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Possible role of Kolaviron, a *Garcinia kola* bioflavonoid in inflammation associated COVID-19 infection

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that belongs to the coronavirus family, remains a pandemic and of public health concern with ascending morbidity and mortality rates worldwide. It continues to affect millions of people despite tremendous social preventive measures and novel vaccines developed recently. The main pathological features of SARS-CoV-2 infection is elevated levels of cytokine release causing "cytokine storm," an aberrant response from the host immune system that induces an exaggerated release of proinflammatory cytokines/chemokines leading to severe acute respiratory distress syndrome. Subsequent cascade of events causes pneumonia and respiratory failure, touted as a major contributor to COVID-19-associated fatality rates. Therefore, effective therapeutic strategy should center on suppression of inflammation, oxidative stress and modulation of immune response. However, certain drugs developed as antivirals and/or immunomodulators have not been very effective against the disease. Recent investigations involving epidemiological and scientific findings show that plant-based phytochemicals with robust anti-inflammatory and anti-infective properties can prevent and manage COVID-19. Garcinia kola and its bioflavonoid-derived phytochemical known as kolaviron have been shown to be relevant traditionally and experimentally in the management and treatment of diseases including viral infection. The emerging understanding of the cellular and molecular mechanisms of kolaviron and the context of the same for SARS-CoV-2 infections suggests that the antioxidant, immunomodulatory, anti-inflammatory, antiviral, and antibacterial properties of Kolaviron can have value added benchmark to anchor the development of nutraceuticals and functional foods as adjuncts for COVID-19 management.

Keywords: Coronavirus disease 2019, Severe acute respiratory syndrome coronavirus 2, Immunomodulators, Cytokine storm, *Garcinia kola*, Kolaviron, Antioxidant, Anti-inflammatory

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, termed coronavirus disease 2019 (COVID-19), is an ongoing pandemic and represents a public health emergency; and pandemic which has affected millions of people worldwide and remain unabated despite frantic efforts at curtailing it including social and physical preventive measures.

However, despite the frightening mortality rate associated with this novel COVID-19, there is currently no absolute therapy to combat the pandemic, but preventive and supportive therapies

(including vaccination) are employed to control further complications and organ damage.[1]

The pathological manifestations of COVID-19 include fever, headache, fatigue, dry cough, sore throat, diarrhea, rashes on the skin, shortness of breath, loss of smell, anorexia, myalgia, and anosmia, identified as the clinical criteria for diagnosis of COVID-19.[2] The severity of infection varies from asymptomatic, pre-symptomatic to symptomatic in patients. Mortality results from complications, such as severe pneumonia, acute respiratory distress syndrome (ARDS), shock, sepsis, and resultant multiorgan failure,[3,4] particularly with extensive involvement of the lungs damage, acute liver injury, acute cardiac injury, and neurological manifestations that may lead to multiorgan failure with poor prognosis.[5,6] Acute lung disease with severe alveolar damage and progressive respiratory failure usually lead to deadly outcomes.[4] Higher complications and deaths are recorded in the elderly with underlying immune disorders, co-morbidities, cardiometabolic diseases, and cancer. In SARS-CoV-2 infection, activation of immune responses and inflammatory cytokines processes result in a dysregulated immune pattern, manifested by a massive rise in the levels of pro-inflammatory cytokines, chemokines, and adhesion molecules.[7] This causes the onset of a "cytokine storm" and the accompanying exaggerated release of inflammatory cytokines which mainly causes ARDS and further leads to pathogenic effects through a quite ubiquitous target at a multiple-organ level [Figure 1].[7-9] Examples of such cytokines implicated in the cytokine storm include interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein (MCP)-1, as well as a decreased number of natural killer cells. In SARS-CoV-2 infection, immune dysregulation has been linked to the massive pro-inflammatory cytokine secretion by alveolar macrophages and subsequent CD4fl and CD8fl T cell dysfunction observed.[10] Therefore, identification of new therapeutics capable of preventing or mitigating the cytokine storm and sequelae is warranted.

Since 2020, following the COVID-19 pandemic, several research efforts involving pharmaceutical, biotechnological, and academic sectors for the discovery of novel drugs, have been made towards solving this global problem. For instance, several antiviral drugs have been approved for use; however, these drugs have a narrow range of activity against many viral infections.[11] This is because viruses can rapidly mutate, causing new strains to emerge that may exhibit resistance to drugs that target a particular viral component.[12] In addition, several drugs based on molecular docking, pharmacological basis of diseases and clinical observations have been considered and repurposed for the management COVID-19[13-15] Remdesivir (an adenosine analog), which was effective against Ebola and some other RNA viruses, was approved by the US Food and Drug Administration on May 1, 2020, and repurposed for emergency treatment of hospitalized COVID-19 patients. Furthermore, hydroxychloroquine, an antimalarial drug in combination with azithromycin was found to produce 93% recovery rate following 8 days treatment.[16] Despite the development of these drugs, COVID-19 continues to ravage the entire world. Furthermore, efforts have also been made to develop vaccines to tackle the disease. Current vaccines that have been available for use through the emergency use authorization have been documented [Table 1].[17] The pandemic still receiving immense consideration at this moment regarding the best courses to take for prevention and/or mitigation of symptoms after onset and addressing emerging variants of the SARS-CoV-2 virus. There are other candidate vaccines under development some of which may offer alternatives to overcome key logistical challenges faced by the leading candidates, including the need for multiple doses, extreme storage temperature requirements, short shelf lifel and possible low public confidence in new vaccine platforms. While current evidence shows that the existing COVID-19 vaccines are effective at stopping disease and therefore very promising, no vaccine is 100% effective. Thus COVID-19 vaccines are by no means a silver bullet. The vaccines can produce significantly milder manifestations and generally prevent hospitalization of the afflicted. With more COVID-19 vaccines already rolled out, available evidence shows that vaccine availability does not equate to vaccine accessibility, nor vaccine efficacy. For instance, some data indicate that approximately nine out of ten individuals living in lower-income countries will not have access to COVID-19 vaccines until 2023 or later. At the same time, higher-income countries, such as the United States, the prevalence of vaccine hesitancy may further compound the situation.[18] In addition, several variants of concern have also arisen following the development of the vaccines thereby compromising their efficacy. The U.S. Government SARS-CoV-2 Interagency Group (SIG) variant classification scheme.

https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html, defines four classes of SARS-CoV-2 variants and have included (1) Variant Being Monitored (VBM) Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), Epsilon (B.1.427 and B.1.429), Eta (B.1.525), Iota (B.1.526) and Kappa (B.1.617.1), 1.617.3, Mu (B.1.621, B.1.621.1), and Zeta (P.2) (2) Variant of Interest (VOI) referring to a variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity; (3) Variant of Concern (VOC), that includes Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages), lastly, (4) the Variant of High Consequence (VOHC). As of November 30, 2021,

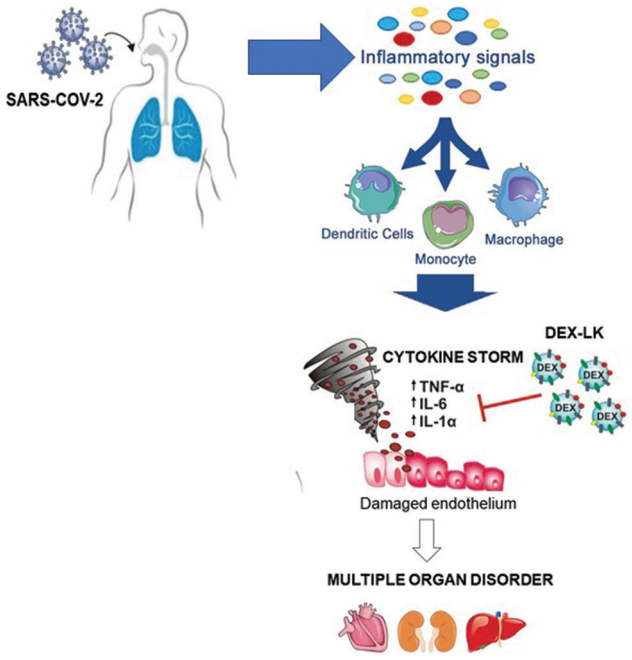

Figure 1: Infection of the pulmonary epithelial by SARS-COV-2 promotes early rapid secretion of pro-inflammatory cytokines resulting in taxis-driven influx, accumulation and activation of innate inflammatory cells, neutrophils, monocytes, dendritic cells and macrophages, resulting in severe immunopathological damage and cytokine storm which in turn triggers ARDS and multi-organ failure a critical factor in COVID-19, illness, or fatality.

the U.S. government SIG classified Omicron as a VOC. This classification was based on the following: Detection of cases attributed to Omicron in multiple countries, including among those without travel history, transmission and replacement of the Delta variant in South Africa, the number and locations of substitutions in the spike protein, available data for other variants with fewer substitutions in the spike protein that indicate a reduction in neutralization by sera from vaccinated or convalescent individuals, and available data for other variants with fewer substitutions in the spike protein that indicates reduced susceptibility to certain monoclonal antibody treatments. The readers is referred to the Center for Disease Control website for updates: https://www.cdc.gov/coronavirus.

Since COVID-19 pathogenesis and its attendant complications mainly involve the immune-inflammatory cascade, therefore, current approaches should, emphasize reduction of inflammation and immune modulation.[19,20] Studies have shown that immunomodulators of natural origin could be valuable for use as preventive as well as therapeutic adjuvant in mitigating the cytokine storm and associated sequelae.[19,20] Natural products have been considered an alternative therapeutic option on account of their antiviral, antibacterial, anti-inflammatory, immunomodulatory, and antioxidant properties. Therefore, identification of novel therapeutic signatures with intrinsic ability against viral components inhibition of viral entry, enhancement

Table 1: Current vaccines that have been available for use through the emergency use authorization. There are other candidate vaccines under development some of which may offer alternatives to overcome key logistical challenges faced by the leading candidates, including the need for multiple doses, extreme storage temperature requirements, short shelf life, and possible low public confidence in new vaccine platforms.

	Pfizer/BioNTech BNT162b2	Moderna mRNA-1273	AstraZeneca/Oxford ChAdOx1-S/AZD1222	Janssen (Johnson & Johnson) Ad26COVS1
Type of vaccine	mRNA in lipid nanoparticles	mRNA in lipid nanoparticles	Non-replicating adenovirus vector	Non-replicating adenovirus vector
Dosage	2 doses 21 days apart	2 doses 28 days apart	2 doses 28 days apart	1 dose or 2 doses 56 days apart
Antibody detection	7 days after booster	14 days after booster	14 days after booster	14 days after booster
Efficacy	95%	95%	70%	N.A.
Planned production volume	50M (2020) 1.3B (2021)	20M (2020) 0.5-1B (2021)	3B (2021)	1B (2021)
Storage requirement	−70°C±10°C	−20°C	2–8°C	2–8°C
Shelf life once thawed	5 days	30 days	180 days	180 days
Phase III trial enrolment	43,000 (age 16–85)	30,000 (age 18+)	11,500 (age 18+)	Single dose 60,000 Two dose 30,000 (age 18+)
Percentage high-risk population in Phase III trial	40.90%	42%	N.A.	N.A.

Source: American Chemical Society, Google image. The reader is referred to the review by Wheatley *et al.* (2021),[17] Trends Immunol, 42: 956–958 that elegantly addresses immune imprinting to define vaccine strategies for combatting global surge in infections due to COVID-19

of immunity, and attenuation inflammatory cytokines could be an attractive and pragmatic strategy at combating COVID-19.

AFRICAN MEDICINAL PLANTS WITH ANTIVIRAL ACTIVITIES

Africa is one of the continents endowed with the richest biodiversity in the world on account of the geographical spread spanning a land mass of approximately 216, 634,000 hectares of closed forest areas. The continent is rich in many food plants used as herbs, health foods and for therapeutic purposes. More than 5000 different species of plant substances with chemotherapeutic properties relevant in the treatment and management of several diseases have been found to occur in these areas.[21] Reports also document diverse plants, with their isolated products and derivatives with antiviral properties including alkaloids, flavonoids, phenolic compounds, terpenes, polysaccharides, and polypeptides.[22,23] In addition, Oladele *et al.* (2020) has documented some of these plants in a recent review.[24]

The efficacy of some of these plants and their derived phytochemicals has been established following their potential to interfere with the replication and transcription machinery of some causative agents of viral infections.[25,26] Thus, the antiviral properties and immuno-modulatory activities of these compounds can be utilized in the prevention, treatment and management of COVID-19. While these medicinal plants and their secondary metabolites await effective, safe, affordable and accessible treatment options, their antiviral potency justifies their selection for further studies as potential agents for prophylactic administration or potential therapeutic intervention against COVID-19.[27] Apart from the antiviral properties exhibited by the phytomedicines and bioactive compounds obtained from these plants, it is documented that they elicit robust anti-inflammatory and immunomodulatory effects which have been linked to their ability to modulate the immune response[28] and to reduce viral or parasite load.[29,30]

In Nigeria, many medicinal plants and phytochemicals have been documented by researchers to elicit significant effects against viral and COVID-19 related diseases. Despite this feat recorded by scientists, the Nigerian government has not approved or authorized the use of any indigenous phytomedicine to combat COVID-19 officially. This is premised on the facts that no herbal remedy currently claimed to prevent, manage or cure the infectious disease has been taken through a rigorous scientific investigation via clinical trials. Meanwhile, the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria has started processing a number of formulations for "safe use" under listing status.[27] These polyherbal formulations, according to NAFDAC, have been claimed to boost immunity with a parallel anti-infective activity capable of providing relief to symptoms associated with COVID-19. For instance, IHP Detox Tea (a special blend of *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae), *Garcinia kola* Heckel (Clusiaceae), and *Psidium guajava* L. (Myrtaceae)) for treatment of COVID-19) has been submitted for clinical trials. The identified main bioactive phytoconstituents of the *A. paniculata* is andrographolide while kolaviron and Garcinia biflavonoids have been reported in *G. kola*.[31,32]

G. kola

G. kola is a largely cultivated tree and highly valued in West and Central Africa for its edible nuts.[33] The seed, commonly known, as bitter kola is eaten by many and it is culturally acceptable in Nigeria. Extracts of the plant have been employed in the African herbal medicine for the treatment of ailments such as laryngitis, liver diseases,[34] cough, and hoarseness of voice.[35]

The seed of *G. kola* [Figure 2] is employed as a general tonic and it is believed to have aphrodisiac properties. The roots and stems are cut into short chew-sticks used for cleaning teeth. *G. kola* extract among ten common Nigerian chewing sticks examined for antibacterial properties, displayed good activity.[36] *G. kola* seeds have also been indicated in the traditional African medicine in the treatment of inflammatory disorders. Extracts of the various parts of the plants have been employed in the treatment of laryngitis[33] and liver disease.[34] Extracts of the seeds gave a remarkable improvement of liver function in patients with chronic hepatitis and cholangitis after treatment for 14 days at a Nigeria herbal home.[34,37] The seeds are used medicinally to treat parasitic, microbial, and viral infections as well as treatment of bronchitis, throat infections, chest colds, and coughs.

KOLAVIRON

The most abundant active constituent of the seed has been reported to be kolaviron [Figure 2], a biflavonoid complex containing bioflavonoids GB-1, GB-2, and kolaflavonone.[38] Kolaviron has been shown by several investigations, in numerous disease models, to scavenge radicals, chelate metals, inhibit carcinogen-induced genotoxicity, and to possess anti-inflammatory properties.[39,40] We demonstrated that kolaviron protected BALB/c mice against influenza A/Perth/H3N2/16/09 (Pr/H3N2) virus infection.[41] This study indicates that kolaviron is effective for delaying the development of clinical symptoms of influenza virus through a mechanism unrelated to those deployed by the existing anti-influenza drugs but closely associated to its antioxidant and immunomodulatory properties. Other studies have demonstrated the molecular mechanisms

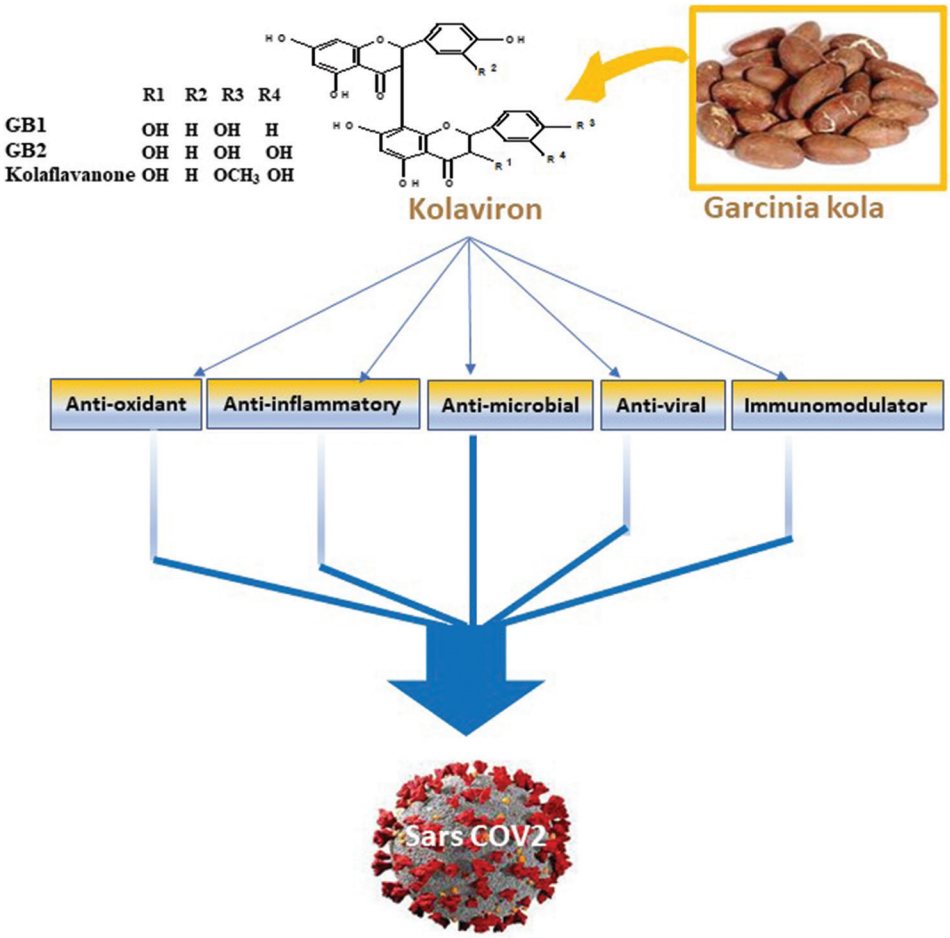

Figure 2: *Garcinia Kola* and Kolaviron: Chemical structure and pharmacological properties.

underlying the chemopreventive abilities of kolaviron to include mitigation of oxidative damage to biomolecules, downregulation of NF-κB and AP-1 DNA binding activities, as well as modulation of inducible nitric oxide synthase (iNOS), and cyclo-oxygenase 2 (COX-2) expressions.[37,40,42] Another compound with potent pharmacological properties is Garcinoic acid, an analog of Vitamin E, characterized from *G. kola* seeds.[43,44] Several studies in various *in vitro* and cell-based models demonstrated Garcinoic acid as a potent anti-inflammatory agent depicted by its ability to inhibit COX-2 and iNOS expressions in lipopolysaccharide (LPS)-stimulated RAW264.7 cells.[44-46]

This review article presents the ability of kolaviron as a novel candidate compound for possible use in COVID-19 on account of its well-researched immunomodulatory, anti-inflammatory, and antiviral properties which may limit the molecular events leading to morbidity and mortality caused by the disease. The emerging understanding of the cellular and molecular mechanisms of kolaviron and the context of the same for SARS-CoV-2 infections suggests that the antioxidant, immunomodulatory, anti-inflammatory, antiviral, and antibacterial properties of kolaviron can have value added benchmark to anchor the development of nutraceuticals and functional foods as adjuncts for COVID-19 management.

Kolaviron as anti-inflammatory agent

In the pathogenesis of SARS-CoV-2 infection, the major molecular events are the release of cytokine storm which plays a key role in the exaggerated and multi organ damaging-inflammation of the disease [Figure 1]. The release of inflammatory mediators by the neutrophils, macrophages, and lymphocytes of the immune system activate adaptive immunity conferring protection against infection but induces inflammation at the same time. Subsequently, T helper cells activate other types of cells such as monocytes and B cells through the release of cytokines, such as TNF-α, IL-1β, and IL-2, promoting and elongating the process of inflammation.[47] Kolaviron is reputed for its potent anti-inflammatory property as demonstrated in various *in vitro* and *in vivo* models.

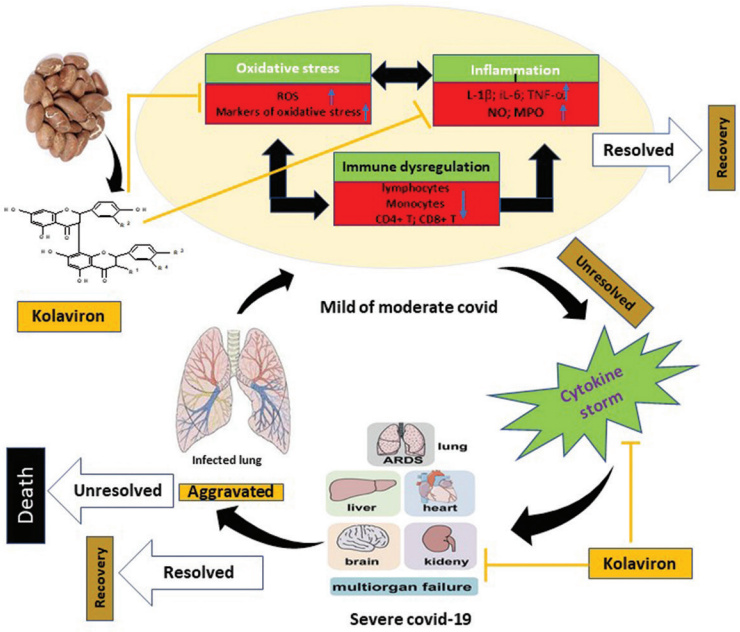

Figure 3: Schematic diagram depicting the pathogenesis of COVID-19 and proposed mechanism of action of kolaviron. On infection of the lung cells by SARS-CoV-2, there is subsequent elevation of oxidative stress leading to uncontrolled inflammation and a dysregulation of immune response accumulating in exaggerated cytokine storm syndrome. ARDS-mediated multi organ damage results from the aberrant cytokine storm causing severe COVID-19. It is proposed that kolaviron may interfere with ROS mediated oxidative stress and uncontrolled inflammation, modulating the immune response, abrogating pro-inflammatory cytokines, and attenuating the resultant cytokine storm.

The anti-inflammatory property of kolaviron through inhibition of IL-6 secretion in lipopolysaccharide stimulation of macrophages was demonstrated.[48] Kolaviron suppressed the DSS-mediated increase in colonic nitric oxide concentration and myeloperoxidase activity, and significantly prevented the increase in inflammatory mediators, IL-1β and tumor necrosis factor alpha in the colon of DSS-treated rats.[49] Kolaviron may therefore be a candidate to modulate the immune-inflammatory cascade presented in COVID-19.

Furthermore Olajide *et al*. (2021a)[50] demonstrated that extract from *G. kola* seeds reduced the production of pro-inflammatory cytokines TNFα, IL-6, IL- 1β, and IL-8 in human PBMCs stimulated with SARS-CoV-2 spike protein S1. This observation has significant clinical implications and the potential ability of kolaviron to attenuate vicious cycle of inflammatory responses which are characterized by excessive release of pro-inflammatory cytokines resulting in the cytokine storm in COVID-19 which ultimately target lung and other tissues.[51,52] It was reported that *G. kola* seed extract prevented toxicity to A549 lung epithelial cells which were co-cultured with SARS-CoV-2 spike protein S1-stimulated PBMCs, suggesting that the anti-inflammatory activity of *G. kola* promoted the prevention of cytokine-mediated damage to A549 lung epithelial cells suggesting that the anti-inflammatory effects of *G. kola* seed extract could represent a pragmatic strategy for the treatment of ARDS and lung damage in patients with severe COVID-19.[50]

Several studies have implicated COVID-19 cytokine storm in lung damage and ARDS.[53,54] In this regard, SARS-CoV-2 is known to activate immune cells leading to the production of a large number of pro-inflammatory cytokines which cause lung damage [Figure 3]. Acute respiratory distress, inducing severe lung injuries characterized, in particular, by elevated levels of inflammatory markers like IL-6 is shown in COVID-19 infected individuals. Several studies have correlated the released cytokines with the severity of the disease pathology, prognosis, and mortality.[55] In COVID-19, acute lung injury presents itself with bilateral pulmonary infiltrates, alveolar-capillary vasculitis with neutrophil infiltration, accompanied by pro-inflammatory cytokine release. In rodents, significant release of IL-6 levels has also been related to acute lung injury,[56] as reported in patients with severe acute respiratory syndrome and those with COVID-19.[56,57] Similarly, in influenza virus infection, on recognition and infection of pulmonary epithelial cells, influenza virus stimulates early, and rapid secretion of cytokines, such as TNF-α, IL-6, and IFN-γ and inflammatory chemokines including MCP-1 and MIP. Together, these two constituents of innate immunity have been directly implicated in lung pathology as they occlude pulmonary parenchyma thus blocking its function.

Release of these chemokines and cytokines subsequently result in taxis-driven influx, accumulation and activation of innate inflammatory cells neutrophils, monocytes, dendritic cells, and macrophages, which if finely orchestrated, may lead

to viral clearance and disease resolution, or when excessively unleashed, result in severe immunopathological damage, illness and fatality.[58-60] Excessive pulmonary activation of neutrophils and macrophages has been reported in influenza virus treated mice.[41] Kolaviron elicited significant modulatory effects on all these immunopathogenic responses as it elicited reduced cellular infiltration and less pathology in the pulmonary tissue. Reduced expression of MCP-1 and iNOS was also observed in kolaviron-treated influenza-challenged mice.[42] In addition, kolaviron abated the high immunostaining signal for the innate cell derived pro-inflammatory cytokine IL-1β, IL-10, and chemokine RANTES in mice infected with influenza virus.[42]

Kolaviron as anti-oxidative agent

ROS, derived from molecular oxygen but more reactive than oxygen itself, play an essential role in viral infections by inducing innate immune responses due to the opening of inter endothelial junctions that allow the migration of inflammatory cells through the endothelial barrier.[61,62] The recruitment of inflammatory cells at the site of infection causes excessive ROS production, which is considered essential for the genesis and progression of inflammatory diseases.[63,64] Furthermore, generation of ROS has been reported to enhance the gravity of viral infections due to their participation in inflammatory processes.[65] Influenza virus and a number of respiratory viruses have been shown to generate ROS on account of overwhelming recruitment of inflammatory cells at the site of infection[66] resulting in disturbance of redox imbalance and oxidative stress with consequent oxidative damage to the cells.[67] In SARS-CoV-2 viral infection, studies have reported increased oxidative stress with attendant migration of neutrophils to the infected area.[68]

Kolaviron has been investigated in a wide range of established *in vitro* assays involving ROS as a potent antioxidant and free radical scavenger. Thus, kolaviron elicited significant reducing power and a dose-dependent inhibition of oxidation of linoleic acid, inhibited H_2O_2, and was more effective than BHA and β-carotene.[69] Kolaviron also significantly scavenged superoxide generated by phenazine methosulfate NADH and scavenged hydroxyl radicals as revealed by significant inhibition of the oxidation of deoxyribose. *In vivo*, kolaviron reduced background levels of protein oxidation marker (2-aminoadipic semialdehyde) in plasma and liver and γ-glutamyl semialdehyde (GGS) as well as malondialdehyde in liver.[70] Furthermore, kolaviron reduced damage to proteins and lipids induced by Fe3+/EDTA/ascorbate mixtures *ex vivo*.[71] Moreover, kolaviron dose dependently inhibited the intracellular ROS production induced by H_2O_2 in HepG2 cells.[72,73]

It has been hypothesized that endogenous GSH deficiency could be one of the causes of severe symptoms in COVID-19 patients. The reduction in GSH and the attendant increase in ROS have been found to correlate with the debilitating symptoms and the slowest recovery times in COVID-19 infected individuals.[74] Likewise, it is known that GSH concentrations are decreased in the elderly,[75] which could explain their susceptibility to the severity of COVID-19. Similarly, and interestingly, in influenza virus infection, intracellular redox imbalance has been shown to be a prominent feature.[76] In addition, viral persistence and expression of late viral proteins have been found to be dependent on increased oxidative environment resulting from persisting depletion of the most prevalent and powerful intracellular antioxidant GSH. Kolaviron elevated GSH level in influenza virus treated mice. During viral infection, the rate of O_2 - coupling to generates OONO. as opposed to its dismutation by superoxide dismutase (SOD) has been reported to be approximately 3 times faster.[77] In influenza virus treated mice, kolaviron was reported to reverse this redox reaction as revealed by few detections of viral particles in the treated mice.[41]

Release of iron into the bloodstream generating ROS leading to oxidative stress has been reported in COVID-19. In SARS-CoV-2 infection, free Fe (III) ions into the bloodstream following attack on the heme groups of hemoglobin in red blood cells, and through the Fenton and Haber–Weiss reactions, the level of ROS is raised.[78] Furthermore, excess ROS oxidize hemoglobin to methemoglobin (iron in the ferric state, Fe (III)) which cannot bind oxygen effectively, resulting poor oxygen transport.[68] The overall effect of oxidative stress on red blood cells results in hypoxia causing respiratory failure commonly seen in COVID-19.[79] Kolaviron has been shown to be effective antioxidant reversing Haber-Weiss and Fenton generating radicals in various models including red blood cells.[70] Thus, kolaviron inhibited the Cu^{2+}-induced as well as Fe^{2+} mediated oxidation of rat serum lipoprotein. Overwhelming oxidative stress induces DNA damage, impairs macromolecules, and causes plasma membrane damage.[47] In lymphocytes incubated with Fe^{3+}/GSH, kolaviron was found to attenuate the oxidant-induced DNA strand breaks as well as base oxidation.[71]

Respiratory viral infections have been associated with dysregulation of several signaling pathways, including the inhibition of Nrf2/Keap1nuclear erythroid factor 2-related factor 2 (Nrf2) and activation of NF-κB signaling, Komaravelli and Casola.[67] For instance, lung biopsies collected from patients with COVID-19, the Nrf2 pathway was found to be inhibited, while agents that stimulate and enhance Nrf2 have been observed to suppress SARS-CoV-2 replication and the inflammatory response.[80] Kolaviron was reported to enhance Nrf2 signaling and offer neuroprotection in BV2 microglia.[81]

Activation of the NF-κB transcription factor signaling pathway has been linked to the pathogenesis of severe

COVID-19.[82] It has been recently shown that NF-κB activation is a mechanism for SARS-CoV-2 spike protein S1-induced exaggerated production of TNFα, IL-6, IL-1β, and IL-8 in PBMCs.[83] On the other hand, inhibition of NF- κB activation, with the resultant reduction in exaggerated production of pro-inflammatory cytokines like TNFα has been associated with the reduction in cytokine storm in severe COVID-19.[84] Kolaviron has been shown to modulate these signaling pathways in a number of disease conditions as well as viral infections. It was reported that the seed extract of *G. kola* inhibited both cytoplasmic activation, DNA binding, and transcriptional activity of NF-κB in SARS-CoV-2 spike protein S1-simulated PBMCs as well as in RAW264 macrophages and BV-2 microglia stimulated with bacterial LPS.[48,50,81] Similarly, in influenza virus mice infection, kolaviron-related redox switch affected NF-κB, the master regulator of pro-inflammatory cytokines/chemokines, as its expression was markedly inhibited as well as its associated stress repines protein COX-2.[42] Furthermore, kolaviron downregulated the expression of NF-κB and COX-2 in dimethyl nitrosamine (DMN)-treated rats.[40]

Kolaviron as hepatoprotective agent

Liver injury is one of the common complications in patients with COVID-19. Liver injury, inflammatory cytokine storm generated by the excessive immune response induced by coronavirus infection has been implicated.[85] Inflammatory cytokines and chemokines such as (IL-2, IL-7, IL-10, MCP1, and TNF-α) have been found to be elevated in COVID-19 patients.[86] Liver ischemia reperfusion injury, a pathophysiological process commonly occurring after rapid recovery of blood circulation, has been ascribed to be an underlying mechanism of COVID-19-associated hepatic injury.[87] Several therapeutics including antibiotics (macrolides and quinolones), antiviral drugs (ribavirin and lopinavir/ritonavir), and nonsteroidal anti-inflammatory widely used to treat COVID-19, have been reported to cause hepatotoxicity.[88] For instance, a report showed that a pooled incidence of drug induced liver injury in patients with confirmed SARS-CoV-2 infection.[89] In addition, a study revealed that a proportion of patients who received lopinavir/ritonavir after admission had abnormal liver function.[90]

The hepatoprotective effects of kolaviron have been demonstrated against hepatotoxicity induced by a wide range of drugs and hepatotoxins such as CCl_4,[91] diclofenac,[92] aflatoxin,[93] 2-acetyl aminofluorene,[94] and dimethylnitrosamine.[95] The underlying mechanism of its heptoprotection involves antioxidant, anti-inflammation, and inhibition of lipid peroxidation.[40,91,93] Kolaviron suppressed certain pro-inflammatory genes whose expression has been shown to be regulated by transcription factors. Thus, kolaviron abolished the expression of COX-2 and iNOS proteins in DMN-treated rat liver and abrogated the DNA binding activity of NF-kB and AP-1 induced by DMN.[40] It also increased levels of antioxidants including glutathione, modulated altered lipid profiles, and restored liver function biomarkers in drug-induced liver toxicity in rodents.[91,94]

Kolaviron as cardioprotective agent

Abounding evidence has identified oxidative stress and inflammation as relevant pathophysiological pathways in the development of cardiovascular diseases (CVDs) involving endothelial dysfunction and thrombosis.[5,95] Several enzyme systems, including nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase (NOX), xanthine oxidase (XO), uncoupled endothelial nitric oxide synthase, and the mitochondrial electron transport chain, have been implicated in the generation of ROS in the cardiovascular system.[96,97] Moreover, inflammation, occurs in the vascular tissue involving inflammatory immune cells, interactions between cell surfaces, and proinflammatory mediators.[98,99] Oxidative stress and inflammation resulting from an increased production of adhesion molecules, following low-density lipoprotein (LDL) oxidation results in the migration and infiltration of inflammatory cells in the vascular tissue.[100] Oxidation of LDL is generally believed to promote atherosclerosis and foam cell formation.[39] Thus, kolaviron inhibited the process of LDL oxidation which may delay the progression of atherosclerosis. Lipoprotein resistance to copper-induced oxidation was highly improved in rats treated with kolaviron (100 mg/kg) for 7 days as demonstrated by significant increase in lag time, a decrease in area under the curve and slope of propagation.[39] Furthermore, kolaviron inhibited the Cu^{2+}-induced oxidation of rat serum lipoprotein and prevented microsomal lipid peroxidation induced by iron/ascorbate in a concentration dependent manner.[39]

SARS-CoV-2 has been shown to alter the host redox balance and elicit a damaging inflammatory response, contributing to cardiovascular complications. Thus, in patients with SARS-CoV-2 an elevated level of cardiac biomarkers, such as homocysteine, troponins, myoglobin, C-reactive protein, IL-2, IL-6, and ferritin, result in myocardial injury.[6,86] In rats, kolaviron attenuated homocysteine-induced atherosclerosis and oxidative stress by increasing the activity of the antioxidant enzymes and reducing the markers of oxidative stress and inflammation. Kolaviron also reduced the serum levels of LDL-C, triglycerides, and total cholesterol with attendant reduction in heart rate as revealed by electrocardiograph data.[101] Antioxidant enzyme systems, such as SOD, catalase, glutathione peroxidases protect vasculature, and cardiomyocytes of cardiovascular system against ROS.[96] Kolaviron elicited antioxidant property and cardioprotective effect on isolated rat heart. In ischemic

reperfusion injury rat heart model, kolaviron elevated plasma levels of FRAP, TEAC, and ORAC in the rats and increased the levels of antioxidant enzymes and attenuated lipid peroxidation. Furthermore, kolaviron inhibited the activation of p38 MAPK, promoted the activation of Akt and promoted inhibition of cardiomyocytes apoptosis signal through reduction in the expressions of Caspase 3, cleaved Caspase 3, and cleaved PARP in rats subjected to reperfusion injury.[102,103] Cardiovascular complications in patients with COVID-19 arise from altered sympathetic activity, coagulation, hemodynamics following infections, oxidative stress, and inflammation. On account of the cardio protective effect of kolaviron and its modulatory effects on biomarkers of CVD, it may have a therapeutic role in cardiovascular risk factors and squeal in COVID-19.

Kolaviron as potential antiviral agent

A plethora of plant-based natural products have been reported to have antiviral properties and are gaining attention of investigators for their therapeutic potential in COVID-19. Thus, phytochemicals isolated from medicinal plants have shown great potential in inhibiting replication and blocking entry of viruses, including coronaviruses.[104,105] Specifically, several models including *in vitro* and animal models have demonstrated antiviral property against SARS-CoV-2.[104,106,107] For instance, the antiviral activities of Limonene against HSV-1, influenza, yellow fever, and dengue virus have been reported.[108-110] The mechanism of the antiviral activity of this compound is mainly through inhibition of viral replication via direct action on the virus.[47] Kolaviron elicited immunomodulatory and immunorestorative properties in *in vitro* and *in vivo* immunocompetent and immunocompromised animal models. which could be harnessed for possible clinical benefits to immunodeficient patients.[111] GB1, a biflavonoid and a component of kolaviron showed antibacterial activities against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci with minimal inhibitory concentrations (MIC) of 32 and 128 mg/ml, respectively.[112] The antibacterial activities of methanol extracts, containing kolaviron, of *G. kola* evaluated using broth microdilution showed MIC of 256 to 1024 μg/mL against multidrug resistant Gram-negative bacteria overexpressing active efflux pumps.[113] Bacteria and pathogens have been reported to exacerbate the effect of corona virus in COVID-19 patients. Examples are *Streptococcus pneumoniae*, *S. aureus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, *Legionella pneumophila*, and *Acinetobacter baumannii*, and viruses such as influenza, coronavirus, rhinovirus/enterovirus, parainfluenza, influenza B virus, and human immunodeficiency virus.[114] The methanol extract and fractions of *G. kola* seed elicited protective effect against *Streptococcus pyogenes*, *S. aureus*, *Plesiomonas shigelloides,* and *Salmonella typhimurium* using agar-well diffusion method and MIC and minimum bactericidal concentration assays.[115]

Influenza A viruses induce cytokine storm and host's intracellular redox imbalance to ensure continuous replication and survival, leading to severe immunopathology and death. We reported the protective role of kolaviron, on BALB/c mice challenged with influenza A/Perth/H3N2/16/09 (Pr/H3N2) virus. Kolaviron administered at 400 mg/kg orally to BALB/c mice for 3 days, 3 h, and 1 h before infection with 1LD50 or 3LD50 (14-day study) and 5LD50 (6-day study) of Pr/H3N2 improved lung aeration, parenchyma integrity with patchy cellular infiltration and reduced lung consolidation, inflammatory cells infiltration as well as overall improvement in morbidity and mortality.[41] Furthermore, excessive pulmonary activation of neutrophils and macrophages in mice infected with Pr/H3N2 were attenuated by Kolaviron.[41,42] While excessive CD4 T cells during influenza infection has been demonstrated to contribute to immunopathology, the pivotal role of CD4+ cells in influenza clearance through direct targeting and elimination of infected cells and activation of adaptive immune response has also been demonstrated[116-118] and the IL-10 secreting prowess of CD4+ which has been implicated in viral infection. In mice infected with influenza virus, kolaviron suppresses IL-10 production, which could selectively fine tune host's CD4+.[42]

CONCLUSION

COVID-19 cases continue to rise globally worldwide. Available vaccines and drugs developed have not been effective enough to combat this dreaded disease. There is therefore an urgent need and search for alternative and effective treatments that would minimize the number of mortalities due to the disease. Aberrant immune host response together with cytokine storm and lymphocytopenia has been considered important in the severity of COVID-19 progression. Thus, modulation of the immune response and cytokine storm resulting from the overproduction of pro-inflammatory cytokines by natural agents that interfere with the production and signaling of these cytokines appear to be a very promising and pragmatic approach for treating severe cases of COVID-19. Phytotherapeutic agents have been found to be effective in the prevention and treatment of certain diseases including viral diseases. Indigenous plants with potent medicinal properties are considered as alternative agents in the treatment of various human illnesses including chronic inflammatory conditions. Several countries especially in Asia have adopted traditional medicine as alternative for the management of COVID-19 pandemic to tackle various symptoms and manifestation of the disease leading to reduced mortality associated with the viral infection. Overall, as

reviewed, kolaviron and *G. kola* possess pharmacological properties relevant in the pathological features of immunological, cardiovascular, neurological, gastrointestinal, hepatocellular, and pulmonary systems, which are the common accompaniments of COVID-19 infection. Due to the potent antioxidant and anti-inflammatory activity of Kolaviron coupled with its interference in multiple pathways of inflammation, including inhibition of pro-inflammatory cytokines and chemokines qualify it as a novel candidate to inhibit cytokine storm, which is a major culprit in the etiology of COVID-19 [Figure 3].

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Dr. Okezie I Aruoma is the Editor-in-Chief and Dr. Olatunde Farombi is the Associate Editor of the journal.

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