

Synergistic efficacy of *Aframomum melegueta* [Roscoe] K. Schum and *Spondias mombin*(Linn), A predictive treatment of SARS-CoV-2 (COVID-19) Infection

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Research Article

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Abstract

SARS-CoV-2 is closely related to the original SARS-CoV. It is thought to have animal based origin from Bats (Betacoronavirus) in subgenus (Sarbecoronavirus) together with two bat-derived strains. The virus is mainly spread between people during physical contact, often through small droplets produced during coughing, sneezing, even talking to patient or infected people. It is primarily spread during close contact and via small droplets produced when infected people cough, sneeze or talk with close contact being within 1–3 m (3 ft 3 in–9 ft 10 in). Those infected with the virus may be asymptomatic (Appearance of No symptoms) or develop flu-like symptom which include fever, cough, fatigue, and shortness of breath. The exposure time to initial symptom is day five (5 days). Majority of cases result in mild symptoms, some progress to viral pneumonia and multiple organ failure. Two medicinal plants may be used for the treatment of SARS-CoV-2, the two medicinal plants are *Aframomum melegueta* and *Spondias mombin* (Linn). Both contains arrays of natural product that may be used for drug formulation to combat SARS-CoV-2, *Aframomum melegueta* medicinal plant belong to the family Zingiberaceae which can be used to detoxify liver and bronchitis during lungs infection. *Aframomum melegueta* contains 6-Gingerol, 8-Gingerol, Methyl-6-Gingerol, 6-Shogaol, 6-Rac-6-Dihydro paradol, 6-Gingeredione, 2-(5 butylfuran-2-yl) ethyl-2-methoxyphenol and 6-Paradol. Secondary metabolite (Phytochemical) investigations of *Aframomum melegueta* extracts revealed the presence of (-)-buplerol, (-)-arctigenin, (E)- 14-hydroxy-15-norlabda-8(17), 12-dien- 16-al, labda-8(17), 12-dien-15, 16-dial, 16-oxo-8(17), 12(E)-labdadien-15-oic acid, 5-hydroxy-7-methoxy flavone and apigenin. The combination of all this novel compound can be used for the treatment of SARS-CoV-2. *Spondias mombin* belongs to the family of Anacardiaceae medicinal plants and contains Catechin and Epigallocatechin, Epicatechin, Stigmasterol and Phytosterol, a very important flavonoid that can be used in drug formulation because of its extensive therapeutic properties which may inhibit specific enzymes, blocking the angiotensin-converting enzyme (ACE) that raises blood pressure of infected patient during elevated fever clinical symptoms of SARS-CoV-2 (COVID-19). *Spondias mombin* extract may act by blocking the “suicide” enzyme cyclooxygenase that breaks down prostaglandins, they also prevent platelet aggregation. Cancer-battling antioxidants, flavonoids, have been found in relative abundance in *Aframomum melegueta* and *Spondias mombin*. Epicatechin have been proven to have diverse benefits to human health. It reduces the risks of diabetes mellitus and cardiovascular diseases, EGC acts as a strong inhibitor of HIV replication in cultured peripheral blood cells and inhibition of HIV-1 reverse transcriptase in vitro. EGC binds directly to CD4 molecules with consequent inhibition of Gp 120 binding and inactivate viruses in vitro by deformation of phospholipids, Epicatechin and other polyphenols decreases the susceptibility of low density lipoprotein to oxidation which prevents the initiation of atherosclerosis, HIV protein (Tat) and gp120. In conclusion. SARS-CoV-2 (COVID-19) pandemic infection should not be a death sentence, it should be an advancement into the scientific world especially the naturally occurring product that can be used in the formulation of new antimicrobial agents.

Keywords: *Aframomum Melegueta*, *Spondias mombin*, SARS-CoV-2 (COVID-19)

Introduction

SARS-CoV-2 is closely related to the original SARS-CoV. It is thought to have animal based origin from Bats, Betacoronavirus and Sarbecoronavirus together with two bat-derived strains [27,28,29]. Coronavirus disease 2019 (COVID-19) is a very infectious symptomatic infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-COV-2) [1]. The infection sequentially was first identified in December 2019 in the china capital called Wuhan [2]. The Common symptoms include high fever, Cough, and shortness of breath, just to mention a few. Other symptoms may include fatigue, muscular pain, diarrhea, sore throat, loss of smell, and abdominal discomfort/pain [3]. The exposure time to initial symptom is day five (5 days), this may range from two to fourteen days as the infection sequentially develop to diseases [4,5]. Majority of cases result in mild symptoms, some progress to viral pneumonia and multiple organ failure, but not in all case all case eventually leads to death of the patient within a short time [6].

The virus is mainly spread between people during close contact (Horizontal transfer) often via droplets produced during coughing, sneezing, or talking [7,8]. While these droplets are produced when breathing out in to the air, they usually fall to the surfaces rather than being infection over large distance [9]. People may also become infected by touching a contaminated surface I.e inanimate object and then their face and nose or the orifice in the body [10]. The virus can survive on surfaces for up to 72 hours within going to the death phase [11,12].

Those infected with the SARS-CoV-2 virus may be asymptomatic (Appearance of No symptom) and develop flu-like symptom during the progession of infection. Other symptoms include high fever, continuous cough, fatigue (Tiredness), and shortness of breath due to congestion of lung cavity, persistent chest pain or pressure, confusion, difficulty waking [17,18]. In some cases, other less commonly symptoms like upper respiratory pain, such as sneezing, runny nose or sore throat. Other such as nausea, vomiting and diarrhea have been observed in varying percentages of infected patient [19].

The incubation period for SARS-CoV-2 (COVID-19) is typically five to six days (5-6 days) but may range from two to 14 days in all, as symptoms progress in subclinical phase II infection [20]. Preliminary evidence suggests asymptomatic cases may contribute to the spread of SARS-CoV-2 (COVID-19), it is primarily spread during close contact and by small droplets produced when people cough, sneeze or talking with close contact (Physical/social contact) being within 1–3 m (3 ft 3 in–9 ft 10 in) [21].

However, SARS-CoV-2 (COVID-19) pandemic infection varies based on the humidity and temperature of the infected country. High humid/ high temperate country as less susceptible to SARS-CoV-2 (COVID-19) compared with less humid/temperate country. To reduce rampaging effect of SARS-CoV-2 (COVID-19) pandemic infection, Surfaces may

be decontaminated with a number of antimicrobial solutions within one minute of exposure to the disinfectant to achieve a sterile inenvironment free of the SARS-CoV-2 (COVID-19) virus. Some of the antimicrobial agent are ethanol, 2-propanol, sodium hypochlorite (bleach), hydrogen peroxide, povidone–iodine, Soap and detergent. 78–95% ethanol (alcohol used in spirits), 70–100% 2-propanol (isopropyl alcohol), the combination of 45% 2-propanol with 30% 1-propanol, 0.21% sodium hypochlorite(bleach), 0.5% hydrogen peroxide or 0.23–7.5% povidone–iodine. Soap and detergent are also effective if correctly used. Soap products can be used to degrade and deactivating the virus fatty protective layers, as well as freeing them from skin and other surfaces [23,24,25].

The standard method of diagnosis the SARS-CoV-2 (COVID-19) pandemic infection is by Real time reverse transcription Polymerase Chain Reaction (Rrt-PCR), by taking a nasopharyngeal swab [13]. Another method of diagnose SARS-CoV-2 is by making use of Chest CT imaging from suspected individual based on symptoms and risk factors but is not recommended for routine screening [14,22].

The lungs are the organs most affected by SARS-CoV-2 (COVID-19) because the virus accesses host cells via the enzyme angiotensin–converting enzymes 2 (ACE2), which is most abundant in the type I and II alveola cells of the lungs. The virus uses a special surface glycoprotein called a “spike” (peplomer) to connect to ACE2 and enter the host cell [29]. The density of ACE2 in each tissue correlates with the severity of the disease in that tissue and some have suggested that decreasing ACE2 activity might be protective, though another view is that increasing ACE2 using angiotensin II receptor blocker medications could be protective and that these hypotheses need to be tested [30]. As the alveolar disease progresses, respiratory failure might develop and death may follow [31]. The virus also affects gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium as well as endotheli cells and Enterocytes of the small intestine [32].

SARS-COV-2 has a tropism for ACE2-expressing epithelial cells of the respiratory tract, infected patients with SARS-CoV-2 (COVID-19) have symptoms of systemic hyper-inflammation. Clinical laboratory findings shows varing degree of elevated IL-2, IL-7, IL-6, granulocyte macrophages stimulating factors (GM-CSF) and this include the interferons-gamma, inducible protein 10(IP-10),macrophage inflammatory protein (Alpha 1(MIP-1Alpha) and tumor necrosis factor alpha that can inductive of cytokine released syndrome [33]. It should be noted that if all this factors can be blocked by a medicinal plants, then, we can say we have a cure and treatment for this world pandemic, this is the basic reason this review becomes very important to the scientific world.

Systemic inflammation results in vasodilation, allowing inflammatory lymphocytic and monocytic infiltration of the lung of the infected patient, it should be noted that the lung and heart of infected patient are mostly affected. In particular,

pathogenic GM-CSF-secreting T-cells were shown to correlate with the recruitment of inflammatory IL-6-secreting monocytes and severe lung pathology in SARS-CoV-2 (COVID-19) infected patients [34]. If there is any medicinal plant that can lower the IL-2, IL-7, IL-6 and pathogenic GM-CSF-secreting T-cells, then we have a breakthrough on SARS-CoV-2 infection prevention is better than cure, so say an adage, Preventive measures can be established to reduce the scourge of SARS-CoV-2, these preventive measures include staying at home, which is mostly recommended in all cases, to prevent the spread of infection and avoiding crowded places, like church gathering, school market places, train station, airport. Washing of hands with soap and water regularly, for at least 20 seconds, practicing good respiratory hygiene and avoiding touching the eyes, nose or mouth and other orifice in the body with unwashed hands [35,36]. People are managed with supportive care which may include fluid therapy, oxygen support and ventilator [37,38]. Those people suspected they carry the virus wear a simple face mask that will cover their mouth and nose. The ability to spread SARS-CoV-2 (COVID-19) varies from individual to individual, and country to country. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold [15,16,39].

Several existing antiviral medications are being evaluated for treatment of COVID-19, including chloroquine and hydroxy-chloroquine [40]. Others are lopinavi, ritonavir with combination of Beta interferon (41). Remdesivir inhibits SARS-CoV-2 in vitro evidence of clinical trial conducted in the United States, Italy and China [42-44]. Chloroquine, previously used to treat malaria fever [43]. Chloroquine phosphate "improves the success rate of treatment and shortens the length of person's hospital stay" and recommended it for people diagnosed with mild, moderate and severe cases of novel coronavirus pneumonia [45]. There are mixed results as to the effectiveness of hydroxychloroquine as a treatment for COVID-19, with some studies showing little or no improvement, hence there is a need of alternative source of treatment this is where medicinal plants come into vintage position.

Medicinal plants has become an obsolete version of the synthetic drug, but come to think of it its uses are limitless, that is the basic reason it will become a veritable tool in the treatment of recalcitrant infection like SARS-CoV-2 (COVID-19). This section of this review will shed more light to just three (3) medicinal plants found in Nigeria which may be used to treat and cure SARS-CoV-2 (COVID-19) and its allies if the foreign world takes cognizant of its uses and various application.

Possible medicinal plants that may be used for the treatment of SARS-CoV-2 (COVID-19).

1. *Aframomum melegueta* [Roscoe] K. Schum

From literature, *Aframomum melegueta* medicinal plant belongs to the family Zingiberaceae which can be used to detoxify liver and bronchitis during lung infection.

Aframomum melegueta contains 6-Gingerol, 8-Gingerol, Methyl-6-Gingerol, 6-Shogaol, 6-Rac-6-Dihydro paradol, 6-Gingeredione, 2-(5-butylfuran-2-yl) ethyl-2-methoxyphenol and 6-Paradol. The combination of all these compounds can be used for the treatment of SARS-CoV-2. It was found from literature that 6-paradol chemical compound has biologically significant beyond its medicinal value especially in the formulation of herbal and synthetic drugs. Cancer-battling antioxidants, flavonoids, have been found in relative abundance in *Aframomum melegueta* [46]. Flavonoids are commonly reported to possess anti-carcinogenic and anti-mutagenic effects (47) in which they interfere with the development of malignant tumors by inhibiting the expression of mutant genes, inactivating carcinogens and enzymes that are involved in the activation of pro-carcinogens, as well as activating enzymatic systems that are involved in the detoxification of xenobiotics [47,48]. Phytochemical investigations of *Aframomum melegueta* revealed the presence of (-)-buplerol, (-)-arctigenin, (E)-14-hydroxy-15-norlabda-8(17), 12-dien-16-al, labda-8(17), 12-dien-15, 16-dial, 16-oxo-8(17), 12(E)-labdadien-15-oic acid, 5-hydroxy-7-methoxy flavone and apigenin in the extract. Among the list, (-)-arctigenin and (-)-buplerol showed the capacity to trigger apoptosis in pancreatic cancer cells [49].



Plate 1: *Aframomum melegueta* Seed, Fruit pulp (Mesocarp), Leaf sheath and Stem
Source (Osuntokun et al., 2020).

The seeds of the *Aframomum melegueta* pepper have been proven to reverse such toxic effects. Its hepatoprotective effect is evaluated based on the changes in ALT, GSH, thiobarbituric acid reactive substances, TNF- α , IL-1 β levels and activities of some enzymes such as caspase 3 and 9 [50].

Aframomum melegueta compounds present in the extract that can be possibly used to treat SARS-CoV-2 (COVID-19) include 3-(S)-acetyl-1-(4'-hydroxy-3', 5'-dimethoxyphenyl)-7-(3'',4'',5''-trihydroxyphenyl)heptane and dihydrogingerone that can suppress TNF- α and IL-1 β levels in the body. These compounds impede the reduction of GSH by trapping free radicals arising from liver hepatocytes. In addition, these compounds also lower the levels of ALT, TNF- α , IL-1 β as well as caspases 3 and 9. Apoptosis of hepatocytes induced by CCl₄ is also inhibited. The hepatoprotective effect of *Aframomum melegueta* is due to its ability to suppress inflammatory responses and apoptosis, as well as the ability to forage free radicals [51].

Secondary metabolite (Phytochemical) of *Aframomum melegueta* investigations revealed the presence of (-)-buplerol, (-)-arctigenin, (E)- 14-hydroxy-15-norlabda-8(17), 12-dien-16-al, labda -8(17),12-dien-15,16-dial, 16-oxo-8(17),12(E)-labdadien-15-oicacid, 5-hydroxy-7-methoxy flav one and apigenin in the extract. Among the list, (-)-arctigenin and (-)-buplerol showed the capacity to trigger apoptosis in pancreatic cancer cells [52].

According to Vinegar et al, the development of the carrageenan induced inflammation is due to the release of cytoplasmic enzymes and serotonin from mast cells during hypersensitive type I reaction and the increase of prostaglandin release to the inflamed area [53]. While the anti-inflammatory activity of diclofenac is mediated chiefly through inhibition of the cyclooxygenase pathway (COX 1 and COX 2), particularly prostaglandins and that of dexamethasone is mediated through their suppressive effects on the inflammatory cytokines and on other lipid mediators of inflammation, It is however possible that the *Aframomum melegueta* extract may inhibit the release of inflammatory mediators released during hypersensitive type I reaction and carrageenan-induced inflammation [54].

The basis of the protective effect of *Aframomum melegueta* containing vitamin D is said to lie in its ability to stimulate innate immunity and to reduce inflammation. Innate immunity differs from adaptive immunity in that the former responds rapidly to microorganisms using genetically encoded effectors, most notably the antimicrobial peptides (AMPs) [52]. As noted, the active form of vitamin D (1,25-dihydroxyvitamin D; 1,25-OH₂D) stimulates the expression of AMPs “endogenous antibiotics” in human monocytes, neutrophils, and epithelial cells [54]. AMPs protect epithelial surfaces by destroying the lipoprotein membranes of microbes such as influenza viruses. If the epithelial mucosal surface barrier is breached, microbes binding to the epithelia promote the expression of inducible AMPs including the defensins and cathelicidin. The defensins inhibit influenza hemagglutinin A-associated carbohydrates [53] and act with cathelicidin as chemoattractants for macrophages and neutrophils [54]. Vitamin D thus enhances the capacity of the epithelium to produce AMPs following exposure to microbes. *Aframomum melegueta* also dampens the proinflammatory peptides interferon gamma, TNF-alpha and IL-12 of the adaptive immune system, especially those responsible for acute inflammation “cytokine storms” [55]. This fact about *Aframomum melegueta*, makes it a choice medicinal plant for the treatment of SARS-CoV-2 (COVID-19), if it is scientifically explored especially during this SARS-CoV-2 (COVID-19) menace.

2. *Spondias mombin*.linn

Spondias mombin belongs to the family of Anacardiaceae, one of the potent medicinal plant that has a very high medicinal value becomes a viral tools in the production of new and novel antimicrobial agent especially during this pandemic era of world history if medically explored because of its various therapeutically advantageous against infectious organism. This will help us to totally eradicate the recalcitrant infection

like SARS-CoV-2 (COVID-19) and HIV, Breast cancer, liver infection just to mention a few [55].

Spondias mombin is a magic bullet against infectious diseases. *Spondias mombin* contains flavonoids also inhibit specific enzymes, which can block the angiotensin-converting enzyme (ACE) that raises blood pressure, which is one of the suppose symptom of SARS-CoV-2 (COVID-19). *Spondias mombin* extract act by blocking the “suicide” enzyme cyclooxygenase that breaks down prostaglandins, they prevent platelet stickiness and hence platelet aggregation [56].



Plate 2: *Spondias mombin* Tree with Developing Fruit and Leaf sheath.

Source Osuntokun et al.,2019 (55)

Spondias mombin contains Catechin and Epigallocatechin, Epicatechin, Stigmasterol, and Phytosterol, a very important flavonoid that can be used in drug formulation because of its extensive therapeutic properties. Catechins inhibites replication of influenza virus on MDCK cells. The inhibitory effect is in a concentration-dependent manner and throughout the virus infection cycle after initial infection. Antiviral effects exerted not only on initially infecting viruses but on newly propagated viruses like SARS-CoV-2 [57].

Epicatechin is a type of flavonoid which is mainly found in green tea (*Camellia sinensis*) and dark chocolate; it has now been discovered in *Spondias mombin* which is good alternative to green tea in places like West Africa where green tea is not found in large quantity [58]. Polyphenols comprise of 30-40% of extractable solids from dried *Spondias mombin* stem bark [58].

Epicatechins have been proven to have diverse benefits to human health and can serve as a predictive treatment of SARS-CoV-2. Epicatechins can be used to reduce the risks of diabetes mellitus and cardiovascular diseases and in the treatment of SARS-CoV-2. Pharmacological effect of Epicatechins content of *Spondias mombin* as well as antihyperlipidemic, anti-inflammatory, antioxidative, anticarcinogenic, and cytoprotective effect should be emphasized [59]. These flavonoids can be used as therapeutic agents individually or in combination with other synthetic drugs and antibiotics to produce a new generation of phytopharmaceuticals which can formulated in synthetic and herbal drug during this pandemic

era of SARS-CoV-2 infection.

Natural product like epicatechin is cost effective, highly biocompatible and has low toxicity [60]. Epicatechin (EC) helps in the inhibition of HIV-1 reverse transcriptase in vitro and binds directly to CD4 molecule with consequent inhibition of gp120 binding [61].

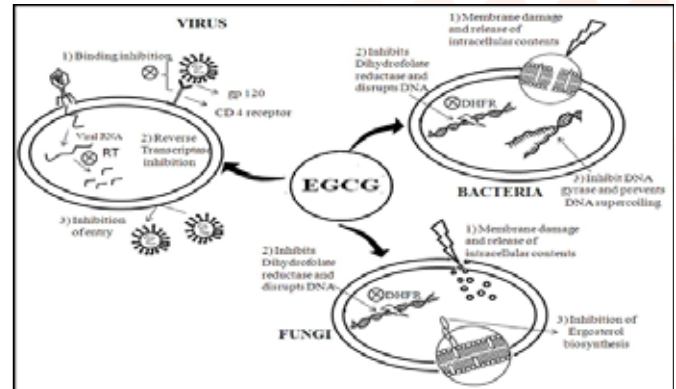
Epigallocatechin (EGC) inhibited plaque forming activity of influenza A and B virus whereas EC exhibited little inhibition. A polyphenol mixture is more efficient than a single compound in plaque inhibition and epicatechin had no antiviral effect and only a little inhibition on plaque formation [62]. (+)-Epicatechin and (-)-epicatechin was found to inhibit Hepatitis C virus (HCV) replication by inactivating Cyclooxygenase-2-dependant signalling pathway. Cyclooxygenase-2 (COX-2) produces various prostaglandins (PG) which result in chronic inflammation and fibrosis. PGE₂, thromboxane B₂ and prostacyclin gives rise to cellular proliferation, cancer invasiveness, angiogenesis and anti-apoptotic. Therefore, leading to hepatocarcinogenesis, (+)-Epicatechin and (-)-epicatechin may suppress the gene expressions of pro-inflammatory enzymes and cytokines that are induced by HCV [63].

Epigallocatechin (EGC) increases lysosomal acidification, regulates autophagy and lipid clearance in liver due to its antisteatotic property [64]. EGC, in dose dependent manner can reduce the release of cytokines/chemokines responsible for inflammation showing anti-inflammatory property [65]. Its antiallergic property strongly inhibits activation of mast cells and expression of high-affinity IgE receptor, which produces an allergic reaction on exposure to certain foreign antigens [66].

The most important antioxidant property is very crucial in treating chronic diseases which are related to oxidative stress, cardiovascular, neurodegenerative diseases and cancer. Research on this property revealed information about its anticardiovascular and anti-hypertensive activity which enables epigallocatechin, epicatechin (EGC, EC) and polysteroids, to prevent platelet aggregation, lower cholesterol level and inhibit lipid peroxidation [67].

Epigallocatechin, Epicatechin (EGC, EC) and polysteroids is also beneficial for preventing aging of brain and other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases as depicted from mouse model studies [68]. EGC and EC also show antihypercholesterolemic (anti-obesity) activity and promote weight loss through fat oxidation. Animal studies have demonstrated that EGC, EC and polysteroids is an efficient agent in preventing the development of diabetes, type 1 or type 2 [69]. EGC affects each step of the HIV life cycle, from cell attachment, entry of virus, replication cycle to the expression of mRNA. It also interferes with the infectivity of the virus by binding to the surface of viral envelope and deforming the phospholipids followed by lysis of the virus particle [70]. The attachment of the gp120

envelope protein to the CD4 receptor on T-helper cells initiates the entry of HIV-1 into the host. EGC blocks the interaction of gp120 and CD4 and prevents the attachment of HIV-1 virions, EGC also inhibits the viral production from infected cells and the level of expression of viral mRNA. EGC acts as a strong inhibitor of HIV replication in cultured peripheral blood cells and inhibition of HIV-1 reverse transcriptase in vitro.



Schematic Diagram of mechanisms of action Epigallocatechin and Epicatechin (EGC, EC)

EGC binds directly to CD4 molecules with consequent inhibition of Gp 120 binding and inactivate viruses in vitro by deformation of phospholipids. It should be mentioned that EC are antioxidant, they are effective scavengers and free radical such a reactive oxygen species (ROS), Reactive nitrogen species and superoxide [71].

Epicatechin have been proven to have diverse benefits to human health. It reduces the risks of diabetes mellitus and cardiovascular diseases this shows the basic important aspect of Spondias mombin tree, which have pharmacological effects such as anti hyperlipidemic, anti-inflammatory, antioxidative effect, anticarcinogenic and cytoprotective. Epicatechin and other polyphenols decreases the susceptibility of low density lipoprotein to oxidation which prevents the initiation of atherosclerosis, HIV protein (Tat) and gp120 is known to cause neurotoxicity in human via mechanisms that activate macrophages and glial cells and finally, oxidative stress it can be suggested that epicatechin are neuroprotective by blocking the neurotoxic effects of the HIV protein which cause oxidative stress [71].

In conclusion, coronavirus disease (COVID-19) pandemic infection should not be a death sentence; it should be an advancement into the scientific world especially the naturally occurring product that can be used in the formulation of new antimicrobial agents. Little is known of this two plants, but their uses, is limitless and it should be explored especially during this time of need which viral infection of COVID 19 becomes a menace

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