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(Special Issue)

“Impact and approach to pandemic covid-19 on various sectors”

A review on Euryale Ferox: Daily dietary regime for Covid -19 patients

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Abstract

In recent pandemic of Covid-19 i.e. Corona Virus disease, patients who are affected by this disease shows symptoms related to different system of body in which most commonly affected parts are lungs which usually results in mortality of patients. It has also seen that older adults and those having COPD, Heart Disease, Diabetes, Chronic Kidney Disease, and obesity are at increased risk for severe COVID -19 requiring hospitalization¹. This Covid 19 can also produce abnormally high blood sugar levels, even in people without diagnosed diabetes. It also causes fluctuation in Blood Pressure by affecting ACE and RAAS system. Fox Nut or Euryale Ferox is rich in protein, fibres and carbohydrates. The Euryale ferox seeds is a grain dish good for baby and also for an old man to prolong life. It has characteristics of strengthening the spleen, nourishing the stomach, supplementing the kidney². Thus, makhana can be used as nutraceutical supplement for Covid -19 Patients. In a daily diet, it is also believed to increase humoral immunity and cell mediated immunity to some extent. The Euryale ferox seeds and glutinous rice are used in 1:3 ratio to prepare rice dumplings in China. These act as super natural food in diet therapy¹¹. Euryale ferox has many bioactive constituents which performs anti-oxidant activity, anti-diabetic activity, Anti-hyper lipidemic activity, Hepatoprotective activity, anti-cytotoxicity, cardioprotective, anti-depressant activity and much more. Thus, Euryale ferox could be an ideal supplement for Covid -19 patients.

Keywords: Euryale Ferox, Daily dietary regime, Covid -19 patients

Introduction

The COVID – 19 pandemic first became apparent in Wuhan, China. This virus has now spread all over the world. The death rate of this disease in India is 1.11 percent^[3]. Persons who are affected by Corona Virus develops clinical illness, it affects respiratory system most commonly. According to WHO complications leading to death may include respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including injury of the heart, liver or kidneys. However, the virus can affect any organ in the body. This virus binds to angiotensin converting enzyme 2 (ACE2) receptors present in vascular endothelial cells, lungs, heart, brain, kidneys, intestine, liver, pharynx, and other tissue^[4].

According to a preprint from scientists at the Wellcome Sanger Institute and elsewhere. They found that cells in the lining of nose are rich in a cell-surface receptor called angiotensin-converting enzyme 2 (ACE2). Throughout the body, the presence of ACE2, which normally helps regulate blood pressure, it marks tissues vulnerable to corona infection, because the virus requires that receptor to enter a cell. Once inside, the virus hijacks the cell's machinery, making many copies of itself and invading new cells^[4].

As virus multiplies, it has ability to transmit to new victims. During this, especially after first week of infection, person may be asymptomatic or may develop mild symptoms like fever, dry cough, sore throat, loss of smell and taste, or head and body aches. If the immune system doesn't respond to SARS-CoV during this initial phase, the virus then moves down to

windpipe and affects lungs. The end part of respiratory tree are air sacs which are lined by a single layer of epithelial cell that are also rich in ACE2 receptor.

When CoV invades inside the body, immune system responds against invader, this war between antigen and antibodies causes disruption of healthy oxygen transfer. WBCs release inflammatory molecules called chemokines, which in turn call more immune cells that target and kill virus – infected cells, it leaves a lather of fluid and dead cells pus. This is the underlying pathology of pneumonia, with its corresponding symptoms: coughing; fever; and rapid, shallow respiration.

Many patients recover with no oxygen support, but in many patients, deterioration happens often quite suddenly, developing a condition called Acute Respiratory Distress Syndrome (ARDS). Oxygen level decrease and patient struggle ever harder to breathe in. Commonly these patients end up on ventilators.

Impact of Covid on Body

SARS-CoV-2 most commonly damage lungs. But the virus, and body response to it, can injure many other organs.

Effect on Lungs

“The real morbidity and mortality of this disease is probably driven by this out of proportion inflammatory response to the virus”, says Jamie Garfield, a pulmonologist who cares for COVID – 19 patients at Temple University Hospital. A cross section study of alveoli shows that cell crowding an inflamed alveolus, whose wall break down during attack by the virus, diminishing oxygen uptake. Patient’s cough, fevers, rise, and breathing becomes labored.

On Chest CT, findings of subpleural and peripheral areas of ground glass opacity and consolidation are present in patients with COVID -19. Most of the patients have bilateral distribution. On chest radiographs, patchy infiltrates are observed that may be distributed asymmetrically.

Cardiac Effect

IN COVID -19, cardiac complications can occur with or without pulmonary and other complications. Patient may reach to Ischaemic condition having any pre existing Coronary Artery Disease (CAD), those with latent CAD or without CAD. The Primary cause of Ischaemic condition is plaque rupture and thrombosis.

Invasion of myocytes by the virus is observed in some patients. Systemic inflammatory response such as cytokines can cause myocarditis without direct viral infiltration. It can cause heart failure and arrhythmias. Respiratory failure dominates in the early phases of disease whereas cardiac damage becomes more critical in the later phases.

In Brescia, Italy, a 53-year-old woman walked into the emergency room of her local hospital with all the classic symptoms of a heart attack, including telltale signs in her electrocardiogram and high levels of a blood marker suggesting damaged cardiac muscles. Further tests showed cardiac swelling and scarring, and a left ventricle—normally the powerhouse chamber of the heart—so weak that it could only pump one-third its normal amount of blood. But when doctors injected dye in the coronary arteries, looking for the blockage that signifies a heart attack, they found none.

A 25 March paper in *JAMA Cardiology* documented heart damage in nearly 20% of patients out of 416 hospitalized for COVID-19 in Wuhan, China. In another Wuhan study, 44% of 36 patients admitted to the ICU had arrhythmias. According to a 10 April paper in *Thrombosis Research*,

among 184 COVID-19 patients in a Dutch ICU, 38% had blood that clotted abnormally, and almost one-third already had clots.

These blood clots can block vital arteries like pulmonary arteries or even can lodge in brain, causing stroke.

Infection may also lead to blood vessel constriction. Reports are emerging of ischemia in the fingers and toes—a reduction in blood flow that can lead to swollen, painful digits and tissue death ^[4].

Effect on Brain

The ACE2 receptors are present in the cerebral cortex and brain stem. A case study in the *International Journal of Infectious Diseases*, from a team in Japan, reported traces of new coronavirus in the cerebrospinal fluid of a COVID-19 patient who developed meningitis and encephalitis, suggesting it, too, can penetrate the central nervous system. Some people with COVID-19 briefly lose consciousness. Many other report losing their sense of taste and smell. In some cases, infection depresses the brain stem reflex that senses oxygen starvation. This can be an ideal explanation for observational incidence that some patients aren’t gasping for air, despite dangerously low blood oxygen levels. Altered O₂ and CO₂ levels may contribute to many neurological manifestations in combination with respiratory and other symptoms. They include dizziness, headache, impaired consciousness including confusion, delirium, and inability to rouse.

In young patients Stroke can occur due to blockage of a cerebral artery even without any prior history. Cerebral haemorrhage has also been observed. Neurological features among patients in ICU with ARDS included encephalopathy, agitation, confusion and depression.

Psychological effect

Many psychological problems are arising due to financial difficulties and social isolation. Some patients who recover shows different mental health problems. These include anxiety, depression, and post – traumatic psychological disease.

Renal Effect

ACE2 receptors are present in kidneys⁵. The virus is found in glomerular cells, tubular epithelium, and podocytes of kidneys. Acute kidney injury is commonly secondary to systemic abnormalities. COVID-19 complicates the management of patients on dialysis and with kidney transplantation. Inflammatory immune response like cytokine storms can cause drastic hypoperfusion as it drastically reduce blood flow to the kidney and cause Acute Kidney Injury.

Acute kidney injury is also caused by rhabdomyolysis due to hyperventilation or medications including antivirals such as remdesivir. And pre existing disease like diabetes can increase the chance of Kidney Injury

According to one preprint, 27% of 85 hospitalized patients in Wuhan had kidney failure. Another reported that 59% of nearly 200 hospitalized COVID-19 patients in China’s Hubei and Sichuan provinces had protein in their urine, and 44% had blood; both suggest kidney damage. Those with acute kidney injury (AKI), were more than five times as likely to die as COVID-19 patients without it, the same Chinese preprint reported ^[4].

Gastro intestinal effect

GI Symptoms include loss of appetite, nausea, vomiting, diarrhea, and abdominal pain or discomfort [6] These symptoms may occur with or without symptoms like fever, myalgias, and cough. Lower GI tract is rich in ACE2 receptors

Some patient’s stool contains infectious virus or only RNA and protein fragments of the virus. Patients who have virus in the stool take longer to clear it. Although a small percentage of patients have GI symptoms, up to one-half shed virus in the stool [7].

In a paper in press at *Gastroenterology*, a Chinese team reported finding the virus’s protein shell in gastric, duodenal, and rectal cells in biopsies from a COVID-19 patient.

Up to half of patients, averaging about 20% across studies, experience diarrhoea and vomiting.

Many patients with COVID-19 show a slight to moderate increase in serum levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) during the course

of infection [8-9]. Autopsies of SARS patients revealed fatty degeneration, hepatocyte necrosis, and cellular infiltration in the liver [10].

Euryale ferox as a diet in Covid -19

Foxnut (*Euryale ferox Salisb.*) commonly known as makhana, Phool Makhana or Gorgon Nut is a flowering plant with gigantic and floating leaves. In Chinese Medicine, it is called Qian Shi. It is the only plant species that is native to Eastern and Southern Asia covering parts of India, Korea and Japan. Traditionally makhana is the delicacy of Mithila, Darbhanga and Madhubani regions of Bihar state.

In Ayurveda and Chinese practices, it has been used for the treatment of the renal disorder, chronic diarrhoea, excessive leucorrhoea and hepatic dysfunctioning. Its bio-active compounds act as antioxidant, antimicrobial, anti-schaemic, anti-diabetic, immunomodulatory, anti-melanogenic, anti-cytotoxic [11]

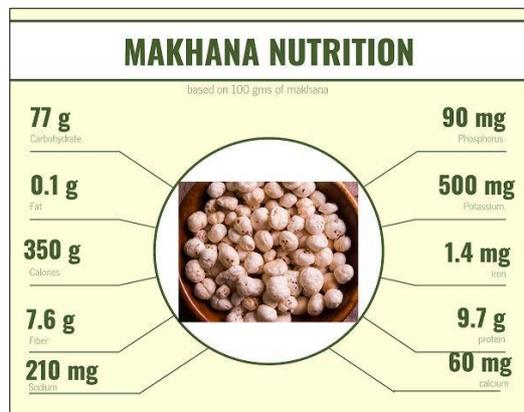
Ayurvedic Properties of Euryale ferox

RASA (Taste)	MADHURA (Sweet)
GUNA (Main Quality)	GURU (Heavy), SNIGADH or SNEHA (Unctuous or Oily)
VIRYA (Potency)	SHEETA (Cool)
VIPAKA (Resultant)	MADHURA (Sweet)
DOSHA KARMA (Effect on Humors)	Pacifies Vata Dosha and Pitta Dosha
Dhatu (Tissue) Effect	RASA, MAMSA, SHUKRA
Organ Effect	Hridya, Balya, Shodit Sthapana, Garbha Sansthapaka

Pharmacological Activity of Euryale ferox

Nutritional value

Foxnut (*Euryale ferox Salisb.*) has low fat content, high carbohydrates contents, protein and minerals. The calorific value of raw seeds and puffed seeds is 328 kcal/100g and 362 kcal/100g respectively. Nutritional studies indicates that edible portion of the seed contains 12.8% moisture, 9.7% protein, 0.1% fat, 76.9% carbohydrate, 0.5% mineral contents and 1.45% iron in addition to a good fraction of sugar, phenol and ascorbic acid. Amino acid index is higher than that of staple foods [17]. They also contain magnesium, potassium and phosphorus in a good amount. A few vitamins in less quantity are also present in makhana.



Antibacterial activity

The methanolic extract of *Euryale ferox* seeds and other plant parts showed significant antibacterial activity against nine clinically isolated bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aureoginosa*, *Citrobacter freundii*, *Shigella flexneri*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Salmonella typhi* and

Salmonella typhimurium), thereby providing a scientific basis for its use in urinary tract infections [12]. Thus it could prevent any secondary infection in CoVID-19 patients.

Effect of Euryale ferox on nCoV-19-RBD/ACE2

A Docking based Virtual Screening was performed on different Chinese Medical and Edible Plant to study there effect as a potent angiotensin converting enzyme 2 inhibitor. This study shows that different compounds like ferotocodimer A, Buddlenol E, [(2S,3R,4E,8E,2'R)]-1-O-(β-glucopyranosyl)-N-(2-hydroxy-docosanoyl)-4,8-sphingadienine] are present in Euryale ferox which are potent as ACE2 inhibitor and may be beneficial in restoring balance to the RAAS network and potentially preventing organ injury. ACE2, an enzyme that physiologically counters RAAS activation, is the functional receptor to SARS-CoV-2, the virus responsible for the Covid-19 pandemic. Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in Covid-19[13].

Cardioprotective activity

Makhana is high in magnesium and potassium and low in sodium. This makes makhana an ideal snack for Covid patients with pre existing Hypertension. High potassium and low sodium is a great combination for patients suffering from hypertension. The potassium brings down the blood pressure and sodium tries to bring it up.

It has antihyperlipidemic property. It helps to improve lipid profile and normalize their plasma levels. In Ayurveda, flowers of Euryale Ferox plant are commonly used for palpitation. Its hot infusion is highly beneficial for regulating and normalizing heartbeat. In addition, its infusion also relieves restlessness [24].

The cardioprotective activity of *Euryale ferox* seeds aqueous and alcoholic extracts were estimated. potent free radical scavenging activity and increased expression of Thioredoxin-1 and Thioredoxin Related Protein-32 (TRP-32) were responsible for the cardioprotective action.

Lab study was performed at male Sprague Dawley rat heart. There hearts were perfused with makhana ethanolic extract. Another feeding model was also set up in which rats were fed with 250 and 500 mg/kg for 21 days and the hearts of rats were isolated, subjected to 30 minutes ischaemia and 2-hour reperfusion. The coronary flow and aortic flow were determined. After 60 and 120 min of reperfusion significant difference was noticed in control and makhana treated rats. Myocardial Infarct size was reduced in both the acute and feeding models. Later thioredoxin-1 (Trx-1) and thioredoxin related protein-32 (TRP32) were found responsible for this action. They were found in makhana treated hearts by antibody array technique [14-15].

Anti oxidant activity

Clinical features of Covid – 19 include over production of reactive oxygen species which induces oxidative stress responses and contribute to acute lung injury. This could be prevented by potential strategic anti – oxidant therapy. An interventional clinical trial was done in Nigeria in collaboration of Obafemi Awolowo university and State ministry of Health on 90 Covid patients. They were given standard care combined with daily anti oxidant supplement for 14 days. There primary outcome measures was better improvement in patients which were treated with daily anti oxidant therapy [16].

There are many methanolic extract of *Euryale ferox* seeds that showed the anti oxidant activity. The ethyl acetate showed highest endogenous enzyme inhibition thereby helps in removing oxidative stress. The antioxidant activity was also evaluated in mesangial cells. The Euryalin B, rel-(2 α ,3 β)-7-O-methylcedrusin, (+)-syringaresinol and buddlenol E were found to have significant antioxidant action.

They carry a flavonoid called kaempferol. Kaempferol reduces inflammation in the body. Flavonoids are antioxidants and reverse the impact of free radicals. It also facilitates cell viability, defends against apoptosis induced by H₂O₂ and enhances the activity of various antioxidant enzymes.

Euryale ferox having strong anti oxidant properties can be utilised as food additive as well as functional on Covid – 19 patients.

Anti diabetic activity

Severe COVID-19 infection is significantly associated with increased blood glucose level. Infection leads to profound alterations in whole-body metabolism¹⁸. Sustained inflammation affects systemic glucose homeostasis and contributes to hyperglycemia¹⁹. Another study found that long-term innate immune activation could impair insulin secretion and action, and play an important role in the pathology of diabetes [20].

Noteworthy, pathological changes in pancreas, mainly focal enlargement of the pancreas or dilatation of the pancreatic duct, were observed in patients with severe COVID-19, indicating SARS-CoV-2 may cause pancreatic injury [21]. This may be one of the reasons that increased blood glucose

was observed in COVID-19 patients without a prior history of diabetes [22].

Therefore, it is observed that there may be a strong relationship between the severity of COVID-19 and glycemic parameters, even in those without diabetes.

Euryale ferox is a sweet and sour dry fruit, as it includes starch and protein that is effective for diabetic patients and acts as an antidiabetic agent, it has active bio constituent Pentacyclic triterpenes in methanolic extract from seeds which has anti diabetic activity and decrease sugar level.

The *Euryale ferox* seed's ethyl acetate extract had phenolic substances such as gallic acid, digallic acid, hexaglycone, picatechin gallate, procyanidine, catechin, gallic acid derivatives. The *Euryale* extract was taken 30 min before the meal, resulted in a decrease of glucose level.

HBAC (2 β -hydroxybetulinic acid 3 β -caprylate) is an efficient antidiabetic agent with numerous restorative effects arbitrated by avoiding the degradation of β cells, preserving the histological composition of the pancreas and liver, and preserving the endogenous antioxidant enzymes in the liver. It is also used as a functional food with HBAC (2 β -hydroxybetulinic acid 3 β -caprylate) as a component in the treatment of diabetes and the alleviation of its complications [23].

A study was performed by injecting Streptozotocin injection which led to the development of hyperglycaemia and then the groups were administered the dosage of ethanolic extract at various concentrations for 4 weeks. A significant reduction was observed in a high dose (600 mg/kg) group by 41% which was compared to standard glimiperide (51% reduction) [11].

Hepatoprotective activity

The active principle extract from *Euryale ferox* 2 β -hydroxybetulinic acid 3 β -caprylate (HBAC) has shown liver protective effect. Study was performed in Wistar rats, the HBAC and HBAO at 60 mg/kg administration could significantly increase the activity of glucose-6-phosphate dehydrogenase which was considered to be an essential enzyme for Hexose Mono Phosphate (HMP) shunt. HBAC exhibits excellent hepatoprotective property [23].

The expression of IRS-1 (insulin resistance substrate-1) and CYP2E1 were also analysed *via* western blotting in a study. There was an increase in the expression of CYP2E1 in rats which were administered by ethanolic extract of *Euryale* seed. Thus it was concluded that overexpression of CYP2E1 leads to hepatoprotective activity in rats after administration of ethanolic seed extract. Further liver activity parameters alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were found to be increased as compared to controlled range [11].

Anti-depression activity

During Covid -19 infection cycle or in post traumatic period many persons came across with clinical symptoms of depression. The petroleum ether fraction of *Euryale ferox* *Salisb.* has significant anti-depressant and neuroprotective effects.

Depression is associated with the death of neural cells. Previous studies have found that autophagy digests and eliminates damaged proteins, the remaining organelles, and cytoplasm during disease. However, autophagy is significantly downregulated when animals are in a depression-like state. Petroleum ether fraction of *Euryale ferox*

Salisb has shown to have neuro-protective effects. Several pathways are likely to be involved in the relationship between depression and the actions of petroleum ether fraction of *Euryale ferox*, including the AMPK pathway, which is a positive regulator of autophagy [25].

Other Properties of *Euryale ferox*

- *Euryale ferox* leaves are used in preparing tea in which golden flower generation concept was preferred so that referred tea would be rich in Eurotium cristatum which regulate immunity, clear heat and invigorate stomach.
- The *Euryale* seed shell extract was used to regularise lipid profile as well to normalise the body weight. Thus proves to be an anti-hyperlipidemic and anti-obesity.
- A skin whitening composition containing *Poria cocos*, *Dioscorea opposita*, *Nelumbo nucifera* and *Euryale ferox* is prepared and its main action is inhibition of tyrosinase enzyme and melanin production. So it also has anti ageing property.
- The medicinal liquor containing 20-40% Chinese medicine liquor, 25-38% *Euryale ferox* seed powder, 20-35% coix seed powder and 5-13% of yeast is reported to possess anti-rheumatoid property.
- A nerve soothing and sleep assisting powder have been prepared with the components of black sesame, oats, brown rice, lotus seeds, lily, *Euryale ferox* and walnut kernels [26].

Conclusion

SARS-CoV-2 virus binds to ACE2 receptors which are present throughout the body and can adversely affect every organ and system of the body. It also causes cytokine storm which can end in death. The lungs are commonly affected leading ARDS. Other complications like heart failure, myocarditis may also present. Neurological problems like meningitis, encephalitis, stroke, delirium are also observed in rare cases. Psychological problems such as depression are more common among these patients even after recovery from this disease. Renal effect are seen in clinical symptoms in pre- existing Kidney Disease or without any kidneys disease. Patients with Chronic kidney disease have more mortality rate. Non fatal GI symptoms are also observed commonly in this disease.

Euryale ferox have many biological natural constituents which shows antioxidant, antimicrobial, anti-ischaemic, anti-diabetic, immunomodulatory, anti-melanogenic, anti-cytotoxic, nephroprotective, hepatoprotective, anti-diarrheal and spermatogenic properties. It also improves strength and stamina, reduce fatigue and palpitation.

Normal Dosage for makhana is 10 to 20 grams per day. In Ayurvedic medicine, its seed powder is advised to take in a dosage of 5 to 10 grams daily with Cow's milk to improve strength or with Arjun twak kheer pak to improve its cardiac property. In SARS – Covid -19 it can be given as a regular daily diet to prevent from complication of this disease or while recovery period to improve strength. We can give *Euryale ferox* seeds in ICU patients who are on ventilator as their dietary regime through Nasogastric tube as prescribed previously.



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