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Potentials of Medicinal Plants with Antiviral Properties: The Need for a Paradigm Shift in Developing Novel Antivirals Against COVID-19

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Review Article

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ABSTRACT

The menace of COVID-19 continues to ravage the world despite deployment of vaccines, and the development of oral antiviral pills whose effectiveness are still being evaluated. As the problems persist, Scientists are continuously searching for new resources and re-evaluating old ones that be used to effectively contain the pandemic. A search through literature has shown a huge amount of scientific resources in medicinal plant research which could be leverage. Many medicinal plants have been demonstrated to possess various antiviral activities against influenza virus, SARS-CoV, herpes simplex virus, vesicular stomatitis virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, simian immunodeficiency virus, echovirus, adenovirus, Newcastle disease virus, duck plague virus, measles virus, polio viruses, yellow fever viruses, Sindbis virus, human cytomegalovirus, Rift valley fever virus, feline herpesvirus, lumpy skin disease virus, and canine

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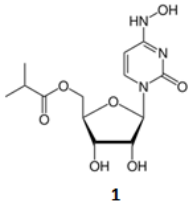
distemper virus. Medicinal plants are known to be a reservoir of bioactive compounds with useful pharmacological actives. This revision has identified one hundred and twelve (112) plants found with various antiviral activities. These plants cut across different families. An intriguing observation is the reported presence of antiviral in different classes of phytochemicals like alkaloids, flavonoids, tannins, anthraquinones, glucosides, polyphenols, saponins, essential oils, peptides and polysaccharides. There is the need for concerted paradigm shift to natural products of plant origin towards developing novel antiviral agents against COVID-19 especially with the reported safety challenge of adverse events and serious adverse events associated with already developed vaccines and pills.

Keywords: Medicinal plants; phytochemicals; antiviral agents; COVID-19; viral infections.

1. INTRODUCTION

Since early 2020 when the World Health Organisation declared COVID-19 a pandemic, the world has struggled with finding effective solution for mitigating it and its associated health problems. Despite the many solutions so far developed, the average case fatality rate (CFR) is still about 2.006%, with over 256,637,065 cases and about 5,148,221 deaths as at 18 November 2021 [1]. About 15 vaccines have been developed with about 7,370,902,499 doses administered worldwide, with the popular ones being Johnson & Johnson's Janssen Ad26.COV2.S, Pfizer's BioNTech, Oxford-AstraZeneca's AZD1222, Moderna's mRNA1273, Spunik V, Sinovac's CoronaVac, Bharat Biotech's BBV152 COVAXIN, and Sinopharm's BIBP [2]. The use of these vaccines are not without adverse events.

The desire for better solution, vaccines hesitancy, desire for better patient's convenience from a less intrusive treatment led to the search for chemical molecules that could be administered as oral pills. Recently, Molnupiravir (MK-4482/EIDD-2801) (**1**, Fig.1) and Paxlovid™ (PF-07321332; ritonavir), two potent oral antiviral pills were developed by Merck and Pfizer respectively. These pills are currently under clinical evaluation with some adverse events and serious adverse events reported in some patients [3,4]. Merck's Molnupiravir is a prodrug of the active analogue, D-N^4-hydroxycytidine which is active in its triphosphate for, (NHC-TP). It acts by promoting widespread mutations in the replication of viral RNA by RNA-directed RNA polymerase [5]. Pfizer's PF-07321332 is a protease inhibitor which blocks the activity of the SARS-CoV-2 3C-like protease enzyme used for replication by coronavirus. It inhibits viral replication at proteolysis stage, which occurs before viral RNA replication [4]. However, vaccines and oral pills so far developed have one or more adverse events or serious adverse events. Some of the possible side effects, adverse events and serious adverse events from these vaccines and synthetic pills are cause of safety concern, which could aggravate patients/consumers hesitancy of their use despite the hugh health benefit. Hence the necessity to develop remedies from safe natural biomolecules is timeless.



1

Fig. 1. Chemical structure of Molnupiravir (1)

The use of natural substances in medicine dates back to pre-historic time [6]. In modern era, natural substances from plant origin have been mostly exploited in alternative medicine for the prevention and treatment of different ailments [7,8]. Modern science has also realized the huge reservoir of bioactive substances in plants and have directed drug development researches towards medicinal plants. It is estimated that about 25% of orthodox medicines contains active ingredients from plant sources [6]. Thus, plants have been sources of antibacterial, antiprotozoal, antifungal, and antiviral agents. These therapeutic agents are obtained from crude plant extracts or isolated and purified.

Many studies have reported the inhibitory effect of some medicinal plants on viral replication since 1952 when the screening of 288 medicinal plants against influenza A virus was first reported [6]. Antiviral activities from plants sources were first reported from their crude aqueous and alcoholic extracts which were not purified or fractionated. Active extracts against herpes

simplex virus type 2 (HSV-2), human immunodeficiency virus (HIV), poxvirus, severe acute respiratory syndrome (SARS) virus, and hepatitis B virus (HBV) have been reported [9-14]. Studies have also demonstrated antiviral activities of plant extracts against virus strains resistant to conventional antiviral medications [15]. This has challenged contemporary approach to drug discovery, and evokes the search for novel natural antiviral agents from medicinal plant sources.

Antiviral compounds are compounds useful in the treatment of viral infectious diseases which include HIV infections, hepatitis B virus (HBV) infections, hepatitis C virus (HCV) infections, herpes virus infections, influenza virus infections, Corona virus, human cytomegalovirus (HCMV) infections, varicella-zoster virus infections, echoviruses, etc [16]. Most of these viruses do not have specific drug or vaccine for their treatment hence the use of phytomedicines and herbal recipes could offer viable treatment alternative [16].

The major symptoms of viral diseases include short span fever, rash and mild to acute upper respiratory syndromes. Clinical presentation may include encephalitis, aseptic meningitis, ataxia, Guillain-Barré syndrome, paralysis, exanthema, respiratory disease, diarrhoea, pericarditis, myocarditis and hepatic disturbance. Viral infections occur mainly via oral and nasal routes transmission. Other routes are sexual or dermal [17].

2. CLASSES OF ANTIVIRAL AGENTS AND THEIR MECHANISM OF ACTION

While synthetic antivirals have been the bedrock of modern treatment for viral diseases, the challenge of their safety profile is of serious concern. Antiviral compounds are grouped into classes such as: protease inhibitors, integrase inhibitors, nucleoside analogues, fusion inhibitors, neuraminidase inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors etc [18]. A nucleoside reverse transcriptase inhibitor (NRTI) e.g Abacavir (**2**) and Didanosine (**3**), acts by inhibiting viral DNA elongation, replication and synthesis [19]. Emtricitabine acts by inhibiting the transcription of viral RNA into DNA, and therefore preventing the virus from incorporating its DNA into host DNA [20,21]. Some other NRTIs include Lamivudine, Stavudine, Telbivudine, Zalcitabine, Zidovudine and Tenofovir Disoproxil Fumarate. There are also non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as Efavirenz, Nevirapin, Etravirine, Rilpivirine and Delavirdine. Protease inhibitors act by binding to the protease active site inhibiting the viral protease enzyme, which prevents cleavage of the gag-pol polyprotein, resulting in noninfectious, immature viral particles. Examples include Indinavir (4), and Saquinavir (5). Others include Ritonavir, Nelfinavir, Lopinavir, Atazanavir, Darunavir, Tipranavir, Fosamprenavir, Amprenavir and Telaprevir [22]. The integrase strand-transfer inhibitors inhibit viral (HIV) integrase by binding to the active site and blocking the strand transfer step of retroviral DNA integration in the host cell [23]. Members of the class include Dolutegravir (6), Elvitegravir (7) and Raltegravir (8). The Nueraminidase inhibitors inhibit viral neuraminidase enzyme which are glycoproteins found on the virion surface and responsible for viral entry into uninfected cells from infected ones, e.g Oseltamivir (9) [24]. The nucleoside analogue such as Aciclovir (10), which is an acyclic guanosine analogue, competitively inhibits viral DNA polymerase by inactivating it. It incorporates into and terminates the growing viral DNA chain [25]. Other acyclic guanosine analogues include Valaciclovir, Ganciclovir and Famciclovir. Ganciclovir (11) is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human cytomegalovirus in vitro and in vivo [26]. Cidofovir (12) and Adefovir dipivoxil (13) are acyclic nucleoside phosphonate analogues. Their diphosphates act as competitive inhibitors and alternate substrates for viral DNA polymerase [27]. It is incorporated into the growing cytomegalovirus (CMV) DNA strand and blocks further viral DNA synthesis leading to non-productive infection [28]. The structures of compounds (2) to (13) are presented in Fig. 2.

Modern antiviral treatment especially in HIV cases uses a combination of different classes of antivirals. The highly active antiretroviral therapy (HAART) combines protease inhibitors and nucleoside or non-nucleoside reverse transcriptase inhibitors. This has not proven to be a cure as patients have to be on continuous use [6]. Although the current conventional strategy to treating virus infections is the use of synthetic chemicals, their side-effects and failure of existing regimes against SARS-CoV-2 infection in humans has necessitated renewed efforts and paradigm shift towards natural biomolecules from medicinal plants [23,29].

In recent studies, many naturally occurring antiviral compounds have been identified and isolated from plants and other natural sources [30]. The associated antiviral molecular mechanisms of action of extracts of medicinal plants and some of these natural agents may differ among viral species. It is interesting to note that most of these active extracts exhibit broad spectrum activities. These activities may arise from the action of a single component or multiple components acting in synergies [22,31,32]. Antiviral agents from plants are suspected to utilize common pathways involving their immune modulatory activities on the human immune system. Studies on the immunomodulatory actions of some antiviral agents from plants sources showed lymphocyte proliferation and secretion of interferon-gamma (IFN-γ) [33], while others revealed their effects on Interleukin 6 (IL-6) production in the macrophage activation assay [34]. Lymphocyte proliferation activity and induced interferon-gamma (IFN-γ) secretion are indicators of cell-mediated immune response modulation [33]. In addition, a product, Sambucol, made from a standardized extract of *Sambucus nigra* L., which is effective against various strains of influenza, had been shown to boost immune responses by secreting inflammatory cytokines (IL-1 beta, TNF-alpha, IL-6, and IL-8) [35].

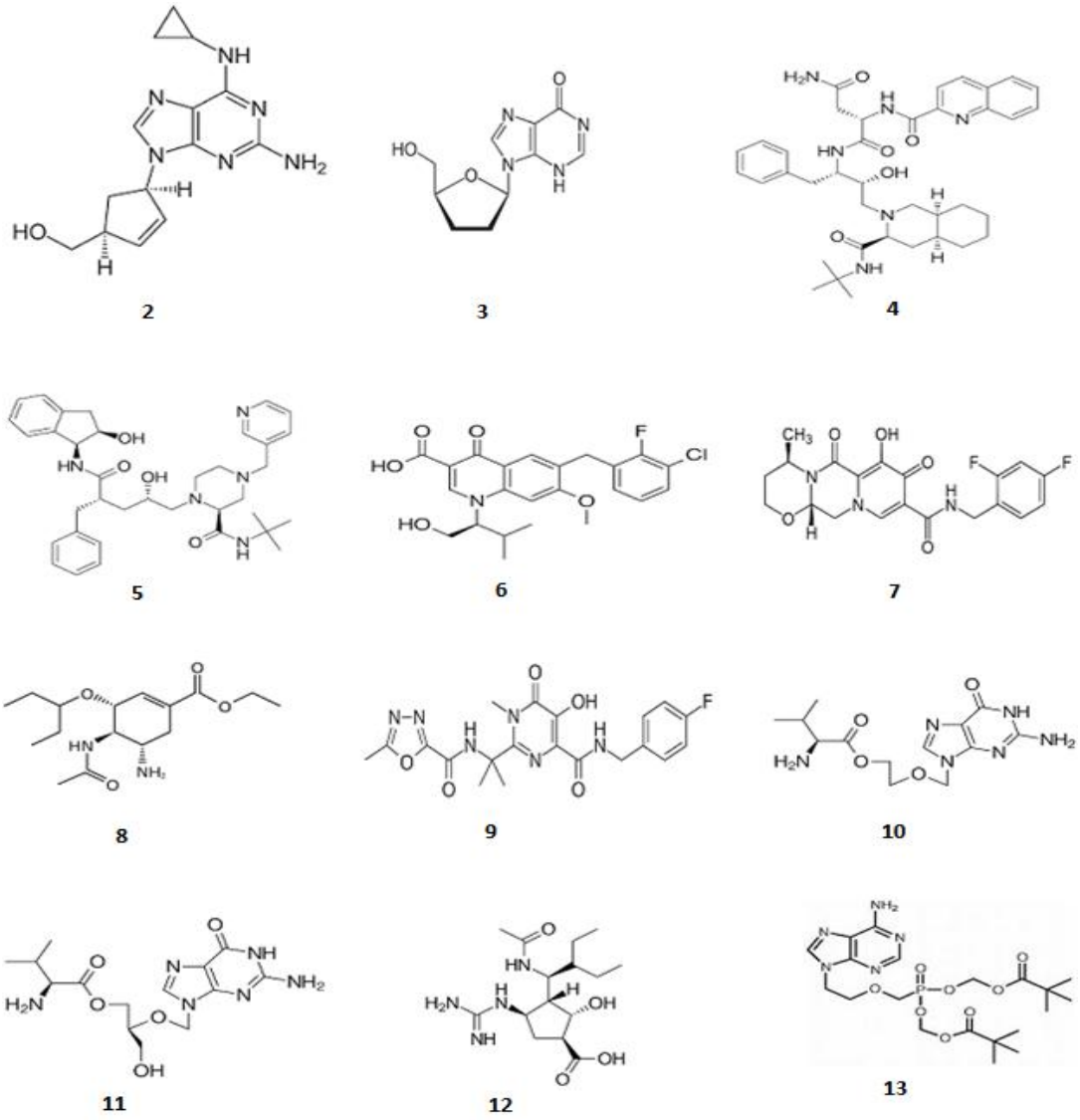


Fig. 2a. Chemical structures of antiviral agents - Abacavir (2), Didanosine (3), Indinavir (4), Saquinavir (5), Dolutegravir (6), Elvitegravir (7), Raltegravir (8), Oseltamivir (9), Aciclovir (10), Ganciclovir (11), Cidofovir (12) and Adefovir dipivoxil (13)

3. PLANTS WITH ANTIVIRAL PROPERTIES

Many plants species with suspected antiviral properties have been studied with interesting antiviral activities of their extracts. The activities of some of these plants have been traced to some wide array of classes of bioactive substances present in these plants. These identified bioactive substances include secondary metabolites like alkaloids, flavonoids, polyphenolics (including lignans), saponins, terpenoids and essential oils. Others include small molecules like coumarins, furyl compounds, polylines (polyynes), sulphides, thiophenes, etc, and larger molecules such as proteins and peptides [36]. Most of these bioactive compounds have been studied in their crude extract form and acts in combination with other to give a synergistic pharmacologic effect. Hence the exact antiviral mechanism of actions of these active crudes is usually multisystemic and multifaceted and may be by either inhibiting viral DNA or RNA formation or replication [36]. In spite of the advances made on antiviral activities of crude extracts, a lot more investigation is required not just in increase the next of plants with potential antiviral activities but also in understanding the mechanisms of action. Table 1 contain a comprehensive list of plants with reported antiviral activities that may guide future research in the development of antiviral agents including COVID-19.

Table 1. Medicinal Plants and their antiviral activity

S/N	Name of Plant	Antiviral activity	References
1.	*Ageratum conyzoides* L	Echoviruses E7 & E19	[16]
2.	*Acacia nilotica* L. Willd ex Delile,	HCV	[37]
3.	*Achillea fragrantissima* (Forssk.) Sch.Bip.	Poliomyelitis-1 virus (POLIO); human and animal ORF virus; small pox viruses	[38]
4.	*Aegle marmelos* (L.)Corr.	Human coxsackieviruses B1-B6, ranikhet disease virus	[38,39]
5.	*Allium sativum* L.	Influenza B, human rhinovirus type 2, human cytomegalovirus (HCMV), Parainfluenza virus type 3, herpes simplex type 1 and 2, vaccinia virus, and vesicular stomatitis virus; Amerliorate conditions associated with HIV infection such as fungal infections (thrush) and parasitic infections (cryptosporidium).	[6,40]
6.	*Aloe barbadensis* miller	HSV-2, HSV-1, Influenza virus, human cytomegalovirus, polio virus	[38]
7.	*Andrographis paniculata* (Burm.f.) Nees.	Simian Retro Virus (SRV), Epstein-Barr virus (EBV), Influenza and HIV	[6]
8.	*Ardisia chinensis* Benth	HBV, DHBV, Coxsackie B3 (Cox B3) virus	[6,41]
9.	*Artocarpus integrifolia* L.f.	Samian (SA-11) and human (HCR3) rotaviruses, HIV.	[38,42]
10.	*Astragalus membranaceus* Bunge	HIV, Avian Influenza H9 virus, Hepatitis B virus, HSV1, NDV, EBV	[6,29]
11.	*Atractylodes macrocephala* Koidz.	H3N2,	[6,43]
12.	*Azadirachta indica* Juss.	Dengue virus type-2 (DEN-2), HSV1, Polio virus, Influenza, HIV, Coxackie B group virus, and Dengue virus at early step of viral genome replication, Duck viral enteritis (DEV), also called duck plague virus (DPV),	[44-49]
13.	*Balanites aegyptiaca* (L.) Del.	VSV T2, HCV, HSV	[38,50]
14.	*Boehmeria nivea* (Linn.) Gaudich	HBV	[9,51,52]
15.	*Boerhavia diffusa* L.	Viral hepatitis (HPV); potato virus X; mung	[53]

S/N	Name of Plant	Antiviral activity	References
		bean (*Vigna radiate*) yellow mosaic virus	
16.	*Boswellia carterii* Birdwood	HCV, HSV	[37,54]
17.	*Bridelia micrantha* (Hochst)	HIV-1	[55,56]
18.	*Bryophyllum pinnatum* (Lam.) Oken	Echoviruses E7 & E19, HSV, Measles (MV),	[16,57]
19.	*Buxus sempervirens* L.	HSV, SINV	[6,58]
20.	*Camellia sinensis* L.	Adenoviruse, HBV, HCV, HSV, Influenza Virus, HIV-1, Bovine coronavirus (BCV), Epstein-Barr virus (EBV), Enterovirus 71 (EV71), Feline Calicivirus (FVS), Chikungunya Virus (CHIKV),	[38,59]
21.	*Cannabis sativa* L.	Newcastle Disease Virus (NDV), HCV, SARS-COV-2	[6, 60-62]
22.	*Capparis spinosa* L.	HSV-2, HIV-1	[38,63,64]
23.	*Carissa edulis* (Forssk.) Vahl.	HSV 1 & 2, HCMV, RVFV, FHV, PV-2, LSDV, CDV	[15,65-67]
24.	*Cassine xylocarpa* Vent.	HIV	[38]
25.	*Chelidonium majus* L.	HSV-1, HIV-1	[6,68,69]
26.	*Cistus incanus* L.	Avian and human influenza strains of different subtypes influenza A (H1N1 H7N7, H5N1); HIV-1 and HIV-2, Ebola virus, Marburg virus	[38,70-72]
27.	*Crinum jagus* (J. Thomps.) Dandy	echoviruses E7 & E19	[16,73,74]
28.	*Curcuma longa* L.	HSV-1, HIV	[38,75]
29.	*Cyperus rotundus* L.	HSV-1 HBV	[38,76]
30.	*Daphne gnidium* L.	HIV	[38,77,78]
31.	*Diospyros kaki* L.	Influenza virus H3N2, H5N3, HSV-1, VSV, Sendai virus, PV, coxsachievirus, adenovirus, rotavirus, feline calicivirus, mouse norovirus, NDV.	[38, 42,79, 80]
32.	Dittrichia viscosa	VSV, HSV-1, poliovirus type 1 U	[38]
33.	*Eclipta alba* L.	Ranikhet disease virus (Alcohol extract of the plant); Viral hepatitis; HIV-1 integrase [HIV-1 IN] (water extract of syn. E. prostrate)	[53, 81-82]
34.	*Embelia schimperi*	HCV	[37]
35.	*Euphorbia hirta*	HIV-1, HIV-2, SIV mac 251	[38]
36.	*Euphorbia spinidens*	HSV-1	[38]
37.	*Ficus benjamina*	HSV-1, HSV-2	[38]
38.	*Ficus carica*	HSV-1 HSV-1, ECV-11, ADV, influenza virus	[38]
39.	*Ganoderma lucidum*	HBV	[83]
40.	*Geranium sanguineum* L.	Influenza virus	[84,85]
41.	*Globularia arabica*	Poliomyelitis-1 virus (POLIO)	[38]
42.	*Glycine max* (L.) Merr	Human adenovirus type 1, coxsackievirus B1	[86]
43.	*Glycyrrhiza glabra*	NDV	[38]
44.	*Glycyrrhiza uralensis*	NDV	[38]
45.	*Glycyrrhiza uralensis* Fisch	SARS-CoV	[87]
46.	*Guazuma ulmifolia* Lam.	Polio virus	[88]
47.	*Haemanthus albiflos*		[89]
48.	*Heracleum maximum* Bartr. (Umbelliferae)	non-specific	[34]
49.	*Humulus lupulus* L. Genbank	Broad spectrum; non-specific	[31]
50.	*Hyssopus officinalis* L.	HSV-1, HIV	[6,38]

S/N	Name of Plant	Antiviral activity	References
51.	*Ipomoea asarifolia* (Desr.) Roem. & Schult.	Echovirus E7	[16]
52.	*Leucojum vernum*	HIV-1	[38]
53.	*Lilium candidum*	HSV-1, HSV-2	[38]
54.	*Lippia multiflora* Moldenke	Echovirus E7	[16]
55.	*Lycoris radiata* L.	SARS-CoV	[87]
56.	*Macaranga barteri* Mull. Arg.	Echoviruses E7 & E19	[16]
57.	*Macaranga kilimandscharica*	Measles; HSV-1; Coxsackie viruses	[90,91]
58.	*Magnolia officinalis*	Dengue virus Type 2	[38]
59.	*Maytenus cuzcoina*	HIV	[38]
60.	*Melissa officinalis*	HSV-1, HSV-2 HIV	[38]
61.	*Mentha pulegium*	HSV-1	[38]
62.	*Mondia whitei* (Hook.f.) Skeels	Echoviruses E7 & E19	[16]
63.	*Moringa peregrina*	HSV-1	[38]
64.	*Myristica fragrans*	Human rotavirus	[38]
65.	*Oenanthe javanica* Blume DC	HBV, DHBV	[6]
66.	*Olea europaea* L.	Influenza virus subtype H9N2, Viral haemorrhagic septicaemia virus (VHSV); HIV	[38,92,93]
67.	*Panax ginseng*	Human rotavirus	[38]
68.	*Panax notoginseng*	Influenza A virus	[38]
69.	*Pandanus amaryllifolius* Roxb	HSV-1 and influenza virus strain H1N1	[32]
70.	*Phyllanthus acidus*	HBV	[38]
71.	*Phyllanthus amarus*	Hepatitis B surface antigen (HBsAg); HBV and HCV; HSV 1 & 2	[53]
72.	*Phyllanthus amarus* Schum. & Thonn.	HIV	[94]
73.	*Phyllanthus emblica*	Influenza A virus strain H3N2, HBV	[38]
74.	*Phyllanthus nanus* L.	HBV, DHBV	[6]
75.	*Phyllanthus niruri* L.	HBV	[6]
76.	*Phyllanthus urinaria*	HSV 1 & 2	[53,95]
77.	*Piper cubeba* L.	HCV	[37]
78.	*Pithecellobium clypearia*	HBV, DHBV	[6]
79.	*Podophyllum peltatum* L	HSV 1	[82,96]
80.	*Polygonum cuspidatum* Sieb.& Zucc.	HBV	[97]
81.	*Prunella vulgaris*	HIV-1, Ebola virus	[38]
82.	*Quercus brantii* L Acorn.	HSV-1	[38]
83.	*Quercus infectoria,*	HCV	[37]
84.	*Quercus persica*	HSV-1	[38]
85.	*Salacia reticulata*	H1N1 influenza	[38]
86.	*Sambucus nigra* L.	Influenza virus	[35,98]
87.	Sanguisorba minor	VSV, HSV-1 HIV	[38]
88.	*Saxifraga melanocentra*	HCV	[56]
89.	*Securigera securidaca*	HSV-1, HSV-2	[38]
90.	*Solanum nigrum*	HCV	[38]
91.	*Sophorae flavescentis*	HBV	[83]
92.	*Spondias lutea*	Human rotavirus	[38]
93.	*Spondias mombin* L.	Echovirus E7	[16]
94.	*Stevia rebaudiana* L.	Human Rhinoviruses (HRV)	[99]
95.	*Stryphnodendron adstringens*	Polio virus	[92]
96.	*Syzygium aromaticum* L.	HCV	[37]
97.	*Tamarix nilotica*	HSV-1	[38]
98.	*Taraxacum officinale*	HCV Influenza virus type A, H1N1.	[38]

S/N	Name of Plant	Antiviral activity	References
99.	*Terminalia ivorensis* A. Chev.	Echovirus E7	[16]
100.	*Tetracera alnifolia* Willd.	Echovirus E7	[16]
101.	*Thymus carmanicus*	HIV-1	[38]
102.	*Thymus daenensis*	HIV-1	[38]
103.	*Thymus kotschyanus*	HIV-1	[38]
104.	*Thymus vulgaris*	HIV-1	[38]
105.	*Trachyspermum ammi* L.	HCV	[37]
106.	*Trichilia glabra* L.	VSV	[100]
107.	*Trifollium species* Secomet-V	HPV, Marburg, influenza, HIV, HBV and HCV	[12]
108.	*Tuberaria lignosa* An	HIV	[38]
109.	*Viola diffusa*	HBV	[38]
110.	*Vitis labrusca*	(SA-11) and human (HCR3) rotaviruses	[38]
111.	*Vitis macrocarpon*	(SA-11) and human (HCR3) rotaviruses	[38]
112.	*Zataria multiflora*	HSV-1	[38]

Key: Herpes Simplex Virus (HSV), Vesicular Stomatitis Virus (VSV), Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV), Simian Immunodeficiency Virus (SIV), Echovirus (ECV), Adenovirus (ADV), Newcastle Disease Virus (NDV), Hepatitis C Virus (HCV), Duck Viral Enteritis (DEV), also called Duck Plague Virus (DPV), Measles Virus (MV), Polio Virus PV, Yellow Fever (YFV) Virus, Sindbis Virus (SINV), Human Cytomegalovirus (HCMV), Rift Valley Fever Virus (RVFV), Feline Herpesvirus (FHV), Poliovirus (PV-2), Lumpy Skin Disease Virus (LSDV), Canine Distemper Virus (CDV), Human Papillomavirus (HPV)

4. DISCUSSION

Medicinal plants have been used since ancient times to manage different diseases, and a number of conventional drugs were developed from these plant resources. Morphine was first isolated in pure form in 1805 from the opium plant [101]. With advancement in science and technology, and the development of more efficient separation techniques, more biologically active compounds were isolated and purified for medical use. Subsequent development of synthetic and purification techniques led to significant reduction, or almost total annihilation, of the use of natural products in medicines in favour of synthetic drugs despite the attendant harmful side effects [102,103].

Natural products remain relevant in contemporary medicine especially in alternative medicine where they are used in crude or partially purified forms. Natural products are also important for the development of new drugs in modern medicine. Some conventional anticancer, antihypertensive, and antimigraine medication, were developed from natural products. For instance, Vinca alkaloids from *Catharanthus roseus*, and the terpene paclitaxel from *Taxus baccata*, are useful anticancer drugs originally derived from plants [104]. Many synthetic medicines have their basic structures from natural products [103]. The usefulness of natural products in medicine is due to the multicomponent nature of their crude, which contain several bioactive compounds. When used in the crude form, these compounds could act synergistically to exact the desired pharmacological effect. In addition, most of the substances are easily biodegradable with minimal or no side effect [103,105]. The bioactivity of these plants lies in their secondary metabolites such as alkaloids, tannins, saponins, terpenes, cardiac glycosides, flavonoids, anthraquinones etc. These metabolites exhibit wide array of pharmacological activities including antioxidant, anti-inflammatory, antimicrobial, anticancer, and immunomodulatory effect, amongst others. An intriguing observation is the presence of anti-influenza activity in a wide variety of phytochemicals, such as alkaloids, flavonoids, glucosides, polyphenols, saponins, anthraquinones and polysaccharides [6,106].

The medicinal plants in Table 1 have been demonstrated to exhibit different antiviral activities along with some other pharmacological activities. While the antiviral actions of some have been partially explained, others are still very obscure. The antiviral activities of most of the plants have been ascribed to the actions of some metabolites like polyphenolics, which also play major roles in antioxidant and immunomodulatory effect of these plants [107,108]. However, some may rely on more than one mechanism since the crude extracts contains several chemical components that may be acting in synergies [72]. The antiviral mechanism of these agents may be explained on basis of their antioxidant activities, scavenging capacities, inhibiting DNA, RNA synthesis,

inhibition of the viral entry, or inhibiting the viral reproduction etc [109]. For instance, some phytochemicals have been investigated as potent inhibitors of COVID-19 main protease. Some of these phytochemicals include kaempferol (14), quercetin (15), luteolin-7-glucoside (16), demethoxycurcumin (17), naringenin (18), apigenin-7-glucoside (19), oleuropein (20), curcumin (21), catechin (22), epigallocatechin-gallate (23), zingerol (24), gingerol (25), allicin (26) and lycorine (27) (Fig. 2) [110]. Catechin and, friedeline (28) and its analogues, act as neurominidase inhibitor preventing the release of the virus from the host cells [110].

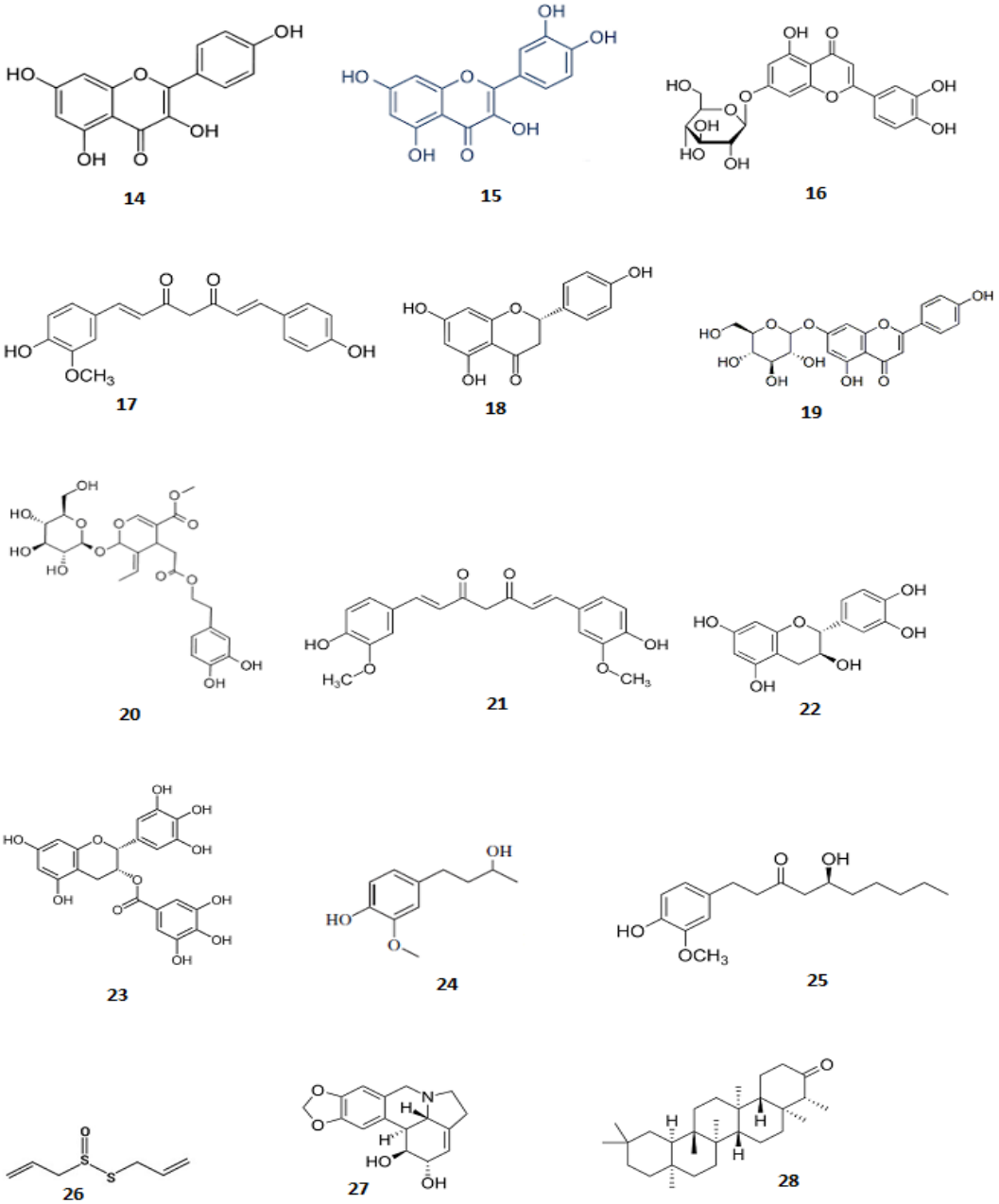


Fig. 2b. Chemical structures of natural compounds from plant sources with antiviral properties- kaempferol (14), quercetin (15), luteolin-7-glucoside (16), demethoxycurcumin (17), naringenin (18), apigenin-7-glucoside (19), oleuropein (20), curcumin (21), catechin (22), epigallocatechin-gallate (23), zingerol (24), gingerol (25), allicin (26) and lycorine (27) and, friedeline (28)

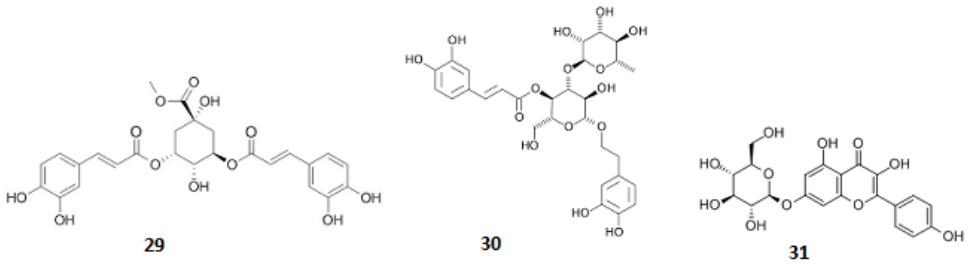


Fig. 3. Structures of compounds with antiviral activities - 3,5-dicaffeoylquinic acid (29), acteoside or verbascoside (30) and kampferol-7-O-glucoside (31)

From the beginning humanity has always relied on nature in solving its health challenges. Despite great advances in science for the synthesis of new drugs for antiviral agents and agents for other infectious diseases, the challenge of finding solution to the COVID-19 pandemic offers yet another opportunity to return to natural products for novel solution. The solution possibly lies in the medicinal plant resources in Table 1. A wide range of phenolics and flavonoids, for example, compounds **14** to **25**, have been shown to possess antiviral activities against a variety of RNA viruses such as poliovirus, sindbis virus, respiratory syncytial virus (RSV), and DNA virus such as herpes simplex virus (HSV) [110, 111]. The proposed antiviral mechanisms of action of flavonoids include inhibition of viral polymerase and binding of viral nucleic acid or viral capsid proteins [112]. The anti-infective activities (antiviral and antimicrobial) of 3,5-dicaffeoylquinic acid (**29**), acteoside or verbascoside (**30**) and kampferol-7-O-glucoside (**31**) had also been reported in literature (Fig. 3) [16,110].

5. CONCLUSION

Medicinal plants offer a reservoir of bioactive substances for the treatment of different diseases. These substances are mostly easily metabolized and safer than their synthetic analogues. This makes natural medicines generally preferable. Modern medicine evolved from medicinal plants which continue to show its relevance today. The failure of existing drugs and newly synthesized molecules to be effective against SARS-CoV-2 shows the limit of synthetic approaches. Synthetic approach to drug discovery is not always enough. It is time to shift focus to natural resources from plants especially those that have shown potentials. The time to shift paradigm to medicinal plant for novel drug against COVID-19 is now.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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