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Chapter

Neurological Complications in COVID-19: Implications on International Health Security and Possible Interventions of Phytochemicals

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Abstract

Global health security or international health security (IHS) includes any natural or man-made phenomenon that challenged human health and well-being including emerging infectious diseases such as the current global pandemic: COVID-19. Since the sudden outburst of COVID-19 pandemic in 2019, many COVID-19 patients have exhibited neurological symptoms and signs. Till now, there is no known effective established drug against the highly contagious COVID-19 infection despite the frightening associated mortality rate. This chapter aims to present the mechanism of action of coronavirus-2 (SARS-CoV-2), the clinical neurological manifestations displayed by COVID-19 patients, impact on the global health system and present phytochemicals with neuroprotective ability that can offer beneficial effects against COVID-19 mediated neuropathology. Reports from COVID-19 clinical studies, case reports, and other related literature were evaluated. Neurological complications of COVID-19 include anosmia, acute cerebrovascular disease, acute disseminated post-infectious encephalomyelitis, encephalitis, etc. Also, SARS-CoV-2 could be a neurotropic virus due to its isolation from cerebrospinal fluid. Multiple neurological damage displayed by COVID-19 patients might be due to hyperinflammation associated with SARS-CoV-2 infections. Kolaviron, resveratrol, vernodalin, vernodalol, and apigenin are natural phytochemicals with proven anti-inflammatory and therapeutic properties that could extenuate the adverse effects of COVID-19. The phytochemicals have been documented to suppress JNK and MAPK pathways which are essential in the pathogenesis of COVID-19. They also showed significant inhibitory activities against SARS-CoV-2 main protease. Taken together, these phytochemicals may offer neuroprotective benefits against COVID-19 mediated neuropathology and suppress the burden of the pandemic on IHS.

Keywords: international health security, Neuropathology, COVID-19, Resveratrol, Kolaviron, Apigenin, Phytochemicals, SARS-CoV-2

1. Introduction

International health security (IHS) is a sum total of any natural, simulated or synthetic phenomenons that pose major threats on human health and well-being including emerging infectious diseases (EIDs) such as the current global pandemic: COVID-19. COVID-19, novel coronavirus pneumonia is ranked amidst the nine most deadly global pandemic ever occurred in the world. It was first recorded in 2019 at Wuhan, a Chinese city and since its first outbreak, the pandemic has dispersed wide to every region of the globe having critical negative impact on many countries both developed and developing nations. This severe acute respiratory disease is highly contagious and transmissible via a pathogenic virus called SARS-CoV-2 to humans and animals. Reports by the WHO team on COVID-19 pandemic as of 25th November 2020 showed that COVID-19 has really inflicted great havoc on human health and constitutes a major danger to global public health. It was reported that over 57.8 million cases of SARS-CoV-2 infections have been recorded with over 1.3 million deaths globally [1, 2]. In Nigeria, the most populous country in Africa, over 66,000 cases had been confirmed and more than 1,160 mortalities recorded [1, 2]. This statistic reveals the impact of this pandemic on the global health system capacity. The emergence of pathogens represents a significant threat to public health, including both high-income regions and low/middle-income regions [3–5].

COVID-19 has an average incubation period of 3 days [6]. The most prevalent medical manifestations of COVID-19 (such as cough, fever, shortness of breath, fatigue, and other complications) are nearly the same to those of other viral pneumonia; multiple organ failures and death were documented in critical and severe cases [7]. These indications are prominently expressed in aged persons perhaps owing to lingering and chronic underlying diseases such as diabetes, hypertension, neurodegenerative disorders, or heart diseases [8]. The spread of the virus (SARS-CoV-2) amid individuals happens when there is an infiltration of infected aerosols from cough, sneeze, or respiratory droplets into the lungs through inhalation in the nose or mouth.

Clinical case reports have documented a spectrum of neuropathological features displayed by COVID-19 patients. These neurological manifestations include anosmia, acute cerebrovascular disease, acute disseminated post-infectiousencephalomyelitis, Encephalitis, Guillain–Barré syndrome, acutedisseminated post-infectiousencephalitis, and viral meningitis [9]. Presence or confirmation of SARS-CoV-2 in cerebrospinal fluid suggest that it could invade and infect the central nervous system (CNS) as a neurotropic virus inducing multiple neurological impairments [9].

2. Methods

This chapter presents the pathogenic mechanism of SARS-CoV-2 and neurological complications of COVID-19. Furthermore, we present the possible intervention of potential anti-COVID-19 phytochemicals in the treatment of neuropathology associated with COVID-19. The literature search for this article was done on Medline, Google Scholar, and PubMed Central using keywords Clinical features, Coronavirus, SARSCOV-2, COVID-19, and complications.

2.1 Neurological damage associated with Covid-19

Several mechanisms have been projected for the neuropathology linked to SARS-CoV-2 in reference to clinical manifestations displayed by COVID-19 patients. Mao

et al. [10] documented hyposmia and anosmia in COVID-19 patients. This indicates that SARS-CoV-2 may be spread directly from the cribriform plate near the olfactory bulb to brain regions [11]. SARS-CoV-2 can diffuse to the CNS via enteric nerve and sympathetic afferent mediated by gastrointestinaltract infection [12]. Furthermore, anterograde and retrograde transmission can mediate neuro-invasion of SARS-CoV-2 through the sensory and motor nerve endings [13], coupled with involvement of motor proteins (dynein and kinesins), in particular through the vagus nerve from the lungs [14].

Brains are more vulnerable to oxidative and neuroinflammation insults due to the low level of cytoprotective endogenous enzymes. The cytokine storm syndrome (hyper-inflammation) accompanying SARS-CoV-2 infections may be one of the causes of the neurological impairments observed in COVID-19 patients. Viral infections have been documented as one of the chief agents that induces secondary haemophagocytic lymphohistiocytosis (sHLH) [15]. sHLH similarly referred to as Macrophage Activation Syndrome (MAS) is a severe health disorder which includes diverse group of hyper-inflammatory condition arisen after an infringement in the interaction between genetic predisposition and initiators such as infections. One of the features of sHLH is an abrupt and severe hyper-cytokinaemia due to inapt persistence of histiocytes and cytotoxic T-lymphocytes which eventually leads to multi-organ failure, haemophagocytosis, and mortality [16]. Other features of sHLH includes persistent fever, cytopenias, and hyper-ferritinaemia; pulmonary involvement occurs in approximately 50% of patients [17].

In the brain, activation of glial cells caused brain damage and severe inflammation with the secretion of pro-inflammatory cytokines including TNF-alpha, interleukin-2, and interleukin-5 [18]. Neuro-invasion of SARS-CoV-2 can activate macrophage via CD4+ cells to produce interleukin-6 which is a principal constituent of cytokine storm syndrome via granulocyte-macrophage colony-stimulating factor. Thus, causing damage to the neuronal cells.

2.2 Modes of action of SARS-CoV-2

Prospective EIDs which are major factor in IHS can emanate from vector-borne, vaccine-preventable, epidemic-prone, food-borne, zoonotic, and/or antibiotic-resistant pathogens or from a lack of access to safe water and sanitation. The experiences had and measures taken from prior outbreaks can enhance interventions and improve future responses to emerging infectious diseases [19, 20]. The genetic investigation on SARS-CoV-2 showed that the comprehensive genome sequence recognition rates of bat SARS coronavirus (SARSr-CoV-RaTG13) and SARS-CoV were 96.2% and 79.5%, respectively [21]. Comparing with other coronaviruses, SARS-CoV-2 proteins for viral replication, spikes formation, and nucleocapsid are initiated in specific genes in ORF1 [22]. The virus (SARS-CoV-2) gain entrance into the host cell and invade it via series of cellular alterations and modifications like other types of beta-coronaviruses. Subsequently, SARS-CoV-2 binds to the Angiotensin-Converting Enzyme 2 (ACE2) receptor in the human and/or host's alveoli of the lungs and respiratory epithelium via theRBM of the S protein [23, 24]. Similar type of receptors has been documented in the viral genome of SARS-CoV and SARS-CoV-2, particularly, the receptor binding motif (RBM) and the receptor binding domain (RBD) [25–27]. Attachment of SARS-CoV to the receptor leads to the recruitment of cellular proteases to split the S protein into S1 and S2 domains. Transmembrane protease serine 2 (TMPRSS2), human airway trypsin-like protease (HAT) and cathepsins are the cellular proteases that cleave the spike protein and enhance additional penetration modifications [28, 29]. The splitting of S protein facilitates the activation of S2 via a conformational modification

thereby allowing the insertion of the internal fusion protein (FP) into the membrane which facilitate the entry of the virus into the host.

There is a prospect that SARS-CoV-2 utilized mechanism similar to that of SARS-CoV as its receptor-binding domain (RBD) binding motif comprises the nucleotides connected to ACE2. Once SARS-CoV-2 enter into its host cell, ACE2 is shed and ADAM metallopeptidase domain 17 (ADAM17) exuviate it into the extra membrane space. This resulted into high concentration of angiotensin II from the transition of angiotensin I to angiotensin II by ACE2 and concomitant respiratory distress because angiotensin II negatively regulates the renin-angiotensin pathway consequently, damage the alveoli by increasing pulmonary vascular permeability [30]. Subsequent to SARS-CoV-2 proteins translation in the host, ORF3a protein is synthesized which codes for a SARS-CoV-2 related calcium (Ca^{2+}) ion channel. It reacts with TNF receptor associated factor 3 (TRAF3) and initiates the transcription of Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NF-kB) pathway, resulting to the secretion of the pro-IL-1B gene [31], ORF3a together with TRAF3 can mobilize the inflammasome complex which includes caspase 1, Nod-like receptor protein 3 (NLRP3) and apoptosis-associated speck-like protein containing a CARD (ASC). Another signaling which include caspases activation, mitochondrial damage, ROS production, and Ca^{2+} influx activates pro-IL-1B to interleukin 1 beta (IL-1B) which enhance cytokine production. Furthermore, ORF8b protein through NLRP3 facilitates the inflammasome pathway. ORF8b protein is longer in SARS-CoV-2 [31]. Further studies are needful to ascertain the benefit or significance of the extra-nucleotides as contained in SARS-CoV-2. The E protein that forms an ion channel is also implicated in the cytokine's over-secretion (an occurrence referred to as cytokine storm syndromes which has been reported to be one of the major causes of respiratory distress in COVID-19) via NLRP3 inflammasome pathway (**Figure 1**) [32].

c-Jun N- terminal kinase (JNK) pathway is also one of the vital SARS-CoV pathogenic pathways. It is activated by ORF3a, ORF3b, and ORF7a. and results in pro-inflammatory cytokines over-secretion. These over-secretions of inflammatory cytokines have deleterious effects on lung and can accelerate lungs damage [33].

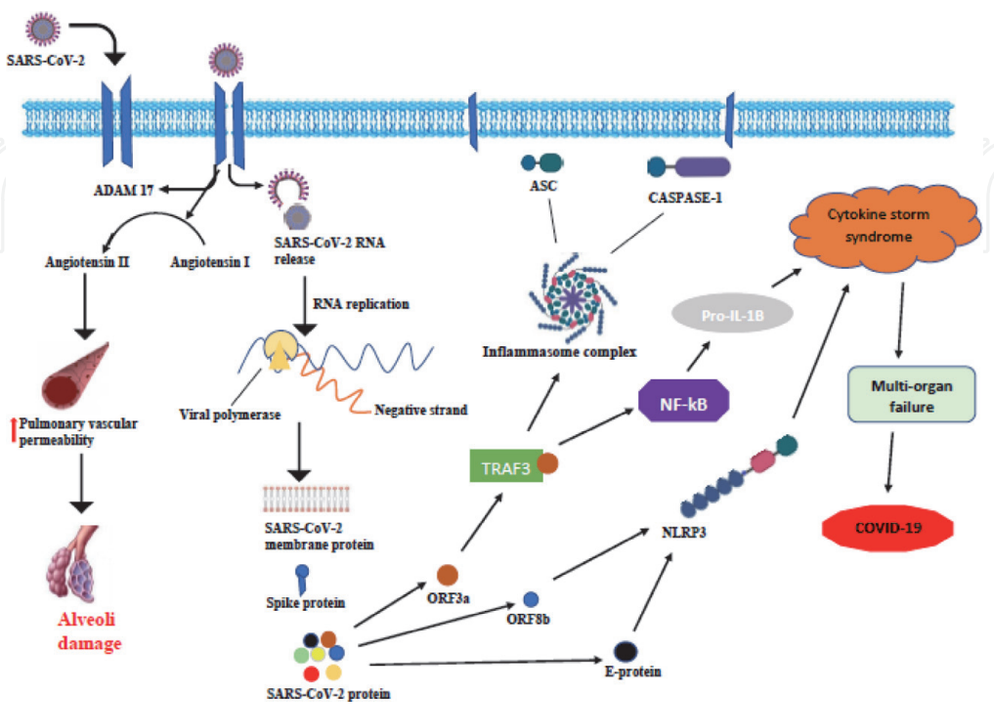

Figure 1.
Proposed mechanism of SARS-CoV-2.

Secondary haemophagocytic lymphohistiocytosis (sHLH) is a cytokine profile with a hyperinflammatory syndrome described by an abrupt hypercytokinaemia with multiorgan failure is related to COVID-19 severity. This also features increased granulocyte-colony stimulating factor, interferon-γ inducible protein 10, tumor necrosis factor-α, interleukin (IL)-2, macrophage inflammatory protein 1-α, IL-7, and monocyte chemoattractant protein 1 [33].

Additionally, SARS-CoV-2 exhibited higher infectivity and transmissibility but lower mortality rate when compared with other types of respiratory syndrome coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The noted increase in virulence of SARS-CoV-2 may be owing to great intensity and affinity at which SARS-CoV-2 attached to ACE2 and noted mutation in its genome sequence. The reported modifications on the SARS-CoV-2 gene include shorter 3b segments, alteration on Nsp 2 and 3 proteins, absent 8a, differences in orf8 and orf10 proteins, and longer 8b [34–37].

3. Phytochemicals with possible SARS-CoV-2 inhibitory and neuroprotective activities

Prevention is one of the predefined frameworks to effectively approach health security threats. To prevent the emergence or re-emergence of potentially life-threatening diseases, necessary measures must be initiated and these measures must be accessible, affordable and effective. Moreover, transmission of IHS threats was able to increase at an accelerating rate due to an overburdening of local health-care systems and widespread poverty where people lacked access to adequate water and waste management infrastructure. Therefore, the preventive and/or curative measures must be affordable by the populace. Furthermore, the remedy must be such that will be generally accepted by all; this will enhance the response and hasten the curb of the pandemic.

Different therapeutic approaches are being used since time immemorial for many health ailments apart from the pharmacological treatments. Approximately eighty percent of the World population still depends upon the use of herbal remedies for their health care. This traditional method of treating ailment is transferred from one generation to the other all over the world. Dependence on plants usage has been attributed to their affordability, effectiveness, safety, cultural preferences, and ample accessibility at all times and when it is needed. Globally, traditional healers are using various medicinal plants for the treatment of COVID-19. We therefore present some of the phytochemicals with therapeutic abilities which may serve as effective treatment for COVID-19 due to their antiviral, anti-inflammatory, antioxidant, antipyretic, immunomodulatory and cytoprotective properties.

3.1 Kolaviron from *Garcinia kola* (Guttiferae)

Since time immemorial, medicinal plants have become a source of novel and affordable drug compounds as plant-derived medicines have made significant impacts to human health and well-being [38, 39]. Garcinia kola (bitter kola) is a medicinal plant and a member of the Guttiferae family. It is an evergreen tree largely cultivated and highly esteemed for its edible nuts in West and Central Africa. Garcinia kola is commonly used by the people due to its ability to improve mouth odour and cause nervous alertness. In African traditional medicine, bitter kola is employed in the treatment and management of laryngitis, throat infections, bronchitis, inflammatory disorders, and as an antibacterial, antiparasitic, and

antipurgative. The seeds have also been used in the treatment of chronic hepatitis and cholangitis with significant improvement of liver functions. Similarly, *Garcinia kola* seeds are used a general tonic to boost the immune system [40, 41].

Many experimental findings have established the traditional medicinal uses of Garcinia kola. Kolaviron, the biflavanone of Garcinia kola (**Figure 2**) have been documented to protect against oxidative stress and hepatotoxicity induced by many xenobiotics which includes aflatoxin, 2-acetylaminofluorene, carbon tetrachloride, dimethylnitrosamine, paracetamol, phalloidin in animal studies [42–45]. Futhermore, the pharmacologically activities of biflavanone of Garcinia kola have been shown with many pharmacokinetic preferences over basic monomeric flavonoids as they pull through first-pass metabolism which incapacitates most flavonoids [40].

Neuroprotective abilities of kolaviron has been reported in many neuronal cell lines. Abarikwu *et al.* [46] documented the protective roles of kolaviron against atrazine induced toxic insult in human dopaminergic SH-SY5Y cells. The findings revealed that the antiapoptotic and antioxidative properties of Kolaviron make it effective to prevent against atrazine-induced toxicities. Similarly, kolaviron was reported to protect against apoptotic cell death in pheochromocytoma derived (PC12) cells exposed to Atrazine [47]. Igado *et al.* [48] reported the biochemical and morphological examination on the potential protective effects of kolaviron in vanadium-induced neuronal damage in rats. Kolaviron has been shown to suppress neuroinflammation in BV2 microglia via the Nrf2/ARE antioxidant protective mechanism [49]. Also, Olajide *et al.* [50] reported multidirectional suppression of cortico-hippocampal neurodegeneration by kolaviron. In another study, Omotoso *et al.* [51] reported that kolaviron ameliorated cuprizone-induced multiple sclerosis in the brain of experimental animals.

In a recent study, we reported the neuroprotective effects of kolaviron in striatal oxidative stress and neuroinflammation associated with rotenone model of neurodegenerative disease [52]. In the study, we showed that kolaviron restored rotenone-associated exploratory deficits, motor/neuromuscular incompetence and locomotor impairment. Also, kolaviron effectively ameliorated the neurobiochemical imbalance, striatal neurodegeneration, neuroinflammation and altered antioxidant defence system in the brain of the neurodegenerative rats. Kolaviron displayed a potential capacity to enhance efficient gait with minimal severity and improved coordination. This shows that kolaviron could be a prospective drug for the effective management and/or treatment of Parkinson's disease.

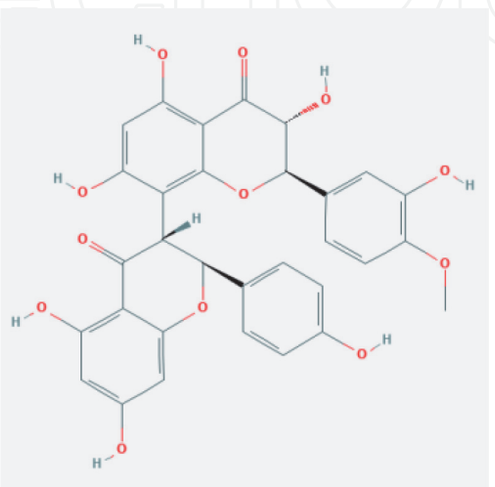

Figure 2.
2D structure of kolaviron (Kolaflavanone).

Kolaviron has been noted to be a potential anti-COVID-19 drug candidate in a computational experimental study aimed to screen phytochemicals in drug repurposing approach to combat COVID-19 [53]. The study employed USCF Chimera in virtual screening and molecular docking for possible inhibitors of SARS-CoV-2. Kolaviron was observed to exhibited a higher docked score with the SARS-CoV-2 major protease (6 LU7) above remdesivir, a recommended drug for the treatment of COVID-19. This showed that kolaviron could offer a better inhibitory effect on SARS-CoV-2 and be a more effective drug candidate in the treatment of COVID-19.

3.2 Apigenin

Apigenin (4′,5,7-trihydroxyflavone) is one of the most explored phenolics and the most commonly disseminated flavonoids in many plant species (**Figure 3**). It is predominantly present in herbs (oregano, thyme, basil, chamomile), phytochemical-based beverages (tea, beer, and wine), in vegetables (parsley, celery, onions), and fruits (oranges). It is also found extensively in Matricaria, Achillea, Artemisia, and Tanacetum [54]. Apigenin has been documented to have anticancer activities as well as theurapeutic effects on depression, Alzheimer's disease, amnesia, and insomnia treatment [54]. The dietary availability of apigenin could facilitate an efficacious intervention to inhibit activation of microglial and prevent onset of Alzheimer's disease.

After absorption, apigenin can easily be transported through the circulatory system, crossing to the blood-brain barrier to the brain, where it acts on the CNS and exhibits interaction with the GABAA-receptor [55, 56]. Sloley *et al.* [57] reported the inhibitory activity of apigenin on neuronal monoamine oxidases. Unregulated activities of monoamine oxidases may be one of the causes of some psychiatric cases and neurological disorders. However, monoamine oxidases inhibitors such as apigenin showed efficacy as antidepressant and anxiolytic agents.

The protective roles of apigenin in the amyloid precursor protein double transgenic Alzheimer's disease mouse has been reported by Zhao *et al.* [58]. Apigenin is also a potent cognition-enhancing, anti-amyloidogenic, antioxidant, neuroprotective, and anti-inflammatory agent with efficacy in the prevention and/or treatment of neurodegenerative diseases [58]. Nabavi et al. [59] in a review article emphasised the therapeutic potentials of apigenin in some human clinical trials and experimental animal models. Furthermore, apigenin's chemical structure, metabolism of action, and pharmacokinetics were elucidated in relation to its medicinal usefulness in depression, Parkinson's and Alzheimer's diseases [59].

Apigenin has also demonstrated strong anti-inflammatory property in lipopolysaccharide -induced macrophages by reducing the level of interleukin 6 (IL-6) {a pro-inflammatory cytokine}. It also inhibited tumour necrosis factor (TNF-α), interleukin 6, and cluster of differentiation 40 (CD40) production via suppression of

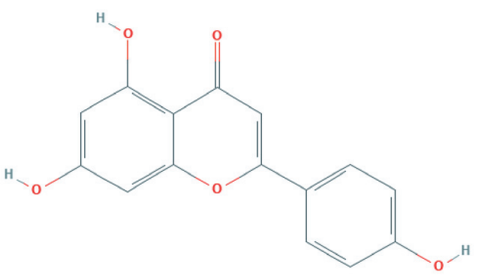

Figure 3.
2D structure of apigenin.

interferon gamma-mediated STAT1 (signal transducers and activators of transcription 1) phosphorylation in microglia [60]. An experimental study has established the inhibitory ability of apigenin on nuclear factor kappa-light-chain-enhancer (NF-kB), facilitated by inhibition of lipopolysaccharide-mediated phosphorylation of the p65 subunit [61]. Apigenin also suppressed the activities of adhesion molecules which is very essential to mitigate oxidative stress and prevent oxidative damage [62].

Apigenin promotes the release of cytoprotective enzymes such as glutathione-s-transferase, superoxide dismutase, and catalase to inhibit and neutralize cellular oxidative. Similarly, apigenin enhances activation of Nrf-2 signaling pathway leading to increase in phase II enzymes production [63, 64]. Anticancer property of apigenin in human cell culture models has been reported to be via suppression of angiogenesis and metastasis by interfering with the main signaling molecules in mitogen-activated protein kinase (MAPK) pathways which include c-Jun N-terminal kinases (JNK), extracellular-signal-regulated kinase (ERK), and p38 [65].

Apigenin has been documented to interact with both S 1 and S2 domains of the spike protein of SARS-COV-2 with substantial binding energies thus unsettling viral attachment and internalization into the host [66]. Similarly, *in silico* study in our laboratory revealed that apigenin displayed a significant binding affinity with the SARS-CoV-2 major protease (6 LU7). The result also suggested that apigenin could be a potential inhibitor of SARS-COV-2 [53].

3.3 Phytochemicals from *Vernonia amygdalina*

Bitter leaf (*Vernonia amygdalina*) is an indigenous African plant with a number of scientific proven medicinal importance [67–70]. Recent study from our laboratory has examined the possible inhibitory activity of selected phytochemical constituents of the leaf extract of *Vernonia amygdalina* (hydroxyvernolide, vernodalin, vernodalol, vernolide, and veronicoside) (**Figure 4**) against SARS-COV2 major protease (6 LU7) [71]. The phytochemicals exhibited significant binding affinity to the binding pocket of SARS-COV2 major protease suggesting them as potential molecules that could mitigate/inhibit SARS-COV2. Binding of these phytochemicalsto SARS-COV2 could inhibit or interfere the pathogenesis of COVID-19 thereby preventing its cellular entryand proliferation.

Veronicoside has been reported to have radical scavenging and antioxidant activities. It has also been documented to have cytotoxicity activities againstHep-2 (human larynx epidermoidcarcinoma), RD (humanrhabdomyosarcoma), andL-20B (transgenic murine cells) cell lines [72]. Severalspecies of plants containing veronicoside are being used in traditional medicine to treat influenza, respiratory diseases, hernia, cough, laryngopharyngitis, cancer, hemoptysis, and are also used as an antiscorbutic and expectorant [73].

Vernodalinandvernolidehave been reported to exhibit antiproliferativeactivities [74] against lung A549 (adenocarcinomic human alveolar basal epithelial cells), HeLa, and MDA-MB-23 (human breast cancer) celllines and induced apoptosis on HepG2 cells with G2/Mphase cell cycle arrest [75]. They have potential to be usedas lead compounds in the development of a therapeutic natural product for treatment of cancers in the lungs, breast or liver. These phytochemicals may also offer help in inhibiting the proliferative activities of SARS-COV2 in the host thereby mitigate the pathogenesis of COVID-19.

Sinisi *et al* [76] has reported vernodalol has a good activator of Nrf2. NF-E2-related factor-2 (NRF2) is a transcriptional factor that bindsto and facilitates the activation of the ARE-dependent gene. Under basal conditions, NRF2 is sequestered in the cytoplasmand its expression is maintained to be low due to constantpolyubiquitination. In response to different kinds of stress, NRF2is significantly induced

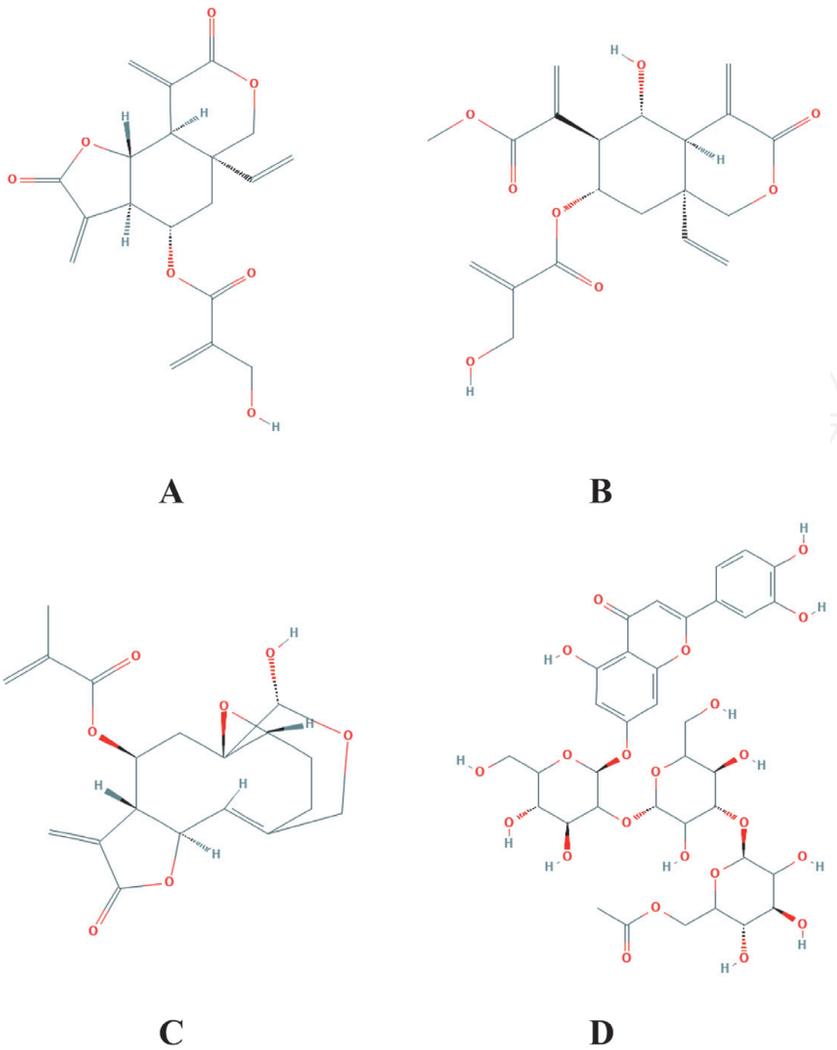

Figure 4.
2D structures of (A) Vernodalin, (B) Vernodalol, (C) Vernolide, (D) Veronicoside A.

andtranslocates into the nucleus, where it activates the antioxidant responseelement (ARE)-dependent gene expression in association with small Maf proteins and other coactivators. Thus, causing the release of phase IIcytoprotective enzymes such as γ-glutamylcysteine ligase (γ-GCS), NAD[P]H:quinone oxidoreductase-1 (NQO1), heme oxygenase-1 (HO-1), and glutathioneS-transferase (GST) which protect the cells against the attack of the stress. Since oxidative stress has been reported as one of the features of COVID-19, vernodalol can help to extenuate it by activation of NRF2.

Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NF-kB) pathway has been implicated in the mode of actions of SARS-COV2 [77, 78] leading to a cytokine profile resembling secondary haemophagocyticlymphohistiocytosis (sHLH) with a hyperinflammatory syndrome characterized by a fulminant and severe hypercytokinaemia with multiorgan failure. This is characterized by increased tumor necrosis factor-α, interleukin (IL)-2, IL-7, interferon-γ inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, and monocyte chemoattractant protein 1 [79]. However, vernolide and vernodalol have been documented to show marked inhibitory activity onSTAT3/NF-κB [76]. Therefore, vernolide and vernodalol could protect against COVID-19-induced multiorgan failure by suppressing the hyperinflammatory syndrome via inhibition of NF-kB.

3.4 Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring lipophilic and phenolic phytochemical found abundantly in edible plants and easily cross the plasma membrane after oral absorption [80–82]. it is a polyphenolic phytoalexin which comprises two aromatic rings linked by a styrene double bond which permit its trans- and cis-isomers formation (**Figure 5**) [83, 84]. Resveratrol has been reported as a possible reason accountable for the French paradox [85, 86], a phenomenon described by an epidemiological study that the French population displayed a comparatively low rate of coronary heart disease, in spite of their high consumption of saturated fat diet [87, 88]. A number of preclinical studies proposes that resveratrol has the capability to influence a variety of human diseases, this is due to its cardioprotective [89, 90] antiviral [91, 92], antiapoptotic [93, 94], anti-inflammatory [95, 96] antidiabetic [97, 98], and antioxidative [97, 99] properties.

Evidences from experimental studies has established the neuroprotective properties of resveratrol which may be beneficial in combating neurological disorders showed in COVID-19 patients. Resveratrol enhances enzymes that are responsible in stress response, for instance quinone reductase 2 (QR2), a cytosolic enzyme which influences the release of destructive activated quinone and ROS, thus, exhibiting a pivotal role in the cellular response [100]. Previous report has showed that QR2 is overproduced in the hippocampus of rat's brain in a model of learning deficits. Hippocampus is a brain region which is seriously affected in Alzheimer disease and it is primarily responsible for memory and learning. This indicates that the overproduction of this enzyme initiates memory impairments [101]. Similarly, neuroprotective effect of resveratrol has been documented to includes inhibition of microglia-mediated neuroinflammation [102]. Resveratrol has been demonstrated to inhibit the activation of NF-κB signaling pathways and mitogen-activated protein kinases (MAPKs) in lipopolysaccharides-induced dopaminergic neuronal death [102].

Activation of microglia is the hallmark of neuroinflammation and play a critical role in the pathogenesis of neurological diseases [103, 104]. Microglia is the neuronal immune cells that perform a vital role in the homeostasis in the central nervous system, and act as the first line of defense during cellular assaults, oxidative damage or progression of neurological diseases in the brain [105]. During microglial activation (microgliosis), different kinds of proinflammatory markers such as chemokines, prostaglandins, reactive nitrogen species, and cytokines are release. The overproduction and accumulation of these proinflammatory factors leads to

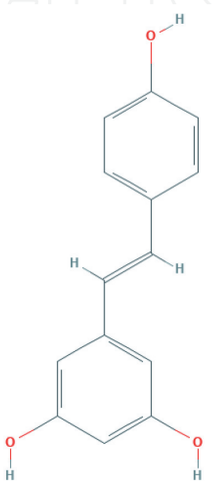

Figure 5.
2D structure of resveratrol.

damage of the neuronal cells and ultimately cause release of soluble factors and debris [106]. Many experimental studies have demonstrated the neuroprotective ability of resveratrol to inhibit the activation microglia [107–109]. Resveratrol has been reported to suppress upsurge expression of IL-1β, nitric oxide and TNFα that accompanied activation of microglia which mediate phosphorylation of p38 and NF-κB signaling [109, 110]. Resveratrol inhibited secretion of TNFα, IL-1β and reactive nitrogen species, and activation of microglia in the ischemic cortex [111].

Anti-covid-19 potentials of resveratrol has been reported in an *in-silico* study designed for drug development targeting SARS-CoV-2 Spike Protein of COVID-19 [66]. The study reported that resveratrol displayed a strong binding ability with the S2 domain of SARS-CoV-2spike protein. This spike glycoprotein, located on the surface of the virus (SARS-CoV-2), is a class I fusion protein which enhance the initial attachment of the virus with ACE2 receptor and itsconsecutive fusion with the host cells [112]. The ability of resveratrol to bind to this spike protein indicates that resveratrol may inhibit or alter the mechanism by which the virus gain entrance into its host. Furthermore, since resveratrol has been reported to modulate phosphoinositide3-kinase (PI3-k), NF-κB signaling and mitogen-activated protein kinases pathways whose end products release cytokines; It may provide beneficial effects in COVID-19 via these pathways to inhibit the over-secretion of inflammatory cytokines which resulted to cytokine storm syndromes that accelerate lungs damage and multiorgan failure is related to COVID-19.

3.5 Quercetin

Quercetin, 3,3′,4′5,7-pentahydroxyflavone (**Figure 6**), is a broadly disseminated plant polyphenol, found as conjugates with residualsugars (quercetin glycosides) in many grains, fruits, seeds, leaves, and vegetables (capers, onions, berries, and apples) [113]. The highest levels of quercetin among vegetables were found in red leaf lettuce, asparagus (*Asparagus officinalis* L.), and onions (*Allium cepa* L.), while peas, green peppers, broccoli, and tomatoes contained lower levels. Quercetin arabinoside, quercetin galactoside, and quercetin glucoside are examples of quercetin glycosides present in vegetables, fruits and other food items. They are first are deglycosylated by gut microbiota-derived betaglucosidase or lactase phlorizin hydrolaseto quercetin aglycone before passive absorption in the small intestine [114]. The quercetin aglycone produced then go through series of metabolic reactions to form methylated, sulphated, and glucuronidated metabolites, signifying participation of the phase II enzymes COMT (catechol-O-methyltransferase), SULT

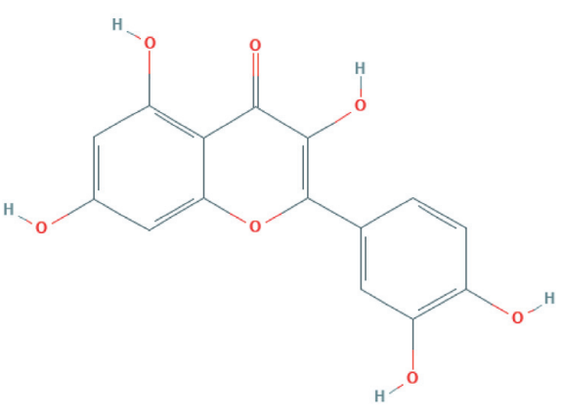

Figure 6.
2D structure of quercetin.

(sulfotransferase) and UGT (uridine 5-diphosphoglucuronosyltransferase) respectively.

Similar toother polyphenols, Studies have reported that quercetin exhibited anti-inflammatory, and immunoprotective [115], antioxidant [116], and antiviral [117], effects. It's medicinal effects on cancer, nervous system disorders, gastrointestinal tract function, infections, inflammatory processes, diabetes, and cardiovascular diseases has been documented [118–120]). Previous findings have documented the inhibitory activities of quercetin against reverse transcriptase [121], proteases [122], and polymerases [123]. Also, it has been studied in modelsof viral infection to bind to viral capsidproteins and inhibit DNA gyrase [124, 125].

During viral infection, entrance of virus into the host cell is a vital step and has been targeted as a possible point of intervention in antiviral treatments [126–128]. Quercetin has been reported to inhibit H1N1 and H3N2 influenza infection ofMDCK cells through binding to hemagglutinin proteins which is accountablefor membrane fusion during virus entry and virus-mediatedhaemolysis [129]. Furthermore, quercetin has been studied to interfere with DNA and RNA polymerases in viral infections. During adenoviruses (ADV-3,−8,−11) and herpesviruses (HSV-1, 2) infections, quercetin was reported to suppress viral DNA and RNA polymerase [123, 130, 131] and inhibit the early stage of viral replication [125, 132]. Li et al. [133] also reported antiviral activities of quercetin against HIV via its ability to suppress protease, integrase and reversetranscriptase. Quercetin upregulated IL-13 and suppressed the levels of Long Terminal Repeat (LTR) gene expression, TNF-α, p24 in HIV infection [115].

Possible antiviral effect of quercetin on many types of Coronaviruses has been described by Yi et al. [134]. Quercetin metabolite have been documented to bind to SARS-Cov 3CL protease and suppressed itsproteolytic activity [135]. Quercetin has been studied through computational studies to interact with the S2 domain of spike protein of SARS-CoV-2, thus altering the virus entry process [66]. The obstruction of virus entrance into the host cell signifies a vital approach in antiviral therapy and quercetin hinders viral membrane fusion for SARS-Cov and influenza in vitro [134].

4. Conclusion

International health security is multifaceted phenomenon that threatened the peace existence of man including emerging infectious diseases such as the current global pandemic: COVID-19. COVID-19 is a highly infectious and severe acute respiratory disorder induced by a morbific virus referred to as SARS-CoV-2. Many COVID-19 patients have displayed neurological symptoms and signs which include anosmia, acute cerebrovascular disease, acute disseminated post-infectiousencephalomyelitis, encephalitis, etc. The underlying mechanisms of pathogenic actions of SARS-CoV-2 includes activated by ORF3a, ORF3b, and ORF7a via the JNK pathway which induces lung damage; reduction of ACE2 to enhance pulmonary vascular permeability and damage the alveoli; immunosuppression; hyper-inflammation characterized by a fulminant and fatal hyper-cytokinaemia with multi-organ failure. Prevention is one of the predefined frameworks to effectively approach health security threats. To prevent the emergence IHS threats, effective measures must be initiated. Moreover, transmission of IHS threats was able to increase at an accelerating rate due to an overburdening of local health-care systems. Therefore, the preventive and/or curative measures must be affordable by the populace. Dependence on plants usage has been attributed to their affordability, effectiveness, safety, cultural preferences, and ample accessibility at all times and

when it is needed. Kolaviron, hydroxyvernolide, vernodalin, vernodalol, vernolide, and veronicoside, resveratrol, quercetin and apigenin are phytochemicals and natural products from medicinal plants with proven antiviral, antipyretic, anti-inflammatory, cytoprotective, antioxidant, immunomodulatory, and pharmacological activities that can inhibit SARS-CoV-2 and mitigate COVID-19. The phytochemicals have been documented to suppress JNK and MAPK pathways which are essential in the pathogenesis of COVID-19. Taken together, these phytochemicals could be potential drug candidates in the treatment/management of COVID-19 mediated neuropathology.

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