ORIGINAL RESEARCH ARTICLE

CUMIN SEEDS: THE FUNCTIONAL FOOD WITH AN ABILITY TO INHIBIT THE DELETERIOUS PHENOMENON OF GLYCATION

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ABSTRACT

Objective: Ageing is the natural process of getting old and involve deleterious phenomenon like glycation and oxidative stress. The quality of life can be improved and maintained for longer duration of time by inhibiting these harmful processes. In this regard, the dietary substances, especially spices hold tremendous potential.

Methods: The present work was designed to assess the anti-ageing potential of five spices i.e. cumin seed, cinnamon, ginger, paprika and garlic, using anti-glycation and anti-oxidant assays along with HPLC fingerprint of the most potent extract.

Results: Our data showed that among all spices, the ethanolic extract (70%) of cumin seeds showed the most significant inhibition of glycation (80%) and oxidative stress (95%) at the tested dose of 1mg/ml. The Venn diagram (set at a threshold of 50%) showed that among all tested extracts, only cumin seed was able to produce 50% inhibition in both assays. The HPLC fingerprint of cumin seed extract was also obtained as the crude reflection of the phytochemicals residing in it.

Conclusion: Hence, the cumin seed presents itself as a promising functional food for the management of age-associated diseases and diabetic complications attributed to the deleterious phenomenon of glycation.

Keywords: Glycation; Oxidative stress; Cumin seeds; Functional food

INTRODUCTION

Senescence or ageing is the natural phenomenon of getting old, which is jeopardizing the human race in an unprecedented manner. The world needs balanced demography to run its machinery. However, the number of old age people shall surpass youth by the year 2050; an event that is unprecedented in known human history (Suzman and Beard, 2011). The scenario is alarming and stresses upon the need to take appropriate measures to increase quality of life over time. Several underlying pathological mechanisms have been reported for the process of ageing (Campisi et al., 2019). Among which, one of them attributes senescence to the buildup of garbage in the body (Sergiev et al., 2015) such as Advance Glycation End products (AGEs) (Ross, 2015) and oxidative stress (imbalance between oxidants and antioxidants) (Pole et al., 2016). Glycation (Maillard reaction) involves interaction between carbohydrates; especially reducing sugar and other bio-molecules i.e. nucleic acids, proteins or lipids, which after a long process produces AGEs (Goldin et al., 2006). The levels of N(6)-carboxymethyl lysine (CML), the predominant AGEs product, co-relates with the phenomenon of ageing, age-linked diseases such as learning & memory impairment (Southern et al., 2007, Igase

and Igase, 2018), kidney injury (Sun et al., 2016), non-alcoholic fatty liver diseases (Leung et al., 2016) and complications associated with diabetes mellitus (Ramasamy et al., 2005). The AGEs binds to its receptor known as Receptor for Advanced Glycation End products (RAGE), thereby leading to activation of Nuclear Factor-kappa B (NF-κB) (Haslbeck et al., 2005); the transcription factor famous for oxidative stress. The stress in this case is specifically termed as glycative stress (Yonei et al., 2020).

In quest of impeding this deleterious phenomenon of glycation, several inhibitors (natural and synthetic) were reported (Reddy and Beyaz, 2006). Despite of their significant effectiveness (e.g. aminoguanidine), they could not make it to the bed side due to their potential to produce adverse effects (Thornalley, 2003, Campbell, 1996). Under this milieu, the field of nutritional pharmacology comes to rescue. This is an emerging field in pharmacy, which uses the concept of functional foods i.e. the food resources which along with nutritional value also offer medicinal value. This concept was formulated by Hippocrates i.e. let food be thy medicine and medicine be thy food (Hasler, 2002). The benefit of using this concept is that it offers fast and inexpensive solutions without needing detailed toxicological assessments as part of drug development process. Furthermore, this type of approach suits well for the indications which grow insidiously.

Dietary spices hold promising potential as functional food and need comprehensive investigations (Dearlove et al., 2008). In this regard, cumin is the famous spice used in folklore for the management of tooth ache, gastrointestinal, inflammatory and neurological disorders (Benelli et al., 2018). Other biological actions attributed to cumin are antioxidant, anticancer, stimulant and carminative (Sharma et al., 2001). Cumin is actually the dried seed obtained from Cuminum cyminum L., a medicinal plant of Apiaceae family, which is native to the Eastern Mediterranean and South Asia (Singh et al., 2017, Zarandi et al., 2017).

Currently, there is no treatment option available in the allopathic system of medicine for the management of glycation. Keeping this in view, the present study was designed to evaluate functional food i.e. spices for their ability to inhibit the deleterious phenomenon of glycation.

MATERIALS & METHODS

Selection of Spices

Five spices i.e. cumin seed, cinnamon, ginger, paprika and garlic were selected for the present study.

Preparation of plant extract

Briefly, 1 kg of each spice was separately soaked in ethanol (70%, 3L) for three days at room temperature, followed by rotary evaporation to yield thick extract, which was freeze dried and stored in refrigerator till further use.

Anti-glycation Assay

The in vitro AGE inhibition assay was performed by incubating BSA (10 mg/ml) and fructose (50mM) together for 24 hours at 60 ˚C. The spice extract was used at the concentration of 1mg/ml. The AGEs were detected using its innate fluorescence (Khan et al., 2017).) All results were tested in triplicate. The percentage inhibition of AGEs was measured using the following formula

% Inhibition = [1-(fluorescence of test)] / (fluorescence of control) x 100

Antioxidant Assay

Free radical scavenging activity of functional foods was assessed by 1-1diphenyl-2-picryl-hydrazyl (DPPH) as reported earlier (Shen et al., 2010). Briefly, DPPH (0.1 mM in methanol) was added (100ul) to spice extracts (1mg/ml, 300ul), vortexed and allowed to stand at room temperature for 30 minutes. The absorbance was measured at 517nm using UV spectrophotometer. Percent free radical scavenging activity was calculated using the following formula (Aiyegoro and Okoh, 2010):

DPPH Scavenging activity (%) = [(Abs control – Abs sample) / Abs control] x 100

Venn Diagram

The Venn diagram was prepared at 50% threshold to observe the effect of spice extracts on both anti-glycation and anti-oxidant assays.

HPLC Fingerprint

The High Performance Liquid Chromatography (HPLC) was used to obtain the fingerprint of the extract. Following were the working conditions:

Extract Strength: 50µg/ml
Column: Hibar® 250-4, 6 LiChrospher® 100 RP-18e (5um) column.
Detector: DAD (SPD-M20A) set at 250nm.
Mobile phase: Methanol (50%)
Flow rate: 0.5ml/min
Injection volume: 10µl

Data analysis

The data is shown as mean ± SEM of percent change.

RESULTS

The results obtained in the present study are as follows:

Anti-glycation Assay

Among the various spices, the cumin seeds extract showed the most promising anti-glycation action with the percent inhibition of 80% (Table-1). Cinnamon, ginger, paprika and garlic showed the percent inhibition of 30%, 25%, 21% and 10% respectively

Table-1 Effect of Various Spice Extracts on Inhibition of Glycation

S. No.	Functional Food	Scientific Name	Free Radical Scavenging (%)
1	Cumin seed	*Cuminum cyminum*	95
2	Cinnamon	*Cinnamomum verum*	87
3	Ginger	*Zingiber officinale*	80
4	Paprika (red)	*Capsicum annum*	85
5	Garlic	*Allium sativum*	41
Ascorbic acid 1 mM (positive control)			95

Antioxidant Assay

Among the various spices, the cumin seeds extract showed the most promising anti-oxidant action with the percent inhibition of 95% (Table-2). Cinnamon, ginger, paprika and garlic showed the percent inhibition of 87%, 80%, 85% and 41% respectively.

Table-2 Effect of Various Spice Extracts on Free Radical Scavenging

S. No.	Functional Food	Scientific Name	Free Radical Scavenging (%)
1	Cumin seed	*Cuminum cyminum*	95
2	Cinnamon	*Cinnamomum verum*	87
3	Ginger	*Zingiber officinale*	80
4	Paprika (red)	*Capsicum annum*	85
5	Garlic	*Allium sativum*	41
Ascorbic acid 1 mM (positive control)			95

Venn Diagram

Among all tested extracts, only cumin seeds showed 50% inhibition in both glycation and anti-oxidant assays as shown in the Venn diagram (Figure-1).

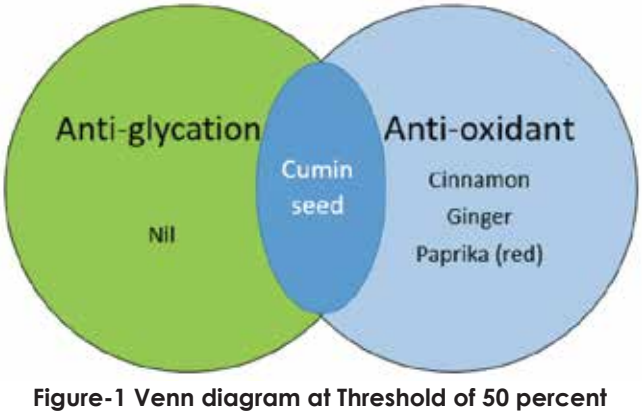

Figure-1 Venn diagram at Threshold of 50 percent

HPLC Fingerprint

The HPLC finger print of cumin seed extract is shown in Figure-2

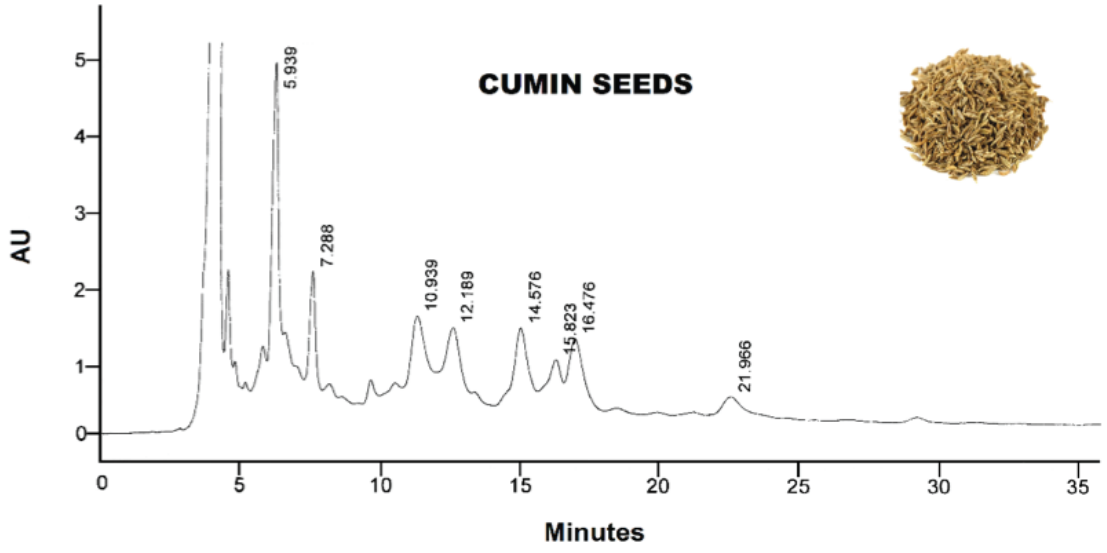

Figure-2 HPLC Fingerprint of Cumin Seed Extract

DISCUSSION

Ageing or senescence has been attributed to capacity loss and emergence of diseases in living beings. Both of which affect the quality of life. The deleterious mechanism like glycation has been reported to underlie the process of ageing and has been the pharmacological target of anti-ageing substances. In this regard, dietary interventions especially through spices appear to be of medicinal value and their evaluation against the said indication was the primary objective of the present study.

Dietary modulation has always been an important tool for the management of ailments, which are either of chronic nature or develop insidiously. Nutritionists often recommend use of specific constituents (Solfrizzi et al., 1999), diet (Berr et al., 2009) or ask to follow specific dietary patterns (Yannakoulia et al., 2015) to manage such situations. Furthermore, the diet based interventions were found to have greater patient compliance. In this context, the dietary spices hold a promising position and their consumption is negatively co-related with ageing and associated ailments especially in our part of the world, which is famous for spicy meals (Kannappan et al., 2011). Keeping this in view, the five commonly used spices were selected (Cumin seed, cinnamon, ginger, paprika and garlic) and their ethanolic extracts (70%) were prepared followed by assessment of their anti-glycation activity. Our data showed that cumin seeds extract was most potent in inhibiting the process of glycation with 80% inhibition (Table-1). Rest of the spices, did not produce a significant inhibition i.e. cinnamon, ginger, paprika and garlic showed the percent inhibition of 30%, 25%, 21% and 10% respectively. This is suggestive of anti-ageing potential of cumin seeds. Search of literature revealed that oxidative stress is also an important factor responsible for deteriorating bodily faculties with age. On similar lines, the spices were reported to hold anti-oxidant potential as well (Srinivasan and nutrition, 2014). Keeping this in view, all extracts were also tested for their ability to scavenge free radicals. It is of note that cumin seeds were again found to be the most potent with inhibition of 95% (Table-2). With an exception of garlic, the other spices i.e. cinnamon, ginger and paprika, also showed promising results with the percent inhibition of 87%, 80% and 85% respectively. The Venn diagram, at threshold of 50% revealed that among all tested extracts, only cumin seed was able to produce more than 50% inhibition in both assays. This suggests that along with inhibition of deleterious phenomenon of glycation, the cumin seeds extract additionally possesses anti-oxidant potential, which shall add value to its medicinal properties against ageing and associated diseases. Additionally, the HPLC fingerprint of cumin seed was also obtained for crude reflection of medicinal constituents residing in it. This shall also be useful for future comparisons in similar studies involving cumin seeds extract.

In conclusion, our data demonstrates that the cumin seed presents itself as the promising functional food for the management of age-associated diseases and diabetic complications attributed to the deleterious phenomenon of glycation.

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REVIEW ARTICLE

FERRITIN LEVELS IN COVID-19: A REVIEW

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ABSTRACT

The corona virus illness 2019 (COVID-19) is a global issue from the day it was first diagnosed in Wuhan, China in December, 2019. Cytokine storm together with higher levels of inflammatory cytokines is associated with death in individuals severely affected with COVID-19 virus. The clinical and laboratory indicators in cases of severe infection are still required to be evaluated in order to appraise the seriousness or death in the severe case. Ferritin is an intracellular protein that accumulate iron as well as possesses serious role in inflammatory diseases like infection, cancer, or neurodegeneration. According to some reports ferritin is found to be an independent risk factor for seriousness of illness in COVID-19 positive individuals. In different studies the ferritin levels have been evaluated in severely ill and patients admitted in intensive care unit (ICU) due to COVID-19.

Keywords: COVID-19; Virus, Ferritin; Hyperferritinemia; Infections

INTRODUCTION

In December 2019 there was an occurrence of pneumonia in the city of Wuhan, Hubei province, China. Its etiology was not known. The health authorities of China, urgently investigated this in order to recognize this outbreak as well as methods to control this disease. The precautions taken included segregation of patients having this disease, deep observation of other people who has been in contact with the patient, collecting patients' data clinically and epidemiologically and establishment of methods that can help in diagnosis and cure.

Chinese scientific scholars found a novel Corona Virus (CoV) from infected people in the city of Wuhan, by 7th January 2020. The DNA sequencing of the 2019 novel Corona Virus (2019-nCoV) became the reason for fast establishment of Point-Of-Care Real-Time (RT-PCR) diagnostic tests specifically for 2019 novel Corona Virus, which was based on full genome sequence data on the Global Initiative on Sharing All Influenza Data [GISA-ID] platform. By this time cases of 2019 novel coronavirus were not only limited to the city of Wuhan, but had also been reported in other countries of the world. 9 export cases of this viral infection were found in the United States of America, Thailand, Japan, Korea, Singapore and Vietnam. Travelling by air was highly probable cause in spreading of this infection.

The reported cases of novel Corona Virus in health care personals, especially those who were involved in the care of infected patients showed that this infection transmitted from person to person and thus chances of spreading was high for this infection. By January 23rd 2020, a sum of 835 cases of 2019 novel Corona Virus infection had been identified in China, among which 23 had lost their lives while 93% were admitted in hospitals (Wang et al., 2020a).

The 2019 novel Corona Virus, is a beta Corona Virus belonging to group 2B and 70% similar to Severe Acute Respiratory Syndrome Corona Virus in genetic sequencing. The 2019 novel Corona Virus differs from both Middle East Respiratory Syndrome Corona Virus and Severe Acute Respiratory Syndrome Corona Virus. It is the 7th member of the family that causes similar human infection. It is believed to have originated from Chinese horseshoe bats that are natural source of Severe Acute Respiratory Syndrome Corona Virus and can transmit from person to person (Song et al., 2020)
The 2019 novel Corona Virus is closely similar to the bat Corona Viruses and it is thought that it is originated from bats but still investigations are ongoing. According to the recent findings it has been suggested that it is transmitted to humans from wild animals that were marketed illegally in the Huanan Seafood Wholesale Market.
Huang and his associates primarily documented 41 cases of 2019 novel Corona Virus–Infected Pneumo-

nia (NCIP), among which many patients were known to be exposed to Huanan Seafood Wholesale Market. The clinical indications from patients included fever, dry cough, shortness of breath, muscular pain, fatigue, usual or lower leukocyte counts and pneumonia confirmed by radiographic test.

Irregular function of organs (like shock, Acute Respiratory Distress Syndrome, Acute Heart Injury and Acute Kidney Dysfunction) and death was also reported in extreme cases. Chen and his associates also documented reports for 99 cases of 2019 Novel Corona Virus Infected Pneumonia (NCIP) from similar hospital and accordingly concluded that the 2019 novel Corona Virus infection, was more likely to be found within groups of people who were in close contact and it affected elderly more especially those with comorbidities and resulted in Acute Respiratory Distress Syndrome.

The distinction in clinical features between severe and mild cases were not documented, however case reports showed person to person transmission of novel Corona Virus Infected Pneumonia (Wang et al., 2020b).

World Health Organization confirmed the COVID-19 as a pandemic on 11th March 2020. The confirmed cases were found to be 30 675 675 including 954 417 deaths by 20th September 2020. Patients having comorbidities like elevated blood glucose levels, heart diseases, respiratory problems as well as cancer are more likely to have serious problems and chances of death. This worldwide calamity needs united struggles of every person to combat it (Cheng et al., 2020).

Findings reveal that in seriously ill patients hyper inflammation was found and it involved increased serum C-reactive Protein (CRP), procalcitonin (PCT), D-dimer as well as hyperferritinemia. These indications proposed a possible essential part of a cytokine chain in pathophysiology of COVID-19. Lab biomarkers to predict the serious illness by COVID-19 are important as resource provision must be wisely planned in the perspective of respiratory treatment. Huang and co-workers performed a systematic analysis as well as meta-analysis to examine the relationship between various biomarkers involving serum C-reactive protein, procalcitonin, D-dimer together with serum ferritin with the seriousness of illness (Huang et al., 2020).

BIOCHEMICAL PARAMETERS:
ELEVATED FERRITIN LEVELS:

Huang and co-workers conducted the data based study and found that in ten studies increased ferritin level was reported in patients who lost their lives due to COVID-19 and also in patients that were severely affected by COVID-19. They also noticed that increased serum ferritin levels were related with Acute Respiratory distress Syndrome, death as well as serious illness of COVID-19. Hence, the existence of secondary hemophagocytic lymphohistiocytosis (sHLH) in COVID-19 patients can be hypothesized. It is a state of increased inflammation characterized by a cytokine storm, which leads to multiple organ damage. The condition is known to be activated by infections caused by the virus (Huang et al., 2020). Ferritin is known to be a major mediator of irregular immune system particularly in severe hyperferritinemia through direct immune-suppression as well as pro-inflammatory effects that contribute in creating cytokine storm. Increased serum ferritin levels are noticed in diabetic patients. Also diabetic patients are most likely to have severe complications due to COVID-19. Vargas and co-workers briefly reviewed proofs in order to support their idea that levels of ferritin can be a key factor that influences COVID-19 severity.

One study based on a sample size of twenty patients of COVID-19 revealed that patients affected severely by COVID-19 showed higher levels of serum ferritin. Also, the group of people that were affected very severely by COVID-19 had marked increase in serum ferritin in comparison to group that were less severely affected by COVID-19.

An additional study showed that the individuals who did not survive due to COVID-19 had higher levels of ferritin at the time they were admitted in the hospital as well as during the time they stayed in the hospital. In addition, it was found that from day 17 of hospitalization the median values of serum ferritin levels in these individuals go beyond the upper limit, showing that levels of ferritin were elevated continuously. Lab results of individuals affected severely by COVID-19, commonly revealed cytokine storm including higher inflammatory markers, involving ferritin, which is related with serious condition. Iron chelators can help to reduce levels of ferritin. Deferoxamine may possibly be an appropriate option because of its safety as well as approval by Food and Drug Administration for clinical use. Non pharmacological management such as reduced intake of iron containing food can be applied, as it showed modification in levels of serum ferritin (Vargas-Vargas and Cortés-Rojo, 2020).

Gao et al reviewed a study that included 141 patients infected by COVID-19. The high levels of serum ferritin (more than 500 microgram per liter) was indicated in individuals severely affected by COVID-19 at the time they were admitted in hospitals while the individuals having mild illness had shown regular mean serum ferritin levels (303 ± 224 microgram per milliliter). In addition, individuals with severe disease as well as patients of Intensive Care Unit showed elevated levels of ferritin in comparison to individuals that had mild illness. One of the studies

reported elevated mean serum ferritin levels in individuals having moderate to severe illness in comparison with individuals suffering from mild illness. Wu and co-workers noted marked increased in serum ferritin levels in individuals having Acute Respiratory Distress Syndrome in comparison with individuals having no comorbidities. Plasma therapy, high-volume hemofiltration and desferrioxamine can be considered to reduce ferritin levels in individuals having COVID-19. These strategies at present are utilized to treat sepsis as well as macrophage activation syndrome (Gao et al., 2021).

Deng and his associates, evaluated hyperferritinemia as an expecting element of death in individuals admitted in hospital due to COVID-19. They collected data of 100 COVID-19 positive patients that were admitted in hospital. They divided these individuals into three groups according to the guidelines given to detect and treat 2019 novel Corona Virus Infected Pneumonia. The group classified as Moderate exhibited fever as well as respiratory indications like dry cough together with chest X-Ray indicating pneumonia. The severe group was classified on the basis of fulfilling the parameters such as shortness of breath, respiration rate greater than or equal to thirty times per minute; oxygen saturation measured by pulse oximeter less than 93% at rest; partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than or equals to 300 mmHg. Critical group was described by parameters such as, respiratory failure as well as need for mechanical ventilation, shock as well as other organ damage that required Intensive Unit Care. Severe as well as critical individuals were kept in Intensive Care Unit for treatment. The results of the study reported that levels of ferritin in critical individuals were markedly elevated in comparison to moderate as well as severe individuals. Moreover, the median concentration of ferritin was markedly increased in mortality group in comparison to survival group. In addition, the ferritin levels in critically ill patients was 2.3 to 4.6 times higher in comparison to patients who were moderately affected. The group containing increased ferritin levels were found to have higher death rate. The study reported higher ferritin levels in COVID-19 positive patients. Although elevated ferritin level is related with death rate, ferritin is not considered a depending factor to predict in-hospital death in individuals who are COVID-19 positive in Intensive Care Unit (Deng et al., 2021).

Table 1: Clinical characteristics and Laboratory results in patients with COVID-19:

Characteristics	Total (n =100)	Moderate (n=17)	Severe (n=40)	Critical (n=43)	Reference
Ferritin (µg/L)	1023.80 (434.45 - 1821.38)	370.70 (89.90 –756.00)	855.75 (434.4 - 1687.2)	1715.8 (965.6 - 2429.2)	15-150

(Deng et al., 2021)

Cao and his co-workers assessed the capability of ferritin to induce liver injury as well as enhance severity of illness on hospital admission and the tool to predict consequences in order to arrange management for successive medical practice. They conducted a study on total 147 COVID-19 positive patients. Ferritin levels were indicated in 79 patients were included in the study. They found that the severity of disease in the group that had increased ferritin concentration was markedly increased in comparison to normal group. Also, the individuals having increased ferritin concentration had greater rate of liver injury in comparison to those individuals who presented normal concentration of ferritin. The study also indicated value of ferritin for diagnosis of patients at the time of hospital admission (Cao et al., 2021).

CONCLUSION

Based on various studies it is concluded that ferritin level is likely to predict mortality and severity of illness. Moreover, it is a valuable detector in COVID-19 and together with other clinical parameters and chemical biomarkers it can be helpful in designing treatment strategies.

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