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Traditional medicinal plants used for the treatment of viral infections: A short review

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ABSTRACT

Viruses are among the most infectious microorganisms and have been present alongside humans throughout history. Viruses infecting humans can be divided into DNA or RNA viruses. It is important to be familiar with the viral replication cycles and the infection mechanisms of each class of viruses şn order to produce efficient vaccines and develop effective treatment regimens, which will help mankind prevent or minimize pandemics such as the current COVID-19 pandemic. Many antiviral drugs are used as broad spectrum to attack common factors of viral infections. However, absence of equal accessibility worldwide and cost of treatments and vaccines, together with the undesirable side effects of these drugs encourages us to venture into alternative treatment modalities. This short review will focus on plants used in traditional medical systems worldwide and their corresponding pharmacological trials, both *in-vitro* and *in-vivo*. Medicinal plants used for Herpesviridae and Hepatitis B virus was addressed when considering DNA viruses, while plants used to treat HIV, influenza, and the Coronaviridae family was discussed under the scope of RNA viruses. Our results indicate that many drugs were developed from natural sources and many plants are yet to be explored for their potential specific and broad-spectrum effects against common viral infections.

Key words: viral infection,medicinal plants,traditional medicine,ethnopharmacology,ethnobotany

ÖZET

İnsanlik tarihi boyunca varlığını muhafaza eden virülser, en bulaşıcı mikroorganizmalardan sayılabilir. İnsanları enfekte eden virüsler DNA veya RNA virüslerine ayrılabilir. İnsanlığın, mevcut COVID-19'a benzer pandemikleri önlemesine veya en aza indirmesine yardımcı olacak etkili tedavi yöntemleri geliştirmesi için, her bir virüs sınıfının viral replikasyon döngülerine ve enfeksiyon mekanizmalarına aşina olması önemlidir. Çoğu antiviral ilaçlar, geniş spektrumlu olup ortak viral enfeksiyon faktörlerini hedef alır. Ancak dünya genelinde eşit erişilebilirlik olmaması ve yüksek maliyet ile istenmeyen yan etkiler, alternatif tedavi yöntemlerine girmemizi teşvik etmektedir. Bu kısa inceleme, dünya çapında viral enfeksiyonları tedavi etmek için geleneksel tıbbi sistemlerde kullanılan bitkiler ve bunların *in-vitro* ve *in-vivo* farmakolojik çalışmalarına odaklanacaktır. DNA virüslerinden Herpesviridae ve Hepatit B virüsü için kullanılan tıbbi bitkiler ele alınırken, HIV, influenza ve Coronaviridae ailesini tedavi etmek için kullanılan bitkiler, RNA virüsleri kapsamında tartışıldı. Sonuçlarımız, doğal kaynaklardan birçok ilacın geliştirildiğini, ve birçok bitkinin yaygın viral enfeksiyonlara karşı potansiyel spesifik ila geniş spektrumlu etkileri için henüz yeterince araştırılmadığını göstermektedir.

Anahtar kelimeler: viral enfeksiyon,tıbbi bitkiler,geleneksel tıp,etnofarmakoloji,etnobotani

INTRODUCTION

Viruses are the most abundant biological entities on Earth and are widely present as parasites in cellular life. They date back to well before humankind's history. They are important agents of many infectious diseases most of which are transmitted from animals. Viruses depend entirely on living cells as hosts for all aspects of their life cycle (Waterson & Wilkinson, 1978).

Apart from their certain benefits, viruses cause a wide range of diseases in humans like the common colds and the rabies. They also play a role in several types of cancer (F. Huang et al., 2016). Viruses do not only cause harm for individuals they can also affect the well-being of societies. Smallpox and Human Immunodeficiency Virus (HIV) are two of the many examples that can be given. For this reason, understanding the nature of viruses, the mechanism of their replication and their pathogenesis is important for taking counteractive measures in the prevention, diagnosis, and treatment of viral ailments through the development of vaccines, diagnostic reagents and anti-viral drugs. Vaccines can save the lives of millions and bring about the end of viral diseases just like in the case of Smallpox virus which was eradicated (WHO, 2014).

Viruses can only replicate and produce new infectious viruses through the attachment and entry into the host cell. Production of viral mRNA and its translation by host ribosomes, genome replication and assembly and release of new viruses containing the genome, all takes place inside the host. The newly formed viruses can then spread and infect other cells (Wagner & Krug, 2020)

Viruses may have DNA or RNA as their genetic material. DNA viruses, such as chickenpox, Hepatitis B and Herpesvirus, can direct the host cell's replication proteins to synthesize new copies of the viral genome and to transcribe and translate that genome into viral proteins. While RNA viruses, such as rabies, hepatitis C and the Coronavirus, encode enzymes that can replicate RNA into DNA, which cannot be done by the host cell. These RNA polymerase enzymes are more likely to make copying errors than DNA polymerases and, therefore, often make mistakes during transcription. For this reason, mutations in RNA viruses occur more frequently than in DNA viruses. This causes them to change and adapt more rapidly to their host (Lodish et al., 2000).

The culturing of the Herpes simplex virus was first carried out in 1925, which paved the way for the development of treatment and possibly prevention methods (Parker Jr & Nye, 1925). Acyclovir is a drug developed and patented in the 70's from nucleosides obtained from the Caribbean sponge, *Cryptotethya crypta*, and together with its derivates forms the basis for herpes treatment (Schaeffer, Gurwara, Vince, & Bittner, 1971). The general idea behind antiviral drug design is identifying targets such as proteins or parts of proteins, preferably those that are common among many viruses. Nowadays, it is possible to develop newer drugs suitable for new targets at the molecular level using computer-aided design programs.

Antiviral drugs usually cause undesired side-effects such as nausea, vomiting, hallucinations, and worsening of asthma conditions (Stiver, 2003). As an example, the use of nucleoside reverse transcriptase inhibitors (NRTIs) in the treatment of AIDS can lead to hepatic failure and lactic acidosis (Lewis, Day, & Copeland, 2003). This, together with the emergence of resistant strains (Sheu et al., 2008; Wyles, 2013) urges the scientific community to explore and research more options for the discovery and development of antiviral drugs for the treatment of diseases and production of possible vaccines (Birkmann & Zimmermann, 2016; Treml et al., 2020). Drug discovery from natural resources is a practice adopted by many traditional medicine systems throughout mankind's history. Some of the major known system include Ayurveda, Unani, traditional Chinese medicine (TCM), Kampo, and Jamu. Although most of medicinal plant usage is recorded in pharmacopoeias and ancient texts, it is possible to access numerous ethnobotanical studies concerning the use of plants as medicines and food in different regions of the world and use these studies as a starting point for drug discovery.

Due to their low toxicity, renewable resources, biodegradability and in most cases low cost, the isolation of biologically active compounds from natural resources has gained more attention (Brahmachari, 2012). With the advent of new technologies in the fields of biology and chemistry – mostly the 'omics' – the pharmacological effects of potential drug substances can now be analyzed more thoroughly. Moreover, the more accurate establishment of synergic effects between natural products enables the development of newer methods for disease treatment and hopefully prevention. Bioactive compounds from medicinal plants were proven to be active against a wide range of virally infectious species, some of these compounds are flavonoids, coumarins, polyphenols, tannins, terpenoids, essential oils, alkaloids, polysaccharides and proteins (Abad, Bedoya, Apaza, & Bermejo, 2012; Bekut et al., 2018; Mukhtar et al., 2008; Naithani et al., 2008).

In light of the abundance of information available to us, this short review will attempt to summarize the available literature in relation to the most infectious viral diseases and the treatment strategies employed in this regard. The focus will be on plants used in traditional medical systems throughout the world, that were documented through ethnobtanical analysis. The active constituents and the related pharmacological studies on biological activity were also included in this study.

1. METHODOLOGY:

Ethnopharmacology is defined as "the interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man" (Bruhn & Helmstedt, 1981; Rivera et al., 2014). Based on this, the present article will explore the treatment methods employed worldwide in traditional medicine systems. The most known databases were researched, namely PubMed, Science Direct, and Web of Science, using the keywords: "plant name", "disease name", "disease family", antiviral, ethnobotany, ethnopharmacology, herbal medicine, traditional, herb, extract. In traditional medical records, plants are recorded based on the symptom they treat. Hence, symptoms of each disease as mentioned in the WHO fact sheets were used as search keywords as well.

The records can be subdivided according to the type of viral infection it addresses. In this article we will be focusing on the pandemic and endemic viral infections mentioned in the World Health Organization (WHO)'s website. Both review articles and scientific articles, based on recorded traditional uses and pharmacological evaluation, were summarized here. Articles were selected based on their metric, coverage, H index, and quartile. Moreover, the general quality and authenticity of the information based on other more reliable literature was taken into consideration.

2. RESULTS AND DISCUSSION:

The results were discussed as shown in the sub sections below. Most research revolved around plants with potential activity against some of the most common viral infections namely those caused by Herpes Simplex virus (HSV), HIV, Hepatitis, A, B, and C viruses (HAV, HBV, HCV), and Influenza virus (IV). The most common DNA viruses were those belonging to the family Herpesviridae and the HBV. As for RNA viruses, the most common ones were IV, HIV, the viruses belonging to the Flaviviridae family, and last but not least, based on current events, the viruses from the Coronaviridae family, which will be discussed in the final part of the article, together with current treatment regimens being adopted during the newest COVID-19 pandemic.

2.1. DNA viruses: Herpesviridae and Hepatitis B

The family Herpesviridae contains viruses such as Herpes Simplex (HSV), chicken pox, cytomegalovirus, Epstein-Barr virus, and Varicella zoster virus. It has a double stranded DNA enclosed in an icosahedral envelope (Denaro et al., 2019). Concurrently to its vast spread in the world, the number of studies on possible cures based on traditional medical systems is quite high. Two of the most common diseases of the Herpesviridae family are HSV-1 and HSV2, and are recorded in WHO fact sheets as a lifelong infection, with an estimate HSV-1 infection for 67% of people under the age of 50 worldwide (WHO, 2017).

Hepatitis B (HB) is an infectious disease caused by the hepatitis B virus (HBV) that affects the liver (Logan & Rice, 1987; WHO, 2019a). It can cause both acute and chronic infections with over 750,000 deaths occurring from hepatitis B each year. *HBV* is a partially double-stranded DNA virus, a species of the genus *Orthohepadnavirus*, and a member of the Hepadnaviridae family of viruses (W.-S. Ryu, 2016). The virus particle (virion) consists of an outer lipid envelope and an icosahedral capsid (Locarnini, 2004). The virus is one of the smallest enveloped animal viruses. Vaccines for the prevention of hepatitis B have been routinely recommended for babies since 1991 in the United States (Schillie et al., 2013) and the first dose is generally recommended within a day of birth (Diseases, 2017).

Euphorbia spp. are known in many folk medicinal systems to possess antiviral, antifungal, and antibacterial activities. While some records, like the Rwandan folk medicine, show antiviral related use of its leaves and stems against poliomyelitis, aphtha, and diarrhea (Vlietinck et al., 1995) other medical systems, like that of the Amazonian people, have records of its use in skin ailments or other seemingly unrelated conditions (MACRAE, HUDSON, & TOWERS, 1988). Dioscorides's *De Materia Medica* contains a depiction of the collection of the latex of a *Euphorbia* plant (Appendino & Szallasi, 1997).

The triterpenes and steroid content of *E. denticulata* Lam., especially betulin, was effective against HSV-1, and it was indicated that the effects were exerted at 2.0 hours post-infection, where it is early on in the replication stage of the virus (Shamsabadipour et al., 2013). Another species named *E. spinidens* Bornm was also able to inhibit the earlier stages of HSV-1 replication (Karimi, Mohammadi-Kamalabadi, Rafieian-Kopaei, Amjad, & Salimzadeh, 2016). A study on the diterpenoids obtained from the acetone extract of *E. milii* Linn. showed promising results against the Epstein-Barr virus's lytic replication (S. N. Liu et al., 2017). Kim and colleagues also recorded effectiveness of *Euphorbia spp.* against the Epstein-Barr virus (D. eun Kim et al., 2018). The tannin isolate named putranjivain A from *E. jolkini* was shown to have antiviral effect against HSV-2 at the later stages of viral replication (H. Y. Cheng et al., 2004).

Belonging to the family of Phyllanthaceae, another plant worth mentioning due to its frequent appearance in the literature is *Phyllanthus urinaria* L.. This plant was used in China's folk medicine as a remedy for hepatitis B, nephrolithiasis, pain, and jaundice (Wei et al., 2005), while in Trinidad and Tobago, it is used to treat diarrhea (Lans, 2007). In the Peruvian Amazon, decoctions of the plant are drunk to treat hepatitis (Roumy et al., 2020). The roots and stem of this plant were also used against HBV among other problems in Korea (Bae, Kim, & Choi, 2009). Recorded pharmacological studies exist on its activity against HSV-1 and HSV-2 due to its tannin content (Hua-Yew Cheng et al., 2011; C.-M. Yang, Cheng, Lin, Chiang, & Lin, 2005; C. M. Yang, Cheng, Lin, Chiang, & Lin, 2007). Other species in the genus *Phyllanthu*s were reviewed recently for their active constituents and biological effects (Qi, Hua, & Gao, 2014). According to a review, there is recorded use of *P. orbicularis* against bovine herpesvirus-1(BHV-1), HSV-2, and adenovirus-7 (AV-7) (Del Barrio & Parra, 2000). Additionally, in another study, the plant was shown to have inhibitory effect against the early replication and DNA synthesis of HSV-2, and this effect was attributed to its epicatechin and procyanidin content (Álvarez et al., 2012). A research was carried out to assess the *in-vitro* and *in-vivo* effects of *P. niruri* L. against HBV. The results indicate that the lignan content named niranthin, could be effective in reducing the viral load and offer hepatoprotective effects (S. Liu et al., 2014). However, one clinical trial was conducted to test the plant on patients with chronic HBV and no significant differences were observed in the viral loads of the treatment and placebo groups (Baiguera et al., 2018).

Morus alba, a plant mentioned in the Chinese pharmacopoeia (Pharmacopoeia Commission of People's Republic of China, 2000) to remove lung heat and relieve asthma, has been studied for the biological activity of its various parts. Of interest is a research conducted in 2003 that aimed to characterize the root bark extract's active constituents and assess its antiviral activity. The results showed potent activity of the flavonoid Leachianone G against HSV-1 (Du et.al, 2003).

The use of *Quercus brantii*'s against diarrhea and stomach ulcers were recorded (Mosaddegh, Naghibi, Moazzeni, Pirani, & Esmaeili, 2012). Although stomach ulcers maybe unrelated to the underlying viral infectious diseases mechanisms, it is well known that diarrhea (acute gastroenteritis) is one of the symptoms in some virally infectious diseases such as norovirus, cytomegalovirus, viral hepatitis, and rotavirus (Grytdal et al., 2016). Thus, it is natural to infer the possible presence of antiviral activity of this plant. Indeed, the activity of *Q. brantii* extract against the herpes simplex virus was studied to reveal its prevention of the viral entry into the host cell due to its condensed tannin content (Karimi, Rafieian-Kopaei, Moradi, & Alidadi, 2017). Additional details can be found in Table 2.1.

2.2: RNA viruses

2.2.1: HIV

Belonging to the Retroviridae family, HIV is a virus that attacks the body's immune system, specifically the white blood cells knows as CD4. HIV is significant due to its major role in Acquired Immunodeficiency Syndrome (AIDS) (Douek, Roederer, & Koup, 2009; Weiss, 1993), which enables the virus to thrive through progressive failure of the immune system via life-threatening opportunistic infections and cancers (Powell et al., 2016).

HIV has a spherical shape around 60 times smaller than a red blood cell, with a diameter of about 120 nm (Harvey, 2007), and two copies of positive-sense single-stranded RNA enclosed in a conical capsid (Kuiken et al., 2009). The treatment regimens include the use of multiple antiretroviral drugs known as antiretroviral therapy (ART) which will reduce the viral load in the blood to an undetectable level and prevent transmission by 96%. Due to the advances, it is now considered a chronic condition with increasingly rarer instances of progression to AIDS. However, the ART should be taken every day in a patient's lifetime, hence with loss of access to ART, alternative medicines must be considered (WHO, 2019b).

One of the methods of suppressing HIV is by inhibiting the virus's reverse transcriptase (RT) enzyme. According to Chinsembu's research, most RT inhibitors were present in plants belonging to the Lamiaceae (13.7%), Fabaceae (10.7%), Euphorbiaceae (9.9%), Clusiaceae (6.1%), Asteraceae (4.6%), Combretaceae (4.6%), and Moraceae (3.0%) families (Chinsembu, 2019). Among the Lamiaceae family, the subfamilies Neptoideae and Lamiodieae containing rosmarinic acid and iridoids respectively have been studied for the antibacterial, antifungal, and antioxidant properties of their essential oils. Among plants that possess anti-RT activity, anti-HIV protease and integrase activities, and DNA copying inhibitory activity for HIV are *Thymus sp.*, *Mentha sp.*, *Rosmarinus sp.*, *Melissa sp.*, *Origanum sp.*, *Ocimum sp.*, *Prunella sp.*, *Hyssopus sp.*, *Salvia sp.*, and *Saturja sp.* (Bekut et al., 2018).

During the early middle ages, it was common for emperors to establish medicinal herb gardens either in their palaces or in monasteries. One such garden was ordered by King Charles the Great (747-814). The garden named *Capitulare de villis* contained majority of the plant species of the family Lamiaceae mentioned above, due to their medicinal value (Heinrich et.al, 2018). *Mentha sp.* were used for headache, bronchitis, lung inflammation, and for improving the general health among Albanians and Serbians from South Kosovo (Mustafa, Hajdari, Pulaj, Quave, & Pieroni, 2020). On the Javor Mountain of Bosnia and Herzegovina Lamiacaea family plants are used for cough, asthma, respiratory infections, fever, and cold (Savić, Mačukanović-Jocić, & Jarić, 2019)

Table 2.1: Plants used traditionally against DNA viruses

Plant Family	Scientific name	Active ingredient(s)	Traditional use / Biological activity	References
Aloaceae	*Aloe spp.*	Aloin B and aloe-emodin	Cold, fever (Zulu medicine) Anticatarrhal (Catalonia) Chest complaints (Namibia) Fever, lung disorders (Pakistan) Fever/malaria (Uganda)	(Hutchings, 1996) (Bonet, Parada, Selga, & Vallès, 1999) (Koenen, 2001) (Yaseen et al., 2015) (Anywar et al., 2020)
			Anti HBV	(Parvez et al., 2019)
Anacardiaceae	*Rhus spp.*	Gallic acid	Arthritis (Thailand) Purgative, lung rejuvenator, anti-asthma (Bhutan)	(Salguero, 2003) (Djakpo & Yao, 2010)
			Anti HSV-1 and HSV-2 activity	(Reichling, Neuner, Sharaf, Harkenthal, & Schnitzler, 2009)
Araliaceae	*Hydrocotyle sibthorpioides*	Asiaticoside	Hepatitis, herpes (TCM)	(Au et al., 2008)
			Anti-HBV	(Q. Huang et al., 2013)
Asteraceae	*Artemisia capillaris* Thunb.	Pumilaside A and enediyne glucosides	Liver disease, indigestion, abdominal pain (South Korea) Liver disease, hepatitis (India) Jaundice, hepatitis (Mauritius)	(H. Kim & Song, 2011) (Thakur et al., 2016) (Suroowan, Pynee, & Mahomoodally, 2019)
			Anti-HBV Anti-HBV	(Zhao et al., 2014) (Geng et al., 2018)
Euphorbiaceae	*Euphorbia spp.*	4,4 dimethyl steroids	Sore throats (China) Cough, bronchial infections, inflammation (Jammu and Kashmir and India) Fungal infections, sores (Jammu and Kashmir)	(Zheng & Xing, 2009) (Gairola, Sharma, & Bedi, 2014) (Shah, Bharati, Ahmad, & Sharma, 2015)
			Anti HSV-1 Anti EV71 and anti HRV	(Shamsabadipour et al., 2013) (B. Wang et al., 2018)
Fagaceae	*Quercus brantii* Lindl	Condensed tannins	Stomach ulcers, diarrhea (Iran)	(Mosaddegh et al., 2012)
			Anti HSV-1	(Karimi et al., 2017)
Rosaceae	*Prunus dulcis* (Mill.) D.A. Webb	Quercetin, epicatechin, and catechin	Buccopharyngeal antiseptic (Catalonia) Sore throat (southern Italy) Cough (southern Italy) Antitussive (eastern Mallorca)	(Agelet & Vallès, 2003) (Pieroni, Quave, & Santoro, 2004) (Scherrer, Motti, & Weckerle, 2005) (Carrió & Vallès, 2012)
			Anti HSV-1 Anti HSV-1	(Bisignano et al., 2017) (Musarra-Pizzo et al., 2019)
Saururaceae	*Houttuynia cordata* Thunb.	Quercetin, quercitrin or isoquercitrin and houttuynoid A	Herpes, smallpox (China) Cold, flu, diarrhea (China) Cough, fever, infant fever (Laos) Common cold (Thailand)	(S. Li et al., 2006) (Au et al., 2008) (De Boer, Lamxay, & Björk, 2012) (Panyadee, Balslev, Wangpakapattanawong, & Inta, 2019)
			Anti HSV-2 Anti HSV-1	(X. Chen et al., 2011) (T. Li et al., 2017)

HSV-1: Herpes Simplex virus type 1; HSV-2: Herpes Simplex virus type 2; EV71: Enterovirus 71; HRV: Human rhinovirus; HBV: Hepatitis B virus.

According to Ibn al-Baytar's (1197-1248) *Kitab al-Yami' li-mufradat al-adwiya wa-*l-*aghdiya* (the *Compendium of Simple Medicaments and Foods*), most members of the Lamiaceae family were used for digestive followed by respiratory illnesses, while the most mentioned plant is *Ocimum basilicum* (El-Gharbaoui, Benítez, González-Tejero, Molero-Mesa, & Merzouki, 2017). The Rasta bush doctors in the Western Cape of South Africa use species of this family for hypertension, cancer, ulcers, gout, general health tonic, respiratory ailments, asthma, bronchitis, cold, fever, cough, and diarrhea (Aston Philander, 2011).

Hyssopus officinalis was shown to inhibit HIV replication due to its polysaccharide type compound content (Kreis, Kaplan, Freeman, Sun, & Sarin, 1990). The use of the whole plant of *Melissa officinalis* L. was recorded as an anti-HIV agent. The extracts of *M. officinalis* L., *Mentha* × *piperita* L., and *Salvia officinalis* L. exhibited strong antirviral effects by inhibiting the viral replication at its earlier stages prior to entry into host (Geuenich et al., 2008). Some studies conducted address the latent HIV which may later resurface and lead to infections. One such drug being considered for human clinical trials is prostratin, which is an ester isolated from the tropical plant *Homalanthus nutans* of the Euphorbiaceae family. This compound can block HIV infections as well as induce the latent virus's expression (Kulkosky et al., 2001; Rullas et al., 2004; Salehi et al., 2018). Triterpenes isolated from *Ocimum labiatum* was shown to have a similar effect on activating latent HIV, and thus having the potential to be used as an adjuvant in ART (Kapewangolo, Omolo, Fonteh, Kandawa-Schulz, & Meyer, 2017).

Artemisinin, a compound isolated from the plant *Artemisia annua* L., which is a famous traditional plant in the Chinese folk systems, has gained popularity, together with its semisynthetic forms, for its major role in the treatment of malaria disease caused by a parasitic worm. Apart from being an approved medicine by the
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Food and Drug Administration (FDA) of the United States, it has produced a Nobel prize in 2015 in medicine for its discoverers. When analyzing the local uses of this plant, a survey conducted by Willcox in 2011 found that most local people of Kenya and Uganda used this plant for conditions other than malaria as well, such as diarrhea, abdominal pain, and HIV/AIDS (Willcox et al., 2011). *A. annua* tea infusions were shown to possess anti-HIV activity *in-vitro* with low toxicity (Lubbe, Seibert, Klimkait, & Van Der Kooy, 2012). A few more plants were included in table 2.2 below.

2.2.2: Influenza viruses

Influenza viruses have originated from the Spanish flu in 1918, and swine flu in 2009 (Sriwilaijaroen et al., 2012). These viruses belong to the Orthomyxoviridae family and have single stranded negative sense RNA enclosed in capsids (Denaro et al., 2019). Due to the high mutation rates of these virus they reoccur seasonally as flu and cold and are an important category of viruses that need continuous attention for cure and vaccine development. Drug development for influenza viruses targets the neuroaminidase (NA) protein present on the virus which is essential for its replication (Denaro et al., 2019). Some of the plants used traditionally and researched for their pharmacological properties will be discussed here.

An interesting study on *Aloe* species was conducted by Glatthaar-Saalmüller and colleagues on the use of Biaron C® (a product containing *Aloe arborescens* Mill., Vitamin C, and *Aronia melanocarpa* Elliot. succus) against viruses causing upper respiratory tract infections. The results showed excellent inhibitory effect against the replicatory ability of orthomyxoviridae – influenza A and influenza B viruses, as well as two non-enveloped RNA viruses belonging to the Picornaviridae family (Glatthaar-Saalmüller et al., 2015).

Table 2.2: Traditional medicinal plants possessing anti-HIV activity

Plant family	Scientific name	Active ingredient(s)	Traditional use / Biological activity	References
Acanthaceae	*Andrographis paniculate* Nees	Andrographolide	Liver disease (Ayurveda) Rid the body of heat in fevers and dispel toxins (TCM) Common colds (Scandinavian countries)	(Chturvedi, Tomar, Tiwari, & Singh, 1983) (Reddy et al., 2005) (Caceres, Hancke, Burgos, & Wikman, 1997)
			Increase in the level of $CD4^+$ lymphocytes Anti-HIV activity	(Calabrese et al., 2000) (Reddy et al., 2005)
Acanthaceae	*Avicenna marina*	Iridoid glycoside	Snakebites, wounds, abscess, blotch (Iran) Ulcers, rheumatism, smallpox (Australasian countries) Skin parasites and gangrenous wounds (India)	(Safa et al., 2013) (Duke, 1991) (Mohan, Rao, & Pragada, 2014)
			Anti-HIV-1 replication	(Behbahani, 2014)
Clusiaceae	*Calophyllum brasiliense*	Tricyclic coumarin	Warts (Brazil) General infections, indigestion (Brazil)	(Lago et al., 2016) (Ribeiro, Bieski, Balogun, & Martins, 2017)
			Inhibits viral replication by suppressing NF-κB activation Inhibits HIV-1 RT*	(Kudo et al., 2013) (César et al., 2011)
Fabaceae	*Acacia spp.*	Acaconin protein, catechins, kaempferol, rutin, ferulic acid and caeffic acid	Flu/cold, cough, headache, chicken pox (Argentina) Diarrhea, chest problems, cold, flu (South Africa)	(Suárez, 2019) (Mhlongo & Van Wyk, 2019)
			Inhibits HIV RT* Inhibits viral protease	(Lam & Ng, 2010) (Modi et al., 2013)

*Reverse transcriptase

Many other studies were conducted on these species and the active constituents were analyzed. For example, the polysaccharide section rich in mannose unit, namely acemamman, was shown to improve wound healing, modulate immunity and exert antiviral effects (Chandegara & Varshney, 2013). The mechanisms studied include prevention of virus adsorption, attachment, and entry into the cell, while immune function is thought to be modulated via its direct effect on the effectivity of T helper cells (Sánchez-Machado, López-Cervantes, Sendón, & Sanches-Silva, 2017)Kampo medicine which was mostly practiced in ancient China and was introduced into Japan in the fifth or sixth century has taken its current form towards the seventeenth century. Kampo drugs consist of a mixture of plants, fungi, minerals, and insects (TSUMURA & CO., 2016). A study conducted on several Kampo drugs (maoto, kakkonto, jinkokato, senkyuchachosan, and bakumondoto) used for common cold and influenza, and the crude drugs *Glycyrrhizae* radix, *Atractylodis lanceae* rhizome, *Rehmanniae* radix, *Citri unshiu* pericarpium, *Cnidii* rhizome, and *Saposhnikoviae* radix. The Kampo drugs were shown to inhibit replication and spread of the virus. *Glycyrrhizae* radix, which was present in all the Kampo drugs tested, showed cytotoxicity at very high concentrations only but had the strongest viral inhibitory effects due to the chalcone isoliquiritigenin and the flavanone liquiritigenin (Nomura et al., 2019). Triterpenoid saponins of the plant were previously reported to have anti-influenza effects (Ji et al., 2016).

A commercially available essential oil blend consisting of oils of orange, clove, cinnamon, eucalyptus, and rosemary were tested to be effective against the influenza virus's proteins (Wu et al., 2010). Eucalyptus was recorded in Zulu medical system as a remedy for headache, diarrhea, cold, and flu (Mhlongo & Van Wyk, 2019) and the leaves are used to treat flu, fever, and common cold as well as an antitussive in Colombian folk medicine (Ceuterick, Vandebroek, Torry, & Pieroni, 2008). Rosemary (*Rosmarinus officinalis* L.) was recorded in the north-eastern Iberian region for its use against colds, to enhance circulation, for pain in muscles, bones and joints, and for laziness (Parada, Carrió, Bonet, & Vallès, 2009).

High throughput screening was conducted on 50 plants used traditionally in different parts of Sarawak, Malaysia. The plants had recorded uses against flu, cold, fever, cough, headache, conjunctivitis, sore throat, and some possible effects against AIDS. Based on the results of the study, 11 plants had significant inhibitory effects against two strains of influenza by inhibiting both the hemagglutinin and NA indication activity against the virus in the early stages of replication. Synergistic effects due to the rich chemical constituents of the extracts were thought to be a reason for the multiple inhibition mechanisms of the extracts towards the viral strains (Rajasekaran et al., 2013).

In southern mountainous regions of Korea, *Thuja orientalis* L. and *Aster sphathulifolius* Maxim. were used in common cold, fever, and generally the respiratory system disorders (H. Kim & Song, 2011). A study conducted on the antiviral activities against these plants showed activity, probably through blockage of the virus attachment to the host cell or the inhibition of viral replication (Won, Lee, Song, & Poo, 2013). Finally, it is worth mentioning that some plants show broad range of activity towards several viruses. One such plant is mentioned in table 2.1 above, namely *Houttuynia cordata* Thunb., which showed anti influenza virus activity due to its polysaccharide and flavonoid contents (Ling et al., 2020).

2.2.3: SARS, MERS, and the novel Coronavirus (COVID-19)

Coronavirus is in the Coronaviridae family causing primarily infections in birds and animals (zoonotic infections) but can also be transmitted to humans and lead to infections in them too. This crossing of the species barrier was evident in the outbreaks of both severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 which caused thousands of deaths (Schoeman & Fielding, 2019).

Both SARS-CoV and MERS-Cov are in the β-coronavirus family (Alimuddin Zumla, David S Hui, 2020). The recent outbreak of COVID-19 at the end of 2019 which happened in Wuhan city, China (Cohen & Normile, 2020), is a result of a highly contagious infection by the SARS-CoV-2 virus among humans (Lu, 2020), has a higher mortality rate than its predecessors, and poses a great problem for humanity as new treatment modalities and a vaccine are trying to be developed to end its killing spree.

The genetic material of the new coronavirus (COVID-19) is a single-stranded positive-sense RNA and belongs to the β-coronavirus family (N. Chen et al., 2020) showing great similarity (%82) to the SARS-CoV (Lu, 2020). Currently, there is no specific treatment for COVID-19. Until the specific antiviral drugs are available, broad-spectrum antivirals like the Nucleoside analogues and HIV-protease inhibitors are used in the hopes to relieve the course of the disease (Lu, 2020). The treatments that have so far been attempted showed that patients were administrated existing antiviral drugs with a course of treatment including twice a day of oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0.25 g ganciclovir for 3–14 days (N. Chen et al., 2020). Another report showed that the broad-spectrum antiviral remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro (M. Wang et al., 2020). However, more research needs to be carried out to find a new specific treatment for the COVID-19. The most recent development was the FDA approval of the anti-parasitic drug ivermectin based on the promising results obtained in *in-vitro* trials. The drug was shown to reduce the viral RNA levels greatly 2 hours post-infection. It was shown to be effective against other viruses such as HIV, influenza A, and dengue (Caly, Druce, Catton, Jans, & Wagstaff, 2020)

Previously saikosaponins (triterpene glycosides) from medicinal plants were shown to be active against the activity of HCoV-22E9 by preventing viral attachment and penetration, as well as earlier stages of replication (P. W. Cheng, Ng, Chiang, & Lin, 2006). Extracts obtained from *Lycoris radiata*, *A.annua*, *Pyrrosia lingua*, and *Lindera aggregate* which are medicinal plants used in TCM have been documented for their activity against SARS-CoV (S. Y. Li et al., 2005). Helicase and protease enzymes together with myricetin, scuttellarein, and other phenolic compounds from *Isatis indigotica* and *Torreya mucifera* were active against the SARS-CoV enzymes (Lin et al., 2005; Y. B. Ryu et al., 2010; Yu et al., 2012). The water extract of *H. cordata* mentioned in table 3.1 has shown inhibition against SARS-CoV by inhibiting the viral protease and RNA-dependent RNA polymerase activities (Lau et al., 2008).

According to a recent review on the use of Chinese traditional medicine for the treatment of the new COVID-19, different herbal drugs were used for the treatment of different stages of the disease (Ang, Lee, Choi, Zhang, & Lee, 2020). For the mild stages, two drugs were mentioned namely *Magnolia officinalis* cortex and *Platycodonis* cortex. These two plants were normally prescribed for gastrointestinal problems and coughs respectively (Xi & Gong, 2017). The *in-vivo* effects of these two plants were previously established for their anti-inflammatory activity in acute lung injury models (Guo et al., 2018; Hu et al., 2017).

It is important to mention *Sambucus spp.* (elderberry) during these times. The species was used in southern Kosovo for respiratory diseases, asthma, and for general health (Mustafa et al., 2020), and in Bosnia and Herzegovina its use for fevers, colds, and high temperatures was recorded (Savić et al., 2019). *S. nigra* was used for pain, bronchitis, stomach infections, headache, diarrhea, and flu in the high river Ter valley of Catalonia (Rigat, Bonet, Garcia, Garnatje, & Vallès, 2007). The plant has been extensively reviewed thanks to the efforts of Porter and Bode, where its active constituents, the related *in-vitro* and *in-vivo* studies, and the approved products that can be accessed currently were reviewed in the research (Porter & Bode, 2017). The plant is mainly used for influenza like conditions, however, a thesis that was recently published mentions the potential use of the plant for viruses like the novel SARS-CoV-2. According to the thesis, the use of *S. nigra* L. extract on chicken coronaviruses with promising results on the inhibition of the earlier replication stages of the virus may indicate its potential effectiveness against human coronaviruses too, if further studied (Wermig-morgan, 2020).

A severe respiratory illness outbreak during the winter of 2017, in a long-term care facility in Louisiana has been reported and was associated with a human coronavirus named HCoV-NL63 (Hand et al., 2018). A study was conducted to assess the effectiveness of another elderberry species named *S. Formosona*Nakai against this virally infectious outbreak (Weng et al., 2019). The study results indicate a significant reduction of the viral yield, plaque formation, and viral attachment to the host cell. The effects were attributed to the caffeic acid, chlorogenic acid, and gallic acid contents of the plant.

The current COVID-19 pandemic is the focus point of the scientific community as of April 2020. On February 17, the Chinese State Council announced its endorsement of the possible beneficial effects of chloroquine phosphate, which is a structural analogue of quinine, the famous anti-malarial drug. The compound is isolated from barks of *Cinchona spp.*. Ancient uses of the tree parts mainly revolve around its use against fevers, such as those tales told in the Peruvian amazon (Urdang, 1945)), and its use in indigenous communities of South America (Thompson, 1928). The antiviral effects of chloroquine phosphate have been tested in more than 10 hospitals in China and has shown to alleviate symptoms and to speed up the virus seroconversion ("Redeploying plant defences," 2020).

CONCLUSION

This review focused on some of the most infectious viral disease that were endorsed by the WHO, and to date, are potential sources of epidemics or pandemics if not studied carefully for the potential treatment and prevention options. We have tried to compile as many plants as we could find that were adopted in traditional medical systems used worldwide, and that were additionally studied for their inhibition of the viruses mentioned.

Due to the vast amount of data available, it is important to apply high throughput screening techniques and make use of the up-to-date technological facilities in order to narrow down and weed out the wealth of information we have on hand in this 21st century. On this note, our suggesting for researchers would be to focus on broad range therapeutics such as *Aloe sp*., *Hottuynia sp*., and *Phyllanthus sp*., just to name a few. The advantage would be to gain a better understanding of the general mechanisms of plant metabolite functions, as well as to produce possible treatment modalities that remind its importance and urgency in times like the current COVID-19 outbreak. The study can be improved by carrying out a more comprehensive and systematic review on more plants and with easier access to ancient traditional medical texts.

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