

## Review article

# IMMUNOMODULATION USING NATURAL PRODUCTS TO PROVIDE INNATE IMMUNITY TO AGEING POPULATIONS AS PREVENTIVE MEASURE FOR COVID-19

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## Abstract

*With the pandemic in its full swing, thousands have lost their lives. The number of COVID-19 has crossed 3 million marks worldwide and more than 75 companies are racing with each other to launch the vaccine for the Coronavirus infections. The major brunt of the viral infection was on the ageing populations around the world. Ageing people, especially with chronic diseases and compromised immunity, were the largest victims with no therapy officially approved by US FDA and /or hopes for a quick vaccine for the prevention is in near sight, there is need for an alternative to seeking a solution to build innate immunity of the ageing populations. Antioxidants from natural resources can be a very good alternative to help the ageing populations and if they can adopt a healthy lifestyle and consistently use natural antioxidants in their diet and as Nutraceuticals, there is a possibility that for the second and third wave of this virus they will be prepared better to face the infections. This review covers various aspects of the innate immunity, and how antioxidants show a promise for ageing populations.*

**Keywords:** Antioxidant; Nutraceuticals; Innate Immunity; Immunomodulation; COVID-19; Viral infections; Inflammatory diseases; Natural products; Ageing population.

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## **Introduction**

The worldwide threat of the pandemic due to Corona Virus-19 has been very imminent. Based on the data of the number of cases and number of deaths happened globally appears to be not only scary but also posing challenges to the scientist's community crossing all the professional barriers. We have collected the data based on St John's University COVID-19 Visualizer on April 29, 2020, enumerated in Table 1. These numbers are growing every day and the end of the pandemic is not visualized in the near end.

Even though many countries have reported that the curve of infections is flattening and many countries have opted to loosen up the lockdown requirements. But the most frightening thing in those countries which are opening the lockdowns is the significant surge in the number of cases as well as deaths.

### **What is Corona Virus?**

Even though people are referring to present 2019-2020 pandemic as COVID-19 coronavirus infections, there have been many coronaviruses existed earlier also.

The term refers to several viruses that are commonly affecting humans and are found to be existing in animals too. Coronaviruses are the reason for more than 30% of cases of the common cold globally. Corona is Latin for "crown" – this specific group of viruses is given its name because its surface appears to be like a crown under an electron microscope [1].

In last few years, two major outbreaks of new diseases in recent history were also attributed to the coronaviruses – SARS in 2003 that resulted in around 1,000 deaths and MERS in 2012 that resulted in 862 deaths [2]. This particular virus named as COVID-19 was first reported in Wuhan, China in 2019 and later was found to be part of the coronavirus species and was termed as COVID-19.

### **The ageing population and COVID -19 infections**

Current data across different part around the globe suggests that the elderly are the most at risk [1].

It's helpful to estimate the risk of death across a population – it is observed that the major group of the population who have succumbed to the COVID-

19 belong to age group 65 and above and especially those who had existed health conditions such as diabetes, blood pressure, heart problems which led to comprising immunity of that individual.

But during an outbreak, it's also crucial to mention that these groups within a population are considered to be most at risk. In many western countries such as Italy, France, Spain, the United Kingdom and the USA, the major fatalities were observed in ageing populations. There are reports where a large population living in old age homes were the target of the COVID-19 and subsequently succumbed to death due to COVID-19 infections.

Table 1: COVID -19 pandemic cases and deaths as reported by John Hopkins COVID-19 visualizer.com data based on April 29, 2020, at 2.30 PM to 3.00 PM

Name of the country	Number of reported deaths	Number of reported active cases	Number of recovered cases
Total world	225617	1976821	986622
United States of America	60495	843987	144352
Italy, Europe	27682	104657	71252
Spain, Europe	24275	79695	132929
France, Europe	23660	95365	46886
Great Britain, Europe	26097	138780	37013
Iran, Middle East	5957	13909	73791
Turkey	3081	70486	44022
Germany, Europe	6376	34167	120400
Brazil	5158	36791	32544
India	1008	22983	7796
Indonesia	784	7596	1391
Australia	89	990	5667
Japan	394	11443	1899
China	4633	647	77578
Argentina	207	2728	1192
Colombia	269	4412	1268
Ethiopia	3	69	58
Kenya	14	241	129
Central African Republic	0	40	10

For COVID-19 cases the opposite seems to be true. The elderly are at the greatest risk of dying if infected with this virus. It was observed that once the patient is transferred in ICU and was kept on a ventilator, almost 80% of these patients died and the majority were ageing patients.

It may not simply be that the older you get, the more you are at risk, people with underlying health conditions – such as cardiovascular diseases, respiratory diseases or diabetes – were at higher risk than for those without it. Elderly people are more likely to have those conditions, which is likely to be part of the reason why the elderly are most at risk from COVID-19. Table 2 shows the data reported of the deaths caused by COVID-19 based on the age of the person as per reports presented in the CDC website [1].

Table 2: Percentage of people died based on age group

Countries Age group	South Korea	Spain	China	Italy
80+ years	13%	15.6%	14.8	20.2 %
70 to 79 years	6.3 %	4.8%	8.0 %	12.8 %
60 to 69 ears	1.8 %	1.9 %	3.6%	3.5 %
50 to 59 years	0.5 %	0.4 %	1.3 %	1.5 %
40 to 49 years	0.1 %	0.3 %	0.4 %	0.4 %

### **An ageing population with compromised immunity**

Early data from China suggests that those with underlying health conditions are at a higher risk. Table 3 here shows the fatality rate for populations within China based on their health status or underlying health condition. This is based on the same data from the Center for Disease Control and Prevention recorded in China in the period up to February 11, 2020.

The researchers reported those with an underlying health condition are much more susceptible to COVID -19 infections than normal healthy individuals. For instance, more than 10% of people with cardiovascular disease and who were diagnosed with COVID-19, died. Diabetes, chronic respiratory diseases, hypertension, and cancer were all risk factors. By comparison, around 0.9% suffered from infections leading to death for those without a preexisting health condition.

Table 3: Fatality per cent of patients with underlying pre-existing health conditions suffered from COVID-19 based on data reported in the CDC website from China on February 20, 2020.

Disease condition	Per cent fatalities	Total deaths and cases reported in China on 20 <sup>th</sup> Feb 2020
Cardiovascular Diseases	10.5 %	2240/76000
Diabetes	7.3 %	2240/76000
Chronic respiratory diseases	6.3 %	2240/76000
Hypertension	6.0 %	2240/76000
Cancer	5.6 %	2240/76000
No pre-existing condition	0.9 %	2240/76000

### **Efforts for drug treatment or vaccine development for COVID -19 patients:**

More than 75 companies are racing to produce vaccines for the COVID-19 and many clinical trials have been already started in human beings and it is expected that the vaccine may be available in 12 to 18 months any time. The USA FDA is pushing for even earlier launching of the vaccine. There are several drugs which have been tried for treating patients with COVID -19 infections including Chloroquine, Hydroxychloroquine and so on. But these were not approved by the US FDA, as it had shown several side effects. Recently, the US FDA has provided an emergency approval to a drug Remdesivir launched by Gilead based preliminary clinical trials which have shown success in reducing the length of the COVID-19 infection time.

Remdesivir (RDV) is a type of broad-spectrum antiviral medication called a nucleotide analogue. It is currently an investigational drug and not approved by any country for any use. COVID-19 is an RNA virus. RNA is the molecular transcription tool organisms use to build proteins using DNA instructions. RNA viruses are dependent on an RNA polymerase enzyme to grow the RNA chain. Remdesivir substitutes this RNA polymerase enzyme, meaning that the RNA can't develop so the virus cannot replicate itself [3]. The only side effects reported are increased concentration of enzymes in the liver causing liver damage, in turn, may also affect the immunity of the patients in the long term but not yet fully established.

Remdesivir is currently under investigation for the treatment of COVID-19; however, safety and efficacy are yet to be established. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. Emergency Use Authorization was issued by USA FDA as of May 1, 2020, for use in hospitalized adults/children with suspected or laboratory-confirmed COVID-19 who have severe disease. The patient must be given a Fact Sheet, be informed of alternatives, that Remdesivir is an unapproved drug, and have a baseline eGFR (or SCR), and LFTs. Healthcare facilities and healthcare providers receiving remdesivir must track serious adverse events. Submitted reports should state, "use of remdesivir was under a EUA" at the beginning of the question "Describe Event" for further analysis.

The open-label study assessed compassionate use in severe COVID-19 hospitalized patients needing O<sub>2</sub> support; 36 of 53 patients (68%) showed clinical improvement, 7 patients (13%) died during 18-day median follow-up. 57% (17 OF 30) on mechanical ventilation were extubated, 75% (3 of 4) receiving ECMO stopped receiving it.

Preliminary results from Adaptive COVID-19 Treatment Trial (ACTT) sponsored by NIAID suggests remdesivir group recovered 31% faster vs. placebo, the median time to recover was 11 days (RDV) vs 15 days (placebo), the mortality rate was 8% (RDV) vs 11.6% (placebo).

SIMPLE Phase III trials evaluating 5-day and 10-day dosing durations in moderate and severe COVID-19 are underway. Initial phase outcomes include comparable time to clinical improvement with 5 and 10-day course (50% of patients improved in 10 vs 11 days, respectively). The most common adverse events occurring in more than 10 per cent of patients in either group were nausea and acute respiratory failure. 7.3% of patients experienced Grade 3 or higher liver enzyme (ALT) elevations, with 3.0% of patients discontinuing remdesivir treatment due to elevated liver tests [4].

### **Immunity boosters for the ageing population to face the future onslaught of COVID-19**

It is expected that the COVID-19 infections will continue for another few months to a few years, nothing is sure as yet and no scientific data is available to support these statements. Based on previous viral epidemics these statements are made by the scientific community but being a very new

virus, very little data is available for scientific predictions. In such a scenario what is left to the ageing patients is to use natural products, which may boost the innate immunity of the ageing population, which may be helpful to fight the viral infections. Unless the vaccine is available which is reliable or some treatment regimens are available which will cure the COVID -19 infections, the patients have no other alternatives to look for.

For centuries natural products have been used and have demonstrated their effectiveness which is helpful to improve metabolic disorders, cardiovascular diseases, inflammation and neurological disorder [5]. Natural products have also been implicated to improve the immune function of the human body using natural fatty acids, herbal medicines and natural antioxidants and probiotics which help to build microbiota, in turn, contributing to innate immunity [5]. Natural products have significant potential to help the ageing populations worldwide to help them in building their immunity using these products as immune modulators. They have shown significant potential to help in inflammatory diseases such as the COVID-19 where the first symptoms are described as an inflammation of the throat and later that of lungs, ultimately leading to death due to many other reasons including cardiovascular failure.

### **Inflammation, Reactive oxygen species (ROS) and Immunity**

Many natural processes happen in our body regularly and these processes can develop free radicals within the body during these processes. These free radicals are part of the reactive oxygen species (ROS), as the concentration of these ROS species grows in the body system it is manifested in the form of inflammation and we see many inflammatory diseases. A consistently high level of ROS within the human body is a precursor to common conditions in older adults including diabetes, hypertension and so on. Most of the chronic diseases tend to develop such ROS within the body leading to some sort of inflammation. Even though our body system has an inbuilt mechanism to create antioxidants to reduce the concentration of ROS but during ageing, this mechanism also get affected and there is a need for external supply of antioxidants which can fight with the ROS reducing their concentration and in return providing relief to the patients. We are constantly exposed to many external sources which enhance the free radical formation such as pollution, smoking, pesticides, radiation and the viruses which cause

an increase in ROS concentrations. COVID-19 also has shown to enhance such mechanisms in the body leading to inflammatory indications.

If the ageing populations are engaged in using such natural products which have antioxidant activity then that can build their innate immunity to fight the probable future COVID -19 infections and they may perform better with increased immunity [6].

### **Immunomodulation using antioxidants**

Immunomodulation is a process where one uses external resources to change the immune and inflammatory reactions of the body to occur due to external or internal triggers in body systems. The immune system of the body is a process of constant surveillance for external attacks, and problems, such as viral infections. Appropriate methods of immunomodulation can help innate immunity, acquired humoral (B cells) and/or T cells or all the three to develop the fighting mechanism of the body for external challenges. Human body immune system is especially sensitive to oxidative stress, excess of ROS induce the production of COX-2, inflammatory cytokines (TNF-alpha, IL-6 and chemokines. In the case of COVID-19, the scientists have described it as a cytokine storm created by COVID-19 in the patient's body.

Hence, natural antioxidants will help the ageing population to fight the viral onslaught in a better way by building the innate immunity. Table 4 lists the commonly used antioxidants which are readily available in the Nutraceuticals market [7].

### **Some interesting research data related to Antioxidant Nutraceuticals:**

Flavonoids are naturally occurring in plants; these molecules are reported to protect against UV –B radiation and pathogen infection [8]. Peterson et al. [9] showed the association between flavonoids and cardiovascular disease incidence or mortality in European and US populations. Johnson has described the role of Carotenoids in human health showing antiviral effects of these plant-based compounds [10]. Flavonoids (including around 6000 phenolic compounds) are considered to be part of the products of the metabolism of plants which can be added to the human diet through consumption of vegetables and edible plants. Flavonoids are classified into



1. Flavonols (such as quercetin, kaempferol, isoquercetin, etc., found in onions, apples, berries, kale, leeks, broccoli, blueberries, red wine and tea),
2. Flavones (such as glycosides of luteolin, chrysin and apigenin, commonly found in fruit skins, parsley and celery),
3. Isoflavones (such as genistein, daidzein and glycitein present in leguminous plants, mainly soy and soy products),
4. Flavanones (such as naringenin, eriodictyol and hesperidin exclusive of citrus fruits),
5. Flavanols (such as epicatechin, catechin, gallic acid, epigallocatechin, epigallocatechin gallate and also polymeric forms of condensed tannins as found in cocoa and tea),
6. Anthocyanidins (such as pelargonidin, cyanidin and malvidin, found in red wine and berry fruits).

Table 4: Readily available antioxidant Nutraceuticals in the market

Group	Examples	Natural sources
Vitamins	Vitamin A and E	Naturally build when exposed to sunlight, Vitamin E capsules available in market
	Vitamin C	Citrus fruits, Strawberries, Sweet peppers
	Vitamin D	Vitamin D capsules available in market
	Beta Carotene	Carrot and other similar natural products
	Folic Acid	Readily available as a marketed product
Phytochemicals	Carotenoids, Saponins, Tacopherols	Carrots, sweet potatoes Apricots, Soybeans, Whole grains, nuts, oils, garlic
	Polyphenols and Flavonoids	Berries, Coffee, tea, legumes
	Allyl Sulphides	Garlic
	Cannabis	Readily available in the market nowadays
Microminerals	Magnesium	Mineral source and markets as product
	Selenium	Mineral source and markets as product
	Zinc	Mineral source and markets as product
Enzymes	Co Q-10	Naturally found in human cells, also available in market
Fatty acids	Omega 3 fatty acids and lipids	Oils, avocados, walnuts, canola oil
	Alpha-Lipoic acid	Synthetically available as capsules in the market
Miscellaneous	Mushrooms	Naturally available

Chemically, flavonoids have a polyphenolic structure due to which they exhibit antioxidant activities. The antioxidant properties of flavonoids have been recognized more than 40 years ago [11] and, in that time (1976–2016) nearly 23,000 publications have appeared (more than 20,000 research articles and 2600 reviews) according to research in the Scopus database (searching ‘flavonoid and antioxidant’) [12].

Reported flavonoid biological activities go much beyond antioxidant properties which include protective effects against cancer, cardiovascular diseases, gastrointestinal alterations, and nervous system-related syndromes, such as depression, epilepsy, Alzheimer’s disease and neurodegenerative disease [12].

*Nutrients* came up with the Special Issue entitled, ‘Flavonoids, Inflammation and Immune System’ which was aimed encouraging researchers to report about the inflammatory response, mainly conducted by macrophages and neutrophils as an expression of the innate immune system activation; and the immune system concerning, and the acquired immunity [12]. We strongly recommend the readers to visit the issue and review all the articles presented by the authors from many different countries [13-16].

A report by Hajian from Iran reported that antioxidants preserve the function of immune cells of the human body against homeostatic disturbances caused by oxidative stress. Since the immune system is an indicator of human health and human longevity, the protection of this system can be afforded by dietary antioxidant. Antioxidant, vitamins and trace elements (Zn and Fe) have important effects on immune responses [17].

An interesting paper recently published mentioned that a strong immune system is an essential precursor for healthy ageing. Several strategies adopted to boost the immune system have been recommended to reduce the incidence and severity of infectious diseases. Simple and powerful tools are already in our hands: the antioxidants which can significantly improve the innate immunity. As we get older, or when we are particularly stressed suffering from chronic diseases caused due to inflammatory symptoms, high levels of reactive oxygen species (ROS) accumulate, promoting oxidative stress in our body. In this situation, normal body functions, in particular the immune systems, are severely impaired by an excess of oxygen radicals and pro-inflammatory molecules. For this reason, blocking the side effects of

ROS with antioxidants may help us improve our immune system performance [18].

### **Conclusion**

Coronavirus -2019 has created a pandemic worldwide and thousands of people have lost their lives. The majority have been ageing populations, especially who had compromised immune systems and suffering from chronic diseases. At present, there are no vaccines or therapeutic treatment for this viral infection. Several clinical trials are undergoing and there will possibly be a solution in near future. There are always threats of new and newer viruses, which will attack human populations. In such a scenario building the innate immunity of the human being will be one important alternative and natural products will play a major role in such efforts. The research clearly shows that antioxidants and many natural products have the potential to build the innate immunity as well as interact with the ROS which is a part of the inflammation caused by viral infections. In the present scenario where neither vaccine nor drugs are available, the only alternative will be to seek such natural products which are safer for use and effective for ageing populations.

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