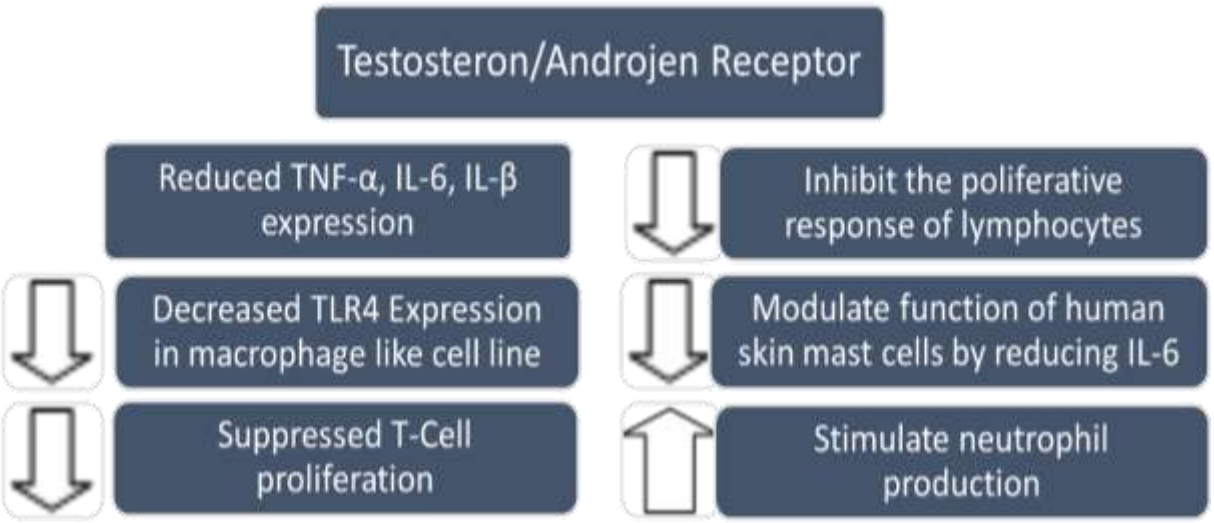

Figure 5. The figure shows the relation between testosterone and the innate-adaptive immune compartments [27].

A review article of studies in sepsis showed that female sex hormones show protective effects, while male sex hormones like androgen can be suppressive on cell-mediated immune responses [24]. CRP-related genetic differences and body image perception could be also causing this gender difference [25]. Studies showed that testosterone levels significantly reduced the gene and protein expression of TNF-alpha in human monocyte-derived macrophages obtained from male and female subjects [26]. When the ferritin levels are high it is associated with cardiovascular disease or insulin resistance. The gender differences in ferritin levels have some possible explanations. Sex hormones, like estrogen and testosterone, could be responsible for causing this difference. Studies reported that testosterone is inversely associated with ferritin. Serum ferritin levels are regulated by hepcidin and hepcidin is related to gender-related hormones like estrogen and testosterone [28].

Angiotensin-converting enzyme receptor 2 and COVID-19

SARS-CoV-2 uses ACE 2 receptors to enter target cells. ACE2 is mostly expressed by the lung, kidneys, heart, blood vessels, and intestine epithelial cells. ACE and ACE2 are a part of the ACE family of dipeptidyl carboxydipeptidases, and they have different functions. ACE is responsible for converting angiotensin I into angiotensin II while ACE2 is responsible for converting angiotensin to Ang-(1-7). ACE2 exists in two different forms: a soluble form and a structural transmembrane protein. SARS-COV-2 uses the transmembrane protein form of the ACE2 to enter the host cells. ACE2 is a relatively newly discovered enzyme in the Renin/Angiotensin/Aldosterone System (RAAS) pathway. In these COVID-19 patients, the RAAS system is often already out of balance, with more Angiotensin II signaling and lower ACE-2 expression levels. To control the ACE2 gene expression, epigenetic mechanisms appear to be crucial [29].

ACE1 and ACE2 are involved in the renin-angiotensin system which controls the homeostatic function of the vascular system. The choice to modify these receptors for other health conditions like the novel COVID-19 infection could have effects on health and to keep the homeostasis it should be done with caution [29]. Studies showed that blocking the renin-angiotensin signaling pathway could be useful in

Table 2. ACE1 and ACE2 inhibitor bioactive compounds [29].

Inhibitors	Plants	Methods	Years
Luteolin	Ailanthus excelsa	In vitro using ACE2 via Elbl and Wagner methods	2007
Kaempferol			
Apigenin			
Quercetin			
Luteolin			
Chrysin	Rheum officinale Polygonum multiflorum	In vitro using ACE2	2007
Rhein			
Delphinidin	Hibiscus sabdariffa	In vitro ACE Inhibition assay	2010
Cyanidin			
Apigenin	Apium graveolens	In vitro using ACE2 isolated from kidney	2010
Rhoifolin	Rhus succedanea	ACE activity was measured by a fluorometric assay	2012
Rutin and Quercetine	Fagopyrum tataricum		
Quercetin	Actinidia macrosperma	In vitro using a fluorescence-based biochemical assay against ACE enzyme	2018
Catechin			
Epigallocatechin			
Epigallocatechin gallate			
δ-Viniferin	Vitis vinifera	Virtual screening against ACE2 using Autodock Vina	2020
Myritilin			
Myricitrin			
Taiwanhomoflavone A	Cephalotaxus wilsoniana		
Nympholide A	Nymphaea lotus		
Afzelin	Cornus macrophylla		
Biorobin	Acalypha indica		
Baicalin	Scutellaria baicalensis	Virtual Screening against ACE2 using molecular docking	2020
Hesperetin	Citrus aurantium		
Scutellarin			
Tangeretin	Citrus aurantifolia	Virtual Screening against ACE2 using MOE molecular docking	2020
Nobiletin			
Naringenin			
Brazilein	Caesalpinia sappan		
Brazilin			
Galangin	Alpinia galanga		

severe acute lung injury caused by the virus in infected patients [30].

The inhibition of ACE2 may prevent the S protein of SARS-CoV-2 to enter host cells. However, as both ACE1 and ACE2 enzymes are related to each other, inhibition of the only ACE2, in this case, would lead to an increase in Ang II blood levels and a parallel reduction in the blood concentration of vasodilators angiotensins 1–7 which would be hard to correct fast. This would create a health issue, especially for vulnerable patients such as the elderly and patients with underlying medical conditions which are ironic, because these people already

have a higher risk to get severe COVID-19 infection [29] (Table 2).

In certain studies, angiotensin system inhibitors showed positive effects in treating non-metastatic cancer patients by activating their immune response. The dysregulation of the renin-angiotensin-aldosterone system to treat COVID-19 could lead to a complication in ways of treatment of cancer patients since the ACE blockers are expected to have a better prognosis [3].

Ace inhibitor and blockers for COVID 19 infection

Increases in ACE2 could be responsible for creating more binding spots for the virus which leads to an increase in the virulence of SARS-COV-2 [31]. Angiotensin receptor blockers (ARBs) and ACE inhibitors are similar; however, ACE inhibitors act by preventing the formation of angiotensin II, not by preventing the binding with blocking [29].

It is possible to hypothesize that there are potential genetic variants that also have an impact on the response to infection in patients. Also, since the RAAS pathway is related to renin, it can be possible to modify ACE2 activity by reducing renin levels [32].

Many flavonoids such as Quercetin can be used to inhibit viral replication and prevent the virus to enter the host cells by inhibiting the ACE2 receptor [33].

Therefore, it is possible to say that consuming flavonoids will have positive effects on both the treatment and prevention of COVID 19.

The use of flavonoids as ACE 2 inhibitor

Epidemiological studies suggest that consuming flavonoid drugs can reduce the development of different diseases. Some flavonoids can interact with enzymes with their poly-pharmacological behavior. Few studies propose to change the design of ACE2 inhibitors to flavonoids, which are a group of compounds that can be found in many plants. Plants synthesize flavonoids as a response when they are under a microbial attack. Therefore, flavonoids have antibacterial and antiviral activities [29].

Other than their anticancer potential, flavonoids are currently used in many different therapeutical applications based on their various structures.

Flavonoids can exhibit antibacterial activity by disturbing the cell wall of the bacteria. They also have antiviral and antimicrobial effects which makes them important new agents derived from nature to develop novel treatment applications.

Studies also show that many flavonoids can inhibit the coronavirus by various mechanisms. A flavonol called Quercetin is one of the most studied among them [33].

From the knowledge we have from previous studies, Quercetin already has beneficial effects to treat other human and bovine coronaviruses. Since the novel COVID-19 is highly similar when compared to SARS-CoV. Therefore, it is possible to use Quercetin to treat SARS-CoV2 as well [34].

Additionally, animal studies show that quercetin does not have mutagenic or genotoxic effects on mice and rats which means they are safe to use for treatment applications [35].

Therefore, few studies propose to change the design of ACE2 inhibitors to flavonoids. [29].

The role of ACE 2 in cancer

An analytical study shows that for most tumors, an increase in ACE2 expression is related to immune infiltration levels. According to the results of the study, for most cancer patients, ACE2 is not related to prognosis however for different types of tumors, particularly breast and lung cancer, ACE2 is related to immune penetration levels. These findings confirm that ACE2 affects the immune infiltration of patients with both COVID-19 and cancer. However,

Table 3. Plants that can inhibit ACE2 receptors [29].

Plant Name	Effective Compound	Inhibition Approach
Rheum officinale (rhubarb)	Emodin	Viral spike protein and human ACE2 receptor inhibitor
Reynoutria multiflora tuber	Emodin	
Citrus accumulate	Naringenin	
Citrus aurantium and Citri Reticulatae Pericarpium	Hesperetin	
Scutellaria baicalensis Georgi	Baicalin	
Citrus	Neohesperidin	
Citrus	Nobiletin	
Erigeron breviscapus (Vant.)	Scutellarin	
Soya bean (Glycine max)	Nicotinamine	
Licorice root (Glycyrrhiza radix)	Glycyrrhizin (saponin)	

some reports show that ACE2 may have both positive and negative effects on the development of cancer. Therefore, their relationship is complicated [37] (Table 3).

Limitations of the study

Due to insufficient data, tests, research, and clinical trials, a complete analysis of the underlying cellular and molecular mechanisms was not conducted for most of the topics of this literature review. The pandemic is still so new for scientists to create theories about its effects in the future. Therefore, it is necessary to verify these results in a larger clinical group in the future to have a better understanding of cancer patients with COVID-19 infection.

Conclusion

To conclude, further studies should be conducted to have a complete understanding of how cancer cells interact with the novel coronavirus. Due to the novelty of the COVID-19 disease, some questions remain unknown such as, are all patients with cancer are at higher risk of getting infected, how to target the SARS-CoV-2 virus by using immunotherapies to treat both COVID-19 infection and cancer, and how ACE2 expression could have an impact in these patients [1]. Furthermore, experiments are needed to be done to find out how affected the COVID-19 vaccines are for immunocompromised cancer patients and would there be any interactions between the COVID-19 vaccine and cancerous cells [38].

Generally, the drugs used today for cancer therapy have some disadvantages such as they have a high cost, and they have toxic effects. Therefore, flavonoids can be an environment-friendly and low-cost alternative with their high biocompatibility and biodegradability properties. They can also show cytotoxic effects specifically on cancer cells [33].

Flavonoids are known to have beneficial effects on the treatment of cardiovascular and respiratory diseases due to their anti-inflammatory activity by inhibition of cytokines. They also have the potential to be used for neurodegenerative diseases like Alzheimer's. They have antidiabetic activity by inhibition of related enzymes. Additionally, they can be used in the treatment of fungal infections by inhibiting fungal growth and disrupting the plasma membrane [33,36].

As discussed before, Quercetin is effective and well-known flavanol to treat and prevent COVID-19. However, its bioavailability is low which a disadvantage for production and application is. However, the formulation of quercetin can be adjusted based on its bioavailability. Additionally, further research must be conducted to determine its dose, duration, and efficiency. Therefore, scientists can fully understand the bioavailability of flavonoids for future treatment applications for both cancer and COVID-19 [34].

Additionally, we can say that using a treatment that relies on flavonoids for COVID-19 would be beneficial due to its many advantages.

Acknowledgement

I would like to thank my mentor, Amrita Tiwari, for guiding me to finalize this literature review.

Also, I wish to extend my sincere thanks to Old Dominion University for giving me this opportunity to be a part of the mentorship program.

Funding: *The author(s) received no financial support for the research, authorship, and/or publication of this article.*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical statement: *Ethics committee approval was not required as the study was a review article.*

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