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Exploration of Some Candidate Plants with Medicinal Properties to Enhance Immunity against Coronavirus Pandemics: A Review

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Abstract

On 11th of March 2020, the World Health Organization (WHO) declared a Global Pandemic named COVID-19, a contagion induced by Severe Acute Respiratory Syndrome (SARS). It is likely suggested that this is a Zoonotic virus, since a group of people infected with virus were unveiled to wet animal market in Wuhan, China. In the preceding decades, two zoonotic coronaviruses; Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndromes (SARS) coronavirus, are analysed that cause lung disorders in human beings and animals and can be fatal too. This pandemic demands the rapid development of vaccines and panacea but till now, no approved vaccine or therapy have been reported against this virus. For the development of some beneficial vaccines and drugs, scientists are working for it across the world. Plants, which possess several antibacterial, antifungal and antiviral properties, are of an utmost importance and becomes even more important when the World is dealing with such a Global pandemic. Plant-based vaccines can be an effective way to cope with this crisis. Plants are integral to well beings of humans. Various molecules, like blancoxanthone, curcumin, etc. separated from plants might be proven effective drug targets. This review paper presents an outlook on various plants with many antiviral properties against COVID 19 and also throws light upon various technologies to establish herbal treatment against it that can be taken into consideration.

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Introduction

The genome of Coronaviruses is enveloped, positive-sensed, ssRNA(+ssRNA), which has over 30,000 nucleotides with three to four structural macromolecules [1]. The word "coronaviruses" is originated from prehistoric word "Corona" meaning "crown-like", because the glycoproteins that are present on the surface of coronavirus appears to be crown-shaped [2]. The Coronaviridae family of the subfamily Orthocoronavirinae divides into the following genera of Coronaviruses (CoVs): AlphaCoV, betaCoV, deltaCoV, gammaCoV [3]. Some human CoVs cause common cold like HCoV-OC43, HCoV-229E that are not prone to severity while other human Coronaviruses like SARS-Coronavirus and MERS-Coronavirus are regarded more virulent and causes severe respiratory diseases leading to pandemics most recent being the SARS-CoV-2. During this widespread, many people faced economic and social disturbance which had catastrophic impact to the society. In such a type of situation, identifying novel drugs with no side effects is very tough to identify so it is beneficial to look for the herbal treatment of COVID-19. [4].

One approach is to evolve inactivation system of viruses by imposing present antiviral agent from therapeutic herbs. Mutation helps viruses to develop resistance against antimicrobial agents, which can increase the need to invent new compounds against SARS-CoV-2 [5,6]. Currently various therapies are suited for SARS-CoV-2. Chemotherapies using Hydroxychloroquine along with Azithromycin are available, but for these, only cellular level invitro studies are there and exact system of actions of these chemicals are not elucidated so far [7,8]. Secondly, Antiviral Therapies using Lopinavir, Ritonivir, Remdesivir, Oseltamivir and Amantadine are also present [9]. There are other therapies also that are available to counteract with COVID-19 using Colchicine and Glucocorticoids. But all these therapies have certain side effects on human beings like Parasthesia, Hepatitis, Diarrhea, Nausea, Hepatotoxicity, Anorexia, CNS toxicity, hepatic and sometimes even death [10-12]. Therefore, we cannot completely rely upon these therapies for curing patients diagnosed with COVID-19. Hence, there is a need to find out certain drugs and vaccines that possess least or no side effects and can be safer to administer to any age group of people. Plants are integral to the well-beings of Humans. Plant-based vaccines are proven to be feasible and they have shown excellent results in the past few decades. Ayurveda is known from ancient times for its use in medicine and curing various diseases in the past. Natural products and plants with medicinal values are used from centuries and are proven potent with time. Studies conclude that extracts from medicinal herbs have advantageous prohibitory effect against coronavirus [13]. Secondary metabolites present in Plants like terpenes, flavonoids, alkaloids and saponins are characterized through antiviral activity assays [14,15]. In this article, we will look upon some plants that may be used to deal with SARS-CoV-2 based upon various research and studies. Plants normally have compounds with cytotoxic potentialities. Plant based medicine production for COVID -19 disease, if possible, can lead to an era of less toxic and side effect free medicine production. These medicines would be in cheap price and easy to access for poor people.

Coronavirus structure and mechanism

It comprises mainly of 4 structural proteins namely, an envelope Protein(E), Membrane protein(M), a Spike protein(S), and a nucleocapsid protein(N) and some nonstructural proteins [16].

CoVs are infectious viruses having diameter of about 70-120 nm having ssRNA [17]. SARS-CoV-2 exhibits nearly 75% resemblance with SARS-CoV-1. It consists of Open Reading Frame (ORFs) [18]. The largest ORF being the ORF1ab which encodes non-structural glycoproteins while other ORFs encodes for four structural proteins. Out of 6 types of mutations that take place in CoVs, a total of 3 mutations are reported in ORF1ab gene (Figure 1) [19].

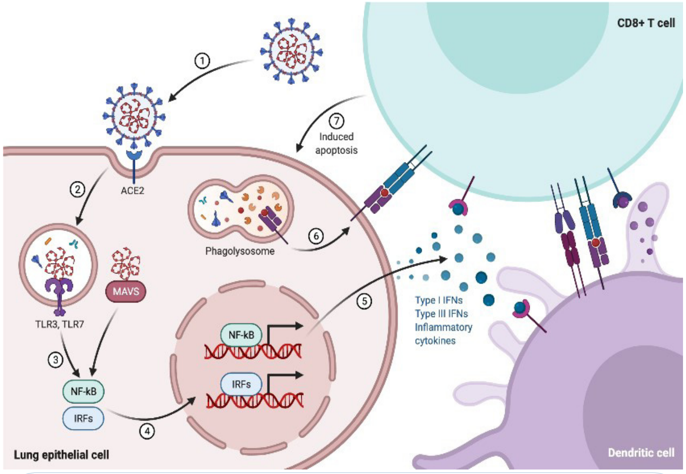

Figure 1: Reprinted from "Acute Immune Responses to Coronaviruses", by BioRender, August 2020, retrieved from https://app.biorender.com/biorender-templates/t-5f17532f2baea000aee86819-acute-immune-responses-to-coronaviruses Copyright 2021 by BioRender [20].

SARS-COV-2 invades the body of a human via mouth and nose and binds to RBD (Receptor-Binding Domain) with the help of glycoproteins on the virions' surface, which seeks to attach to the human Angiotensin-Converting Enzyme 2 (ACE2) receptor. Further research revealed that SARS-COV-2 recognises ACE-2 more strongly than SARS-COV, boosting ability of SARS-CoV-2 to spread one-to-one. [21]. As a result, it was stated that the spike proteins of SARS-CoV-2 had a strong binding ability for human ACE2. In summary, on the surface of the host cell, the spike proteins of SARS-CoV-2 are strongly binded making virus entrance and replication easier [22].

SARS CoV-2 and plants- based therapeutics with antiviral properties

Plants have secondary metabolites, which derives from primary plant compounds. Plant metabolites have potentiality to combat viral diseases (Figure 2). A detailed approach is given below.

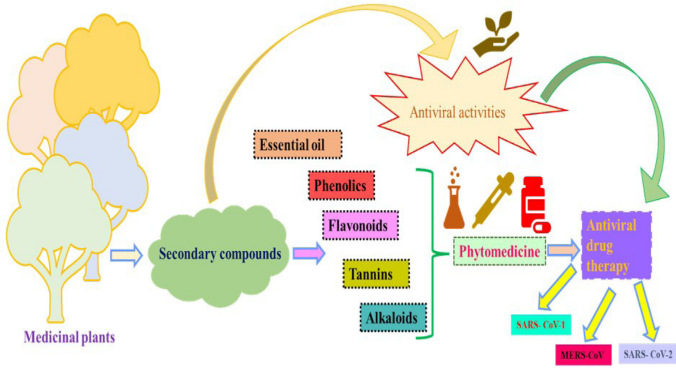

Figure 2: Illustration depicting the role of plant secondary compounds in the production of phytomedicines that could be effective as antiviral drug therapy and COVID -19 controls subsequently.

Activity of andrographis paniculata

Andrographis paniculata also termed mas Kalmegh has its wide used in Ayurvedic medicines. It is included in the family of Acanthaceae, indigenous to Sri Lanka and India. It is mostly grown in Southern Asia, where it is used as a treatment against many bacterial and other diseases.

After conducting in silico studies, it was discovered that chemical ingredients of Andrographis paniculata, such as andrographolide and dihydroxy dimethoxy flavone, bind to the SARS CoV-2 active site, produce remarkable activity, and are used to treat various viruses, particularly SARS-COV-2.

Research also indicates that natural medicinal plants like *Andrographis paniculata* have a number of biological assets and is used in serving various disorders, because they have least or no side effects compared to allopathic medicines [23]. From the literature, *Andrographis paniculata* has been used to treat liver illnesses, hepatitis, diarrhea, fever, malaria, hypertension and anti-cancer [24]. "Inhibitory Activities of Methanol Extracts of *Andrographis paniculata* and *Ocimum sanctum* against Dengue-1 Virus," 2014 determined notable amount of DEN-1 inhibition based upon cytopathic effects that was observed in HepG2 cells [25]. The degree of inhibition decided the antiviral activity on the basis of Cytopathic Effects (CPE) as well as plaque inhibition assay. *Andrographis paniculata* is a habitat to many varieties of molecules mainly Andrographolide ($C_{20}H_{30}O_5$) and its by-products. Clinical attributes include antiretroviral activity that can be used in the treatment of patients diagnosed with Coronavirus [26].

Activity of *aloe vera* (L.)

Aloe vera and its certain phytochemicals have been shown to have antiviral action [27]. At doses of 0.21 and 0.02 g/mL, *A. vera* chrysophanic acid inhibits microorganism (virus) replication in type 2 and 3 polioviruses, according to [28]. The virostatic effect on HSV (Hemorrhagic Rhabdovirus septicemia Virus) is present in Aloin ($C_{21}H_{22}O_9$). Acemannan has antiviral activity in cats affected by the immunological disease Virus, according to a study (HIV). Using the alcohol extract of *Aloe vera*, the autocannibalism by influenza in the MDCK cells was repressed [29].

[30] Qualitatively tested tannins, saponins, flavonoids, and terpenoids were found to be positive in *A. vera*, while phlobactanins and steroids were found to be negative. The carbohydrates found in *Aloe vera* includes pure mannan ($C_{24}H_{42}O_{21}$), acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan ($C_{14}H_{26}O_{11}$), arabinogalactan ($C_{20}H_{36}O_{14}$), cellulose substrate, xylan, and polyose [31]. Many vitamins and enzymes are also found in the plant [32]. Anthraquinones ($C_{14}H_8O_2$) are responsible for antiviral activity in most cases. However, several antiviral chemicals found in burn plants, such as quercetin, catechin hydrate, kaempferol, acemannan were previously unknown. The effect of *Aloe vera* on COVID-19 can be confirmed with the need of clinical trials.

Activity of *crocus sativus* (Iranian Saffron)

[33] Explored the anti-HSV-1 properties of Iranian saffron extract as well as key constituents, such as crocin and picrocrocin, in vitro, as well as cytotoxicity. The aqueous extract of saffron was found to be inert against HSV-1 and HIV-1 virions, with less activity than crocin ($C_{44}H_{64}O_{24}$) and picrocrocin ($C_{16}H_{26}O_7$), which had noticeable antiviral effect against HSV-1 and HIV-1 virions. Crocin and picrocrocin have the capability to be used as anti-HSV and anti-HIV drugs in herbaceous medicine [34].

Activity of *azadirachta indica*

It is included under the family of Meliaceae and is widely utilized in Ayurveda and Unani remedies all over the world, particularly in India, due to its diverse qualities in the treatment of diseases such as group B coxsackieviruses [35]. The effect against coxsackievirus B-4 virus is demonstrated by the Neem (NCL-11) [36]. At dose ranging from 50 to 100 g/mL, the bark of *Azadirachta indica* (Neem) extract (NBE) strongly inhibited HSV-1 entrance into cells [37]. Furthermore, when extract was used with viruses, the inhibiting action of NBE was noted but not with the target cells, which indicated that the bark of neem has an anti-HSV-1 attribute [38].

Activity of withania somnifera

Withania Somnifera (WS) named Ashwagandha, is a regenerator that has been used to improve physical and mental health. It is thought to revitalize the body in debilitated situations and extend life [39]. It has anti-inflammatory, antimicrobial, analgesic, anti-tumour, anti-diabetic, anti-stress and rejuvenating properties [40]. Withania somnifera's active ingredient, withanolides, is said to comprise certain chemical compounds like alkaloids, saponins and steroidal lactones [40].

Activity of *tinospora cordifolia*

The Menispermaceae family includes *Tinospora cordifolia*. It's a climbing herbaceous vine that's deciduous and spreads widely. It is regarded as a very helpful herbal plant, particularly in Indian medicine [41]. In Sanskrit, it's called Chakralakshanika, Gurcha in Hindi language and in Kannada, it's called Amritaballi [42,43]. *Tinospora cordifolia* silver nanoparticles were found to be beneficial in combating the Chikungunya virus in studies [44]. *Tinospora cordifolia* is also a key ingredient in Shilajatu Rasayana, an Ayurvedic preparation that has been shown to boost therapy efficacy in HIV patients [45,46] used molecular docking to investigate the effectiveness of pure products from *Tinospora cordifolia* against SARS-CoV-2 and discovered that it is used to prevent SARS-CoV-2 to attach to the host cell. The validation of *Tinospora cordifolia*'s pharmacological activities against SARS-CoV-2 is important. *Tinospora cordifolia*, a natural substance thanks to the long history of usage in Ayurveda, can be rapidly modified for therapeutic use to treat COVID-19 [47].

Some other plants that can be useful for COVID -19 is demonstrated below in table 1. Chemical structures of useful bioactive compounds of stated plants and the photoplates are given also (Figure 3,4).

Table 1: Table displaying therapeutic plants, their local names, useful plant parts and potential secondary compounds.

SN	Plants' Scientific Name	Local Name	Parts of the Plant that are/ can be used	Secondary compounds
1	*Ocimum sanctum* Linn.	Tulsi (hindi)	Leaves, stem, flower, root, seeds and even whole plant	Flavonoids, Terpenoids, Polyphenol
2	*Acacia arabica* (Lam.) Willd.	Babul, Kikar (hindi) Black babool, Indian gum arabic(English)	Bark, root, gum, leaves, pod and seeds	Flavonoid, Polyphenol
3	*Allium sativum* Linn.	Garlic (English), Srngaveram (Sanskrit)	Leaves, (scapes), flowers (bulbils). garlic	Organosulfur compounds like S-allylcysteine ($C_6H_{11}NO_2S$) and diallyl trisulfide ($C_6H_{10}S_3$)
4	*Curcuma longa* Linn.	Turmeric, Haldi (hindi) Haridra (Sanskrit:)	Rhizome	Polyphenolic curcumin
5	*Phyllanthus niruri* Linn.	Gale Of Wind (English) Bahupatra, Bhumyaamalaki (Sanskrit)	Whole plant or the leaves	Rutin (C27H30O16), gallic acid (C7H6O5) and corilagen
6	*Plumbago indica* Linn.	Chitrak (hindi), Indian leadwort or scarlet leadwort (English)	Root and its constituents	Plumbagin, flavonoids. proteins, saponins
7	*Pongamia pinnata* (L.) pierre.	Karanj (hindi), Indian beech and Pongame oiltree (English)	Roots, leaves, stems, seeds and even whole plant	polyphenols, oils
8	*Swertia chirata* Buch.-Ham. ex Wall.	Chiretta/ Chirayata (hindi)	Whole plant	Ophelic acid, two bitter glucosides, chiratin and amarogentin ($C_{29}H_{30}O_{13}$), gentiopicrin ($C_{16}H_{20}O_9$), two yellow crystalline phenols, a neutral, yellow crystalline compound, and a new xanthone ($C_{13}H_8O_2$), swerchirin
9	*Hypericum connatum* Linn.	St. John's wort (English and german)	Flower tops and the leaves	Flavonoids, polyphenols
10	*Eurycoma longifolia* Jack.	Tongkat ali (Malaysian) or Pasak bumi (Indonesian)	Root extract	Flavonoids, polyphenols and volatile oils

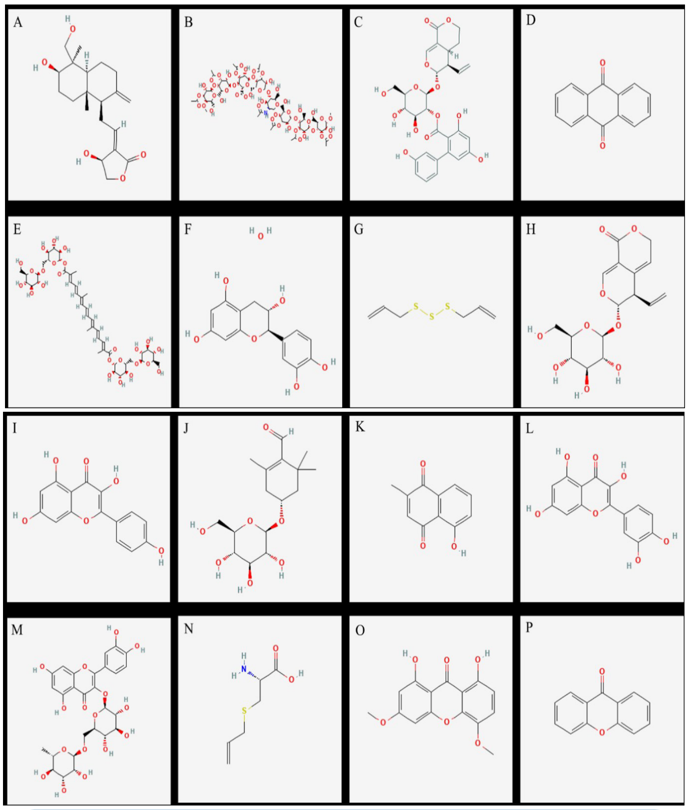

Figure 3: Some useful bioactive compounds that could be possibly effective for combating the COVID – 19 pandemic A. Andrographolide; B. Acemannan; C. amarogentin; D. Anthraquinone; E. Catechin hydrate; F. Crocin; G. Diallyl trisulfide; H. gentiopicrin; I. Kaempferol; J. Picrocrocin; K. Plumbagin; L. Plumbagin; M. Rutin; N. S-Allyl-L-cysteine; O. Swerchirin; P. Xanthone; Q. Aloin; R. Gallic acid; S. Galactan; T. Mannan; U. Aloin.

Figure 4: Photoplates of some important medicinal plants with possible potentiality to fight against COVID-19 A. Acacia Arabica; B. Allium sativum; C. *Aloe vera*; D. Andrographis paniculata; E. *Azadirachta indica*; F. *Crocus sativus*; G. *Curcuma longa*; H. *Eurycoma longifolia*; I. *Hypericum connatum*; J. *Ocimum sanctum*; K. *Phyllanthus niruri*; L. *Plumbago indica*; M. *Pongamia pinnata*; N. *Swertia chirata*; O. *Tinospora cordifolia*; P. *Withania somnifera.*

Plant-based therapeutics over chemically synthesized drugs against SARS-CoV 2

Vaccines such as Covishield, Covaxin, Pfizer nTech, Moderna, and others are currently in clinical trials to eradicate this virus [48]. Remdesivir, ritonavir, favipiravir, and ribavirin prove to be beneficial for treatment of SARS CoV-2 [49-51]. Although these existing coronavirus vaccines and medications can be regarded first-line treatments, they cannot be called the panacea to combat pandemic. The development of medicinal medications is still a pressing necessity, and experts from all over the world are paying close attention to it. Scientists and researchers are working to discover therapeutics. While some therapies, such as peptide vaccines, are still in clinical studies, plasma therapy has gotten a lot of interest after demonstrating promising outcomes [52]. Chemically produced pharmaceuticals, in practice, always have side effects, either direct or indirect, which reduces their efficacy and, as a result, reduces their reliance on synthetic drugs. As a result, there is still a pressing need for safe, effective, dependable, and affordable therapeutic medications with little or no adverse effects to tackle the deadly COVID-19 virus.

Techniques helpful in developing plantibodies

Virus-like particles (VLPs)

While emerging a plantibody, the utilization of VLPs is an important strategy. These macromolecular complexes look like viruses but don't have their own genomes. They replicate the virus structure using the host's machinery, but they are not contagious [53]. VLPs (Virus-Like Particles) are a type of particle that looks like a virus. VLPs imitate the original structure of viruses in this way, but they do not appear to be infectious. In the literature, there are numerous reports on the generation of VLPs, including cases of respiratory disease virus, human papillomavirus, and serum hepatitis virus [54]. SARS-CoV-1 VLPs were studied in a copy of mouse that enabled nasal/intraperitoneal immunization, with tissue layer routes being the most relevant for vaccination. Immunoglobulin G levels were higher in the teams that were vaccinated intraperitoneally. There can be the induction of liquid body substance IgA responses in the gastrointestinal system, saliva, and lungs due to nasal immunization. Within aforementioned research Intraperitoneal delivery of IgA to the viscus tract produced more IgA than intranasal administration [55,56].

Immune complexes

Another method for making highly immunogenic substances is to produce Immune Complexes (ICs) in plants [57]. As a result, probable bodily substance and cell-mediated immune responses are induced. They utilise the machinery of plant cells for supermolecule processing and their synthesis, which are used as Antibodies (Ab). In transgenic tobacco plants, for example, ICs supporting the tetanus toxin fragment C combined with an antibody were created. These ICs were strongly immunogenic, causing immunoprotected effects in mice when supplied below the skin without the use of adjuvants [58]. This method has also been used to study Ag85B and Acr mycobacterial matters, as well as the GP1 antigen from the Ebola virus [59].

Discussion

The appearance of coronavirus has triggered a global emergency that necessitates the use of current medications, notably vaccinations, to combat the threat. In this situation, a plant-based vaccination could be a viable option for dealing with the crisis. This method paves the way to establish vaccinations against COVID-19. Because they have high immunogenicity, conservation of substance determinants, and lack of replicative capability; VLPs are a promising technique for the advamcement of cost-effective and safe vaccines. As a result, VLPs that promote the most SARS-CoV-2 structural proteins are promising medium for coronavirus medication development. An event of vaccines that supported transplastomic lines that were modified at the nuclear level and were expected to end in oral vaccines, notably uplifting agents to induce membrane immunity, might be considered of as long-term goal. However, they require attention due to low value and capable for use as enhancing agents, which could result in captivating immunological profiles characterized by body substance response within membrane compartments and long-term protection.

Corresponding to these, the assembly of plant antibodies is one of the alternative, which can represent an occasional value and safer endogenous treatment for infected patients. Therefore, plant-based vaccines can be used as a possible option to combat this pandemic.

As the outbreak spreads, using plant-based vaccines could be the best way to develop low-cost and a potent vaccine to combat the pandemic. COVID-19 has caused a major disaster in the entire world. There isn't any cure for this pandemic. It is also critical to seek out other options, particularly for African countries. The main focus of our study was to look into the antiviral properties of different plants. Thus, findings demonstrate that certain plants not only have antiviral properties but can help in the treatment of COVID-19. These favourable effects are required to be confirmed through molecular testing and clinical trials (Figure 5).

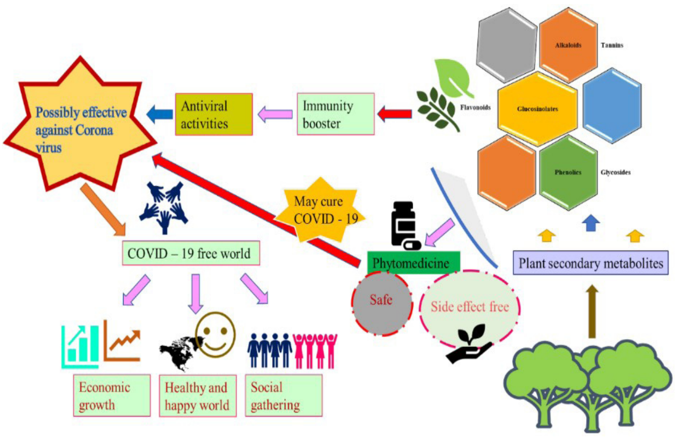

Figure 5: A conceptual figure showing the possible effectiveness of plant based secondary metabolites to fight against COVID -19 and to make world happy and healthy.

Conclusion and future direction

After reviewing a lot of research and review papers, it is clear that plant-based therapeutics can be a safer option to cure patients diagnosed with COVID-19. The key findings from this review paper are that there are many plants which possesses antiviral properties and they have been used for treating other viruses in the past. These plants and compounds isolated from them also possess less side effects compared to chemically synthesized drugs and vaccines. Plantibodies (basically the plant-based antibodies) can also be effective to when the World is dealing with such a deadly virus, it is important to find a safer and cost-effective vaccine which can be administered to any age group of people. In plants, antibodies production is effective and acquires low cost. These types of vaccines are easy to store and are thus convenient. We the authors of this article, strongly believe that plant-based vaccines can be helpful to combat this pandemic.

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