

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



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

*Johnson Olaleye Oladele, Oluwaseun Titilope Oladele, Oyedotun M. Oyeleke and Adenike T. Oladiji*

## 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 phenomena 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-infectious encephalomyelitis, Encephalitis, Guillain–Barré syndrome, acute disseminated post-infectious encephalitis, 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 gastrointestinal tract 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 the RBM 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 ( $\text{Ca}^{2+}$ ) 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- $\kappa$ B) pathway, resulting to the secretion of the pro-IL-1 $\beta$  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  $\text{Ca}^{2+}$  influx activates pro-IL-1 $\beta$  to interleukin 1 beta (IL-1 $\beta$ ) 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].

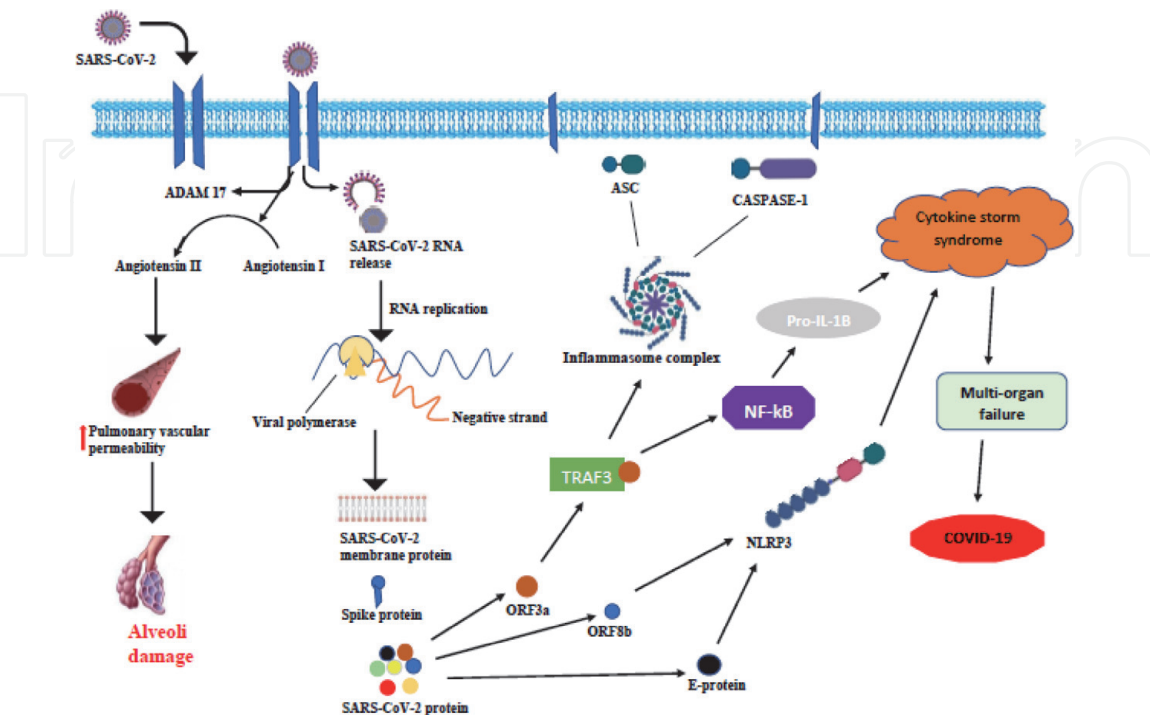


Figure 1.  
Proposed mechanism of SARS-CoV-2.

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- $\gamma$  inducible protein 10, tumor necrosis factor- $\alpha$ , interleukin (IL)-2, macrophage inflammatory protein 1- $\alpha$ , 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

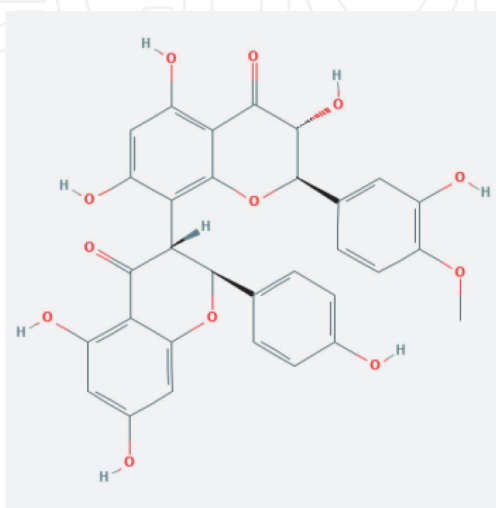
antipurgative. The seeds have also been used in the treatment of chronic hepatitis and cholangitis with significant improvement of liver functions. Similarly, *Garcinia kola* seeds are used a general tonic to boost the immune system [40, 41].

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.

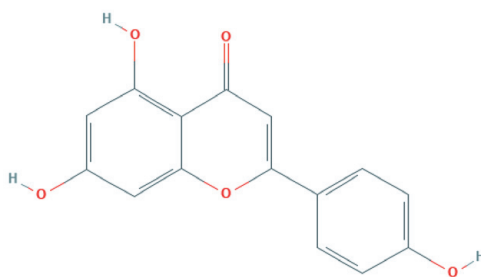
### 3.2 Apigenin

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 therapeutic 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- $\alpha$ ), 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- $\kappa$ B), 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 S1 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].

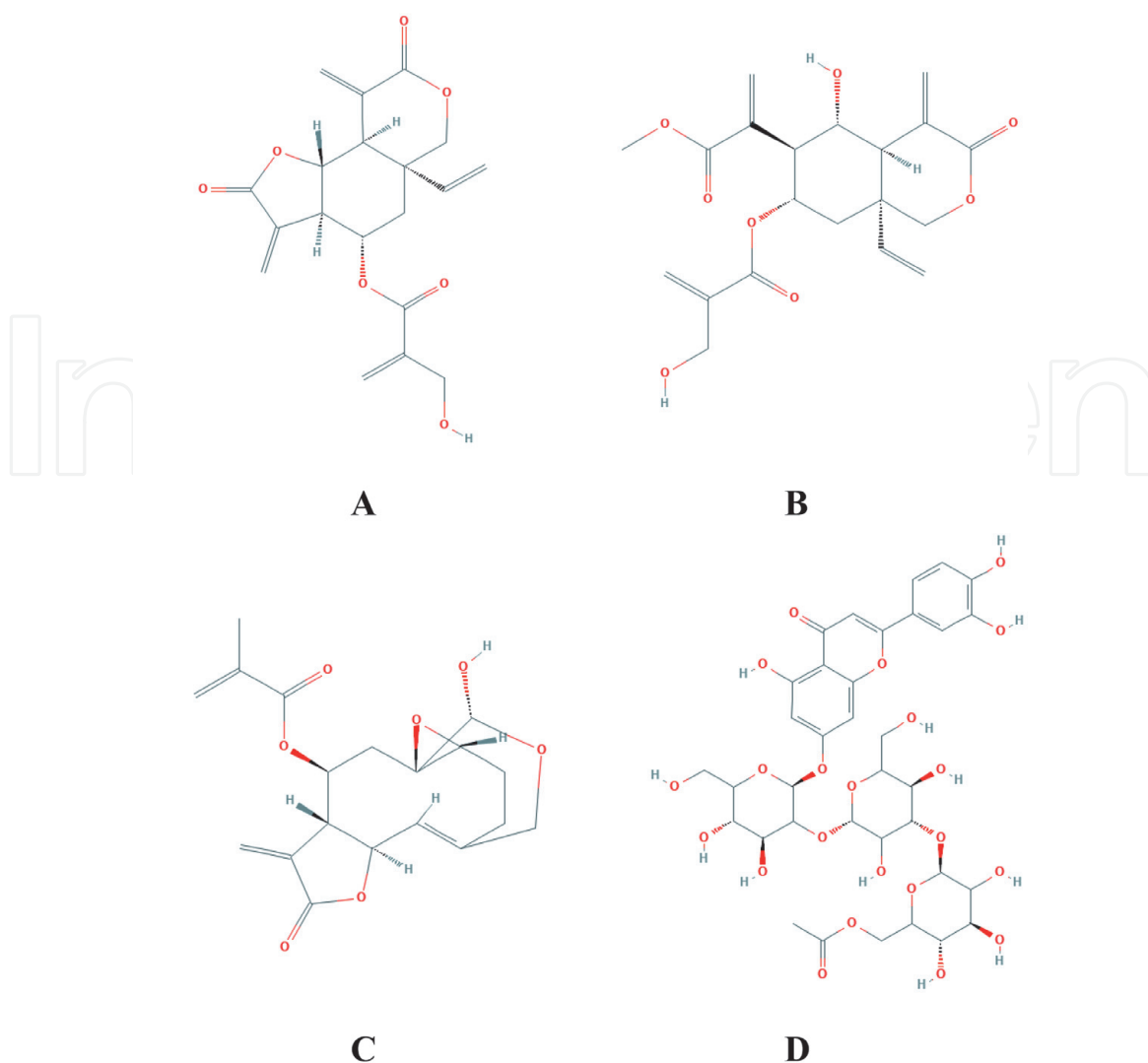
### 3.3 Phytochemicals from *Vernonia amygdalina*

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, vernodalol, 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 phytochemicals to SARS-COV2 could inhibit or interfere the pathogenesis of COVID-19 thereby preventing its cellular entry and proliferation.

Veronicoside has been reported to have radical scavenging and antioxidant activities. It has also been documented to have cytotoxicity activities against Hep-2 (human larynx epidermoid carcinoma), RD (human rhabdomyosarcoma), and L-20B (transgenic murine cells) cell lines [72]. Several species 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].

Vernodalol and vernolide have been reported to exhibit antiproliferative activities [74] against lung A549 (adenocarcinomic human alveolar basal epithelial cells), HeLa, and MDA-MB-23 (human breast cancer) cell lines and induced apoptosis on HepG2 cells with G2/M phase cell cycle arrest [75]. They have potential to be used as 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 binds to and facilitates the activation of the ARE-dependent gene. Under basal conditions, NRF2 is sequestered in the cytoplasm and its expression is maintained to be low due to constant polyubiquitination. In response to different kinds of stress, NRF2 is significantly induced



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

and translocates into the nucleus, where it activates the antioxidant response element (ARE)-dependent gene expression in association with small Maf proteins and other coactivators. Thus, causing the release of phase II cytoprotective enzymes such as  $\gamma$ -glutamylcysteine ligase ( $\gamma$ -GCS), NAD[P]H:quinone oxidoreductase-1 (NQO1), heme oxygenase-1 (HO-1), and glutathione S-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.

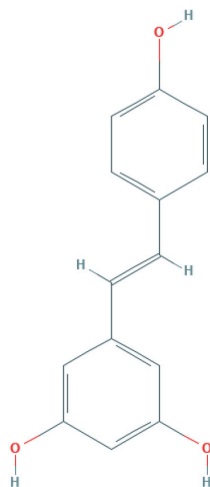
Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NF- $\kappa$ B) pathway has been implicated in the mode of actions of SARS-COV2 [77, 78] leading to a cytokine profile resembling secondary haemophagocytic lymphohistiocytosis (sHLH) with a hyperinflammatory syndrome characterized by a fulminant and severe hypercytokinaemia with multiorgan failure. This is characterized by increased tumor necrosis factor- $\alpha$ , interleukin (IL)-2, IL-7, interferon- $\gamma$  inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein 1- $\alpha$ , and monocyte chemoattractant protein 1 [79]. However, vernolide and vernodalol have been documented to show marked inhibitory activity on STAT3/NF- $\kappa$ B [76]. Therefore, vernolide and vernodalol could protect against COVID-19-induced multiorgan failure by suppressing the hyperinflammatory syndrome via inhibition of NF- $\kappa$ B.

### 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- $\kappa$ B 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



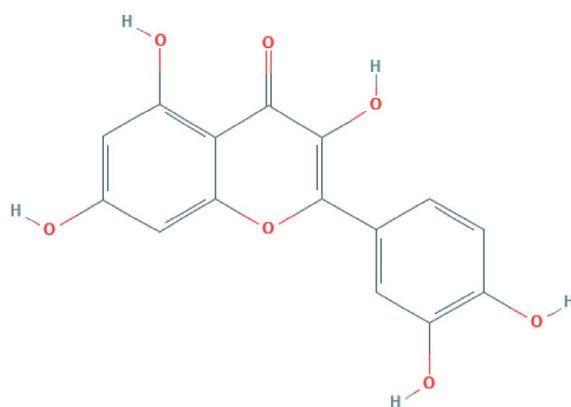
**Figure 5.**  
2D structure of resveratrol.

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-1 $\beta$ , nitric oxide and TNF $\alpha$  that accompanied activation of microglia which mediate phosphorylation of p38 and NF- $\kappa$ B signaling [109, 110]. Resveratrol inhibited secretion of TNF $\alpha$ , IL-1 $\beta$  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-2 spike 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 its consecutive 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- $\kappa$ B 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 residual sugars (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 hydrolase to 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 to other polyphenols, studies have reported that quercetin exhibited anti-inflammatory, and immunoprotective [115], antioxidant [116], and antiviral [117], effects. Its 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 models of viral infection to bind to viral capsid proteins 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 of MDCK cells through binding to hemagglutinin proteins which is accountable for membrane fusion during virus entry and virus-mediated haemolysis [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 reverse transcriptase. Quercetin upregulated IL-13 and suppressed the levels of Long Terminal Repeat (LTR) gene expression, TNF- $\alpha$ , p24 in HIV infection [115].

Possible antiviral effect of quercetin on many types of Coronaviruses has been described by Yi et al. [134]. Quercetin metabolites have been documented to bind to SARS-CoV 3CL protease and suppressed its proteolytic 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 a multifaceted phenomenon that threatens the peace and 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 morbid 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-infectious encephalomyelitis, encephalitis, etc. The underlying mechanisms of pathogenic actions of SARS-CoV-2 include 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; hyperinflammation 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 of 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, hydroxyveranolide, 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.

## Author details

Johnson Olaleye Oladele<sup>1\*</sup>, Oluwaseun Titilope Oladele<sup>2</sup>, Oyedotun M. Oyeleke<sup>1</sup> and Adenike T. Oladiji<sup>3</sup>


<sup>1</sup> Biochemistry Unit, Department of Chemical Sciences, Kings University, Ode-Omu, Osun State, Nigeria

<sup>2</sup> Phytomedicine and Molecular Toxicology Research Laboratories, Department of Biochemistry, Osun State University, Osogbo, Nigeria

<sup>3</sup> Department of Biochemistry, University of Ilorin, Ilorin, Nigeria

\*Address all correspondence to: [oladelejohn2007@gmail.com](mailto:oladelejohn2007@gmail.com); [jo.oladele@kingsuniversity.edu.ng](mailto:jo.oladele@kingsuniversity.edu.ng)

## IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] WHO COVID-19 weekly epidemiological update- 24<sup>th</sup> November 2020. <https://who.int/publications/m/item/weekly-epidemiological-update—24-november-2020>.
- [2] NCDC. Coronavirus COVID-19. <https://covid19.ncdc.gov.ng>
- [3] Nicole K. Le, Manish Garg, Ricardo Izurieta, Sona M. Garg, Thomas J. Papadimos, Bonnie Arquilla, Andrew C. Miller, Abbas M. Khan, Tamara Worlton, Michael S. Firstenberg, Sagar C. Galwankar, Sunil Raina, Harry L. Anderson III, Rebecca Jeanmonod, Donald Jeanmonod, Ijeoma Nnodim Opara, Kristiana Kaufmann, Juan A. Asensio and Stanislaw P. Stawicki. International Health Security: A Summative Assessment by ACAIM Consensus Group. 2020. DOI: <http://dx.doi.org/10.5772/intechopen.93214>
- [4] De Cock KM et al. The new global health. *Emerging Infectious Diseases*. 2013; 19 (8):1192–1197
- [5] Sikka V et al. The emergence of Zika virus as a global health security threat: A review and a consensus statement of the INDUSEM Joint Working Group (JWG). *Journal of Global Infectious Diseases*. 2016; 8(1):3–15
- [6] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2002032.
- [7] World Health Organization (WHO). Q&A on coronaviruses (COVID-19); 2020. Available from: <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses>. Accessed March 6, 2020.
- [8] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395:507–513.
- [9] Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, Karim AH and Sattar A (2020) Neurological Manifestations of COVID-19 (SARS-CoV-2): A Review. *Front. Neurol.* 11:518. doi: 10.3389/fneur.2020.00518
- [10] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020). e201127. doi: 10.1001/jamaneurol.2020.1127
- [11] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* (2020) 11:995–998. doi: 10.1021/acscchemneuro.0c00122
- [12] Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. *J Gastroenterol Hepatol.* (2020) 35:744–748. doi: 10.1111/jgh.15047
- [13] Swanson PA 2nd, McGavern DB. Viral diseases of the central nervous system. *Curr Opin Virol.* (2015) 11:44–54. doi: 10.1016/j.coviro.2014.12.009
- [14] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:552–5. doi: 10.1002/jmv.25728
- [15] Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; 383: 1503–1516.
- [16] Henter JI, Samuelsson-Harne A, Arico M, Egeler RM, Elinder G,

Filipovich AH, et al. Treatment of haemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood*. 2002; 100: 2367–2373.

[17] Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest* 2016; **149**: 1294–1301.

[18] Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci*. (2018) 12:386. doi: 10.3389/fncel.2018.00386

[19] Kalra S et al. The emergence of Ebola as a global health security threat: From 'lessons learned' to coordinated multilateral containment efforts. *Journal of Global Infectious Diseases*. 2014; 6 (4):164

[20] Abramowitz S et al. The opposite of denial: Social learning at the onset of the Ebola emergency in Liberia. *Journal of Health Communication*. 2017; 22 (suppl 1):59–65.

[21] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507–513.

[22] van Boheemen S, de Graaf M, Lauber C, Bestebroer TM, Raj VS, Zaki AM, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. *MBio* 2012;3(6): e00473–e0e512.

[23] Phan, T., 2020. Novel coronavirus: from discovery to clinical diagnostics. *Infect. Genet. Evo.* 79, 104211. <https://doi.org/10.1016/j.meegid.2020.104211>.

[24] Liu, Z., Xiao, X., Wei, X., Li, J., Yang, J., Tan, H., Zhu, J., Zhang, Q.,

Wu, J., Liu, L., 2020b. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. *J. Med. Virol.* <https://doi.org/10.1002/jmv.25726>.

[25] Yin, Y., Wunderink, R.G., 2018. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology* 23, 130–137. <https://doi.org/10.1111/resp.13196>.

[26] Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., Zuo, W., 2020. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. *BioRxiv* <https://doi.org/10.1101/2020.01.26.919985>.

[27] Tai, W., He, L., Zhang, X., Pu, J., Voronin, D., Jiang, S., Zhou, Y., Du, L., 2020. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. *Cell. Mol. Immunol.*, 1–8 <https://doi.org/10.1038/s41423-020-0400-4>.

[28] Glowacka I, Bertram S, Müller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *J Virol* 2011;85(9): 4122–4134.

[29] Bertram S, Glowacka I, Müller MA, Lavender H, Gnirss K, Nehlmeier I, et al. Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. *J Virol* 2011;85 (24):13363–13372.

[30] Chan JF, To KK, Tse H, Jin DY, Yuen KY. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends Microbiol* 2013; 21:544–555.



- [31] Siu, K.L., Yuen, K.S., Castaño-Rodriguez, C., Ye, Z.W., Yeung, M.L., Fung, S.Y., Yuan, S., Chan, C.P., Yuen, K.Y., Enjuanes, L., 2019. Severe acute respiratory syndrome coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. *FASEB J.* 33, 8865–8877. <https://doi.org/10.1096/fj.201802418R>.
- [32] Nieto-Torres, J.L., Verdiá-Báguena, C., Jimenez-Guardeño, J.M., Regla-Nava, J.A., Castaño-Rodriguez, C., Fernandez-Delgado, R., Torres, J., Aguilera, V.M., Enjuanes, L., 2015. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. *Virology* 485, 330–339. <https://doi.org/10.1016/j.virol.2015.08.010>.
- [33] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497–506.
- [34] Wu, A., Peng, Y., Huang, B., Ding, X., Wang, X., Niu, P., Meng, J., Zhu, Z., Zhang, Z., Wang, J., 2020a. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. *Cell Host Microbe* 27, 325–328. <https://doi.org/10.1016/j.chom.2020.02.001>.
- [35] Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., 2020b. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm. Sin. B* <https://doi.org/10.1016/j.apsb.2020.02.008>.
- [36] Xu, J., Zhao, S., Teng, T., Abdalla, A.E., Zhu, W., Xie, L., Wang, Y., Guo, X., 2020a. Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses* 12, 244. <https://doi.org/10.3390/v12020244>.
- [37] Xu, X., Yu, C., Qu, J., Zhang, L., Jiang, S., Huang, D., Chen, B., Zhang, Z., Guan, W., Ling, Z., 2020b. Imaging and clinical features of patients with 2019 novel coronavirus SARSCoV-2. *Eur. J. Nucl. Med. and Mol. Imaging*, 1–6 <https://doi.org/10.1007/s00259-020-04735-9>.
- [38] Oladele, J.O., Oyewole, O.I., Bello, O.K., Oladele, O.T. (2017). Hepatoprotective Effect of Aqueous Extract of *Telfairia occidentalis* on Cadmium Chloride-Induced Oxidative Stress and Hepatotoxicity in Rats. *Journal of Drug Design and Medicinal Chemistry*. 3(3): 32–36.
- [39] Oyewole, O.I., Oladele, J.O., and Oladele, O.T. (2017). Methanolic leaf extract of *Ficus Exasperata* Leaf attenuates Arsenate-Mediated hepatic and renal oxidative stress in rats. *Res. J. of Health Sci.* 5(2): 115–123.
- [40] Iwu MM (1985). Antihepatotoxic constituents of *Garcinia kola* seeds. *Experientia* 41: 699–670.
- [41] Taiwo, O.; Xu, H.-X.; Lee, S.F. (1999). Antibacterial activities of extracts from Nigerian chewing sticks. *Phytother. Res.*, 13, 675–679.
- [42] Farombi EO, Tahnteng JG, Agboola AO, Nwankwo JO, and Emerole GO (2000). Chemoprevention of 2-acetylaminofluorene-induced hepatotoxicity and lipid peroxidation in rats by kolaviron-a *Garcinia kola* seed extract. *Food Chem Toxicol*; 38: 535–541.
- [43] Farombi, E O Adepoju, B F Ola-Davies O E and Emerole, G O. (2005). Chemoprevention of aflatoxin B1-induced genotoxicity and hepatic oxidative damage in rats by kolaviron, a natural biflavonoid of *Garcinia kola* seeds. *European Journal of Cancer Prevention*, 14, No. 3:207–214.
- [44] Farombi, E. O. (2000). Mechanisms for the hepatoprotective action of

kolaviron: studies on hepatic enzymes, microsomal lipids and lipid peroxidation in carbontetrachloride-treated rats Pharmacological Research, Vol. 42, No. 1, 2000.

[45] Farombi, E. O., Shrotriya, S., and Surh, Y. J. (2009). Kolaviron inhibits dimethyl nitrosamine-induced liver injury by suppressing COX-2 and iNOS expression via NF- $\kappa$ B and AP-1. Life Sciences. Volume 84, Issues 5–6, Pages 149–155.

[46] Abarikwu, S O., Farombi E. O, Kashyap, M. P., and Pant, A. B. (2011). Kolaviron protects apoptotic cell death in PC12 cells exposed to Atrazine *Free Radical Research*, September 2011; 45 (9): 1061–1073

[47] Abarikwu, S.O., Farombi, E.O., and Pant, A.B. (2011)b.Biflavanone-kolaviron protects human dopaminergic SH-SY5Y cells against atrazine induced toxic insult Toxicology in Vitro 25 848–858.

[48] Igado, O. O, Olopade, J O, Adesida A, Aina, O. O., and Farombi, E. O. (2012). Morphological and biochemical investigation into the possible neuroprotective effects of kolaviron (*Garcinia kola* bioflavonoid) on the brains of rats exposed to vanadium. Drug and Chemical Toxicology, 35(4): 371–380.

[49] Onasanwo, S.A., Velagapudi, R., El-Bakoush, A., Olajide, O.A., 2016. Inhibition ofneuroinflammationin BV2 microglia by the biflavonoid kolaviron is dependent on theNrf2/ARE antioxidant protective mechanism. Mol. Cell. Biochem. 414, 23–26.

[50] Olajide, O.J., Asogwa, N.T., Moses, B.O., Oyegbola, C.B., 2017. Multidirectional inhibitionof cortico-hippocampal neurodegeneration by kolaviron treatment in rats.Metab. Brain Dis. <https://doi.org/10.1007/s11011-017-0012-6>.

[51] Omotoso, G.O., Ukwubile, I.I., Arietarhire, L., Sulaimon, F., Gbadamosi, I.T., 2018.Kolaviron Protects the brain in Cuprizone-induced Model of Experimental MultipleSclerosis viaenhancement of intrinsic antioxidant mechanisms: Possible TherapeuticApplications? Pathophysiology 25, 299–306. <https://doi.org/10.1016/j.pathophys.2018.04.004>.

[52] Farombi EO, Awogbindin IO, Farombi TH, Oladele JO, Izomoh ER, Aladelokun OB, Ezekiel IO, Adebambo OI, Abah VO (2019) Neuroprotective role of kolaviron in striatal redo-inflammation associated with rotenone model of Parkinson's disease. Neurotoxicology 73:132–141. <https://doi.org/10.1016/j.neuro.2019.03.005>

[53] Oladele JO, Oyeleke OM, Oladele OT, Olowookere BD, Oso BJ, Oladiji AT. (2020). Kolaviron (Kolaflavanone), apigenin, fisetin as potential Coronavirus inhibitors: *In silico* investigation

[54] Dewick, P.M. Chimica, Biosintesi e BioattivitàdelleSostanzeNaturali; Piccin: Roma, Italy, 2001.

[55] Campbell, E.L.; Chebib, M.; Johnston, G.A.R. The dietary flavonoids apigenin and (–)-epigallocatechingallate enhance the positive modulation by diazepam of the activation by GABA of recombinant GABA(A)receptors. Biochem. Pharmacol. **2004**, 68, 1631–1638.

[56] Jäger, A.K.; Krydsfeldt, K.; Rasmussen, H.B. Bioassay-guided isolation of apigenin with GABA benzodiazepine activity from Tanacetum parthenium. Phytother. Res. **2009**, 23, 1642–1644.

[57] Sloley, B.D.; Urichuk, L.J.; Morley, P.; Durkin, J.; Shan, J.J.; Pang, P.K.T.; Coutts, R.T. Identification ofkaempferol

- as a monoamine oxidase inhibitor and potential neuroprotectant in extracts of Ginkgo bilobaleaves. *J. Pharm. Pharmacol.* **2000**, 52, 451–459.
- [58] Zhao, L.; Wang, J.; Liu, R.; Li, X.X.; Li, J.; Zhang, L. Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model. *Molecules* **2013**, 18, 9949–9965.
- [59] Nabavi, S.F.; Khan, H.; D'onofrio, G.; Šamec, D.; Shiroomie, S.; Dehpour, A. R.; Argüelles, S.; Habtemariam, S.; Sobarzo-Sanchez, E. Apigenin as neuroprotective agent: Of mice and men. *Pharm. Res.* **2018**, 128, 359–365.
- [60] Rezai-Zadeh, K.; Ehrhart, J.; Bai, Y.; Sanberg, P.R.; Bickford, P.; Tan, J.; Douglas, R.D. Apigenin and luteolin modulate microglial activation via inhibition of STAT1-induced CD40 expression. *J. Neuroinflamm.* **2008**, 5, 41–51.
- [61] Nicholas, C.; Batra, S.; Vargo, M.A.; Voss, O.H.; Gavrilin, M.A.; Wewers, M. D.; Guttridge, D.C.; Grotewold, E.; Doseff, A.I. Apigenin blocks lipopolysaccharide-induced lethality in vivo and proinflammatory cytokine expression by inactivating NF-kappaB through the suppression of p65 phosphorylation. *J. Immunol.* **2007**, 179, 7121–7127.
- [62] Myhrstad, M.C.W.; Carlsen, H.; Nordström, O.; Blomhoff, R.; Moskaug, J.Ø. Flavonoids increase the intracellular glutathione level by transactivation of the -glutamylcysteine synthetase catalytic subunit promoter. *Free Radic. Biol. Med.* **2002**, 32, 386–393.
- [63] Paredes-Gonzalez, X.; Fuentes, F.; Jeffery, S.; Saw, C.L.L.; Shu, L.; Su, Z.Y.; Kong, A.N.T. Induction of NRF2-mediated gene expression by dietary phytochemical flavones apigenin and luteolin. *Biopharm. Drug Dispos.* **2015**, 36, 440–451.
- [64] Huang, C.S.; Lii, C.K.; Lin, A.H.; Yeh, Y.W.; Yao, H.T.; Li, C.C.; Wang, T. S.; Chen, H.W. Protection by chrysin, apigenin, and luteolin against oxidative stress is mediated by the Nrf2-dependent up-regulation of hemeoxygenase 1 and glutamate cysteine ligase in rat primary hepatocytes. *Arch. Toxicol.* **2013**, 87, 167–178.
- [65] Peng, Q.; Deng, Z.; Pan, H.; Gu, L.; Liu, O.; Tang, Z. Mitogen-activated protein kinase signaling pathway in oral cancer. *Oncol. Lett.* **2017**, 15, 1379–1388.
- [66] Jitendra S. R., Aroni C., Abhijeet K., Shashikant R. (2020): Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: An in silico study for drug development. *ChemRxiv. Preprint.* <https://doi.org/10.26434/chemrxiv.12094203.v1>.
- [67] Oladele J.O., Oyeleke O.M., Oladele O.T., Babatope O.D., Awosanya O.O. (2020). Nitrobenzene-induced hormonal disruption, alteration of steroidogenic pathway, and oxidative damage in rat: protective effects of *Vernonia amygdalina*. *Clinical Phytoscience*.
- [68] Oladele JO., Oyeleke OM., Oladele OT. Olaniyan MD. (2020). Neuroprotective mechanism of *Vernonia amygdalina* in a rat model of neurodegenerative diseases. *Toxicology report.* <https://doi.org/10.1016/j.toxrep.2020.09.005>.
- [69] Oladele JO., Oyeleke OM., Akindolie BO., Olowookere BD., Oladele OT. (2021). *Vernonia amygdalina* abates oxidative hepatic damage and inflammation associated with nitrobenzene in rat. *Jordan Journal of Biological Sciences. in press.*
- [70] Oladele JO., Oyeleke OM., Olowookere BD., Babatope OD., Olaniyan MD., Akindolie BO., Oladele OT. (2020). Bitter leaf



(*Vernonia amygdalina*) modulates nitrobenzene-induced renal damage in rats via suppression of oxido-inflammatory activities. *Serbian Journal of Experimental and Clinical Research*. in press.

[71] Oladele JO, Oyeleke OM, Oladele OT, Oladiji AT. (2020). Covid-19 treatment: Investigation on the phytochemical constituents of *Vernonia amygdalina* as potential Coronavirus-2 inhibitors. *Computational toxicology*.

[72] IclalSaracoglu, F. Handan Oztunca, AkitoNagatsu, and U. SebnemHarput. Iridoid content and biological activities of *Veronica cuneifolia* subsp. *cuneifolia* and *V. cuneifolia* and *V. cuneifolia*. *CymbalariaPharmaceutical Biology*, 2011; 49(11): 1150–1157

[73] Graham JG, Quinn ML, Fabricant DS, Farnsworth NR. (2000). Plants used against cancer - an extension of the work of Jonathan Hartwell. *J Ethnopharmacol*, 73, 347–377.

[74] T. Ito, S. Aimaiti, N.N. Win, T. Kodama, H. Morita, New sesquiterpene lactones, vernonilides A and B, from the seeds of *Vernonia anthelmintica* in Uyghur and their antiproliferative, *Bioorg. Med. Chem. Lett.* 26 (2016) 3608–3611, <https://doi.org/10.1016/j.bmcl.2016.06.009>.

[75] SanitThongneta, PornsudaChawengrumb, SiripornKeeratichamroen, KriengsakLirdprapamongkol, ChatchakornEurtivong, JutatipBoonsombat, PrasatKittakoo, JisnusunSvasti, SomsakRuchirawata. Vernodalidimer L, a sesquiterpene lactone dimer from *Vernonia extensa* and anti-tumor effects of vernodalin, vernolepin, and vernolide on HepG2 liver cancer cells *Bioorganic Chemistry* 92 (2019) 103197.

[76] Annamaria Sinisi, Estrella Millán, Solomon M. Abay, Annette Habluetzel,

Giovanni Appendino, Eduardo Muñoz, and Orazio Tagliatella-Scafati. Poly-Electrophilic Sesquiterpene Lactones from *Vernonia amygdalina*: New Members and Differences in Their Mechanism of Thiol Trapping and in Bioactivity. *Journal of Natural Products* DOI: 10.1021/acs.jnatprod.5b00179

[77] Siu, K.L., Yuen, K.S., Castaño-Rodriguez, C., Ye, Z.W., Yeung, M.L., Fung, S.Y., Yuan, S., Chan, C.P., Yuen, K.Y., Enjuanes, L., 2019. Severe acute respiratory syndrome coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. *FASEB J*, 33: 8865–8877.

[78] Oladele JO, Ajayi EIO, Oyeleke OM, Oladele OT, Olowookere BD, Adeniyi BM, Oyewole OI (2020) Curative potentials of Nigerian medicinal plants in COVID-19 treatment: A Mechanistic approach. *Jordan Journal of Biological Science*. in press.

[79] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.

[80] Jeandet, P., Douillet-Breuil, A. C., Bessis, R., Debord, S., Sbaghi, M., and Adrian, M. (2002) Phytoalexins from the Vitaceae: Biosynthesis, phytoalexin gene expression in transgenic plants, antifungal activity, and metabolism. *J. Agric. Food Chem.* 50, 2731–2741.

[81] de Santi, C., Pietrabissa, A., Mosca, F., and Pacifici, G. M. (2000) Glucuronidation of resveratrol, a natural product present in grape and wine, in the human liver. *Xenobiotica* 30, 1047–1054.

[82] De Santi, C., Pietrabissa, A., Spisni, R., Mosca, F., and Pacifici, G. M. (2000) Sulphation of resveratrol, a natural compound present in wine, and its



inhibition by natural flavonoids.  
*Xenobiotica* 30, 857–866.

[83] Ribeiro de Lima, M. T., Waffo-Teguo, P., Teissedre, P. L., Pujolas, A., Vercauteren, J., Cabanis, J. C., and Merillon, J. M. (1999) Determination of stilbenes (trans-astringin, cis- and trans-piceid, and cis- and trans-resveratrol) in Portuguese wines. *J. Agric. Food Chem.* 47, 2666–2670.

[84] BerzasNevado, J. J., Contento Salcedo, A. M., and CastanedaPenalvo, G. (1999) Simultaneous determination of cis- and transresveratrol in wines by capillary zone electrophoresis. *Analyst* 124, 61–66.

[85] Kopp, P. (1998) Resveratrol, a phytoestrogen found in red wine. A possible explanation for the conundrum of the 'French paradox'? *Eur. J. Endocrinol.* 138, 619–620.

[86] Hengst, J. A., and Yun, J. K. (2012) Sphingosine kinase: A key to solving the 'French Paradox'? *Br. J. Pharmacol.* 166, 1603–1604.

[87] Ferrieres, J. (2004) The French paradox: Lessons for other countries. *Heart* 90, 107–111.

[88] Constant, J. (1997) Alcohol, ischemic heart disease, and the French paradox. *Coron. Artery Dis.* 8, 645–649.

[89] Wang, Z., Zou, J., Cao, K., Hsieh, T. C., Huang, Y., and Wu, J. M. (2005) De-alcoholized red wine containing known amounts of resveratrol suppresses atherosclerosis in hypercholesterolemic rabbits without affecting plasma lipid levels. *Int. J. Mol. Med.* 16, 533–540.

[90] Szmitko, P. E., and Verma, S. (2005) Cardiology patient pages. Red wine and your heart. *Circulation* 111, e10–e11.

[91] Berardi, V., Ricci, F., Castelli, M., Galati, G., and Risuleo, G. (2009)

Resveratrol exhibits a strong cytotoxic activity in cultured cells and has an antiviral action against polyomavirus: potential clinical use. *J. Exp. Clin. Cancer Res.* 28, 96.

[92] Clouser, C. L., Chauhan, J., Bess, M. A., Oploo, J. L., Zhou, D., Dimick-Gray, S., Mansky, L. M., and Patterson, S. E. (2012) Anti-HIV-1 activity of resveratrol derivatives and synergistic inhibition of HIV-1 by the combination of resveratrol and decitabine. *Bioorg. Med. Chem. Lett.* 22, 6642–6646.

[93] Nicolini, G., Rigolio, R., Miloso, M., Bertelli, A. A., and Tredici, G. (2001) Anti-apoptotic effect of trans-resveratrol on paclitaxel-induced apoptosis in the human neuroblastoma SH-SY5Y cell line. *Neurosci. Lett.* 302, 41–44.

[94] Baarine, M., Thandapilly, S. J., Louis, X. L., Mazue, F., Yu, L., Delmas, D., Neticadan, T., Lizard, G., and Latruffe, N. (2011) Proapoptotic versus anti-apoptotic properties of dietary resveratrol on tumoral and normal cardiac cells. *Genes Nutr.* 6, 161–169.

[95] Udenigwe, C. C., Ramprasath, V. R., Aluko, R. E., and Jones, P. J. (2008) Potential of resveratrol in anticancer and anti-inflammatory therapy. *Nutr. Rev.* 66, 445–454.

[96] Chen, G., Shan, W., Wu, Y., Ren, L., Dong, J., and Ji, Z. (2005) Synthesis and anti-inflammatory activity of resveratrol analogs. *Chem. Pharm. Bull. (Tokyo)* 53, 1587–1590.

[97] Chang, C. C., Chang, C. Y., Huang, J. P., and Hung, L. M. (2012) Effect of resveratrol on oxidative and inflammatory stress in liver and spleen of streptozotocin-induced type 1 diabetic rats. *Chin. J. Physiol.* 55, 192–201.

[98] Dao, T. M., Waget, A., Klopp, P., Serino, M., Vachoux, C., Pechere, L.,

- Drucker, D. J., Champion, S., Barthelemy, S., Barra, Y., Burcelin, R., and Seree, E. (2011) Resveratrol increases glucose-induced GLP-1 secretion in mice: A mechanism which contributes to the glycemic control. *PLoS One* 6, No. e20700.
- [99] Spanier, G., Xu, H., Xia, N., Tobias, S., Deng, S., Wojnowski, L., Forstermann, U., and Li, H. (2009) Resveratrol reduces endothelial oxidative stress by modulating the gene expression of superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPx1) and NADPH oxidase subunit (Nox4). *J. Physiol. Pharmacol.* 60 (Suppl 4), 111–116.
- [100] F. Vella, G. Ferry, P. Delagrè, J. A. Boutin, NRH:quinone reductase 2: an enzyme of surprises and mysteries, *Biochem. Pharmacol.* 71 (2005) 1–12.
- [101] C.E. Benoit, S. Bastianetto, J. Brouillette, Y. Tse, J.A. Boutin, P. Delagrè, T. Wong, P. Sarret, R. Quirion, Loss of quinone reductase 2 function selectively facilitates learning behaviors, *J. Neurosci.* 30 (2010) 12690–12700.
- [102] F. Zhang, J. Liu, J.S. Shi, Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation, *Eur. J. Pharmacol.* 636 (2010) 1–7.
- [103] Block, M. L., and Hong, J. S. (2007) Chronic microglial activation and progressive dopaminergic neurotoxicity. *Biochem. Soc. Trans.* 35, 1127–1132.
- [104] Gao, H. M., Liu, B., Zhang, W., and Hong, J. S. (2003) Novel anti-inflammatory therapy for Parkinson's disease. *Trends Pharmacol. Sci.* 24, 395–401.
- [105] Ransohoff, R. M., and Perry, V. H. (2009) Microglial physiology: Unique stimuli, specialized responses. *Annu. Rev. Immunol.* 27, 119–145.
- [106] Zhang, F., Liu, J., and Shi, J. S. (2010) Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation. *Eur. J. Pharmacol.* 636, 1–7.
- [107] Candelario-Jalil, E., de Oliveira, A. C., Graf, S., Bhatia, H. S., Hull, M., Munoz, E., and Fiebich, B. L. (2007) Resveratrol potentially reduces prostaglandin E2 production and free radical formation in lipopolysaccharide-activated primary rat microglia. *J. Neuroinflammation* 4, 25.
- [108] Lorenz, P., Roychowdhury, S., Engelmann, M., Wolf, G., and Horn, T. F. (2003) Oxyresveratrol and resveratrol are potent antioxidants and free radical scavengers: Effect on nitrosative and oxidative stress derived from microglial cells. *Nitric Oxide* 9, 64–76.
- [109] Bi, X. L., Yang, J. Y., Dong, Y. X., Wang, J. M., Cui, Y. H., Ikeshima, T., Zhao, Y. Q., and Wu, C. F. (2005) Resveratrol inhibits nitric oxide and TNF- $\alpha$  production by lipopolysaccharide-activated microglia. *Int. Immunopharmacol.* 5, 185–193.
- [110] Bureau, G., Longpre, F., and Martinoli, M. G. (2008) Resveratrol and quercetin, two natural polyphenols, reduce apoptotic neuronal cell death induced by neuroinflammation. *J. Neurosci. Res.* 86, 403–410.
- [111] Shin, J. A., Lee, H., Lim, Y. K., Koh, Y., Choi, J. H., and Park, E. M. (2010) Therapeutic effects of resveratrol during acute periods following experimental ischemic stroke. *J. Neuroimmunol.* 227, 93–100.
- [112] Oladele JO, Ajayi EIO, Oyeleke OM, Oladele OT, Olowookere BD, Adeniyi BM, Oyewole OI, Oladiji AT. (2020). A systematic review on COVID-19 pandemic with special emphasis on Curative potentials of medicinal plants.

- Heliyon. <https://doi.org/10.1016/j.heliyon.2020.e04897>.
- [113] Li Y, Yao J, Han C, Yang J, Chaudhry MT, Wang S, et al. Quercetin, inflammation and immunity. *Nutrients*. (2016) 8:167. doi: 10.3390/nu8030167
- [114] Y. Guo and R. S. Bruno, "Endogenous and exogenous mediators of quercetin bioavailability," *The Journal of Nutritional Biochemistry*, vol. 26, no. 3, pp. 201–210, 2015.
- [115] Nair MP, Kandaswami C, Mahajan S, Chadha KC, Chawda R, Nair and Schwartz SAH. The flavonoid, quercetin, differentially regulates Th-1 (IFN $\gamma$ ) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. *Biochim Biophys Acta*. (2002) 1593:29–36. doi: 10.1016/S0167-4889(02)00328-2
- [116] Robaszkiewicz A, Balcerzyk A, Bartosz G. Antioxidative and prooxidative effects of quercetin on A549 cells. *Cell Biol Int*. (2007) 31:1245–1250. doi: 10.1016/j.cellbi.2007.04.009
- [117] Uchide N, Toyoda H. Antioxidant therapy as a potential approach to severe influenza-associated complications. *Molecules*. (2011) 16:2032–2052. doi: 10.3390/molecules16032032
- [118] G. S. Kelly, "Quercetin. Monograph," *Alternative Medicine Review*, vol. 16, no. 2, pp. 172–194, 2011.
- [119] M. Russo, C. Spagnuolo, I. Tedesco, S. Bilotto, and G. L. Russo, "The flavonoid quercetin in disease prevention and therapy: facts and fancies," *Biochemical Pharmacology*, vol. 83, no. 1, pp. 6–15, 2012.
- [120] A. W. Boots, G. R. M. M. Haenen, and A. Bast, "Health effects of quercetin: from antioxidant to nutraceutical," *European Journal of Pharmacology*, vol. 585, no. 2–3, pp. 325–337, 2008.
- [121] Spedding G, Ratty A, Middleton E Jr. Inhibition of reverse transcriptases by flavonoids. *Antiviral Res*. (1989) 12:99–110. doi: 10.1016/0166-3542(89)90073-9
- [122] Bachmetov L, Gal-Tanamy M, Shapira A, Vorobeychik M, Giterman-Galam T, Sathiyamoorthy P, et al. Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity. *J Viral Hepat*. (2012) 19:e81–8. doi: 10.1111/j.1365-2893.2011.01507.x
- [123] Shinozuka K, Kikuchi Y, Nishino C, Mori A, Tawata S. Inhibitory effect of flavonoids on DNA-dependent DNA and RNA polymerases. *Experientia*. (1988) 44:882–885. doi: 10.1007/BF01941188
- [124] Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. *Int J Antimicrob Agents*. (2005) 26:343–356. doi: 10.1016/j.ijantimicag.2005.09.002
- [125] Debiaggi M, Tateo F, Pagani L, Luini M, Romero E. Effects of propolis flavonoids on virus infectivity and replication. *Microbiologica*. (1990) 13: 207–213.
- [126] Liu S, Wu S, Jiang S. HIV entry inhibitors targeting gp41: from polypeptides to small-molecule compounds. *Curr Pharm Des*. (2007) 13: 143–162. doi: 10.2174/138161207779313722
- [127] Yang J, Li M, Shen X, Liu S. Influenza A virus entry inhibitors targeting the hemagglutinin. *Viruses*. (2013) 5:352–373. doi: 10.3390/v5010352
- [128] Xia S, Liu Q, Wang Q, Sun Z, Su S, Duand L, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) entry inhibitors targeting spike protein. *Virus Res*. (2014) 194:

200–210. doi: 10.1016/j.virusres.2014.10.007

pharmacophore features. *Bioorg Med Chem.* (2006) 14:8295–8306. doi: 10.1016/j.bmc.2006.09.014

[129] Wu W, Li R, Li X, He J, Jiang S, Liu S, et al. Quercetin as an antiviral agent inhibits Influenza A Virus (IAV) entry. *Viruses.* (2015)8:6. doi: 10.3390/v8010006

[130] Ono K, Nakane H. Mechanisms of inhibition of various cellular DNA and RNA polymerases by several flavonoids. *J Biochem.* (1990) 108:609–613. doi: 10.1093/oxfordjournals.jbchem.a123251

[131] Ono K, Nakane H, Fukushima M, Chermann JC, Barré-Sinoussi F. Differential inhibitory effects of various flavonoids on the activities of reverse transcriptase and cellular DNA and RNA polymerases. *Eur J Biochem.* (1990)190:469–76. doi: 10.1111/j.1432-1033.1990.tb15597.x

[132] Chiang LC, Chiang W, Liu MC, Lin CC. In vitro antiviral activities of *Caesalpinia pulcherrima* and its related flavonoids. *J Antimicrob Chemother.* (2003) 52:194–198. doi: 10.1093/jac/dkg291

[133] Li BW, Zhang FH, Serrao E, Chen H, Sanchez TW, Yang LM, et al. Design and discovery of flavonoid-based HIV-1 integrase inhibitors targeting both the active site and the interaction with LEDGF/p75. *Bioorg Med Chem.* (2014)22:3146–58. doi: 10.1016/j.bmc.2014.04.016

[134] Yi L, Li Z, Yuan K, Qu X, Chen J, Wang G, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *J Virol.* (2004) 78:11334. doi: 10.1128/JVI.78.20.11334-11339.2004

[135] Chen L, Li J, Luo C, Liu H, Xu W, Chen G, et al. Binding interaction of quercetin-3-beta-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): structure-activity relationship studies reveals salient