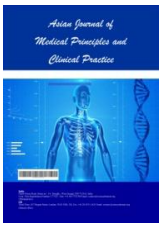

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Immunomodulatory Foods and Functional Plants for COVID-19 Prevention: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Coronavirus disease (COVID-19) has swept across the globe, affecting over 179 countries, with about 650,805 thousand deaths globally and over 16,341,920 million reported cases in the world. Hence, the need for novel drugs and different approaches for high quality treatment of the novel coronavirus may be a necessity. Since, the commencement of the coronavirus spread, significant efforts have been made to forestall and cure the virus by World Health Organization (WHO). However, no particular treatment has been certified, although, therapeutic methods have been outlined but, these therapeutic approaches have different drawbacks and lack the specified performance for the treatment of the new coronavirus disease. Thus, in response to these therapeutic drawbacks, this review helps to suggest possible immunomodulatory foods and plant species which could be used as anti-SARS-Cov2 therapy to forestall infection and strengthen immunity of the masses against SARS-CoV-2 and in COVID-19 patients.

Keywords: Coronavirus; SARS-CoV-2; immunomodulatory foods; functional plants; antiviral compounds.

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1. INTRODUCTION

Coronaviruses (CoVs) are groups of viruses common among many animals, including humans. They cause respiratory illnesses in humans and gastrointestinal illnesses in animals [1]. Under the microscope, virions of CoVs have large peplomers that make it appear as a crown, hence the name corona, meaning “crown” or “halo” [2,1,3]. Before 2003, human CoVs weren't considered a deadly virus because the circulating strains then were causing mild symptoms in immunocompetent people. Typically, coronavirus symptoms include runny nose, cough, pharyngitis, headache, and fever which will last for several days. However, in immunocompromised patients, there's a possibility that the virus could cause a lower respiratory disease like pneumonia and bronchitis [2,1]. In 2003, the world was shocked by the primary pandemic of the 21st century; the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) emerged in Guangdong, China, leading to 774 deaths and quite 8000 patients [4,1,5]. Nine years later, a strain of CoV evolved in Saudi Arabia to cause the center East Respiratory Syndrome Coronavirus (MERS-CoV), approximately 2500 cases are confirmed, including 861 deaths with a fearful case–fatality rate of 34.4% [5].

The first cases of coronavirus disease 2019 (COVID-19) was reported to occur from a zoonotic transmission in Wuhan, China in December 2019, and linked to an outsized seafood market that traded in live wild animals. The causative virus, severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) is capable of human- to- human transmission and spread rapidly to other parts of China then to other countries. Table 1 shows the global number of cases and deaths emerging from

Table 1. Coronavirus Disease (Covid-19) global cases

Continents	Cases	Deaths
Africa	726,105	12,257
Americas	8,728,962	339,651
Eastern Mediterranean	1,494,697	38,371
Europe	3,261,042	210,897
South-East Asia	1,838,380	41,366
Western Pacific	291,993	8,250
Globally	16,341,920	650,805

Source: WHO. [6]

Table 2. Potentials of functional plants against new coronavirus disease

Methodology	Bioactive substances	Plant	References
Use of plant extract/ lectin	Utricadioica Agglutinin	*Utricadioica* (Stinging nettle)	[34,35]
	Allium porrum	*Allium porrum* (Leek)	[34]
	Agglutinin (APA)	*Psoelea corylifolia*	[36]
	Plant extract	*T. nucifera* (Japanese nutmeg-yew)	[37]
Use of plant secondary metabolites	Quercetin	*Allium cepa* (Onion) *Allium sativum* (Garlic)	[38,39,19]
	Cephrarenthine	*Stephania spp*	[40]
	Glycyrrhizin	*Glycyrrhiza glabra* (Licorice)	[41,42,43]
	Diarylheptenol	*Alnus japonica* (Alder)	[44]
	Flavoniod	*Pterogyne Nitens*	[45]
	Aloe-emodin	*Aloe vera*	[46,47,48,49,50]
Use of plants to express vaccinal proteins	Viral N Antigen	*Nicotiana tabacum* (Tobacco)	[51,52]

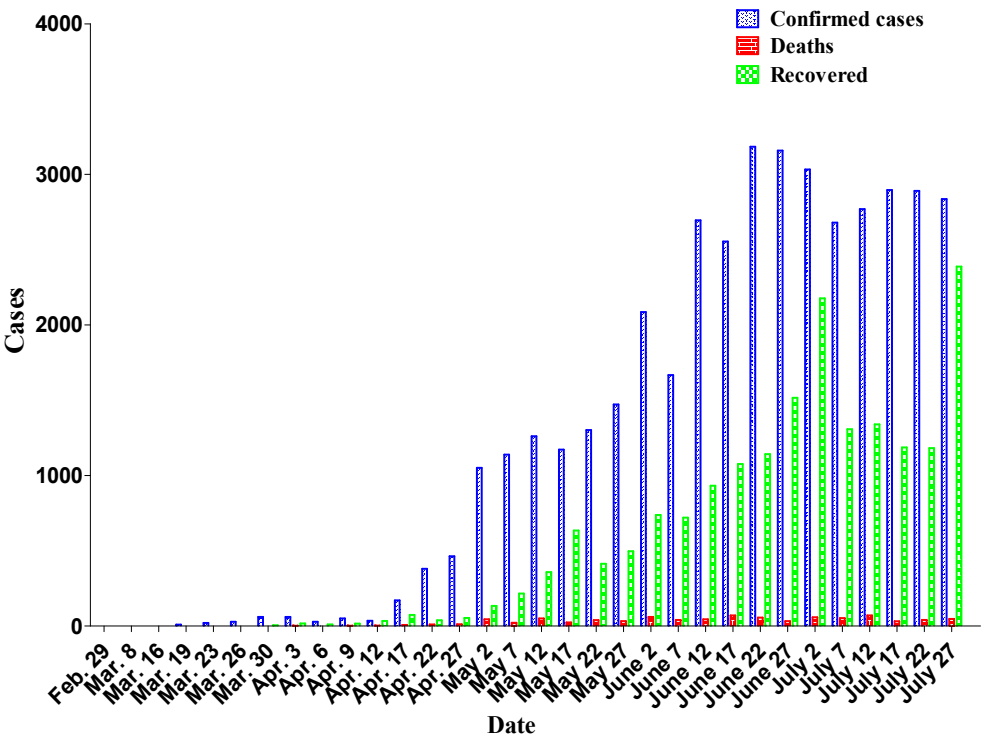

Fig. 1. Covid-19 cases in Nigeria
Source: NCDC. [22]

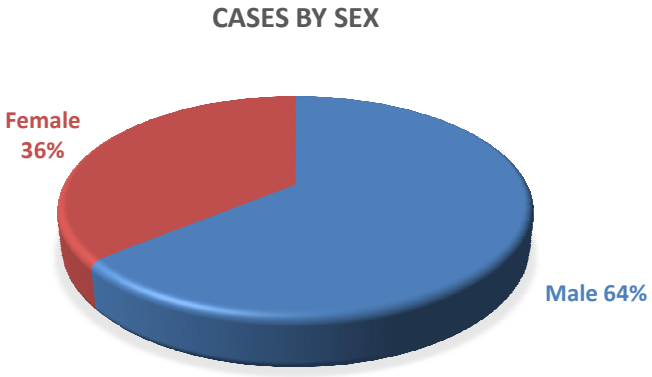

Fig. 2. Coronavirus cases by sex in Nigeria
Source: NCDC. [22]

different continents as at 28th July 2020. While Fig. 1 shows the coronavirus cases in Nigeria between February 29th to July 27th 2020. From the figure, it was observed that there's a sharp increase within the number of latest cases, recovery rate and death rate. The sharp increase observed might be as a result of the convenience on lockdown, thanks to the poverty rate, and unemployment within the country and the ineffective laid down rules by the government. Covid-19 showed a difference in death rate between males (64%) and females (36%) as at July 27th 2020. The differences might be as a result of ACE2 which is found on the X chromosome, there could also be alleles that confer resistance to COVID-19, explaining the

lower death rate in females [12]. Alternatively, the oestrogen and testosterone sex hormones have different immunoregulatory functions, which could have influence immune protection or disease severity [21].

The features of covid-19 are its apparent ability to spread readily and its propensity to cause severe disease in older adults and patients with existing health conditions [7]. Just like the other respiratory coronaviruses, SARS-CoV-2 is transmitted primarily via respiratory droplets, with a possible, but unproven, fecal–oral transmission route. On infection, the median time period is approximately 4–5 days before symptom onset [8,9,10,11] with 97.5% of symptomatic patients developing symptoms within 11.5 days [10].

On hospital admission, patients with covid-19 typically exhibit a fever and dry cough; less commonly, patients also experience difficulty in breathing, muscle or joint pain, headache/dizziness, diarrhoea, nausea and expulsion of blood [8,12,13,14,15,16], within 5–6 days of symptom onset, SARS- CoV-2 viral load reaches its peak, significantly before that of the related SARS- CoV, where viral load peaks at about 10 days after symptom onset [17,18,19, 20]. Severe covid-19 cases progress to acute respiratory distress syndrome (ARDS), on average around 8–9 days after symptom onset [15,1].

1.1 The Current Methods Applied for the Treatment of the New Coronavirus

The present methods of COVID-19 treatment are composed of the administration of medicine like Remdesivir, Chloroquine, Arbidol and Favipiravir and, approaches like interferon therapy [23,24]. A variety of the targets considering the inhibition of the RNA transcription, RNA modification, virus packaging enzymes, the capsid and therefore the surface proteins assist the virus to diffuse into the cells and may be a considered strategy to deactivate or prohibit the propagation of RNA virus in cells and tissues [23]. Currently, further studies are been investigated on the biochemical materials that would inhibit the most proteases of the virus or the compounds that would inhibit the propagation rate of the virus within the cells. The plants provide an ultimate, natural source of enzyme and viral propagation inhibitors to be implicated as a treatment method of disorders caused by SARS-Cov and SARS-Cov2. Fortunately, there's a substantial similarity between the SARS-Cov and SARS-Cov2 virus which is 80% identity and 96% similarity of the genome [25,7]. It's also observed that there's a 76.10% identity between the mentioned viruses [26]. Based on this similarity, it is expected that the results of the studies about the SARS-Cov could be implied for the research in the SARS-Cov2 to a high degree.

2. IMMUNOMODULATORY EFFECT OF FOODS AND NATURAL PLANT AGAINST SARS-COV-1 AND SARS-COV-2

Coronavirus can be treated using nutrition, the common cold, SARS-CoV-1, and SARS-CoV-2 fall under the same coronavirus family; hence, are regarded as the same viral type [27]. An evidence has showed that vitamin D decreased the risk of COVID-19 outbreak in winter, which is a time when 25-hydroxyvitamin D (25(OH)D) level is low. Thus, vitamin D intake may reduce the risk of influenza and COVID-19 infections and related deaths [28]. Many foods and herbs have been known to display antiviral and immunomodulatory activities such as; Aloe vera, *Angelica gigas* (Korean angelica), *Astragalus membranaceus* (Mongolian milkvetch), *Ganoderma lucidum* (lingzhi mushroom), *Panax ginseng* (ginseng), and *Scutellaria baicalensis* (Chinese skullcap) has been reported to exhibit immunomodulatory properties [29]. Their activities are based on selectively stimulating cytokines, activating lymphocytes, increasing natural killer cell counts and enhancing macrophage actions. Rice bran, wheat bran, *Lawsonia alba* (hina), *Echinacea purpurea* (eastern purple coneflower), *Plumbago zeylanica* (Ceylon leadwort), and *Cissampelos pareira Linn* (velvetleaf) also exhibit immunomodulatory properties by stimulating phagocytosis. Eucalyptus essential oil has been reported to improve the innate cell-mediated immune response that can be used as an immunoregulatory agent against infectious diseases [30]. Collectively, using these immunomodulatory foods and herbs could enhance the immune system and protect the body against COVID-19. Numerous studies, although limited to *in vitro*, *in vivo* studies, reported the bioactive components of foods and herbs against SAR-CoV-1 but only a few clinical studies have been carried on the effects of specific foods and herbs against the SAR-CoV-1, as most clinical studies have been done on food and herb combinations, or the traditional Chinese formulas [31].

2.1 Functional Plants Potentials for the Management of the Coronavirus Related SARS Disease

Plants provide a good source of viral protein inhibitors for the treatment of SARS. Generally, they will express metabolites which will provide an inhibitory effect on the enzymes, proteins and therefore the propagation of the virus. Although, numerous studies have focused on the SARS 2003, there are a lower number of studies with the main target on the COVID-19 disease and articles are limited in the studies of the functional plant compounds [32,33]. The fact that the majority of the active proteins in the infection cycle of SARS-Cov2 are conserved, it is expected that the results from the other researches about previous generations of coronaviruses especially SARS-Cov might be applicable to the new coronavirus.

2.2 Plant Lectins

The plant immunity is an elaborate system which will efficiently detect and deactivate the invading pathogens with a spread of tools considering cell surface and intracellular receptor proteins. Plant lectins are carbohydrate-binding proteins which will act as immunologic receptors and defense proteins and, are found in some plant species like tobacco, soy, and leek. Plant lectins are considered among the plant-based compounds that would be targeted as one of the treatments for COVID-19.

2.2.1 *Utrica dioica* agglutinin lectin

Stinging nettle (*Utrica dioica*) has been utilized in various countries as traditional medicine for years. This plant has been reported to possess therapeutic effects on cardiovascular, immunity, neuronal and digestive systems [53]. The agglutinin lectin is extracted from the rhizomes of the common *Urtica dioica*. Previously, it had been indicated that from the lectins that were extracted from the selective plant species, the Allium porrum Agluttinin (APA) of leek, *Utrica dioica* Agglutinin (UDA) of *Urtica dioica* and NICTABA lectin of Tobacco (*Nicotiana tabacum*) were able to show the very best inhibition tendency to ban the proliferation rate of the virus to 50% (EC50) at 1.3 µg/ml, pure extract with low toxicity *in-vitro* [34]. Similarly, further studies also confirmed that the UDA have an impression on the inhibition of the SARS-Cov virus *in-vitro* [54]. Experiments have proposed and show that the lectins will interrupt the viral attachment and lectins has the very best performance effects once they are delivered at the first stages of the infection cycle [34]. The study also showed that the UDA prevents the virus attachment by inhibition of the SARS-CoV spike (S) glycoprotein [35]. The evidence from the previous research showed that UDA are often an appropriate compound for further research within the COVID-19 arena.

2.2.2 Aloe-emodin

Aloe vera (L.) Burm.f. considered as a “miraculous plant” or “wonder plant” is a medicinal plant that has been used for more than 3000 years in various cultures [55]. *Aloe vera* is a high-potential anti- COVID-19 plant drug and has been used for the management of the disease in the Democratic Republic of the Congo. Several experimental studies have shown that the *Aloe vera* plant is endowed with formidable virucidal properties with a broad spectrum of action. From the point of view of toxicity, the innocuousness of the extracts of this plant has been proven experimentally both *in vitro* and *in vivo*. For instance, *Aloe vera* contains virucidal secondary metabolites such as anthraquinones and some antiviral drugs (Lopinavir, ritonavir), which may act alone or in synergy with pharmacological targets like SARSCov -2 protease 3CLPro [56,57,58]. In addition to intrinsic antiviral properties, *Aloe vera* is also endowed with anti-inflammatory and immunomodulatory properties [59]. To this effect, it is not excluded that a phyto-drug based on *Aloe vera* extracts can attenuate in the patient, the expression of pro-inflammatory factors and receptors is likely to induce acute respiratory distress which is the main cause of mortality associated with COVID-19 while strengthening the immune system. As combination of therapies based on viral protease inhibitors are the best therapeutic option, *Aloe vera* and its major secondary metabolites may play an important role in the management of COVID-19. These data pave the way for clinical research on anti-COVID-19 herbal medicine. Indeed, in addition to its secondary metabolites endowed with virucidal properties, *Aloe vera* contains zinc (40.8 ppm) [60]. This chemical element, although indispensable as an enzymatic co-factor, a slight increase in its intracellular concentration inhibits the replication of retroviruses including SARSCoV-1 which is important in the management of COVID-19.

2.2.3 *Psoralea corylifolia*

Psoralea corylifolia belongs to the Leguminosae family, the seeds of which are a permitted food

additive in many countries, especially South Korea. The major bioactive components of the seeds of *P. corylifolia* are flavonoids and chalcones, including bavachinin, psoralidin, and isobavachalcone [36]. Moreover, the constituents of *P. corylifolia* have been found to exhibit antioxidant, antibacterial, anti-inflammatory and antidepressant activities [61,62,63]. *Psoralea corylifolia* has also been reported to have inhibitory activities of baculovirus-expressed BACE-1, DNA polymerase and topoisomerase II [64,65]. It was also reported that glycosidase inhibitory phenolic compounds are found in this species [65]. During an intensive research program into biologically active metabolites from *Psoralea corylifolia*, it was found that the ethanol extract showed significant inhibition against SARS-CoV PLpro. In the study, six aromatic compounds were isolated and targeted against SARS-CoV PLpro from the seeds of *P. corylifolia*. The isolated compounds were evaluated separately for their inhibitory activities against PLpro. Their inhibition mechanisms were ascertained using Lineweaver–Burk and Dixon plots.

2.2.4 *T. nucifera* (Japanese nutmeg-yew)

T. nucifera, a Taxaceae tree found in snowy areas near the Sea of Jeju Island in Korea has been used in traditional Asian medicine as a remedy for stomachache, hemorrhoids and rheumatoid arthritis [66]. As part of an ongoing investigation of potential SARS-CoV 3CLpro inhibitors from medicinal plants, ethanol extracts of the leaves of *Torreya nucifera* was done using a fluorescence resonance energy transfer (FRET) assay. The isolation of 12 phytochemicals—eight diterpenoids and four biflavonoids—with SARS-CoV 3CLpro inhibitory activity from the ethanol extracts of the leaves of *T. nucifera* was done and the starting material by virtue of its observed 3CLpro inhibition (62% at 100 lg/mL). All isolated compounds were examined for their 3CLpro inhibitory activities by enzymatic inhibition assay. The isolated compounds, biflavonoid amentoflavone [67] was identified as a potent inhibitor of SARS-CoV 3CLpro, exhibiting an IC50 value of 8.3 lM.

2.3 Natural Plant Secondary Metabolites

Secondary metabolites are always considered as non-necessary compounds for plant living cells, such metabolites are expressed in response to biotic and abiotic stresses. There are sorts of plant secondary metabolites that are studied for the inhibition of SARS-Cov and are found to possess a robust antiviral and anti-SARS-Cov activity [42,68,35]. Examples of such compounds are discussed below.

2.3.1 Quercetin

Allium genus plant contains Organosulfur compounds like onions (e.g. *Allium cepa*), garlic (e.g. *Allium sativum*) and leek (*Allium porrum*), an organic macromolecule that contain sulfur in their biochemical structure. During a recent study for SARS-Cov2, it had been revealed that the organosulfur materials from the *A. porrum* can have significant potential in inhibition of the Human ACE2 enzymes and thus features a potential to inhibit and to attach the SARS-Cov2 to the cells [69]. Quercetin may be a flavonoid that's abundantly available in onion and garlic species and is found as sulfonic substituents (although less occurring) [39]. Quercetin-3-β-galactoside was observed by Chen et al. [3] to possess inhibition activity of 3CLPro of SARS-Cov. Further studies have also confirmed the inhibition of 3CLPro of the SARS-Cov by both Quercetin and Quercetin-3-β-galactoside in-vitro [38,19]. It had been also confirmed that quercetin 3-β-D-glucoside has the potential to inhibit the 3CLPro of the MERS-Cov [19]. This compound is found to possess low toxicity to the cells *in-vitro*, and it's one among the main natural components that are targeted for the treatment of the COVID-19 disease.

2.3.2 Cepharanthine

Cepharanthine is a natural alkaloid (secondary metabolite) derived from plants of the genus Stephania native to Southeast Asia. Over the years, numerous members of the plant species have been used in Asia as typical treatment for delirium [40]. Cepharanthine is an agent that has proven preclinical promise in the treatment of SARS. An *in vitro* experiment was once performed to examine the extent of anti-SARS-CoV activity using VeroE6 cells infected with SARS-CoV [70]. The researchers split the cells into four groups where cells in the first group were pre-treated with cepharanthine prior to infection and cells in the second group were treated with cepharanthine post-infection with the virus. The third group had cells co-treated with cepharanthine and the virus.

The fourth group of cells was also co-treated with cepharanthine and the virus but the mixture of cepharanthine and virus were incubated at 37℃

for 2 hrs prior to application on the VeroE6 cells. Following treatment, viral cytopathic effect was inhibited by a cepharanthine concentration of 10 µg/ml across all groups, with the 50% inhibitory concentration (IC 50) ranging between 6.0 µg/ml and 9.5 µg/ml for the four treatments. Even though Zhang et al. [45] had no clear explanation for their findings, their results were not totally surprising as cepharanthine has also been demonstrated to inhibit similar human coronaviruses such as the human coronavirus type OC43 (HCoV-OC43).

Given the excellent impact of cepharanthine on HCoV-OC43 and SARS-CoV; there is a likelihood that cepharanthine will exhibit comparable results on the newly observed SARS-CoV-2.

2.3.3 Glycyrrhizin

Glycyrrhizin is the major component within the licorice (*Glycyrrhiza glabra*) root [71,72]. The compound has been used traditionally for the treatment of gastritis, bronchitis, and jaundice and is reported to possess antioxidant and anti-inflammatory activity which will stimulate the formation of interferons within the body [73]. It's been shown that Glycyrrhizin can decrease the attachment of the SARS-Cov agents to the cells especially during the initial phase of the virus infection cycle [74].

Glycyrrhizin are composed of flavonoids, glycyrrhetinic acid, β-sitosterol and hydroxyl coumarins [73] and has been observed to possess an anti-SARS-Cov activity by Cinatl et al. [75]. Pilcher [74] later regarded the licorice plant and Glycyrrhizin as a prospective method of creating a billboard drug against SARSCov, adding to the very fact that there's an extended way until a billboard drug for the SARS-Cov is formed. Chen et al. [41] further confirmed that Glycyrrhizin possess anti-SARS-Cov and various review articles are published as results of positive antiviral activity of Glycyrrhizin [76,77,78].

A case study of using 30 µg/mL of glycyrrhizin in *in-vivo* behavior for COVID-19 disease, has noted the glycyrrhizin as a possible inhibitor of SARS-Cov2 [33,78]. However, no studies are found on the SARSCov, for approval of the *in-vivo* effectiveness of the glycyrrhizin. Yet, haven supported the positive results of the mentioned studies, this compound could be a possible for the event of an anti-COVID-19 disease drug.

2.3.4 Diarylheptanoids

Diarylheptanoids are found in Alder**,** Alder bark contains the anti-inflammatory salicin, which is metabolized into salicylic acid in the body [79]. Some Native American cultures use red alder bark (*Alnus rubra*) to treat poison oak, insect bites and skin irritations. Blackfeet Indians have traditionally used an infusion made from the bark of red alder to treat lymphatic disorders and tuberculosis. Park et al. [47] studied inhibitory potential of 9 diarylheptanoid derivatives (platyphyllenone, hirsutenone, platyphyllone, platyphyllonol-5-xylopyranoside, hirsutanonol, oregonin, rubranol, rubranoside B and rubranoside A) isolated from *Alnus japonica* Steud (Betulaceae) of Korean origin in the same manner against both SARS-CoV $3CL^{pro}$ and PL^{pro} using a continuous fluorometric assay.

Firstly, the stem bark ethanol extract of the plant was identified with a marked PL^{pro} inhibition, which led to isolation of the afore mentioned diarylheptanoids containing basically 1,7-diphenylheptane skeleton. Among them, hirsutenone ($IC_{50} = 3.0 \pm 1.1$ µM), hirsutanonol ($IC_{50} = 24.1 \pm 2.0$ µM), oregonin ($IC_{50} = 44.5 \pm 5.3$ µM), rubranol ($IC_{50} = 35.2 \pm 1.7$ µM), rubranoside B ($IC_{50} = 7.2 \pm 2.2$ µM) and rubranoside A ($IC_{50} = 14.4 \pm 3.0$ µM) were found to be the promising inhibitors of SARS-CoV PL^{pro} in deubiquitination activity assay in comparison to that of curcumin ($IC_{50} = 5.7$ µM) as the reference compound. α, β-Unsaturated carbonyl group with a catechol moiety was correlated with the higher inhibition in these molecules, whereas monohydroxyl substitution led to diminish of the inhibitory effect. Within the same work, the glycoside derivatives of these diarylheptanoids were also tested and found to exhibit poorer inhibition than the diarylheptanoids. When they were tested against recombinant SARS-CoV $3CL^{pro}$, the findings showed that the diarylheptanoids displayed a noteworthy selectivity towards the coronaviral proteases.

2.3.5 Flavonoids

Flavonoids are an important class of natural products and have several subgroups, which include chalcones, flavones, flavonols and isoflavones [80]. Flavonoids have many functions besides antioxidant effects and they also have antiviral abilities. Shimizu et al. [81] had found that flavonoids from Pterogyne Nitens could inhibit the entry of the hepatitis C Virus. Jo et al. [82] had suggested that the anti-coronavirus

activity of some flavonoids (Herbacetin, rhoifolin and pectolinarin) was due to the inhibition of 3C like protease (3CLpro). Other flavonoids (Herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, and helichrysetin) were also found to be able to block the enzymatic activity of MERS CoV/3CLpro [83]. Moreover, Ryu et al. [37] had reported that biflavonoids from Torreya nucifera also brought inhibition effect of SARS CoV/3CL (pro).

2.3.6 Nicotianamine

Nicotianamine is an important metal ligand in plants and it is found in a novel angiotensin converting enzyme 2 inhibitor in soybean [82]. It has also showed to be another potential option to be used to reduce the infection of COVID 19.

2.4 The Effectiveness of the Anti-viral Plants' Oral Delivery

The uses of plant cells as a bioreactor are normally subjective to several ethical and environmental considerations. This process normally, will leads to the generation of a new transgenic plant, it's probable that the propagation of plant species as a result of the uncontrolled breeding might affect the species within the ecosystems, create an imbalanced niche or even cause poisoning to the species which may consume the plant randomly. Consequently, the transgenic plant culture should be done monitored and administered under restricted control [84]. However, the question is usually whether the direct oral delivery of the compounds is going to be also effective in terms of getting antiviral activities. It had been confirmed by several studies that the majority of the plant that possess anti-SARS agents can inhibit the connection of the viral agents to the cells [74]. However, it is often postulated that the majority of plant anti-viral agents might apply a protective behavior against the doorway and propagation of the viral agents within the host body. During this case, adding the edible plant species that produce anti-SARS-Cov compounds like leek, onion, garlic and Urtica dioica root (the common nettle) against infection to the food diet might be a good strategy against infection of the new COVID-19 disease.

3. CONCLUSION

Considering the high similitude of the genome, receptors of SARS-Cov and SARS-Cov2. Functional plant could as well provide a natural, cost effective and less side effects approaches of drug discovery against covid-19 disease. This study suggests that plant species like *Utricadioica dioica* and *T. nucifera* (Japanese nutmeg-yew*)* could help manage, prevent infections and strengthen immunity of the masses against SARS-CoV-2 and in COVID-19 patients. Overall, more studies are needed to further assess the anti-viral ability of these plant species and functional foods.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wang LF, Shi Z, Zhang S, Field H, Daszak P, Eaton BT. Review of bats and SARS. Emergency Infection District. 2016;12: 1834–1840.
2. Ge XY, Li J, Yang X, Chmura A, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature. 2013;503:535–538.
3. Chen Y, Guo D. Molecular mechanisms of coronavirus RNA capping and methylation. Virol. Sin. 2016;31:3–11.
4. Drexler JF, Corman VM, Drosten C. Ecology, evolution and classification of bat coronaviruses in the aftermath of SARS. Antivir. Res. 2014;101:45–56.
5. Cui J, Li F, Daszak P. Origin and evolution of pathogenic coronaviruses. Nat. Rev. Genet. 2018;17:181–192.
6. World Health Organization (WHO). Coronavirus disease; situation report. 2020;189. Available:https://www.who.int/emergencies/diseases/novel-coronavirus 2019/situation-reports
7. Zhou P, Yang XL, Wang XGW, Hu B, Zhang L, Zhang W, Si HR. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. BioRxiv; 2020.

8. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo JL, Ye CJ, Zhu SY, Zhong NS. Clinical characteristics of Coronavirus disease 2019 in China; 2020.
9. Pung R. Investigation of three clusters of COVID-19 in Singapore: Implications for surveillance and response measures. 2020;395:1039–1046.
10. Lauer SA, Grantz KH, Qifang BI, Forrest K, Zheng Q, Meredith HR, Andrew S, Nicholas G, Lessler J. The incubation period of Coronavirus disease 2019 (COVID-19) from publicly reported confirmed dases; estimation and application. Ann. Intern. Med; 2020.
11. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KS, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early transmission dynamics in Wuhan, China, of Novel Coronavirus infected pneumonia. Journal of Medicine. 2020;382:1199–1207.
12. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunologic features of severe and moderate; 2020.
13. Phan LT, Huong V, Quang C, Thinh V, Hieu T, Hung Q, Thuc T, Thang M, Quang D. Pham. Importation and human- to-human transmission of a novel coronavirus in Vietnam. Journal of. Medicine. 2020;382:872–874.
14. Hung C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng X, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel Coronavirus pneumonia in Wuhan, China: A descriptive study. 2020;395:507–513.
16. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Cheng CZ, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L. Clinical and biochemical indexes from 2019 nCoV infected patients linked to viral loads and lung injury. Sci. China Life Sci. 2020;63:364-374.
17. Peiris JS, Chu CM, Cheng VCC, Chan KS, Hung IFN, Poon LLM, Law KI, Tang BSF, Hon TYW, Chan CS, Chan KH, Ng JSC, Zheng BJ, Ng WL, Lai RWM, Guan Y, Yuen KY. Clinical progression and viral load in a community outbreak of coronavirus associated SARS pneumonia: A prospective study. 2003;361:1767–1772.
18. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS- CoV-2 in clinical samples. 2020;3099-30113.
19. Kim JY, Ko JH, Kim Y, Kim YJ, Kim JM, Chung YS, Kim HM, Myung-Han G, Kimand SO, Chin BS. Viral load kinetics of SARS- CoV-2 infection in first two patients in Korea. Journal of Korean Medicinal Science. 2020;35-86.
20. Zou L. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N. Engl. J. Med. 2020;382:1177–1179.
21. Taneja V. Sex hormones determine immune response. Frontal Immunomodulatory. 2020;9:19-31.
22. Nigeria Centre for Disease Control (NCDC). An update of COVID-19 outbreak in Nigeria; An update of COVID-19 outbreak in Nigeria for Week 30; 2020. Available:https://ncdc.gov.ng/diseases/sitreps/?cat=14&name=An%20update%20of%20COVID-19%20outbreak%20in%20Nigeria
23. Dinesh DC, Tamilarasan S, Rajaram K, Bouřa D. Antiviral drug targets of single stranded RNA viruses causing chronic human diseases. Current Drug Targets. 2020;21(2):105-124.
24. Dong S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discoveries & Therapeutics. 2020;14(1):58-60.
25. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with

human respiratory disease in China. 2020;7798:265-269.
26. Xu Xintian, Ping Chen, Jingfang Wang, Jiannan Feng, Hui Zhou, Xuan Li, Wu Zhong, Pei Hao. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Science China Life Science. 2020;3:457-460.
27. Saul AW. Nutritional treatment of coronavirus. Orthomol Med News Ser. 2020.
28. Grant WB, Lahore H, McDonnell SL. Evidence that vitamin d supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12(4):988.
29. Tan BKH, Vanitha J. Immunomodulatory and antimicrobial effects of some traditional Chinese medicinal herbs: A review. Curr Med Chem. 2004;11:1423-1430.
30. Saldon AE, Lamson DW. Immune-modifying and antimicrobial effects of eucalyptus oil and simple inhalation devices. Alternative Medicinal Review. 2010;15(1):33-42.
31. Luo H, Tang QL, Shang YX. Can Chinese medicine be used for prevention of Coronavirus Disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. Chin J Integrated Medicine. 2020;26(4):243-250.
32. Qamar MT, Alqahtani SM, Alamri MA, Chen LL. Structural basis of SARSCoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. Analysis; 2020.
33. Mohammadi N, Shaghaghi N. Inhibitory effect of eight secondary metabolites from conventional medicinal plants on COVID_19 virus protease by molecular docking analysis; 2020.
34. Kayaerts E, Vijgen L, Pannecouque C, Van Damme E, Peumans W, Egberink H, Balzarini J, Ranst MV. Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antiviral Research. 2007;75(3):179-187.
35. Kumaki Y, Wanderseea MK, Smitha AJ, Zhoub Y, Simmons G, Nelsona NM, Baileya KW, Vest ZG, Joseph KK, Chane PKS, Smeea DF, Barnarda DL. Inhibition of severe acute respiratory syndrome coronavirus replication in a lethal SARS-CoV BALB/c mouse model by stinging nettle lectin, *Urtica dioica* agglutinin. Antiviral Research. 2011;90(1):22-32.
36. Guo JM, Weng XC, Wu H, Li Q, Bi KS. Antioxidants from a Chinese medicinal herb *Psoralea corylifolia L.* Food Chemistry. 2005;91:287–92.
37. Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY, Kim D, Nguyen TTH, Park JS, Chang JS, Park KH, Rho MC, Lee WS. Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL(pro) inhibition. Bioorgan Medical Chemistry. 2010;18: 7940-7947.
38. Nguyen TTH, Woo HJ, Kang HK, Nguyen VD, Kim YM, Kim DW, Ahn SA, Xia Y, Kim D. Flavonoid mediated inhibition of SARS coronavirus 3C-like protease expressed in Pichia pastoris. Biotechnology Letters. 2012;5:831-838.
39. Massi A, Bortolini O, Ragno D, Bernardi T, Sacchetti G, Tacchini M, De Risi C. Research progress in the modification of quercetin leading to anticancer agents (ineng). Molecules. 2017;8:12-70.
40. Bailly C. Cepharanthine: An update of its mode of action, pharmacological properties and medical applications. Phytomedicine. 2019;62:152956.
41. Chen F, Chan KH, Jiang Y, Kao, Lu HT, Fan KW, Cheng VCC, Lee TSW, Guan Y, Peiris JSM. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. Journal of Clinical Virology. 2004;31(1):69-75.
42. Hoever G, Lidia BL, Michaelis M, Kondratenko R, Baltina L, Genrich A, Tolstikov, Hans W, Cinatl J. Antiviral activity of glycyrrhizic acid derivatives against SARS coronavirus. Journal of Medicinal Chemistry. 2005;48(4):1256-1259.
43. Yeh CF, Wang KC, Chiang LC, Shieh DE, Yen MH, Chang JS. Water extract of licorice had anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. Journal of Ethnopharmacology. 2013;2:466-473.
44. Park JY, Jeong HJ, Kim JH, Kim YM, Park SJ, Kim DKH, Park KH, Lee W, Ryu YB. Biol. Pharm. Bull. 2012;35:2036–2042.
45. Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. Journal of Enzyme Inhibition and Medicinal Chemistry. 2020;1:145-151.
46. Kuo PL, Lin TC, Lin CC. The antiproliferative activity of aloe-emodin is through P53 dependent and P21 apoptotic

pathway in human hepatoma cell lines. Life Sciences. 2002;71:1879-1892.
47. Keivan Z, Moloud AZ, Kohzad S, Zahra R. Antiviral activity of *Aloe vera* against herpes simplex virus type 2: An *in vitro* study. African Journal of Biotechnology. 2007;6(15):1770-1773.
48. Zandi K, Zadeh MA, Sartavi K, Rastian Z. Antiviral activity of *Aloe vera* against herpes simplex virus type 2: An *in vitro* study. Afr J Biotechnol. 2007;6:1770-1773.
49. Morin E. *Aloe vera* (L.) Burm. f.: Aspects pharmacologiques et cliniques. Thèse de doctoratenpharmacie, Faculté de Pharmacie, Université de Nantes. 2008;224.
50. Rezazadeh F, Moshaverinia M, Motamedifar M, Alyaseri M. Assessment of anti HSV 1 activity of *Aloe vera* gel extract: an *in vitro* study. J Dent Shiraz University of Medical Science. 2016;17:49-54.
51. Wang Y, Zhaorui C, Jing O, Haiyan W, Renquan Y, Yangong C, Jianguo Q, Jianwei W, Tao H. Profiles of IgG antibodies to nucleocapsid and spike proteins of the SARS associated coronavirus in SARS patients. DNA and Cell Biology. 2005;8:521-527.
52. Franconi R, Illiano E, Paolini F, Massa S, Venuti A, Demurtas OC. Rapid and low cost tools derived from plants to face emerging/re-emerging infectious diseases and bioterrorism agents. In Defence against Bioterrorism, Dordrecht V. Radosavljevic, I. Banjari, and G. Belojevic, Eds., 2018// 2018: Springer Netherlands. 2018;123-139.
53. Dhouibi R, Affes H, Ben Salem M, Hammami S, Sahnoun Z, Zeghal KM, Ksouda K. Screening of pharmacological uses of *Urtica dioica* and others benefits. Progress in Biophysics and Molecular Biology. 2020;150:67-77.
54. Van der Meer FJUM, Haan CAM, Schuurman NMP, Haijema BJ, Verheije MH, Bosch BJ, Balzarini J, Egberink HF. The carbohydrate-binding plant lectins and the non peptidic antibiotic pradimicin A target the glycans of the coronavirus envelope glycoproteins. Journal of Antimicrobial Chemotherapy. 2007;4:741-749.
55. Mukherjee PK, Nema NK, Maity N, Mukherjee K, Harwansh RK. Phytochemical and therapeutic profile of *Aloe vera*. Journal of Natural Remedies. 2014;14(1):1-26.
56. Kahlon JB, Kemp MC, Carpenter RH, McAnalley BH, McDaniel HR, Shannon WM. Inhibition of AIDS virus replication by acemannan *in vitro*. Mol Biother. 1991;3:127-35.
57. Bernard SG, Hughes BG, Sidwell RW. Evaluation of the antiviral activity of anthraquinones, anthrones and anthraquinone derivatives against human cytomegalovirus. Antiviral. Res. 1992;35:2463-2466.
58. Semple SJ, Pyke SM, Reynolds GD, Flower RL. *In vitro* antiviral activity of the anthraquinone chrysophanic acid against poliovirus. 2001;49:169-178.
59. Bhalsinge RR, Rajbhoj SR, Limaye MV, Vaidya MU, Rane PS, Tilak AV. Anti-inflammatory and immunomodulatory activity of ethanol extract of *Aloe vera* gel. IJPSR. 2017;9(2):832-835.
60. te velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity *in vitro* and zinc ionophores block the replication of these viruses in cell culture. Plos Pathogens. 2010;6(11):1-10.
61. Khatune NA, Islam ME, Haque ME, Khondkar P, Rahman MM. Antibacterial compounds from the seeds of *Psoralea corylifolia*. Fitoterapia. 2004;75:228–30.
62. Xu Q, Pan Y, Yi LT. Antidepressant-like effects of psoralen isolated from the seeds of *Psoralea corylifolia* in the mouse forced swimming test. Biol Pharm Bull. 2008;31:1109–14.
63. Choi YH, Yon GH, Hong KS, Park WH, Kim YH, Ry SH, Choi CH, Cha MR, Kim YS. *In vitro* BACE-1 inhibitory phenolic components from the seeds of *Psoralea corylifolia*. *Planta Med*. 2008;74:1405–8.
64. Sun NJ, Woo SH, Cassady JM, Snapka RM. DNA polymerase and topoisomerase II inhibitors from *Psoralea corylifolia*. 1998;61:362–6.
65. Oh KY, Lee JH, Curtis-Long MJ, Kim JY, Ryu HW, Jeong TS, Park KH, Kim JY. Glycosidase inhibitory phenolic compounds from the seed of *Psoralea corylifolia*. Food Chem. 2010;121:940–5.
66. Katsuki T, Luscombe D. *Torreya nucifera*. The IUCN Red List of Threatened Species. IUCN. 2013;298-7599.
67. Kao RY, Tsui WHW, Lee TSW, Tanner JA, Watt RM, Huang JD, Hu L, Chen G, Chen Z. Zhang L, He T, Chan KH, Tse H, To APC, Ng LWY, Wong BCW, Tsoi HW,

Yang D, Ho DD, Yuen KY. Chemical Biology; 2004.
68. Yeun KY. Baicalin as a treatment for SARS infection. Ed: Google Patents; 2009.
69. Thuy BTP, Tran TAM, Nguyen TTH, Le TH, Tran TH, Huynh TPL, Nguyen TT, Tran TVA, Phan TQ, Pham VT, Nguyen VH, Duong TQ, Nguyen TT, Vo TT, Lam KH, Nguyen TA. Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil. ACS Omega; 2020.
70. Zhang CH, Wang YF, Liu XJ, Lu JH, Qian CW, Wan ZY. Antiviral activity of cepharanthine against severe acute respiratory syndrome coronavirus *in vitro*. Chin Med; 2005.
71. Kim DE, Min JS, Jang MS, Lee JY, Shin YS, Park CM. Natural Bis benzylisoquinoline alkaloids-tetrandrine, fangchinoline, and cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells. Biomolecules. 2019;9(11):696.
72. St-Jean JR, Jacomy H, Desforges M, Vabret A, Freymuth F, Talbot PJ. Human respiratory coronavirus OC43: Genetic stability and neuroinvasion. Journal of Virology. 2004;16:8824–34.
73. Ramos-Tovar E, Muriel P. Chapter 9 - phytotherapy for the liver. In Dietary Interventions in Liver Disease, R. R. Watson and V. R. Preedy Eds.: Academic Press. 2019;101-121.
74. Pilcher H. Liquorice may tackle SARS. Nature. 2003;030-609.
75. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr, HW. Glycyrrhizin, an active component of liquorice roots and replication of SARS associated coronavirus. The Lancet. 2003;361(9374): 2045-2046.
76. Fiore C, Eisenhut M, Ragazzi E, Zanchin G, Armanini D. A history of the therapeutic use of liquorice in Europe. Journal of Ethnopharmacology. Antiviral effects of Glycyrrhiza species. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2008;22(2):141-148.
77. Pu J, He L, Wu S, Zhang P, Huang X. Anti-virus research of triterpenoids in licorice. Bing du Xue Bao. Chinese Journal of Virology. 2013;6:673-679.
78. Chen H, Du Q. Potential natural compounds for preventing 2019-nCoV infection. Preprints; 2020.
79. Ewing S. The great Alaska nature factbook: A guide to the state's remarkable animals, Plants and Natural Features (2nd Ed.). Graphic Arts Books. 2012;106:142-80.
80. Parchen AN, Diwan AD, Chandra SR. Flavonoids: An overview. Journal of Nutrition Science. 2016;5-47.
81. Shimizu JF, Lima CS, Pereira CM, Bittar C, Batista MN, Nazaré AC, Polaquini CR, Zothner C, Harris M, Rahal P. Flavonoids from *Pterogyne nitens* inhibit hepatitis C virus entry. Science. Representative. 2017;7:16-127.
82. Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. Enzyme Inhib Med Chem. 2020;35:145-151.
83. Jo S, Kim H, Kim S, Shin DH, Kim MS. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. Chemical Biology Drug Description. 2019;94:2023-2030.
84. Yoresi M, Rezazadeh A, Mousai MM. The considerations and the required steps for production of the plant seeds vaccines with focus on the oral delivery. Plant Cell Biotechnology and Molecular Biology. 2020;36-51.

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