ROLE OF NATURAL NUTRACEUTICAL INGREDIENTS IN HOLISTIC RECOVERY OF AFFECTED HUMAN ORGANS DUE TO COVID 19 INFECTION AND ITS TREATMENT

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ABSTRACT

Nutraceutical industry has emerged as a research-oriented sector and its demand during the Covid 19 pandemic has increased tremendously. There is a rapid change in the consumer health consciousness and their lifestyle post covid which have led to a swift growth in a Natural nutraceutical Market. Nutraceuticals are now looked upon as important supplements that are on the priority list of monthly expenses, which, like food, cannot be skipped and has wide range of nutritional as well as therapeutic benefits.

Antiviral drugs such as remdesivir, ritonavir, and lopinavir are also being used; however, they are known to cause severe side effects on different organs [56].

After first phase of Covid-19, the second wave affects a lot to the Indians with mysterious fungal infection known as Mucor mycosis.

The purpose of this study was to understand post covid 19 effects during the treatment and post treatment on specific organs such as brain, lungs, heart, bones, liver, kidneys, skin etc. and effectiveness of natural nutraceutical ingredients to nourish that specific organ and boost overall immunity including side effects of medications provided during the treatment and long-term side effects.

This is a review paper of COVID-19's extensive effects on virtually all the organs and how do natural nutraceutical ingredients will help in recovering fast.

Keywords: Post Covid 19, Natural ingredients, Nutraceutical, health, side effects of medication, Immunity, multiple organs, Mucor mycosis

INTRODUCTION

The regional office of World Health Organization (WHO) in China was first alerted to the virus infection in Wuhan on December 31, 2019 and termed the infection as an epidemic on March 11, 2020. Since then, scientists team working with laboratories across the globe have been collaborating to develop vaccines, therapeutic agents and best ingredients for this novel coronavirus.

As the world entered the COVID-19 pandemic, the market has shifted the food sector towards safety, security, resilience, and sustainability including bioactivity. [16] The demand for foods containing bioactive compounds increased rapidly, as consumers were looking to adopt healthier diets and boost their immune systems. [15] Also **pandemic has generated exceptional opportunities for the Indian Nutraceutical Industry because of its safety and minimal or no side effects.**

In past 20 years more scientific focus has been trained on the identification for novel, health promoting ingredients from nutraceutical and food sector (e.g., Vitamins, Antioxidants) which will be beneficial for human health and useful to boost immunity within the human body. Dr Stephen DeFelice coined the term "Nutraceutical" from "Nutrition" and "Pharmaceutical" in 1989. The philosophy behind nutraceuticals is to focus on prevention, according to the saying by a Greek physician Hippocrates who is known as the father of medicine, said "let food be your medicine". According togenerally accepted definition, functional food includes whole foods and fortified, as well as enriched or enhanced dietary components that may reduce the risk of chronic disease and provide a

health benefit beyond the traditional nutrients it contains by providing nourishment and giving nutrimental value. COVID-19 is characterized by collapsed immune balance, hyperinflammation, cytokine storm, and multiorgan failure. [45]

In this article we give an overview of the present understanding of during the treatment and post Side effects of COVID 19, which would form the basis for selecting nutraceuticals and natural products that can be potentially explored both as therapeutic and preventive interventions for the COVID 19 infection during the treatment and after the medication has been given to support the organ functioning and boost the immunity from within.

Side effects of COVID 19:

WHO 16 October 2021 **– Post covid 19 conditions (Long Covid)**[30]

According to WHO Newsroom, most people who develop COVID-19 infection are fully recover, but current evidence suggests approximately 10%-20% of people experience a variety of mid- and long-term effects after they recovery from their initial illness. These mid- and long-term effects like fatigue, breathlessness and cognitive dysfunction (for example, confusion, forgetfulness, or a lack of mental focus and clarity) are collectively known as post COVID-19 condition or "long COVID."Some people also experience psychological effects as part of post COVID-19 condition.Post COVID-19 condition can affect a person's ability to perform daily activities such as work or household chores.At present, there is no specific medication therapy for people with post COVID-19 condition. However, there is data suggesting that holistic care, including rehabilitation, can be helpful.

People with post COVID-19 condition, also known as "long COVID", may have difficulty functioning in everyday life. Their condition may affect their ability to perform daily activities such as work or household chores. At present, the minimum time before a person is diagnosed with post COVID-19 condition is usually three months after they first developed symptoms of COVID-19. [38]

EFFECT OF COVID-19 ON THE ORGANS

Main part of the human organ which is being mostly affected during Covid 19 infection is the Respiratory system. However, the virus can affect any organ in the body. In critically ill patients, multiple organs are often affected. The virus binds to angiotensin converting enzyme 2 (ACE2) receptors present in vascular endothelial cells, lungs, heart, brain, kidneys, intestine, liver, pharynx, and other tissue [22]. It can easily injure these organs affecting their functionality. In addition, the virus can also lead to organ malfunctioning. Cardiac and renal dysfunction is common among the patients who died because of infection and malfunctioning of organ during the treatment. Injury to the organs may become apparent extended after the acute infection has subsided. Different organs may be affected at different times. Chronic injury may occur. Rehabilitation can be prolonged and difficult.

1. Cardiac effect

According to CardiologistWendy Susan Post, M.D., M.S.John Hopkins medicine, COVID-19, the disease caused by the SARS-CoV-2 coronavirus, can damage heart muscle and affect heart function. There are several reasons

for this. The cells in the heart have angiotensin converting enzyme-2 (ACE-2) receptors where the coronavirus attaches before entering cells. Heart damage can also be due to high levels of inflammation circulating in the body. As the body's immune system fights off the virus, the inflammatory process can damage some healthy tissues, including the heart.

Coronavirus infection also affects the inner surfaces of veins and arteries, which can cause blood vessel inflammation, damage to very small vessels and blood clots, all of which can compromise blood flow to the heart or other parts of the body. "Severe COVID-19 is a disease that affects endothelial cells, which form the lining of the blood vessels".

Type 2 heart attacks are more common with COVID-19"Blood tests have shown that during COVID-19, some people have elevated levels of a substance called troponin in their blood, along with EKG changes and chest pain." Elevated troponin levels are a sign of damaged heart tissue. Sometimes this is from a heart attack. This is less commonly seen after COVID-19."During acute COVID-19, elevated troponin levels with an abnormal EKG are linked to higher mortality, but not in patients with a normal EKG". [27]

Respiratory failure dominates in the early phases of the disease whereas cardiac injury becomes more critical in the later phases.

Myocarditis is more likely the cause in younger patients. Arrhythmias include tachycardia, bradycardia, and asystole. They can be due to inflammation, myocarditis, hypoxemia, metabolic abnormalities, or medications. Cardiovascular complications may occur long after viral clearance and recovery. [31]

People who have high blood pressure, diabetes, or obesity are more likely to have problem from their heart to covid 19.

Valentina O et al. examined the cardiac MRIs of 100 people who had recovered from Covid-19 and compared them to heart images from 100 people who were similar but not infected with the virus. Their average age was 49 and two-thirds of the patients had recovered at home. More than two months later, infected patients were more likely to have troubling cardiac signs than people in the control group: 78 patients showed structural changes to their hearts, 76 had evidence of a biomarker signalling cardiac injury typically found after a heart attack, and 60 had signs of inflammation. [52]

2. Heart failure

In an early study from Wuhan involving 799 patients, heart failure was one of the most commonly observed complications of COVID-19, with a reported incidence of 24% in all patients and 49% in patients who died. [9]

Similarly, in another study of 191 patients in Wuhan, heart failure was identified in 23% of all patients and in 52% of patients who died. [62]

Patients with depressed immunity are at a higher risk of infectious diseases. The effect of COVID-19 on the cardiovascular system in immunocompromised means depends on person-to-person immunity response. [36]

Medication effect: At present, many research teams worldwide are focused on the development of drugs for the prevention and treatment of COVID-19. Of note, the development and testing of new drugs are time-consuming processes [43] and not a viable strategy during this COVID-19 pandemic. Drug, in which existing medications that have already been approved for a disease are tested for a new condition, is currently the main approach in the search for new drugs for COVID-19. [46]

Several medications used for the treatment of COVID-19 have uncertain safety and efficacy profiles.Commonly used medications including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers have

not been demonstrated to increase the risk of COVID-19infection or its complications and should not be discontinued [50].

Finally, medications that have been proposed as treatments for COVID-19 such as hydroxychloroquine and azithromycin have pro-arrhythmic effects. [36]

3. Effect on Kidney

"Sperati, who also conducts research on kidney disease, says the Johns Hopkins Division of Nephrology is exploring exactly how SARS-CoV-2 — and the body's response to it — is affecting kidney health."

The impact of COVID-19 on the kidneys isn't yet clear. Here are some possibilities doctors and researchers are exploring:

- **Coronavirus might target kidney cells**
- **Too little oxygen can cause kidneys to malfunction**
- **Cytokine storms can destroy kidney tissue**
- **COVID-19 causes blood clots that might clog the kidneys[8]**

COVID-19 complicates the management of patients on dialysis and with kidney transplantation [10]. In Britain about 15% of the patients who expired had chronic kidney disease. ACE2 receptors are present in kidneys [42]. The virus is found in glomerular cells, tubular epithelium, and podocytes of kidneys.

Benjamin Bowe et al. (November 2021), his **result analysis was** compared with non-infected controls, 30-day survivors of COVID-19 exhibited excess eGFR decline, in non-hospitalized, hospitalized, and those admitted to intensive care during the acute phase of COVID-19 infection.

His conclusion on this was patients who survived COVID-19 exhibited increased risk of kidney outcomes in the post-acute phase of the disease. Post-acute COVID-19 care should include attention to kidney disease. [6]

Medication: Acute kidney injury is also caused by rhabdomyolysis due to hyperventilation or medications. Rhabdomyolysis is a serious syndrome due to a direct or indirect muscle injury. It results from the death of muscle fibres and release of their contents into the bloodstream. This can lead to serious complications such as renal (kidney) failure. This means the kidneys cannot remove waste and concentrated urine.

Including antivirals such as remdesivir. In New York, about 90% of patients who were onmechanical ventilation developed AKI [21]. AKI occurs in temporal association with respiratoryfailure.

4. Effect on brain

It is clearlyrecognized that COVID-19 infection represents a multiorgandisease that can affect almost every organ, including the brain. [48]

The ACE2 receptors are present in the cerebral cortex and brain stem. Some patients have meningitis and encephalitis indicating viral invasion of the central nervous system (CNS). Neurological manifestations may be the only ones observed or may occur in combination with respiratory or other symptoms [19, 35, 50]. Neurological manifestations are more common in people with more severe disease. Altered oxygen and carbon dioxide levels may contribute to them. They include dizziness, headache, impaired consciousness including confusion, delirium,and inability to rouse.Brains of dead patients demonstrate hypoxic changes but encephalitis or other changes due to the virus are rare [47].A systematic review of neurological manifestations in COVID-19 describes headache and anosmia as the most common symptoms. [58]

5. Effect on eyes

Both ACE2 receptors and TMPRSS2 proteases that are necessary for infection by SARS-CoV-2are found in ocular surface cells in cornea, inside the eyelids and in the white of the eye. [61]

About one-third of hospitalized patients develop ocular abnormalities includingconjunctivitis [59]. Conjunctivitis is more common in the sicker patients. Ocular involvementmay occur early. Ocular surface cells are portals of entry and reservoirs of the virus. Ocular virusshedding is a source of infection. Infectious virus can persist in the eye for up to threeweeks [11].

6. Gastrointestinal effect

Gastrointestinal (GI) symptoms include loss of appetite, nausea, vomiting, diarrhoea, and abdominal pain or discomfort [18, 38]. These symptoms might start before or occur with or without other symptoms such as fever, myalgias, and cough. Lower GI tract is rich in ACE2 receptors.

More than one half of COVID-19 hospitalized patients have elevated lactate dehydrogenase and other liver enzymes indicating injury to the liver or bile ducts. This is likely to be due to an overactive immune system or due to drugs causing liver damage. [31]

7. Effect on skin

Patients may develop livedo reticularis. It is a purplish net-like discoloration of the skin, often a result of blood clotting abnormalities. Lacy, dusky rashes, including dead skin cells are observed on the arms, legs, and buttocks. They are associated with hypercoagulability. Petechiae are present. COVID toes and fingers have frostbite-like areas with red or purple rash or hive-like eruption.[31]

8. Psychological effects

Because of financial difficulties and social isolation due to COVID-19, many psychological problems can arise. They can be delayed by months. There is an increase in "deaths of despair" from substance abuse or suicide. The risk is greater among persons with dementia, mental illness, and autism. In person and online communication with friends and support professionals is beneficial.[31]

Some patients who recover from COVID-19 develop mental health problems [41]. These includeanxiety, depression, and post-traumatic stress disorder (PTSD). Long term effects can includedevelopment of Alzheimer's or Parkinson's disease.

DRUG THERAPY GIVEN TO COVID 19 PATIENTS

COVID-19 was treated primarily with corticosteroids, remdesivir, or both. Favipravir, doxycycline, azithromycin, ivermectin, and zinc were also common treatments. Amphotericin B, posaconazole, and surgery were the most common antifungal treatments. Among 53 patients with available follow-up data at 42 days, 17 (32.1%) had an incomplete recovery, 20 (37.8%) had a full recovery, 10 (18.9%) had vision loss, and 6 (11.3%) had died. [5]

TABLE 1: Drugs and their role in treatment and side effects

Drugs	Mechanism of action	Side effects	References
Antimalarialagents (chloroquine [CQ] and hydroxy-chloroquine	Preventing virus penetration to cells	heart rhythm problems	**25**
Azithromycin (antibacterial drug)	Influences intracellular mitogen-activated protein kinase (MAPK),	Cardiac Arrhythmias	**32**
Fabiflu/fabipiravir	elective inhibition of RNA-dependent RNApolymerase enzyme in RNA viruses	nausea and vomiting, hyperuricemia,diarrhea, reduced neutrophil	**1**

Remdesivir	Adenosine analog, insertion into viral RNA chains,and termination of replication	respiratory failure and organ dysfunction,low albumin, low potassium, low red blood cell count low platelet count, which helps clots, and yellow skin discoloration	**60**

Many other drugs (oseltami-vir, lopinavir/ritonavir, and ribavirin) are metabolized in the liver andexcreted through urine. [12]The Liverpool Drug Interaction Group shares drug- drug interaction report for hydroxychloroquine and azithromycin.[23]

A case series was reported of 40 patients with COVID-19 who were treated with hydroxychloroquine with or without azithromycin. Thirty-seven (93%) patients experienced a prolongation of QTc, with 14 (36%) experiencing an increase > 60 ms and 7 (17.5%) ≥ 500 ms. Of those prescribed both hydroxychloroquine and azithromycin, 6 (33%) experienced QTc prolongation ≥ 500 ms. The authors raise concerns about the use of hydroxychloroquine (with or without azithromycin) in settings where clinical monitoring is not available.[7]

Coadministration of hydroxychloroquine and azithromycin was associated with a greater prolongation of QTc than administration of hydroxychloroquine alone. The authors advise risk assessment before co-administering hydroxychloroquine and azithromycin with close monitoring of QTc.

WHAT IS THE DISEASE MUCOR MYCOSIS OR THE BLACK FUNGUS?

Mucor mycosis or the black fungus is a rare fungal infection caused by the fungi of the class zygomycetes that affects patients whose immunity is compromised. It is fatal if not identified and treated in the early stage. It affects the brain, lungs, sinuses and can be life threatening in diabetic or severely immunocompromised individuals such as Cancer patients and HIV/AIDS patients. [28]

Although rare, it is a serious infection. It is caused by a group of moulds known asmucoromycetes present naturally in the environment. It mainly affects people who are on medication for health problems that reduces their ability to fight environmental pathogens, say experts from the Covid-19 task force task force.

Usually, mucoromycetes does not pose a major threat to those with a healthy immune system.

Who is at a risk?

Patients most vulnerable to Mucor mycosis are those who have been treated with steroids and other drugs for Covid 19 to reduce inflammation. [24]

Role of various natural Nutraceutical Ingredients on affected organs:

The Role of Food Ingredients and Active Compounds in Supporting the Human Immune System

Several nutritional supplements and natural products with immunomodulatory properties have been tested as potential therapeutic adjuvants in the fight against COVID-19. They have already been tested with some successes in clinical trials targeting various diseases

Curcumin

Curcumin and other curcuminoids are the main bioactive ingredients of turmeric (Curcuma longa). They have been used for millennia in the traditional medicines of multiple cultures due to their anti-inflammatory, antioxidant, antibacterial, antiviral, antidiabetic, and neuroprotective properties. [51]Curcuminoids have received approval from the USA Food and Drug Administration (FDA), and these compounds have good tolerability and

safety [20].Ahmadi, Iran, 2020, have studied the Treatment duration: 2 weeks Follow-up: 2 weeks after treatment 30 mild to moderate COVID-19 patients 27 mild to moderate COVID-19 patients, Sinacurcumin® soft gel 40 mg - Intervention group received 2 soft gels after breakfast and 2 soft gels after dinner daily for 2 weeks. - Placebo soft gels were prepared by the same company, with the same appearance containing all ingredients of medicine soft gel except curcumin with same dosing (2 soft gels twice daily after meal).

Positive effect of curcumin therapy observed. All symptoms except sore throat resolved faster in the treatment group, and the difference was significant for chills, cough, and smell/taste disturbances. CRP serum level was lower in the treatment group at the end of two weeks, and lymphocyte counts were significantly higher in the intervention group. [2]

Curcumin administered with piperine

Pawar, India, 2020, Randomized double-blind placebo-controlled clinical trial, treatment duration: 2 weeks &70 mild to severe COVID-19 patients; Mild (n = 30) Moderate (n = 25), and severe (n = 15). Curcumin administered with piperine - Intervention group received Curcumin (252 mg) Complex® (SamiDirect, India) dietary with (2.5 mg) Bioperine® (SamiDirect, India) twice a day for 14 days from the day of admission. - Control group received a dose of probiotics (Nutrolin B Plus, which contains lactic acid Bacillus and Vitamin B; Ciplamed) twice a day for 14 days. Positive effect of curcumin therapy. Showed early symptomatic recovery and could substantially reduce the duration of hospitalization in patients with moderate to severe symptoms, and fewer deaths observed in the intervention group. [39]

The conclusion part of Fatemeh Babaei, (2020) et. al. "Curcumin has several therapeutic effects including antiviral, antinociceptive, anti-inflammatory, antipyretic, and antifatigue effects with several molecular mechanisms such as antioxidant, antiapoptotic, antifibrotic effects, and inhibitory effects on NF-κB, inflammatory cytokines and chemokines, Toll-like receptors, and bradykinin. The importance of this review is due to the fact that curcumin is a nutraceutical that could be a new treatment option to combat the COVID-19 pandemic." [14]

Ashwagandha

Ayurvedic medicines, especially Ashwagandha (*Withaniasomnifera* (L.) Dunal, WS), may be beneficial in the management of COVID-19. WS is a widely prescribed Ayurvedic botanical known as an immunomodulatory, antiviral, anti-inflammatory, and adaptogenic agent. The chemical profile and pharmacological activities of WS have been extensively reported. Several clinical studies have reported its safety for use in humans. The experimental literature indicates that WS has the potential for 1) maintaining immune homeostasis, 2) regulating inflammation, 3) suppressing pro-inflammatory cytokines, 4) organ protection (nervous system, heart, lung, liver, and kidney), and 5) anti-stress, antihypertensive, and antidiabetic activities. [45]

The chemical profile of several extracts and formulations of WS has been well documented in previous studies. Briefly, withanolides (steroidal lactones), the main phytochemical of WS, play a central role in exhibiting multimodal effects synergistically. These are a group of C28-steroidal lactone triterpenoids, which majorly include withaferin A, withanolide A, B, and D, withanoside IV and V, withasomniferin A, withanone, sitoindoside IX and X, 12-deoxywithastramonolide, etc. Moreover, other polyphenols including catechin, naringenin, syringic acid, and p-coumaric acid were also found in significant quantities in WS extracts. A combination of such versatile phytochemicals potentiates WS as a strong therapeutic agent. [33, 3]

According to Hindustan Times news, "Recently, the minister of state for Ayush, Mahendrabhai Munjapara, informed the Rajya Sabha that the ministry is conducting wide research on the effectiveness of Ayush medicines to curb the Covid-19 outbreak. Scientific studies, as cited by the ministry, have found Ayush 64 useful in

asymptomatic, mild and moderate Covid-19 infection as standalone and adjunct to standard care. AYUSH-64 is a an Ayurvedic formulation which was developed by the Central Council for Research in Ayurvedic Sciences for the management of Malaria. But it is a repurposed drug and the ministry recommended it for Covid-19 too." [26] Ashwagandha has emerged as a widely acclaimed organ-protective drug capable of potentiating several organs to fight against infections and inflammation.

Table no. 2: Inflammation-Induced Organ Failure and role of Ashwagandha

Organ with Inflammation due to Covid 19	Role of Ashwagandha ingredients	Reference
Brain	1.extract can be a promising candidate to prevent neuroinflammation. 2. Several withanolides can cross the blood–brain barrier, which promote their usage in developing a therapeutic and preventive drug for neurological disorders (Vareed et al., 2014).	[17] [53]
Liver	Withanolide-rich fraction isolated from WS root methanolic extract found to restore the marker enzyme levels in druginduced hepatic cytotoxicity in rat models of cytokines	[13]
Heart	WS leaf normalized troponin I release in the blood and thereby preserved structural and functional integrity of contractile myocardium in a rat model	[34]
Gastrointestinal Tract	root aqueous extract expressed antidiarrheal activity and maintained gastrointestinal mobility in the rat model by inhibiting cyclooxygenase and regulating inflammatory markers induced by NF-κB transcription factor	[40]
Kidney	1.WS normalizing histopathological changes in the kidney 2.Withaferin A balances apoptotic markers to prevent cytotoxicity of bromobenzene in the kidney cells	[54] [55]
Muscles	Several clinical trials involving the administration of WS aqueous extract found an increase in the overall muscle strength	[57] [63]
Pancreas	Withaferin A (Tiruveedi et al., 2018) and aqueous extract of WS roots (Anwer et al., 2012) showed protective effects against acute pancreatitis through enzymatic modulation of oxidative stress and inflammation in animal model.	[49] [4]

Resveratrol

Network Pharmacology Reveals That Resveratrol Can Alleviate COVID-19-Related Hyperinflammation.According to some reports published by L.H. Ramdani et. al. Resveratrol could be proposed as potential therapeutics in the treatment of SARS-CoV-2.Resveratrol has been the subject of more than 4,000

studies for its anti-aging, anti-oxidant, anti-inflammatory, anti-viral and cardio-protecting propertiesPotential role of the Resveratrol in mitigating the major effects of SARS-CoV-2. Indeed, Resveratrol was reported to downregulate the main signalling pathways of inflammation by increasing activity of both SIRT1 and p53, two proteins involved in anti-viral activities. It was also shown to boost immune system through activation of CTLs and NK cells and regulation of pro-inflammatory cytokines as IL-1β, IFN-γ and TNF-α. Furthermore, Resveratrol was demonstrated to activate ACE2 and reduce oxidative stress causing lung injury in SARS-CoV-2 infection. Regarding these findings, this report suggests that Resveratrol could be used as therapeutic agent or adjuvantagainst SARS-CoV-2.[44]Mina T. Kelleni suggested resveratrol- zinc nanoparticles possess a major pharmacokinetic advantage for COVID- 19. [37]

RESULT AND CONCLUSION

Coronavirus disease (COVID-19) rapidly spread throughout the world leading to high mortality rates specially people with low immunity. Mitigating or managing a specific disease is essential but it is not sufficient to provide a body with complete recovery and wellness. As a result, it is essential to combine the benefits of modern medicine treatment with natural Nutraceutical ingredients to simultaneously boost immunity and create a holistic recovery. Ingredients such as Curcumin, Peprine, withanolides from Ashwagandha, Resveratrol etc can be used as potential treatment and as nourishing supplement for post covid 19 effects on multiple organs this reduces the natural capability of the body to fight against the virus.

The multidimensional research on Ashwagandha with a deeper understanding of biological mechanisms is a promising area for future exploration as a therapeutic adjuvant.

India has already registered many deaths due to Black Fungus in patients recovering from compromised immune systems. According to WHO, Prevention of COVID-19 associated Mucor mycosis needs to focus on aiming for better glycaemic control in COVID-19 patients and monitoring the use of systemic corticosteroids in treating severe cases. So here can be a great opportunity for Nutraceutical sector to innovate natural form of supplements which can boost immune system.

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