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Review article

Possible Health Benefits of Polyphenols in Neurological Disorders Associated with COVID-19

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SUMMARY

Novel coronavirus disease 2019 (COVID-19) represents an emerging global health burden that has challenged the health systems worldwide. Since its sudden upsurge in 2019, many COVID-19 patients have exhibited neurological symptoms and complications. Till now, there is no known effective established drug against the highly contagious COVID-19 infection despite the frightening associated mortality rate. This article aims to present the mechanism of action of coronavirus-2 (SARS-CoV-2), the clinical neurological manifestations displayed by COVID-19 patients, and present polyphenols 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 for this review. 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 damages displayed by COVID-19 patients might be due to hyperinflammation associated with SARS-CoV-2 infections. Resveratrol, kolaviron, quercetin and apigenin are polyphenols with proven anti-inflammatory and therapeutic properties that can extenuate the adverse effects of COVID-19. These polyphenols have been documented to suppress c-Jun N- terminal kinase (JNK), phosphoinositide-3-kinase (PI3-K), extracellular-signal-regulated kinase (ERK), nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB) and mitogen-activated protein kinase (MAPK) pathways which are essential in the pathogenesis of COVID-19. They also showed significant inhibitory activities against SARS-CoV-2 proteins. Taken together, these polyphenols may offer neuroprotective benefits against COVID-19 mediated neuropathology via modulation of the pathogenic pathways.

Key words: **neuropathology, polyphenols, COVID-19, SARS-CoV-2, kolaviron; apigenin, quercetin**

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INTRODUCTION

COVID-19 novel coronavirus pneumonia is ranked amidst the nine deadliest global pandemics that 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 of 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 world health organization (WHO) team on COVID-19 pandemic as of 25 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).

COVID-19 has an average incubation period of 3 days (3). 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 pneumonias; multiple organ failures and death were documented in critical and severe cases (4). 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 (5). 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 (6). The presence or confirmation of SARS-CoV-2 in cerebrospinal fluid suggests that it could invade and infect the central nervous system (CNS) as a neurotropic virus inducing multiple neurological impairments (6).

This article 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 the key words: clinical features, coronavirus, SARSCOV-2, COVID-19, and complications.

POSSIBLE MECHANISM BY WHICH SARS-COV-2 INDUCED NEUROLOGICAL DAMAGE

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. (7) 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 (8). SARS-CoV-2 can diffuse to the CNS via enteric nerve and sympathetic afferent mediated by gastrointestinal tract infection (9). Furthermore, anterograde and retrograde transmission can mediate neuro-invasion of SARS-CoV-2 through the sensory and motor nerve endings (10), coupled with involvement of motor proteins (dynein and kinesins), in particular through the vagus nerve from the lungs (11).

The brain is more vulnerable to oxidative and neuroinflammation insults due to the low level of cytoprotective endogenous enzymes. The cytokine storm syndrome (hyperinflammation) 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 induce secondary haemophagocytic lymphohistiocytosis (sHLH) (12). sHLH similarly referred to as macrophage activation syndrome (MAS) is a severe health disorder which includes a diverse group of hyperinflammatory conditions arising 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 hypercytokinaemia due to inapt persistence of histiocytes and cytotoxic T-lymphocytes, which eventually leads to multi-organ failure, haemophagocytosis, and mortality (13). Other features of sHLH include

persistent fever, cytopenias, and hyperferritinaemia; pulmonary involvement occurs in approximately 50% of patients (14).

In the brain, the activation of glial cells cause brain damage and severe inflammation with the secretion of pro-inflammatory cytokines, including TNF-alpha, interleukin-2, and interleukin-5 (15). Neuroinvasion 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.

SARS-COV-2 MECHANISM OF ACTION

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 (16). Compared with other coronaviruses, SARS-CoV-2 proteins for viral replication, spikes formation, and nucleocapsid are initiated in specific genes in ORF1 (17). 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 (18, 19). A 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) (20-22). 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 (23, 24). 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 facilitates the entry of the virus into the host.

There is a prospect that SARS-CoV-2 utilized the 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 enters 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, and consequently damage the alveoli by increasing pulmonary vascular permeability (25). 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 in the secretion of the pro-IL-1B gene (26). 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 includes caspases activation, mitochondrial damage, ROS production, and Ca^{2+} influx activates pro-IL-1B to interleukin 1 beta (IL-1B) which enhances cytokine production. Furthermore, ORF8b protein through NLRP3 facilitates the inflammasome pathway. ORF8b protein is longer in SARS-CoV-2 (26). 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) (27).

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 (28). Secondary haemophagocytic lymphohistiocytosis (sHLH) is a cytokine profile with a hyperinflammatory syndrome described by an abrupt hypercytokinaemia with multi-organ failure, which has been reported in COVID-19 severity. This also features increased granulocyte-col-

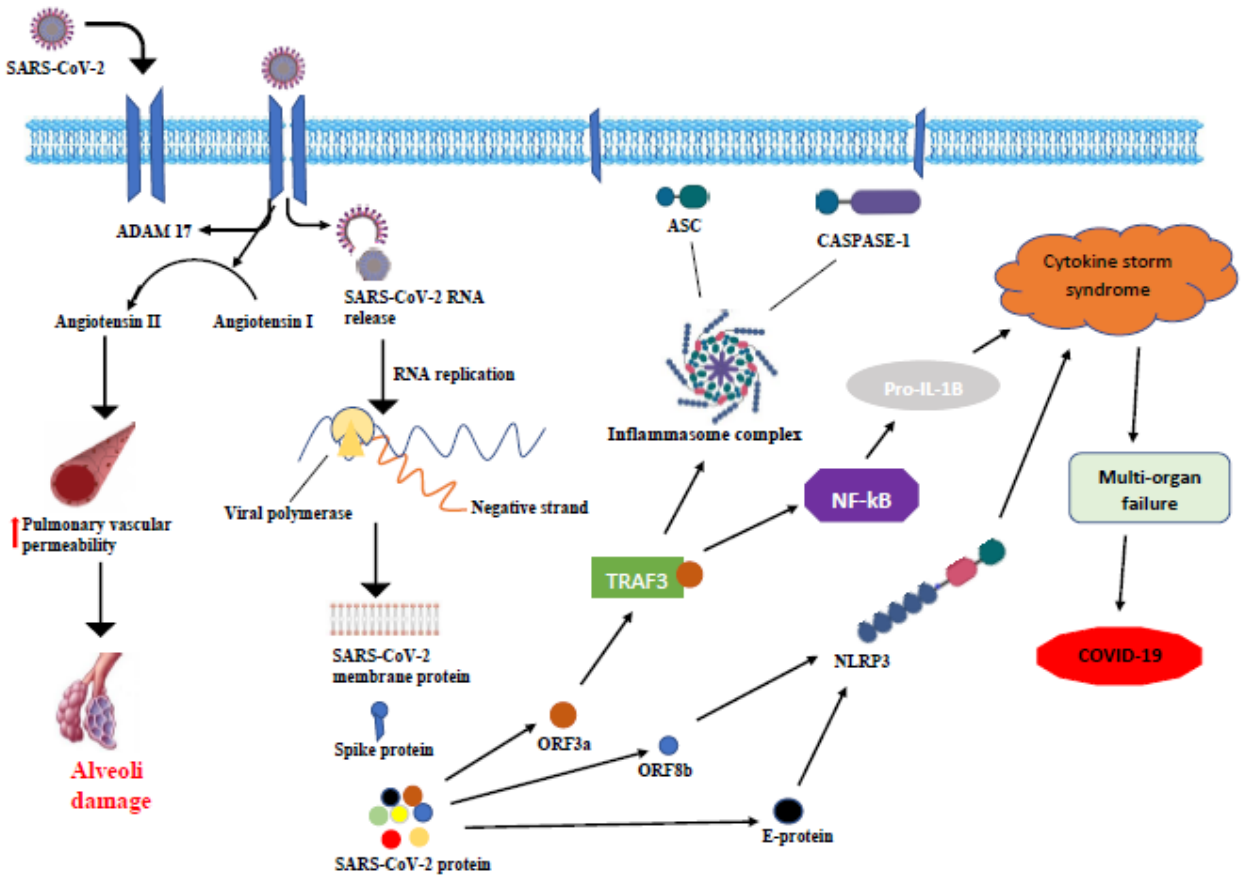

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Figure 1. *SARS-CoV-2 mechanism of action*

ony 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 (28).

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 (29 - 32).

POLYPHENOLS WITH NEUROPROTECTIVE EFFECTS AND SARS-COV-2 INHIBITORY ACTIVITIES

Quercetin

Quercetin, 3,3′,4′5,7-pentahydroxyflavone (Figure 2) 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) (33). 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 contain lower levels. Quercetin arabinoside, quercetin galactoside, and quercetin glucoside are the

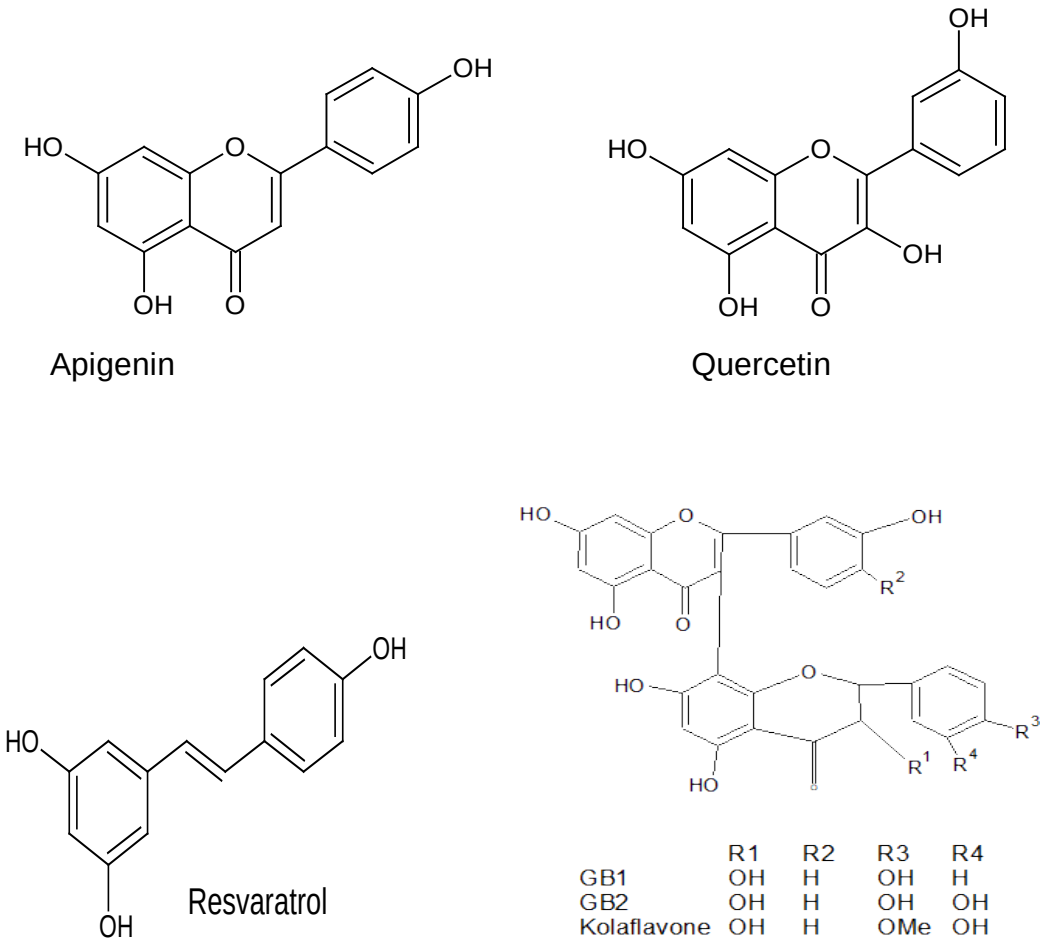

Figure 2. *Basic structure of apigenin, quercetin, resveratrol and kolaviron*

tables, fruits and other food items. They are first deglycosylated by gut microbiota-derived betaglucosidase or lactase phlorizin hydrolaseto quercetin aglycone before passive absorption in the small intestine (34). 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 (sulfotransferase) and UGT (uridine 5-diphospho glucuronosyl transferase), respectively.

Studies have reported that quercetin exhibited anti-inflammatory, immunoprotective (35), antioxidant (36), and antiviral (37) effects. Its medicinal effects on cancer, nervous system disorders, gastrointestinal tract function, infections, inflammatory processes, diabetes, and cardiovascular diseases have been documented (38-40). Previous findings have documented the inhibitory activities of quercetin against reverse transcriptase (41), proteases (42), and polymerases (43). Also, it has been studied in models of viral infection to bind to viral capsid-proteins and inhibit DNA gyrase (44, 45).

During viral infection, the entrance of virus into the host cell is a vital step and has been targeted as a possible point of intervention in antiviral treatments (46 - 48). 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 (49). Furthermore, quercetin has been studied to interfere with DNA and RNA polymerases in viral infections. During adenoviruses (ADV-3,–8,–11) and herpes viruses (HSV-1, 2) infections, quercetin was reported to suppress viral DNA and RNA polymerase (43, 50, 51) and inhibit the early stage of viral replication (45, 52). Li et al. (53) also reported anti-

viral 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-α, p24 in HIV infection (35).

Possible antiviral effect of quercetin on many types of coronaviruses has been described by Yi et al. (54). Quercetin metabolite have been documented to bind to SARS-CoV 3CL protease and suppressed its proteolytic activity (55). 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 (56). 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* (54).

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring lipophilic and phenolic phytochemical found abundantly in edible plants and easily crosses the plasma membrane after oral absorption (57 - 59). It is a polyphenolic phytoalexin which comprises two aromatic rings linked by a styrene double bond which permits its trans- and cis-isomers formation (60, 61). Resveratrol has been reported as a possible reason accountable for the French paradox (62, 63), 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 (64, 65). A number of preclinical studies proposes that resveratrol has the capability to influence a variety of human diseases, this is due to its cardioprotective (66, 67), antiviral (68, 69), anti-apoptotic (70,71), anti-inflammatory (72, 73) anti-diabetic (74, 75), and antioxidative (74, 76) properties.

Evidences from experimental studies has established the neuroprotective properties of resveratrol which may be beneficial in combating neurological disorders shown 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 (77). 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 (78). Similarly, neuroprotective effect of resveratrol has been documented to include the inhibition of microglia-mediated neuroinflammation (79). 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 (79).

Activation of microglia is the hallmark of neuroinflammation and plays a critical role in the pathogenesis of neurological diseases (80, 81). Microglia are 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 (82). During microglial activation (microgliosis), different kinds of proinflammatory markers such as chemokines, prostaglandins, reactive nitrogen species, and cytokines are released. The overproduction and accumulation of these proinflammatory factors lead to the damage of the neuronal cells and ultimately cause a release of soluble factors and debris (79). Many experimental studies have demonstrated the neuroprotective ability of resveratrol to inhibit the activation of microglia (83-85). Resveratrol has been reported to suppress upsurge expression of IL-1β, nitric oxide and TNFα that accompanied the activation of microglia which mediate phosphorylation of p38 and NF-κB signaling (85, 86). Resveratrol inhibited secretion of TNFα, IL-1β and reactive nitrogen species, and activation of microglia in the ischemic cortex (87).

Anti-covid-19 potentials of resveratrol have been reported in an in-silico study designed for drug development targeting SARS-CoV-2 Spike Protein of COVID-19 (55). 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 enhances the initial attachment of the virus with ACE2 receptor and its consecutive fusion with the host cells (88). 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, resveratrol has been reported to

modulate phosphoinositide-3-kinase (PI3-k), NF-κB signaling and mitogen-activated protein kinases pathways whose end products release cytokines. These modulatory effects may provide beneficial effects in COVID-19 by inhibiting the over-secretion of inflammatory cytokines, which resulted in the occurrence of cytokine storm syndromes that accelerate lungs damage and multi-organ failure, which is related to COVID-19.

Apigenin

Apigenin (4',5,7-trihydroxyflavone) is one of the most explored phenolics and the most commonly disseminated flavonoid in many plant species. It is predominantly present in herbs (oregano, thyme, basil, chamomile), phytochemical-based beverages (tea, beer, and wine), in vegetables (parsley, celery, onions), and fruits (guava, oranges). It is also found extensively in the plant species of the genus: *Matricaria, Achillea, Artemisia, and Tanacetum* (89). Apigenin has been documented to have anticancer activities as well as theurapeutic effects on depression, Alzheimer's disease, amnesia, and insomnia (89). The dietary availability of apigenin could facilitate an efficacious intervention to inhibit activation of microglial and prevent the onset of Alzheimer's disease.

After absorption, apigenin can easily be transported through the circulatory system, crossing the blood-brain barrier to the brain, where it acts on the CNS and exhibits an interaction with the GABAA-receptor (90, 91). Sloley et al. (92) 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. (93). 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 (93). Nabavi et al. (94) 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 (94).

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 interferon gamma-mediated STAT1 (signal transducers and activators of transcription 1) phosphorylation in microglia (95). 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 (96). Apigenin also suppressed the activities of adhesion molecules which is very essential to mitigate oxidative stress and prevent oxidative damage (97).

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 (98, 99). 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 (100).

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 (56). Similarly, in silico study in our laboratory revealed that apigenin displayed a significant binding affinity with the SARS-CoV-2 major protease (6LU7). The result also suggested that apigenin could be a potential inhibitor of SARS-COV-2 (101).

Kolaviron

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 (102 - 107). 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 as general tonic to boost the immune system (108, 109).

Many experimental findings have established the traditional medicinal uses of Garcinia kola. Kolaviron, the biflavanone of Garcinia kola, has 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 (110-113). Furthermore, 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 (108).

Neuroprotective abilities of kolaviron has been reported in many neuronal cell lines. Abarikwu et al. (114) 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 (115). Igado et al. (116) 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 (117). Also, Olajide et al. (118) reported multidirectional suppression of cortico-hippocampal neurodegeneration by kolaviron. In another study, Omotoso et al. (119) 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 (120). 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.

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 (101). 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 (6LU7) above remdesivir, a recommended drug for the treatment of COVID-19. This showed that kolaviron could offer an effective inhibitory effect on SARS-CoV-2 and be a more effective drug candidate in the treatment of COVID-19.

CONCLUSION

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-infectious encephalomyelitis, encephalitis, etc. The underlying mechanisms of pathogenic actions of SARS-CoV-2 include those 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. Resveratrol, quercetin, kolaviron and apigenin are polyphenols from medicinal plants with proven antioxidant, anti-inflammatory, and pharmacological activities that can inhibit SARS-CoV-2 and mitigate COVID-19. These polyphenols

have been documented to suppress JNK and MAPK pathways which are essential in the pathogenesis of COVID-19. SARS-Cov-2 virus infection dysregulate and exacerbate inflammatory process in the lung leading to increased secretion of IL-6 which ultimately results to a "cytokine-storm". The polyphenols with their robust anti-inflammatory properties may suppress cytokine-induced organ impairment and enhance survival in lethal infections. Taken together, resveratrol, quercetin, kolaviron and apigenin could be potential drug candidates in the treatment/management of COVID-19 mediated neuropathology.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Mogući zdravstveni benefiti polifenola kod neuroloških poremećaja udruženih sa kovidom-19

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SAŽETAK

Pojava nove bolesti izazvane korona virusom (COVID-19) predstavlja opterećenje i izazov za globalni zdravstveni sistem. Od iznenadne i nagle pojave ovog virusa 2019. godine, kod mnogih kovid-19 bolesnika javili su se neurološki simptomi i komplikacije. Do sada nije pronađen efikasan lek protiv ove visokozarazne infekcije uprkos zastrašujućoj stopi smrtnosti. Cilj ovog rada je predstavljanje mehanizma delovanja korona virusa 2 (COVID-19), kliničkih neuroloških manifestacija zabeleženih kod kovid-19 bolesnika, kao i polifenola sa neuroprotektivnim karakteristikama, koji imaju blagotvorne efekte kod neuropatologije izazvane kovidom-19. Izveštaji kliničkih studija o kovidu-19, prikazi slučajeva i slični izvori u literaturi pregledani su zbog potreba ovog rada. Neurološke komplikacije kovida-19 uključuju anosmiju, akutnu cerebrovaskularnu bolest, akutni diseminovani postinfektivni encefalomijelitis, encefalitis itd. Takođe, COVID-19 može biti i neurotropni virus zbog izolacije iz cerebrospinalne tečnosti. Mnogobrojna neurološka oštećenja mogu se javiti kod kovid-19 bolesnika zbog hiperinflamacije udružene sa SARS-CoV-2 infekcijama. Rasveratrol, kolaviron, kvercetin i apigerin su polifenoli sa dokazanim antiinflamatornim i terapeutskim svojstvima, koja mogu da ublaže neželjene efekte kovida-19. Potvrđeno je da ovi polifenoli suprimiraju c-Jun N-termalnu kinazu (JNK), fosfatidilinozitol 3-kinazu (PI3-K), ekstracelularnim signalom regulisanu kinazu (ERK), nuklearni faktor kapa B ćelija (NF-kB) i mitogenom aktiviranu protein kinazu (MAPK), što je esencijalno u patogenezi kovida-19. Takođe pokazali su značajnu inhibitornu aktivnost usmerenu ka SARS-CoV-2 proteinima. U celini, ovi polifenoli mogu da ispolje neuroprotektivne efekte u slučaju neuropatologije izazve kovidom-19, preko modulacije puteva patogeneze.

Ključne reči: **neuropatologija, polifenoli, COVID-19, SARS-CoV-2, kolaviron, apigenin, kvercetin**