Review Article

POTENTIALS OF MEDICINAL PLANTS WITH ANTIVIRAL PROPERTIES: THE NEED FOR A PARADIGM SHIFT IN DEVELOPING NOVEL ANTIVIRALS AGAINST COVID-19

Abstract

The menace of COVID-19 continues to ravage the world despite the development of vaccines whose effectiveness is still being evaluated. As the problems persist, Scientists are continuously searching for new and old resources 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 distemper virus. Medicinal plants are known to be a reservoir of bioactive compounds with useful pharmacological actives. This revision has identified one hundred and thirty-one (131) plants found with various antiviral activities. These plants cut across different families and genus. 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.

Keywords: Medicinal Plants; Antiviral agents; COVID-19; HSV; HCV; HIV; Influenza virus

Introduction

The use of natural substances in medicine dates back to per-historic time [1]. In modern era, natural substances from plant origin have been mostly exploited in alternative medicine for the prevention and treatment of different ailments [2,3]. 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 [1]. 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 [1]. Antiviral activities from plants sources were first reported from their crude aqueous and alcoholic extracts which were not purified of 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 [4-9]. Studies have also demonstrated antiviral activities of plant extracts against virus strains resistant to conventional antiviral medications [10]. 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 includes: HIV infections, hepatitis B virus (HBV) infections, hepatitis C virus (HCV) infections, herpes virus infections, influenza virus infections, Corona virus, human cytomegalovirus (HCV) infections, varicella-zoster virus infections, echoviruses, etc. 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 [11]. Better to focus on the traditional medicinal plants

Comment [u1]: citations ….?

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 infection occurs via oral and nasal routes transmission [12].

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 [13]. A nucleoside reverse transcriptase inhibitor (NRTI) e.g Abacavir (**1**) and Didanosine (**2**), acts by inhibiting viral DNA elongation, replication and synthesis [14]. Emtricitabine acts by inhibiting the transcription of viral RNA into DNA, and therefore preventing the virus from incorporating its DNA into host DNA [15,16]. 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 (**3**), and Saquinavir (**4**). Others include Ritonavir, Nelfinavir, Lopinavir, Atazanavir, Darunavir, Tipranavir, Fosamprenavir, Amprenavir and Telaprevir [17]. 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 [18]. Members of the class include Dolutegravir (**5**), Elvitegravir (**6**) and Raltegravir (**7**). 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 (**8**) [19]. The nucleoside analogue such as Aciclovir (**9**), which is an acyclic guanosine analogue, competitively inhibits viral DNA polymerase by inactivating it. It incorporates into and terminates the growing viral DNA chain [20]. Other acyclic guanosine analogues include Valaciclovir, Ganciclovir and Famciclovir. Ganciclovir (**10**) is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of human cytomegalovirus in vitro and in vivo [21]. Cidofovir (**11**) and Adefovir dipivoxil (**12**) are acyclic nucleoside phosphonate analogues. Their diphosphates act as competitive inhibitors and alternate substrates for viral DNA polymerase [22]. It is incorporated into the growing cytomegalovirus (CMV) DNA strand and blocks further viral DNA synthesis leading to non-productive infection [23].

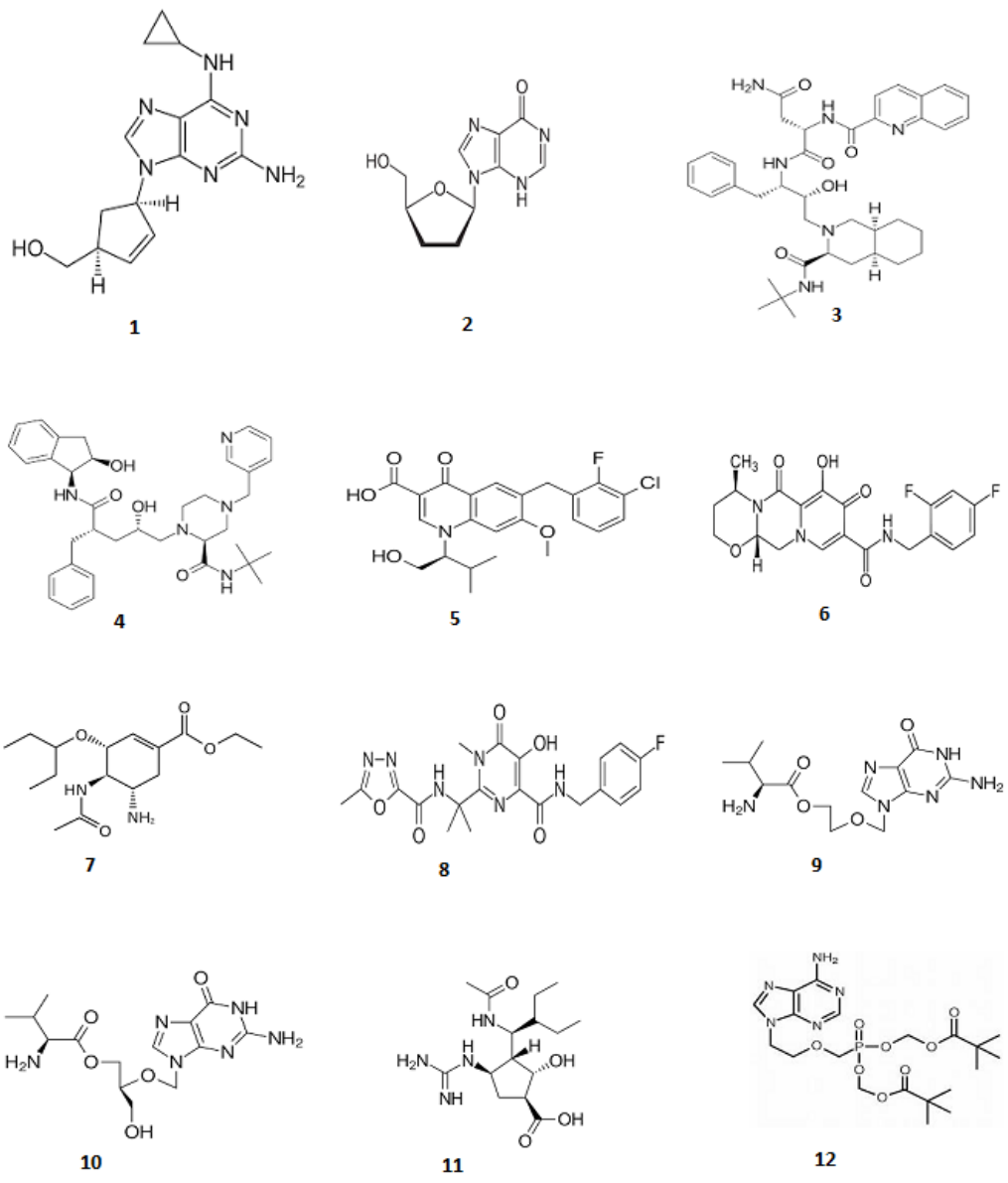

Fig. 1. Chemical structure of antiviral agents

Comment [u2]: Citation…?

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 [1]. 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 [18,24].

In recent studies, many naturally occurring antiviral compounds have been identified and isolated from plants and other natural sources [25]. 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 [17,26,27]. 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) [28], while others revealed their effects on Interleukin 6 (IL-6) production in the macrophage activation assay [84] (Webster, 2006). Lymphocyte proliferation activity and induced interferon-gamma (IFN-γ) secretion are indicators of cell-mediated immune response modulation [28]. 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) [29].

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 [30]. 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 [30]. 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	[11]
2.	*Acacia nilotica* L. Willd ex Delile,	HCV	[31]
3.	*Achillea fragrantissima* (Forssk.) Sch.Bip.	Poliomyelitis-1 virus (POLIO); human and animal ORF virus; small pox viruses	[32]
4.	*Aegle marmelos* (L.)Corr.	Human coxsackieviruses B1-B6, ranikhet disease virus	[32, 33]
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)	[1, 34]
6.	*Aloe barbadensis* miller	HSV-2, HSV-1, Influenza virus, human cytomegalovirus, polio virus	[32]
7.	*Andrographis paniculata* (Burm.f.) Nees.	Simian Retro Virus (SRV), Epstein-Barr virus (EBV), Influenza and HIV	[1]
8.	*Ardisia chinensis* Benth	HBV, DHBV, Coxsackie B3 (Cox B3) virus	[1, 35]
9.	*Artocarpus integrifolia* L.f.	(SA-11) and human (HCR3) rotaviruses, HIV	[32, 36]
10.	*Astragalus membranaceus* Bunge	HIV, Avian Influenza H9 virus, Hepatitis B virus, HSV1, NDV, EBV	[1, 24]
11.	*Atractylodes macrocephala* Koidz.	H3N2,	[1, 37]
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),	[38-43]
13.	*Balanites aegyptiaca* (L.) Del.	VSV T2, HCV, HSV	[32,44]
14.	*Boehmeria nivea* (Linn.) Gaudich	HBV	[4, 45, 46]
15.	*Boerhavia diffusa* L.	Viral hepatitis (HPV); potato virus X; mung bean (*Vigna radiate*) yellow mosaic virus	[47]
16.	*Boswellia carterii* Birdwood	HCV, HSV	[31, 48]

17.	*Bridelia micrantha* (Hochst)	HIV-1	[49, 50]
18.	*Bryophyllum pinnatum* (Lam.) Oken	Echoviruses E7 & E19, HSV, Measles (MV),	[11, 51]
19.	*Buxus sempervirens* L.	HSV, SINV	[1, 52]
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),	[32, 53]
21.	*Cannabis sativa* L.	Newcastle Disease Virus (NDV), HCV, SARS-COV-2	[1, 54-56]
22.	*Capparis spinosa* L.	HSV-2, HIV-1	[32, 57, 58]
23.	*Carissa edulis* (Forssk.) Vahl.	HSV 1 & 2, HCMV, RVFV, FHV, PV-2, LSDV, CDV	[10, 59-61]
24.	*Cassine xylocarpa* Vent.	HIV	[32]
25.	*Chelidonium majus* L.	HSV-1, HIV-1	[1, 62, 63]
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	[32, 64-66]
27.	*Crinum jagus* (J. Thomps.) Dandy	echoviruses E7 & E19	[11, 67, 68]
28.	*Curcuma longa* L.	HSV-1, HIV	[32, 69]
29.	*Cyperus rotundus* L.	HSV-1 HBV	[32, 70]
30.	*Daphne gnidium* L.	HIV	[32, 71, 72]
31.	*Diospyros kaki* L.	Influenza virus H3N2, H5N3, HSV-1, vesicular stomatitis virus, Sendai virus, poliovirus, coxsachievirus, adenovirus, rotavirus, feline calicivirus, mouse norovirus, Newcastle disease virus	[32, 36, 73, 74]
32.	Dittrichia viscosa	VSV, HSV-1, poliovirus type 1 U	[32]
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)	[47, 75-76]
34.	*Embelia schimperi*	HCV	[31]
35.	*Euphorbia hirta*	HIV-1, HIV-2, SIV mac 251	[32]
36.	*Euphorbia spinidens*	HSV-1	[32]
37.	*Ficus benjamina*	HSV-1, HSV-2	[32]
38.	*Ficus carica*	HSV-1 HSV-1, ECV-11, ADV, influenza virus	[32]
39.	*Ganoderma lucidum*	HBV	[77]
40.	*Geranium sanguineum* L.	Influenza virus	[78, 79]
41.	*Globularia arabica*	Poliomyelitis-1 virus (POLIO)	[32]
42.	*Glycine max* (L.) Merr	Human adenovirus type 1, coxsackievirus B1	[80]
43.	*Glycyrrhiza glabra*	NDV	[32]
44.	*Glycyrrhiza uralensis*		[32]

45.	*Glycyrrhiza uralensis* Fisch	SARS-CoV	[81]
46.	*Guazuma ulmifolia* Lam.	Polio virus	[82]
47.	*Haemanthus albiflos*		[83]
48.	*Heracleum maximum* Bartr. (Umbelliferae)	non-specific	[84]
49.	*Humulus lupulus* L. Genbank	Broad spectrum; non-specific	[26]
50.	*Hyssopus officinalis* L.	HSV-1, HIV	[1, 32]
51.	*Ipomoea asarifolia* (Desr.) Roem. & Schult.	Echovirus E7	[11]
52.	*Leucojum vernum*	HIV-1	[32]
53.	*Lilium candidum*	HSV-1, HSV-2	[32]
54.	*Lippia multiflora* Moldenke	echovirus E7	[11]
55.	*Lycoris radiata* L.	SARS-CoV	[81]
56.	*Macaranga barteri* Mull. Arg.	echoviruses E7 & E19	[11]
57.	*Macaranga kilimandscharica*	Measles; HSV-1; Coxsackie viruses	[85, 86]
58.	*Magnolia officinalis*	Dengue virus Type 2	[32]
59.	*Maytenus cuzcoina*	HIV	[32]
60.	*Melissa officinalis*	HSV-1, HSV-2 HIV	[32]
61.	*Mentha pulegium*	HSV-1	[32]
62.	*Mondia whitei* (Hook.f.) Skeels	Echoviruses E7 & E19	[11]
63.	*Moringa peregrina*	HSV-1	[32]
64.	*Myristica fragrans*	Human rotavirus	[32]
65.	*Oenanthe javanica* Blume DC	HBV, DHBV	[1]
66.	*Olea europaea* L.	Influenza virus subtype H9N2, Viral haemorrhagic septicaemia virus (VHSV); HIV	[32, 87, 88]
67.	*Panax ginseng*	Human rotavirus	[32]
68.	*Panax notoginseng*	Influenza A virus	[32]
69.	*Pandanus amaryllifolius* Roxb	HSV-1 and influenza virus strain H1N1	[27]
70.	*Phyllanthus acidus*	HBV	[32]
71.	*Phyllanthus amarus*	Hepatitis B surface antigen (HBsAg); HBV and HCV; HSV 1 & 2	[47]
72.	*Phyllanthus amarus* Schum. & Thonn.	HIV	[89]
73.	*Phyllanthus emblica*	Influenza A virus strain H3N2, HBV	[32]
74.	*Phyllanthus nanus* L.	HBV, DHBV	[1]
75.	*Phyllanthus niruri* L.	HBV	[1]
76.	*Phyllanthus urinaria*	HSV 1 & 2	[47, 90]
77.	*Piper cubeba* L.	HCV	[31]
78.	*Pithecellobium clypearia*	HBV, DHBV	[1]
79.	*Podophyllum peltatum* L	HSV 1	[76, 91]
80.	*Polygonum cuspidatum* Sieb.& Zucc.	HBV	[92]
81.	*Prunella vulgaris*	HIV-1, Ebola virus	[32]
82.	*Quercus brantii* L Acorn.	HSV-1	[32]
83.	*Quercus infectoria*,	HCV	[31]
84.	*Quercus persica*	HSV-1	[32]
85.	*Salacia reticulata*	H1N1 influenza	[32]

86.	*Sambucus nigra* L.	Influenza virus	[29, 93]
87.	Sanguisorba minor	VSV, HSV-1 HIV	[32]
88.	*Saxifraga melanocentra*	Hepatitis C virus (HCV)	[50]
89.	*Securigera securidaca*	HSV-1, HSV-2	[32]
90.	*Solanum nigrum*	HCV	[32]
91.	*Sophorae flavescentis*	HBV	[77]
92.	*Spondias lutea*	Human rotavirus	[32]
93.	*Spondias mombin* L.	echovirus E7	[11]
94.	*Stevia rebaudiana* L.	human rhinoviruses (HRV)	[94]
95.	*Stryphnodendron adstringens*	Polio virus	[87]
96.	*Syzygium aromaticum* L.	HCV	[31]
97.	*Tamarix nilotica*	HSV-1	[32]
98.	*Taraxacum officinale*	HCV Influenza virus type A, H1N1.	[32]
99.	*Terminalia ivorensis* A. Chev.	echovirus E7	[11]
100.	*Tetracera alnifolia* Willd.	echovirus E7	[11]
101.	*Thymus carmanicus*	HIV-1	[32]
102.	*Thymus daenensis*	HIV-1	[32]
103.	*Thymus kotschyanus*	HIV-1	[32]
104.	*Thymus vulgaris*	HIV-1	[32]
105.	*Trachyspermum ammi* L.	HCV	[31]
106.	*Trichilia glabra* L.	Vesicular stomatitis virus (VSV)	[95]
107.	*Trifollium species* Secomet-V	human papillomavirus, Marburg, influenza, HIV, HBV and HCV	[7]
108.	*Tuberaria lignosa* An	HIV	[32]
109.	*Viola diffusa*	HBV	[32]
110.	*Vitis labrusca*	(SA-11) and human (HCR3) rotaviruses	[32]
111.	*Vitis macrocarpon*	(SA-11) and human (HCR3) rotaviruses	[32]
112.	*Zataria multiflora*	HSV-1	[32]

Key: HSV herpes simplex virus, VSV vesicular stomatitis virus, HBV hepatitis B virus, HIV human immunodeficiency virus, SIV simian immunodeficiency virus, ECV echovirus, ADV adenovirus, NDV Newcastle disease virus, HCV hepatitis C virus; Duck viral enteritis (DEV), also called duck plague virus (DPV), Measles (MV), polio PV and yellow fever (YFV) viruses, 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)

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 [96]. 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 [97, 98].

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 [99]. Many synthetic medicines have their basic structures from natural products [98]. 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 compound could act synergistically to exact the desired pharmacological effect. In addition, most of the substances are easily biodegradable with minimal or no side effect [98, 100]. The bioactivities 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 [1, 101].

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 [102, 103]. However, some may rely on more than one mechanism since the crude extracts contains several chemical components that may be acting in synergies [66]. 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 [104].

From the beginning humanity has always rely 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 flavonoids 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) [105]. The proposed antiviral mechanisms of action of flavonoids include inhibition of viral polymerase and binding of viral nucleic acid or viral capsid proteins [106]. The anti-infective activities (antiviral and antimicrobial) of 3,5-dicaffeoylquinic acid (DCQA), acteoside (verbascoside) and kampferol-7-O-glucoside had been reported in literature [11].

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.

References

[1] Mukhtar M, Arshad M, Ahmad M, Pomerantz RJ, Wigdahl B, Parveen Z. Antiviral potentials of medicinal plants. Virus Research (Elsevier) 131 (2008) 111–120.

[2] Mohammed FS, Şabik AE, Sevindik E, Pehlivan M, Sevindik M (2020a). Determination of Antioxidant and Oxidant Potentials of Thymbra spicata Collected from Duhok-Iraq. Turkish Journal of Agriculture-Food Science and Technology 8(5):1171-1173.

[3] Mohammed FS, Günal S, Şabik AE, Akgül H, Sevindik M (2020b). Antioxidant and Antimicrobial activity of Scorzonera papposa collected from Iraq and Turkey. Kahramanmaraş Sütçü İmam Üniversitesi Tarım ve Doğa Dergisi 23(5):1114-1118.

[4] Huang KL, Lai YK, Lin CC, Chang JM. Inhibition of hepatitis B virus production by Boehmeria nivea root extract in HepG2 2.2.15 cells. *World J Gastroenterol*. 2006;12(35):5721-5725. doi:10.3748/wjg.v12.i35.5721

[5] Kwon, D.H., Kwon, H.Y., Kim, H.J., Chang, E.J., Kim, M.B., Yoon, S.K., Song, E.Y., Yoon, D.Y., Lee, Y.H., Choi, I.S., Choi, Y.K., 2005. Inhibition of hepatitis B virus by an aqueous extract of Agrimonia eupatoria L. Phytother.Res. 19 (4), 355–358.

[6] Asres, K., Bucar, F., 2005. Anti-HIV activity against immunodeficiency virus type 1 (HIV-I) and type II (HIV-II) of compounds isolated from the stem bark of Combretum molle. Ethiop. Med. J. 43 (1), 15–20.

[7] Kotwal, G.J., Kaczmarek, J.N., Leivers, S., Ghebremariam, Y.T., Kulkarni, A.P., Bauer, G., C, D.E.B., Preiser, W., Mohamed, A.R., 2005. Anti-HIV, anti-Poxvirus, and anti-SARS activity of a nontoxic, acidic plant extract from the Trifollium Species Secomet-V/anti-Vac suggests that it contains a novel broad-spectrum antiviral. Ann. NY Acad. Sci. 1056, 293–302.

[8] Vermani, K., Garg, S., 2002. Herbal medicines for sexually transmitted diseases and AIDS. J. Ethnopharmacol. 80 (1), 49–66.

[9] Debiaggi, M., Pagani, L., Cereda, P.M., Landini, P., Romero, E., 1988. Antiviral activity of Chamaecyparis lawsoniana extract: study with herpes simplex virus type 2. Microbiologica 11 (1), 55–61.

[10] Tolo, F.M., Rukunga, G.M., Muli, F.W., Njagi, E.N., Njue, W., Kumon, K., Mungai, G.M., Muthaura, C.N., Muli, J.M., Keter, L.K., Oishi, E., Kofi- Tsekpo,M.W. Anti-viral activity of the extracts of aKenyan medicinal plant Carissa edulis against herpes simplex virus. J. Ethnopharmacol. 2006;104 (1/2), 92–99.

[11] Ogbole OO, Akinleye TE, Segun PA, Faleye TC and Adeniji AJ. In vitro antiviral activity of twenty-seven medicinal plant extracts from Southwest Nigeria against three serotypes of echoviruses. Virology Journal (BMC), 2018, 15:110. https://doi.org/10.1186/s12985-018-1022-7.

[12] Abedi GR, Watson JT, Pham H, Nix WA, Oberste MS, Gerber SI. Enterovirus and human parechovirus surveillance—United States, 2009–2013. MMWR Morb Mortal Wkly Rep. 2015;64(34):940–3.

[13] Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. Cold Spring Harb Perspect Med. 2012 Apr;2(4):a007161. doi: 10.1101/cshperspect.a007161. PMID: 22474613; PMCID: PMC3312400.

[14] Cruciani M, Martí-Carvajal AJ, Mengoli C, Serpelloni G, Bovo C, Moyle G. Abacavir versus other nucleoside reverse transcriptase inhibitor (NRTI) backbone therapies for treatment of HIV infection. Cochrane Database Syst Rev. 2018 Feb 2;2018(2):CD009390. doi: 10.1002/14651858.CD009390.pub2. PMCID: PMC6491294.

[15] Patel PH, Zulfiqar H. Reverse Transcriptase Inhibitors. [Updated 2021 Jun 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

[16] Orkin C, Llibre JM, Gallien S, Antinori A, Benrens G, Carr D (2018). Nucleoside reverse transcriptase inhibitor reducing strategies in HIV treatment: assessing the evidence. HIV. Med 19(1):18-32

[17] Lv Z, Chu Y, Wang Y. HIV protease inhibitors: a review of molecular selectivity and toxicity. HIV AIDS (Auckl). 2015;7:95-104. https://doi.org/10.2147/HIV.S79956

[18] Lepik KJ, Yip B, Ulloa AC, Wang L, Toy J, Akagi L, Lima VD, Guillemi S, Montaner JSG, Barrios R. Adverse drug reactions to integrase strand transfer inhibitors. AIDS. 2018 Apr 24;32(7):903-912. doi: 10.1097/QAD.0000000000001781. PMID: 29424784.

[19] McNicholl IR, McNicholl JJ. Neuraminidase inhibitors: zanamivir and oseltamivir. Ann Pharmacother. 2001 Jan;35(1):57-70. doi: 10.1345/aph.10118. PMID: 11197587.

[20] Seley-Radtkem KL and Yates MK. The evolution of nucleoside analogue antivirals: A review for chemists and non-chemists. Part 1: Early structural modifications to the nucleoside scaffold. Antiviral Res. 2018 Jun; 154: 66–86. doi: 10.1016/j.antiviral.2018.04.004

[21] Galar A, Valerio M, Catalán P, García-González X, Burillo A, Fernández-Cruz A, Zataráin E, Sousa-Casasnovas I, Anaya F, Rodríguez-Ferrero ML, Muñoz P and Bouza E. Valganciclovir–Ganciclovir Use and Systematic Therapeutic Drug Monitoring. An Invitation to Antiviral Stewardship. Antibiotics, 2021; 10, 77. https://doi.org/10.3390/antibiotics10010077

[22] De Clercq E. (2003). Clinical potential of the acyclic nucleoside phosphonates cidofovir, adefovir, and tenofovir in treatment of DNA virus and retrovirus infections. Clinical microbiology reviews, 16(4), 569–596. https://doi.org/10.1128/CMR.16.4.569-596.2003

[23] Dando, T.M., Plosker, G.L. Adefovir Dipivoxil. Drugs 63, 2215–2234 (2003). https://doi.org/10.2165/00003495-200363200-00007

[24] Khan HM, Raza SM, Anjum AA, Ali MA and Akbar H. Antiviral, embryo toxic and cytotoxic activities of Astragalus membranaceus root extracts. Pak. J. Pharm. Sci., 2019; 32(1): 137-142.

[25] Perez R.M. (2003) Antiviral Activity of Compounds Isolated From Plants, Pharmaceutical Biology, 41:2, 107-157, DOI: 10.1076/phbi.41.2.107.14240

[26] Buckwold, V.E., Wilson, R.J., Nalca, A., Beer, B.B., Voss, T.G., Turpin, J.A., Buckheit III, R.W.,Wei, J.,Wenzel-Mathers, M.,Walton, E.M., Smith, R.J., Pallansch, M., Ward, P., Wells, J., Chuvala, L., Sloane, S., Paulman, R., Russell, J., Hartman, T., Ptak, R., 2004. Antiviral activity of hop constituents against a series of DNA and RNA viruses. Antiviral Res. 61 (1), 57–62.

[27] Ooi, L.S., Sun, S.S., Ooi, V.E., 2004. Purification and characterization of a new antiviral protein from the leaves of Pandanus amaryllifolius (Pandanaceae). Int. J. Biochem. Cell Biol. 36 (8), 1440–1446.

[28] Chiang LC, Cheng HY, Liu MC, Chiang W, Lin CC (2003). In vitro antiherpes simplex viruses and anti-adenoviruses activity of twelve traditionally used medicinal plants in Taiwan. Biol Pharm Bull 2003; 26: 1600-4.

[29] Barak, V., Halperin, T., Kalickman, I., 2001. The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. Eur. Cytokine Netw. 12 (2), 290–296.

[30] Jassim S, Naji MA. Novel antiviral agents: a medicinal plant perspective. J Appl Microbiol. 2003;95(3):412–27.

[31] Hussein, G., Miyashiro, H., Nakamura, N., Hattori, M., Kakiuchi, N., Shimotohno, K., 2000. Inhibitory effects of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. Phytother. Res. 14 (7), 510–516.

[32] Ben-Shabat S, Yarmolinsky L, Porat D and Dahan A. Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies. Drug Delivery and Translational Research (2020) 10:354–367.

[33] Dhankhar S, Ruhil S, Balhara M, Dhankhar S and Chhillar AK. *Aegle marmelos* (Linn.) Correa: A potential source of Phytomedicine. Journal of Medicinal Plants Research, 2011; 5(9): 1497-1507.

[34] Batiha GE, Beshbishy AM, Wasef LG, Elewa YHA, Al-Sagan AA , Abd-El-Hack ME, Taha AE, Abd-Elhakim YM and Devkota HP. Chemical Constituents and Pharmacological Activities of Garlic (Allium sativum L.): A Review. Nutrients, 2020; 12: (872):1-21; doi:10.3390/nu12030872

[35] Su M, Li Y, Leung KT, Cen Y, Li T, Chen R, Ooi VEC. Antiviral activity and constituent of Ardisia chinensis benth against coxsackie B3 virus. Phytother Res., 2006;20(8):634-9. doi: 10.1002/ptr.1912.

[36] Behl T, Rocchetti G, Chadha S, Zengin G, Bungau S, Kumar A, Mehta V, Uddin MS, Khullar G, Setia D, Arora S, Sinan KI, Ak G, Putnik P, Gallo M, Montesano D. Phytochemicals from Plant Foods as Potential Source of Antiviral Agents: An Overview. Pharmaceuticals (Basel). 2021 Apr 19;14(4):381. doi: 10.3390/ph14040381.;

[37] Gu S, Li L, Huang H, Wang B, Zhang T. Antitumor, Antiviral, and Anti-Inflammatory Efficacy of Essential Oils from Atractylodes macrocephala Koidz. Produced with Different Processing Methods. Molecules. 2019;24(16):2956. Published 2019 Aug 15. doi:10.3390/molecules24162956,

[38] Ahmad, A., Javed, M.R., Rao, A.Q. et al. Designing and screening of universal drug from neem (Azadirachta indica) and standard drug chemicals against influenza virus nucleoprotein. BMC Complement Altern Med 16, 519 (2016). https://doi.org/10.1186/s12906-016-1469-2

[39] Alzohairy MA. Therapeutics Role of Azadirachta indica (Neem) and Their Active Constituents in Diseases Prevention and Treatment. Evidence-Based Complementary and Alternative Medicine, vol. 2016, Article ID 7382506, 11 pages, 2016. https://doi.org/10.1155/2016/7382506

[40] Sujarwo W, Keim AP, Caneva G, Toniolo C, Nicoletti M. Ethnobotanical uses of neem (Azadirachta indica A.Juss.; Meliaceae) leaves in Bali (Indonesia) and the Indian subcontinent in relation with historical background and phytochemical properties. J Ethnopharmacol. 2016 Aug 2;189:186-93. doi: 10.1016/j.jep.2016.05.014. Epub 2016 May 10. PMID: 27178630.

[41] Xu J., Song X., Yin Z.Q., Cheng A.C., Jia R.Y., Deng Y.X., Ye K.C., Shi C.F., Lv C., Zhang W. Antiviral activity and mode of action of extracts from neem seed kernel against duck plague virus in vitro. Poultry Science, 2012; 91(11): 2802-2807.

[42] Tiwari V, Darmani NA, Yue BY, Shukla D. In vitro antiviral activity of neem (Azardirachta indica L.) bark extract against herpes simplex virus type-1 infection. Phytother Res. 2010;24(8):1132-1140. doi:10.1002/ptr.3085

[43] Parida et al. (2002)

[44] Abdelaziz SM, Lemine FMM, Tfeil HO, Filali-Maltouf A and Boukhary AOMS. Phytochemicals, Antioxidant Activity and Ethnobotanical Uses of Balanites aegyptiaca (L.) Del. Fruits from the Arid Zone of Mauritania, Northwest Africa. Plants, 2020; 9(3), 401; **https://doi.org/10.3390/plants9030401**

[45] Wei J, Lin L, Su X, Qin S, Xu Q, Tang Z, Deng Y, Zhou Y and He S: Anti-hepatitis B virus activity of Boehmeria nivea leaf extracts in human HepG2.2.15 cells. Biomed Rep 2: 147-151, 2014

[46] Chang J, Huang KL, Yuan TTT, Lai Y and Hung L. The Anti-hepatitis B Virus Activity of Boehmeria nivea Extract in HBV-viremia SCID Mice. Evidence-based Complementary and Alternative Medicine: eCAM, 2010; 7(2):189-195

[47] Anbazhagan GK, Palaniyandi S and Joseph B. Antiviral Plant Extracts. Book chapter, IntechOpen, 2019. DOI: 10.5772/intechopen.85126

[48] Badria FA. Frankincense (Heaven's Gift) — Chemistry, Biology, and Clinical Applications. Book Chapter, IntechOpen. 2015. DOI: 10.5772/59006.

[49] Maroyi A. Ethnopharmacology and Therapeutic Value of Bridelia micrantha (Hochst.) Baill. in Tropical Africa: A Comprehensive Review. Molecules. 2017;22(9):1493. Published 2017 Sep 8. doi:10.3390/molecules22091493

[50] Zuo, G.Y., Li, Z.Q., Chen, L.R., Xu, X.J., 2005. In vitro anti-HCV activities of Saxifraga melanocentra and its related polyphenolic compounds. Antivir. Chem. Chemother. 16 (6), 393–398.

[51] Obi RK and Shenge JA. 2018. In vitro antiviral activities of Bryophyllum pinnatum (Odaa opuo) and Viscum album (awuruse). Res. J. Microbiol., 2018; 13: 138-146.

[52] Hudson J.B., Lee M.K., Sener B. & Erdemoglu N. (2000) Antiviral Activities in Extracts of Turkish Medicinal Plants, Pharmaceutical Biology, 38:3, 171-175, DOI: 10.1076/1388-0209(200007)3831-SFT171

[53] Mahmood MS , Mártinez JL , Aslam A , Rafique A, Vinet R , Laurido C , Hussain I , Abbas RZ, Khan A & Ali S. Antiviral effects of green tea (Camellia sinensis) against pathogenic viruses in human and animals (A mini-review). Afr J Tradit Complement Altern Med. (2016) 13(2):176-184

[54] Lowe H, Steele B, Bryant J, Fouad E, Toyang N, Ngwa W. Antiviral Activity of Jamaican Medicinal Plants and Isolated Bioactive Compounds. Molecules. 2021; 26(3):607. https://doi.org/10.3390/molecules26030607

[55] Abubakar YU, Taura DW, Yushau M, Muhammad AU. An in ovo investigation on antiviral activity of Cannabis sativa extracts against Newcastle Disease Virus (NDV). Advance Pharmaceutical Journal 2020; 5(1):21-30.

[56] Bouarfa M, Lebtar S , Boukhira S, Bousta D. An Ethnobotanical and Ethnopharmacological Survey of Cannabis Sativa of Taounate Region in Northern Morocco. Int. J. Pharm. Sci. Rev. Res., 2020; 64(2): 116-122.

[57] Mohammad SM, Kashani HH, Azarbad Z. Capparis spinosa L. Propagation and Medicinal uses. Life Science Journal 2012; 9(4):684-686.

[58] Arena A, Bisignano G, Pavone B, Tomaino A, Bonina F, Saija A, Cristani M, D'Arrigo, M, Trombetta D. Antiviral and immunomodulatory effect of a lyophilized extract of Capparis spinosa L. buds. Phytotherapy Research, 2008; 22(3):313-7.

[59] More, G.K.; Makola, R.T.; Prinsloo, G. In Vitro Evaluation of Anti-Rift Valley Fever Virus, Antioxidant and Anti-Inflammatory Activity of South African Medicinal Plant Extracts. Viruses 2021, 13, 221. https://doi.org/10.3390/v13020221

[60] Al-Youssef HM and Hassan WHB. Phytochemical and pharmacological aspects of Carissa edulis Vahl: A review. Int. J. Curr.Res.Chem.Pharma.Sci. 1(9): (2014):12–24

[61] Tolo FM , Rukunga GM, Muli FW, Ochora J, Eizuru Y, Muthaura CN , Kimani CW, Mungai GM and Kofi-Tsekpo MW. In vitro anti-viral activity of aqueous extracts of Kenyan Carissa edulis Prunus africana and Melia azedarach against human cytomegalovirus.. African Journal of Health Sciences, 2007; 14(3-4): 143-148.

[62] Monavari SH, Shahrabadi MS, Keyvani H and Bokharaei-Salim F. Evaluation of in vitro antiviral activity of Chelidonium majus L. against herpes simplex virus type-1. African Journal of Microbiology Research, 2012; Vol. 6(20), pp. 4360-4364, 30 May, 2012

[63] Gerencer M, Turecek PL, Kistner O, Mitterer A, Savidis-Dacho H, Barrett NP. In vitro and in vivo anti-retroviral activity of the substance purified from the aqueous extract of Chelidonium majus L. Antiviral Res. 2006 Nov;72(2):153-6. doi: 10.1016/j.antiviral.2006.03.008. Epub 2006 Apr 18. PMID: 16647765.

[64] Zalegh, I.; Akssira, M.; Bourhia, M.; Mellouki, F.; Rhallabi, N.; Salamatullah, A.M.; Alkaltham, M.S.; Khalil Alyahya, H.; Mhand, R.A. A Review on Cistus sp.: Phytochemical and Antimicrobial Activities. Plants 2021, 10, 1214. https://doi.org/10.3390/plants10061214

[65] Viapiana A, Konopacka A, Waleron K, Wesolowski M. Cistus incanus L. commercial products as a good source of polyphenols in human diet. Industrial Crops & Products 107 (2017) 297–304.

[66] Rebensburg, S., Helfer, M., Schneider, M. et al. Potent in vitro antiviral activity of Cistus incanus extract against HIV and Filoviruses targets viral envelope proteins. Sci Rep 6, 20394 (2016). https://doi.org/10.1038/srep20394

[67] Alawode TT, Lajide L, Owolabi BJ, Olaleye MT. Evaluation of Extracts of Leaves of Crinum jagus for Antimicrobial Properties. J. Appl. Sci. Environ. Manage., 2020; Vol. 24 (7) 1197-1201.

[68] Noubissi PA, Tagne MAF, Fankem GO, Mukam JN, Wambe H, Kamgang R, "Effects of Crinum jagus Water/Ethanol Extract on Shigella flexneri-Induced Diarrhea in Rats", Evidence-Based Complementary and Alternative Medicine, vol. 2019, Article ID 9537603, 10 pages, 2019. https://doi.org/10.1155/2019/9537603

[69] Chanda S and Ramachandra TV. Phytochemical and Pharmacological Importance of Turmeric (Curcuma longa): A Review. Research & Reviews: A Journal of Pharmacology. 2019; 9(1): 16–23.

[70] Sivapalan SR. Medicinal uses and Pharmacological activities of Cyperus rotundus Linn – A Review. International Journal of Scientific and Research Publications, 2013; 3(5): 1-8.

[71] Sovrlić, Miroslav M. and N. Manojlovic. "Plants from The Genus Daphne: A Review of its Traditional Uses, Phytochemistry, Biological and Pharmacological Activity." Serbian Journal of Experimental and Clinical Research 18 (2017): 69 - 80.

[72] Chaabane F, Boubaker J, Loussaif A, Neffati A, Kilani-Jaziri S, Ghedira K, Chekir-Ghedira L. Antioxidant, genotoxic and antigenotoxic activities of daphne gnidium leaf extracts. BMC Complementary and Alternative Medicine, 2012; 12(1):153

[73] Khouchlaa A, El-Menyiy N, Guaouguaou FE, El-Baaboua A, Charfi S, Lakhdar F, El-Omari N, Taha D, Shariati MA, Rebezov M, El-Shazly M, Bouyahya A, Ethnomedicinal use, phytochemistry, pharmacology, and toxicology of Daphne gnidium: A review,Journal of Ethnopharmacology, 2021; 275; 114124, https://doi.org/10.1016/j.jep.2021.114124.

[74] Ueda K, Kawabata R, Irie T, Nakai Y, Tohya Y, Sakaguchi T. Inactivation of pathogenic viruses by plant-derived tannins: strong effects of extracts from persimmon (Diospyros kaki) on a broad range of viruses. PLoS One. 2013;8(1):e55343. doi: 10.1371/journal.pone.0055343. Epub 2013 Jan 25. PMID: 23372851; PMCID: PMC3555825.

[75] Satish, A.B., Deepa, R.V., Nikhil, C.T. and Vaibhav, R.M. (2013). Eclipta alba (L.): An Overview. International Journal of Bioassays, 2(11): 1443 – 1447.

[76] Jagessar, R.C. (2020). Plant extracts as antiviral agents. Modern Approaches in Drug Designing, 3(1): 1 – 5.

[77] Li, Y., Yang, Y., Fang, L., Zhang, Z., Jin, J., Zhang, K., 2006. Anti-hepatitis activities in the broth of Ganoderma lucidum supplemented with a Chinese herbal medicine. Am. J. Chin. Med. 34 (2), 341–349.

[78] Pantev, A., Ivancheva, S., Staneva, L., Serkedjieva, J., 2006. Biologically active constituents of a polyphenol extract from Geranium sanguineum L. with anti-influenza activity. Z Naturforsch. [C] 61 (7/8), 508–516.

[79] Serkedjieva, J., 2003. Influenza virus variants with reduced susceptibility to inhibition by a polyphenol extract from Geranium sanguineum L. Pharmazie 58 (1), 53–57.

[80] Yamai, M., Tsumura, K., Kimura, M., Fukuda, S., Murakami, T., Kimura, Y., 2003. Antiviral activity of a hot water extract of black soybean against a human respiratory illness virus. Biosci. Biotechnol. Biochem. 67 (5): 1071–1079.

[81] Li, S.Y., Chen, C., Zhang, H.Q., Guo, H.Y.,Wang, H.,Wang, L., Zhang, X., Hua, S.N., Yu, J., Xiao, P.G., Li, R.S., Tan, X., 2005. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res. 67 (1), 18–23.

[82] Felipe, A.M., Rincao, V.P., Benati, F.J., Linhares, R.E., Galina, K.J., de Toledo, C.E., Lopes, G.C., de Mello, J.C., Nozawa, C., 2006. Antiviral effect of Guazuma ulmifolia and Stryphnodendron adstringens on Poliovirus and Bovine Herpesvirus. Biol. Pharm. Bull. 29 (6), 1092–1095.

[83] Husson, G.P., Vilagines, P., Sarrette, B., Vilagines, R., 1994. Study of antiviral action of total alkaloids from Haemanthus albiflos. Ann. Pharm. Fr. 52 (6): 311–322.

[84] Webster, D., Taschereau, P., Lee, T.D., Jurgens, T., 2006. Immunostimulant properties of Heracleum maximum Bartr. J. Ethnopharmacol. 106 (3), 360–363.

[85] Cos P, Hermans N, De Bruyne Y, Apers S, Sindambiwe JB, Vanden BB, Pieters L, Vlietinck AJ. Further evaluation of Rwandan medicinal plant extracts for their antimicrobial and antiviral activities. J Ethnopharmocol. 2002;79:155–63.

[86] Magadula JJ. Phytochemistry and pharmacology of the genus Macaranga: a review. J Med Plants Res. 2014;8(12):489–503.

[87] Micol, V., Caturla, N., Perez-Fons, L., Mas, V., Perez, L., Estepa, A., 2005. The olive leaf extract exhibits antiviral activity against viral haemorrhagic septicaemia rhabdovirus (VHSV). Antiviral Res. 66 (2/3), 129–136.

[88] Lee-Huang, S., Zhang, L., Huang, P.L., Chang, Y.T., Huang, P.L., 2003. Anti-HIV activity of olive leaf extract (OLE) and modulation of host cell gene expression by HIV-1 infection and OLE treatment. Biochem. Biophys. Res. Commun. 307 (4), 1029–1037.

[89] Notka, F., Meier, G., Wagner, R., 2004. Concerted inhibitory activities of *Phyllanthus amarus* on HIV replication in vitro and ex vivo. Antiviral Res. 64(2), 93–102.

[90] Yang, C.M., Cheng, H.Y., Lin, T.C., Chiang, L.C., Lin, C.C., 2007. The in vitro activity of geraniin and 1,3,4,6-tetra-O-galloyl-beta-d-glucose isolated from Phyllanthus urinaria against herpes simplex virus type 1 and type 2 infection. J. Ethnopharmacol. 110 (3), 555–558.

[91] Bedows, E., Hatfield, G.M., 1982. An investigation of the antiviral activity of Podophyllum peltatum. J. Nat. Prod. 45 (6), 725–729.

[92] Chang, J.S., Liu, H.W., Wang, K.C., Chen, M.C., Chiang, L.C., Hua, Y.C., Lin, C.C., 2005. Ethanol extract of Polygonum cuspidatum inhibits hepatitis B virus in a stable HBV-producing cell line. Antiviral Res. 66 (1), 29–34.

[93] Zakay-Rones, Z., Thom, E.,Wollan, T.,Wadstein, J., 2004. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. J. Int. Med. Res. 32 (2), 132–140.

[94] Takahashi, K., Matsuda, M., Ohashi, K., Taniguchi, K., Nakagomi, O., Abe, Y., Mori, S., Sato, N., Okutani, K., Shigeta, S., 2001. Analysis of anti-rotavirus activity of extract from Stevia rebaudiana. Antiviral Res. 49 (1), 15–24.

[95] Cella, M., Riva, D.A., Coulombie, F.C., Mersich, S.E., 2004. Virucidal activity presence in Trichilia glabra leaves. Rev. Argent Microbiol. 36 (3), 136–138.

[96] Hamilton, G.R.; Baskett, T.F. In the arms of Morpheus the development of morphine for postoperative pain relief. Can. J. Anaesth. 2000, 47, 367–374

[97] Joo, Y.E. Natural product-derived drugs for the treatment of inflammatory bowel diseases. Intest. Res. 2014, 12, 103–109

[98] Newman, D.J.; Cragg, G.M.; Snader, K.M. Natural Products as Sources of New Drugs over the Period 1981–2002. J. Nat. Prod. 2003, 66, 1022–1037.

[99] Yuan H, Ma Q, Ye L, Piao G. The Traditional Medicine and Modern Medicine from Natural Products. Molecules. 2016;21(5):559. Published 2016 Apr 29. doi:10.3390/molecules21050559

[100] Winter, J.M.; Tang, Y. Synthetic biological approaches to natural product biosynthesis. Curr. Opin. Biotechnol. 2012, 23, 736–743

[101] Wang, X., Jia,W., Zhao, A.,Wang, X., 2006. Anti-influenza agents from plants and traditional Chinese medicine. Phytother. Res. 20 (5), 335–341.

[102] Choi JG, Lee H, Kim YS, Hwang YH, Oh YC, Lee B, Moon KM, Cho WK and Ma JY. Aloe vera and its Components Inhibit Influenza A Virus-Induced Autophagy and Replication. The American Journal of Chinese Medicine, 2019; 47(06): 1307-1324.

[103] Churiyah C, Pongtuluran OB, Rofaani E, Tarwadi T. Antiviral and Immunostimulant Activities of Andrographis paniculata. Hayati Journal of Biosciences, 2015; 22 (2): 67-72.

[104] Naithani R, Huma LC, Holland LE, Shukla D, McCormick DL, Mehta RG and Moriarty RM. Antiviral Activity of Phytochemicals: A Comprehensive Review. Mini-Reviews in Medicinal Chemistry, 2008; 8(11):1106-33. https://doi.org/10.2174/138955708785909943

[105] Middleton JE, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev. 2000;52:673–751.

[106] Ogbole OO, Ajaiyeoba EO, Adeniji JA, Kamdem SR, Sajan S, Muhammad IC. Bioassay-guided isolation of poliovirus-inhibiting constituents from Zephyranthes candida. Pharm Biol. 2015;53(6):882–7.