Bioactive Natural Antivirals: An Updated Review of the Available Plants and Isolated Molecules

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Abstract: Viral infections and associated diseases are responsible for a substantial number of mortality and public health problems around the world. Each year, infectious diseases kill 3.5 million people worldwide. The current pandemic caused by COVID-19 has become the greatest health hazard to people in their lifetime. There are many antiviral drugs and vaccines available against viruses, but they have many disadvantages, too. There are numerous side effects for conventional drugs, and active mutation also creates drug resistance against various viruses. This has led scientists to search herbs as a source for the discovery of more efficient new antivirals. According to the World Health Organization (WHO), 65% of the world population is in the practice of using plants and herbs as part of treatment modality. Additionally, plants have an advantage in drug discovery based on their long-term use by humans, and a reduced toxicity and abundance of bioactive compounds can be expected as a result. In this review, we have highlighted the important viruses, their drug targets, and their replication cycle. We provide in-depth and insightful information about the most favorable plant extracts and their derived phytochemicals against viral targets. Our major conclusion is that plant extracts and their isolated pure compounds are essential sources for the current viral infections and useful for future challenges.

Keywords: HIV; HSV; Hepatitis C virus; influenza virus; COVID-19; plant extracts; phytochemicals

1. Introduction

A virus is a tiny parasite that has no capacity to replicate itself. Once infected in a host agent or living cell, it produces more viruses using host machinery. With their complexity and diversity, it survives for a long time in the host, bypassing the treatments, and it causes devastating issues such as pandemics [1]. They have RNA or DNA as genetic material with single or double-stranded nucleic acid. Using unique physical properties such as phospholipid layers, ligands, and configurations, they invaded into host cells easily [2]. Viral infections can lead to acute as well as chronic conditions. Acute infections happen in an out of balance way; for instance, it is a non-equilibrium process whereby the virus and host change its process until the destruction of the host or control over the infection. The ineffective function of specific genes related to the immunity of the host or effective reduction...
of host immunity by the viral genes is a niche in this infection and leads to the development of overwhelming consequences [3]. On the other hand, chronic viral infections occur in metastable equilibrium with viral and host genes balancing one another. Sometimes, the virus can persist in the healthy and immune host, which is deprived of any sign of infection [4].

Viral infections and associated diseases are responsible for a substantial number of mortality and public health problems around the world. Each year, infectious diseases kill 3.5 million people worldwide [5]. Even though there are different therapeutic strategies available in the clinical practice, a lack of specificity toward the virus, and the limited efficacy of drugs makes the vaccines a gold standard prophylactic to viral infections. Moreover, the synthetic drugs often do not meet the treatment expectation via either unwanted drug side effects or drug resistance to nucleoside analogues via mutation [6,7]. The drug failure and resistances have led to a growing interest in natural products, especially plants, and investigation into antiviral agent discovery. According to the World Health Organization (WHO), 65% of the world population is in the practice of using plants and herbs as part of the treatment modality [8]. Human use of plants as medicine, including viral infections, dates back 60,000 years to the Paleolithic age [9]. Hence, plants have an advantage in drug discovery based on their long-term use by humans, and lesser toxicity and plenty of bioactive compounds can be expected from them.

Hence, the aim of the present retrospective review is an update on the discovery regarding different plants and lead compounds isolated from them against the essential and clinically significant virus such as the human immunodeficiency virus (HIV), herpes simplex virus (HSV), influenza, and hepatitis c, clarifying their indication with viruses and mechanisms of action.

2. Methodology

To obtain the appropriate literature, we have used relevant keywords such as plants, viruses, phytochemicals, HIV, HSV, influenza, hepatitis-c, HIV integrase, HIV-reverse transcription, HIV-protease, virucidal action, virus replication imbibition, viral attachment, inhibition of hemagglutination, HCV infection replication, etc. These keywords were searched in relevant databases such as Google Scholar, PubMed, Scopus, Scielo, etc. We have collected information from research articles, review articles, PhD theses, books, chapters, and conference abstracts from 1975 to 2020. A total of 207 species have been reported in this review article. The taxonomy of the plant species was properly identified from http://www.theplantlist.org and http://www.ipni.org websites.

3. Human Immunodeficiency Virus (HIV)

The main target of the human immunodeficiency virus (HIV) is our immune system, where it affects and destroys the immune system function. At present, more than 35 million people are suffering from HIV; so far, it caused more than 39 million HIV-related deaths worldwide [10]. The overwhelming adverse effects of HIV continue globally. The treatment for HIV involves antiretroviral therapy (ART), which is a combination of HIV medicines. Since the year 2000, there has been a significant decrease in HIV-related patient deaths, which accounted for about 50% of all cases. This achievement maybe because of the successful use of ART regimen among the patients and new preventive strategies [11]. Regardless of this progress in HIV treatment with ART and the global measures taken for HIV prevention still, the newly infected HIV patient numbers have been increasing with the rate of 2 million every year [12].

HIV is a member of the genus Lentivirus, part of the family Retroviridae [13]. HIV contains two copies of single-strand RNA, which is the contributory agent of acquired immunodeficiency syndrome (AIDS) by a progressive decline of the immune system. In this condition, the infections take advantage of the weaker immune system, where the immune system is no longer in a stage to fight back. HIV is an enveloped positive-sense virus, which is meticulously focused on the immune system by infecting CD4+ T cells [14,15]. This T helper cell is the core of the immune system, whereby it handles signal transduction toward the rest of the immune cells and thereby protects the whole system against
life-threatening infections and endangering subjects. The first stage of infection is the attachment of HIV to the CD4+ lymphoid cell surface. After the viral capsid enters the cell, reverse transcriptase liberates a positive sense single-stranded RNA, coping it into a complementary DNA. Then, the nuclei of host cells become integrated with the viral RNA. The integrated DNA is then transcribed into RNA in the presence of transcription factors such as NF-kB, which is then spliced into messenger RNA (mRNA) [16–18]. Then, the structural protein is generated and made into a new virus particle (Figure 1).

![Figure 1. Human immunodeficiency virus structure and replication mechanism. The HIV structure in this figure has been modified from the source www.istockphoto.com.](image)

The antiviral treatments explicitly target these key areas of virus multiplication. Nonetheless, the infection rate of HIV is increasing in spite of ART [19]. Moreover, the ART has become more important, since there is no vaccine available against HIV. However, again, ART is not a panacea for HIV, due to the various side effects and resistance [20,21]. Hence, significant attempts have been employed by natural product biologists to find an alternative for ART. Even the WHO suggests and supports these initiatives. Many plants and plant products such as secondary metabolites have shown significant effects in these targets [22].

Natural products have been explored in finding anti-HIV agents with a critical focus in four mechanisms. They are HIV integrase strand transfer inhibitors [23], Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors (PIs) [24]. Integrase is a key enzyme by which HIV inserts (integrate) its viral DNA (proviral) into the DNA of the host CD4 cell. Thus, inhibiting the integrase in the cellular level is a significant target for anti-HIV drug discovery [25]. As per the Food and Drug Administration (FDA), Raltegravir was the first integrase strand inhibitor (INSTI) to be approved in 2007, followed by elvitegravir in 2012 and dolutegravir in 2014. [26]. Natural product discovery has been conducted much time by specifically inhibiting the integrase target [27]. Another target of anti-HIV drugs is reverse transcriptase inhibitors. The reverse transcriptase, a RNA-dependent DNA-polymerase, has been used by the virus to convert RNA to DNA, which is called reverse transcription. Hence, blocking reverse transcription will inhibit HIV replication [28]. In the last phase of viral replication, a viral protease is necessary for the cleavage of a large precursor polyprotein. This cleavage of a
protein precursor is crucial for the viral particle maturation and infectivity. Saquinavir, indinavir, ritonavir, and nelfinavir are a few examples of approved protease inhibitors by the WHO [29,30]. Thus, inhibiting protease is also considered as a significant target of anti-HIV natural products.

In our search for natural products in the mentioned databases, we have observed that the majority of the natural products are evaluated for anti-HIV properties up to the crude extraction level only. So, we found a few major secondary metabolites isolated from plants, which have good activity against HIV. A list of plant species with inhibition studies is summarized in Table 1.
Table 1. Review of the plants that have shown anti-HIV activities with their prospective family, part, type of extract, and inhibition target.

| No. | Plant Family     | Part      | Extract | Inhibition Target          | Ref.   |
|-----|------------------|-----------|---------|---------------------------|--------|
| 1   | Alchornea laxiflora | Euphorbiaceae | Root    | Methanol                  | HIV integrase [31] |
| 2   | Mimuseps elengi  | Sapotaceae | Leaf    | Ethanol                   | HIV integrase [32] |
| 3   | Sceletium tortuosum | Aizoaceae | Whole plant | Ethanol               | HIV integrase [33] |
| 4   | Hoodia gordonii | Apocynaceae | Whole plant | Ethanol               | HIV integrase [34] |
| 5   | Panax notoginseng | Araliaceae | Whole plant | Methanol             | HIV integrase [35] |
| 6   | Arctium lappa   | Asteraceae | Aerial   | Methanol                 | HIV integrase [35] |
| 7   | Blumea balsamifera | Asteraceae | Whole plant | Ethanol               | HIV integrase [36] |
| 8   | Chrysanthemum indicum | Asteraceae | Capitulum | Ethanol             | HIV integrase [35] |
| 9   | Chrysanthemum morifolium | Asteraceae | Capitulum | Ethanol             | HIV integrase [37] |
| 10  | Eclipta prostrata | Asteraceae | Whole plant | Chloroform           | HIV integrase [37] |
| 11  | Senecio scandens | Asteraceae | Whole plant | Methanol             | HIV integrase [34] |
| 12  | Boraginacea Cordia | Spinescens | Leaf    | Methanol, Aqueous       | HIV integrase [38] |
| 13  | Calophyllum inophyllum | Clusiaceae | Bark   | Methanol                 | HIV integrase [39] |
| 14  | Dioscorea bulbifera | Dioscoreaceae | Whole plant | Methanol             | HIV integrase [40] |
| 15  | Allizia procura | Fabaceae  | Whole plant | Methanol             | HIV integrase [35] |
| 16  | Caesalpinia sappan | Fabaceae  | Stem    | Methanol                 | HIV integrase [35] |
| 17  | Agastache rugosa | Lamiaceae | Whole plant | Aqueous methanol | HIV integrase [41] |
| 18  | Salvia miltiorrhiza | Lamiaceae | Root    | Aqueous                   | HIV integrase [42] |
| 19  | Lindera aggregate | Lamiaceae | Stem    | Methanol                 | HIV integrase [43] |
| 20  | Aglata lawii    | Lamiaceae | Leaf    | Methanol                 | HIV integrase [44] |
| 21  | Bersama abyssinica | Meliaceae | Root    | Aqueous                   | HIV integrase [45] |
| 22  | Articennia officinalis | Acanthaceae | Leaf    | Methanol                  | HIV-reverse transcription [46] |
| 23  | Justicia gendarussa | Acanthaceae | Aerial   | Ethanol                   | HIV-reverse transcription [47] |
| 24  | Rhinacanthus nasutus | Acanthaceae | Aerial   | Hexane                    | HIV-reverse transcription [48] |
| 25  | Acorus calamus  | Acoraceae | Rhizome | Hexane                    | HIV-reverse transcription [48] |
| 26  | Sambucus nigra  | Adoxaceae | Whole plant | Methanol             | HIV-reverse transcription [49] |
| 27  | Sambucus racemosa | Adoxaceae | Leaf    | Methanol                 | HIV-reverse transcription [50] |
| 28  | Aerva lanata   | Amaranthaceae | Root    | Hexane                    | HIV-reverse transcription [51] |
| 29  | Crinum amabile | Amaryllidaceae | Bulb   | Methanol                 | HIV-reverse transcription [52] |
| 30  | Ancistrocladus korupensis | Annonaceae | Root    | Methanol                  | HIV-reverse transcription [53] |
| 31  | Polyalthia sabrosa | Annonaceae | Stem    | Methanol                 | HIV-reverse transcription [47] |
| 32  | Ridolfia segetum | Apioaceae | Whole plant | Essential oil | HIV-reverse transcription [54] |
| 33  | Hemidesmus indicus | Apocynaceae | Whole plant | Methanol             | HIV-reverse transcription [55] |
| 34  | Tabernaemontana stapfi ana | Apocynaceae | Whole plant | Ethanol             | HIV-reverse transcription [56] |
| 35  | Calendula officinalis | Asteraceae | Leaf    | Dichloromethane          | HIV-reverse transcription [57] |
| No. | Plant                   | Family         | Part            | Extract | Inhibition Target       | Ref. |
|-----|-------------------------|----------------|-----------------|---------|------------------------|------|
| 36  | Gamochaeta simplicicaulis | Asteraceae     | Whole plant     | Pet ether | HIV-reverse transcription | [58] |
| 37  | Lobostemon trigonus     | Boraginaceae   | Whole plant     | Aqueous  | HIV-reverse transcription | [59] |
| 38  | Brassica rapa           | Brassicaceae   | Whole plant     | Methanol | HIV-reverse transcription | [60] |
| 39  | Lonicera japonica       | Caprifoliaceae | Flower          | Ethanol  | HIV-reverse transcription | [61] |
| 40  | Gymnosporia buchananii  | Celastraceae   | Whole plant     | Methanol | HIV-reverse transcription | [56] |
| 41  | Salacia chinensis       | Celastraceae   | Stem            | Methanol | HIV-reverse transcription | [48] |
| 42  | Combretum molle         | Combretaceae   | Root            | Aqueous  | HIV-reverse transcription | [62] |
| 43  | Ipomoea aquatic         | Convolvulaceae | Whole plant     | 80% ethanol | HIV-reverse transcription | [47] |
| 44  | Ipomoea cairica         | Convolvulaceae | Aerial          | Water    | HIV-reverse transcription | [47] |
| 45  | Ipomoea carnea          | Convolvulaceae | Aerial          | Water    | HIV-reverse transcription | [47] |
| 46  | Chamaesyce hyssopifolia | Euphorbiaceae  | Whole plant     | Methanol | HIV-reverse transcription | [38] |
| 47  | Acalypha Indica         | Euphorbiaceae  | Whole plant     | Methanol | HIV-reverse transcription | [63] |
| 48  | Euphoria polyacantha    | Euphorbiaceae  | Whole plant     | Aqueous  | HIV-reverse transcription | [52] |
| 49  | Mallotus philippensis   | Euphorbiaceae  | Flower          | Methanol | HIV-reverse transcription | [48] |
| 50  | Bauhinia variegata      | Fabaceae       | Whole plant     | Ethanol  | HIV-reverse transcription | [60] |
| 51  | Phaseolus vulgaris      | Fabaceae       | Seed            | Methanol | HIV-reverse transcription | [64] |
| 52  | Pterocarpus marsupium   | Fabaceae       | Whole plant     | Aqueous  | HIV-reverse transcription | [65] |
| 53  | Tripetospermum lanceolatum | Gentianaceae  | Whole plant     | Methanol | HIV-reverse transcription | [66] |
| 54  | Hypericum hircinum      | Hypericaceae   | Whole plant     | Ethanol  | HIV-reverse transcription | [67] |
| 55  | Ajuga decumbens         | Lamiaceae      | Whole plant     | Methanol | HIV-reverse transcription | [68] |
| 56  | Hyssopus officinalis     | Lamiaceae      | Leaf            | Methanol | HIV-reverse transcription | [69] |
| 57  | Ocimum kilimandscharicum | Lamiaceae      | Whole plant     | Methanol | HIV-reverse transcription | [70] |
| 58  | Ximenia caffra          | Olacaceae      | Whole plant     | Ethanol  | HIV-reverse transcription | [71] |
| 59  | Phyllanthus amarus       | Phyllanthaceae | Whole plant     | Aqueous  | HIV-reverse transcription | [72] |
| 60  | Scoparia dulcis         | Plantaginaceae | Leaf            | Ethanol  | HIV-reverse transcription | [73] |
| 61  | Canthium coromandelicum | Rubiaceae      | Leaf            | Methanol | HIV-reverse transcription | [74] |
| 62  | Alisma plantago-aquatica | Alismataceae   | Rhizome         | Aqueous  | HIV-protease            | [75] |
| 63  | Toxicodendron acuminatum | Anacardiaceae | Whole plant     | Methanol | HIV-protease            | [76] |
| 64  | Xylopia frutescens      | Annonaceae     | Bark            | Aqueous  | HIV-protease            | [38] |
| 65  | Ammi visnaga            | Aiphaeae       | Fruit           | Methanol | HIV-protease            | [77] |
| 66  | Anethum graveolens      | Aiphaeae       | Seed            | Methanol | HIV-protease            | [76] |
| 67  | Angelica grosseserrata  | Aiphaeae       | Aerial          | Aqueous  | HIV-protease            | [78] |
| 68  | Torilis japonica        | Aiphaeae       | Seed            | Methanol | HIV-protease            | [78] |
| 69  | Gymnema sylvestre       | Apocynaceae    | Whole plant     | Methanol | HIV-protease            | [79] |
| 70  | Garcinia buchieri       | Clusiaceae     | Steam           | Methanol | HIV-protease            | [80] |
| 71  | Garcinia kiongoensis    | Clusiaceae     | Steam           | Methanol | HIV-protease            | [80] |
The screening of medicinal plants has delivered plenty of secondary metabolites with anti-HIV properties. They include alkaloids, triterpenoids, flavonoids, coumarins, phenolics, tannins, saponins, phospholipids, xanthones, quinones, etc. [81]. There is a large pool of natural compounds with diverse structures, which target different viral targets. Some of them have been found to inhibit HIV integrase and some show RT inhibition (Table 2). The compounds for which we could not establish the mechanism of action will not be included in this review.

Table 2. Bioactive compounds derived from plants with anti-HIV activities.

| No. | Compound                          | Activity                      | Dose/IC$_{50}$ | Ref. |
|-----|-----------------------------------|-------------------------------|----------------|------|
| 1   | Ellagic acid                      | Inhibition of HIV integrase   | 90.23 µM       | [30] |
| 2   | Gallocatechin                     | Inhibition of HIV integrase   | 35.0 µM        | [31] |
| 3   | Hernandumine                      | Inhibition of HIV integrase   | 16.3 µM        | [82] |
| 4   | Laurolistine                      | Inhibition of HIV integrase   | 7.7 µM         | [82] |
| 5   | 7-oxohernangerine                 | Inhibition of HIV integrase   | 18.2 µM        | [82] |
| 6   | Lindechunine A                    | Inhibition of HIV integrase   | 21.1 µM        | [82] |
| 7   | Quercitrin                        | RT inhibition                 | 60 µM          | [83] |
| 8   | Gallic acid                        | Viral infection inhibition    | 0.36 µg/mL     | [84] |
| 9   | Erythro-7′-methylcarolignan E      | Viral infection inhibition    | 6.3 µM         | [83] |
| 10  | Ascalin                           | RT inhibition                 | 10 µM          | [85] |
| 11  | Justiprocumins A                  | RT inhibition                 | 200 µg/mL      | [47] |
| 12  | Robustaflavone                    | RT inhibition                 | 65 µM          | [86] |
| 13  | Hinokiflavone                     | RT inhibition                 | 65 µM          | [86] |
| 14  | Agathisflavone                    | RT inhibition                 | 119 µM         | [86] |
| 15  | Morelloflavone                    | RT inhibition                 | 100 µM         | [86] |
| 16  | Michellamines A                   | RT inhibition                 | 1 µM           | [87] |
| 17  | Betulinic acid                    | RT inhibition                 | 13 µM          | [88] |
| 18  | Michellamines A2                  | RT inhibition                 | 29.6 µM        | [89] |
| 19  | Michellamines A3                  | RT inhibition                 | 15.2 µM        | [89] |
| 20  | Michellamines A4                  | RT inhibition                 | 35.9 µM        | [89] |
| 21  | Michellamines B                   | RT inhibition                 | 20.4 µM        | [89] |
| 22  | Lupeol                            | RT inhibition                 | 3.8 µM         | [55] |
| 23  | Lupeol acetate                    | RT inhibition                 | 6.4 µM         | [55] |
| 24  | Chlorogenic acid                  | RT inhibition                 | 4.7 µM         | [55] |
| 25  | Artemisinin                       | RT inhibition                 | 100 µM         | [90] |
| 26  | Luteolin                          | RT inhibition                 | 12.8 µM        | [91] |
| 27  | Gossypetin                        | RT inhibition                 | 2 µg/mL         | [92] |
| 28  | Xanthonolomul                     | RT inhibition                 | 0.5 µg/mL       | [93] |
| 29  | Kaempferol 3-rhamnosyl-rutinosid  | RT inhibition                 | 0.23 µM        | [94] |
| 30  | Robustaflavone                    | RT inhibition                 | 65 µM          | [95] |
| 31  | Protostanes                       | RT inhibition                 | 5.8 µg/mL       | [96] |
| 32  | Morelloflavone                    | RT inhibition                 | 86 µM          | [97] |
| 33  | Anolignan A                       | RT inhibition                 | 156 µg/mL       | [95] |
| 34  | Cucurbitacins                     | RT inhibition                 | 28 µM          | [98] |
| 35  | Oleanolic acid                    | RT inhibition                 | 2 µg/mL         | [99] |
| 36  | p-cymene                          | RT inhibition                 | 7.6 µg/mL       | [99] |
| 37  | Baicalein                         | RT inhibition                 | 2 µg/mL         | [100]|

4. Herpes Simplex Virus

The herpes simplex virus (HSV) infection, otherwise known as genital herpes (GH), is the most frequent cause of genital ulceration worldwide. In general, herpes can appear commonly in the mouth and genitals. The primary cause of oral herpes is the HSV-1 type strain, but genital herpes is commonly caused by the HSV-2 type strain [101]. HSV-seronegative persons (vulnerable group) develop a primary infection on their first HSV-1 or HSV-2 exposure. HSV-1 and HSV-2 are normally spread by different routes and affect different areas of the body, however, the signs and symptoms that they cause overlap. The infection happens through primary contact with mucocutaneous surfaces of an infected person, whereas the virus enters the nerve cells to create latency in the sacral dorsal root.
ganglion and lesions at the point of entry. Even though HSV is rarely fatal, most people who have been infected and dormant viruses can reactivate; thus, an extensive of HSV pool is available to spread to vulnerable individuals in the society [102]. The estimated worldwide prevalence of HSV-1 is 67%, whereas HSV-2 is less common, infecting ~11% of the world population with the highest prevalence in Africa [103].

HSV is a member of Herpesviridae, which is a large family of enveloped double-stranded DNA viruses that causes diseases in both human and animals [104]. Even though Herpesviridae viruses vary in tissue tropism and host interaction mechanisms, they have a much-conserved tool by which they replicate their DNA in infection. Among the members of this family, HSV has been much exploited to study its mechanism of replication. It is well understood that other viruses of this family follow similar replication pathways, but they differ in the pace of activity [105]. Initially, the host cell attachment happens with the HSV virus. This attachment occurs at the heparan sulfate moieties of cellular proteoglycans with the glycoprotein present in the virus envelope, where they bind with the secondary cellular receptors. After the attachment, the viral envelope is released into the cytosol. This will facilitate the movement of capsid toward the nuclear pore, where the viral DNA will be released via the capsid portal. Once in the nucleus, viral DNA transcription leads to mRNA by cellular RNA polymerase II. This viral gene expression is tightly regulated, which is comprised of three kinetic expressions such as early, intermittent, and late mRNA formation. All mRNA transcripts are translated into proteins and travel into the cytoplasm from the nucleus by exocytosis (Figure 2).

![Herpes simplex virus structure and replication mechanism](https://pnghut.com)

**Figure 2.** Herpes simplex virus structure and replication mechanism. The HSV structure in this figure has been modified from the source https://pnghut.com.

There is no ultimate cure for HSV, but the current strategies are mainly focused on symptomatic relief. Both innate and adaptive immune systems can control HSV infections. In fact, the nature of HSV infection is dependent upon how the virus bypasses the host innate immune system. In the current system of practice, antiviral drugs are classified as virucidal, immunomodulators, and chemotherapeutic agents [108]. There is a starting treatment for HSV with acyclovir, valacyclovir, or famciclovir for 7–10 days for primary HSV infections [109]. After that, the treatment will be started only when the recurrence of HSV occurs, and the treatment will be episodic for five
days to prevent the symptoms and prevent recurrence [110]. These drugs act via a mechanism of inhibition of DNA polymerase. Even though these drugs are in practice, they can fail to meet the treatment expectation via either unwanted drug side effects or drug resistance to nucleoside analogues via mutation. Therefore, clinicians and microbiologists are always looking for a better alternative.

The natural products always served as a trustable source for new compounds with antiviral properties. Many studies have been carried out since 1995 to isolate bioactive antiviral compounds from plants and functional foods. Accordingly, a large number of plant-derived anti-HSV drugs have been described in several studies. A list of plant species with inhibition studies is summarized in Table 3.
## Table 3. Review of the plants that show anti-herpes simplex virus activities with their prospective family, part, type of extract, and inhibition target.

| No. | Plant                | Family             | Part       | Extract       | Mode of Action                           | Ref.       |
|-----|----------------------|--------------------|------------|---------------|------------------------------------------|------------|
| 1   | *Peganum harmala*    | Nitrariaceae       | Seed       | Methanol      | Virucidal action/HSV2                    | [111]      |
| 2   | *Pistacia vera*      | Anacardiaceae      | Seed       | Methanol      | Viral DNA synthesis inhibition/HSV1      | [112]      |
| 3   | *Rhus aromatica*     | Anacardiaceae      | Root       | Aqueous       | Inhibit the virus penetration/HSV1       | [113]      |
| 4   | *Quercus brantii*    | Cynipidae          | Aerial     | Chloroform    | Inhibit virus entry/HSV1                 | [114]      |
| 5   | *Tanacetum partitum* | Asteraceae         | Aerial     | Aqueous       | Virus replication imbibition/HSV1        | [115]      |
| 6   | *Cenella asiatica*   | Umbelliferae       | Aerial     | Aqueous       | Inhibit viral replication/HSV2           | [116]      |
| 7   | *Pistacia lentiscus* | Anacardiaceae      | Stem       | Methanol      | Virus absorption imbibition/HSV2         | [117]      |
| 8   | *Mangifera indica*   | Anacardiaceae      | Leaves     | Aqueous       | Inhibit of viral replication/HSV2        | [118]      |
| 9   | *Eucalyptus denticulata* | Asteraceae      | Aerial     | Acetone       | Inhibit virus entry/HSV1                 | [119]      |
| 10  | *Aglia odorata*      | Meliaceae          | Leaf       | Ethanol       | Inhibition of viral replication/HSV2     | [120]      |
| 11  | *Euphorbia coopire*  | Euphorbiaceae      | Flowers    | Chloroform/methylene chloride | Inhibition of viral replication/HSV1 | [121]      |
| 12  | *Rhus aromatica*     | Anacardiaceae      | Leaf       | Aqueous       | Inhibit virus entry/HSV2                 | [122]      |
| 13  | *Anacardium occidentale* | Anacardiaceae    | Leaf       | Aqueous       | Inhibit of viral replication/HSV2        | [123]      |
| 14  | *Phoradendron cassifolium* | Loranthaceae    | Leaf       | Ethanol       | Inhibit viral replication/HSV2           | [124]      |
| 15  | *Morus alba*         | Moraceae           | Leaf       | Aqueous methanol | Inhibition of viral replication/HSV1 | [125]      |
| 16  | *Aloe vera*          | Liliaceae          | Leaf       | Gel           | Replication inhibition/HSV1             | [126]      |
| 17  | *Annona muricata*    | Annonaceae         | Stembark   | Petroleum ether | Inhibition of viral replication/HSV2 | [127]      |
| 18  | *Petunia nyctaginiflora* | Solanaceae      | Stembark   | Petroleum ether | Inhibition of viral replication/HSV2 | [128]      |
| 19  | *Cuphea chartegegensis* | Lythraceae     | Aerial     | Ethanol       | Inhibition of viral replication/HSV1     | [129]      |
| 20  | *Graptopetalum paraguayense* | Crassulaceae  | Leaf       | Methanol/water | Inhibition of viral replication/HSV1 | [130]      |
| 21  | *Prunus dulcis*      | Rosaceae           | Almond skin | Methanol/HCl | Block virus entry                      | [131]      |
| 22  | *Equisetum giganteum* | Equisetaceae     | Root and stem | Ethanol/water | Inhibition of viral cell attachment and entry/HSV2 | [132]      |
| 23  | *Schinus terebinthifolia* | Anacardiaceae  | Bark       | Ethanol/water | Inhibition of viral attachment and penetration/HSV1 | [133]      |
| 24  | *Nepeta nuda*        | Lamiaceae          | Aerial     | Aqueous       | Inhibition of viral absorption and replication/HSV1 | [134]      |
| 25  | *Corus canadensis*   | Cornaceae          | Leaf       | Aqueous       | Virus absorption inhibition/HSV1        | [135]      |
| 26  | *Streptococcus pseudoquina* | Loganiaceae   | Stem       | Ethyl acetate | Interference with various steps of virus cycle/HSV1 | [136]      |
| 27  | *Tillandsia usnoides* | Bromeliaceae      | Fruits     | Ethanol       | Inhibition of viral replication/HSV1     | [137]      |
| 28  | *Copaifera reticulata* | Fabaceae         | Leaf       | Ethanol/water | Inhibition of viral cell attachment and entry/HSV2 | [138]      |
| 29  | *Spondias mombin*    | Anacardiaceae      | Leaf       | Methanol      | Inhibition of viral cell attachment/HSV1 | [139]      |
| 30  | *Solanum melongena*  | Solanaceae         | Peel       | Ethanol       | Reduction of viral protein              | [140]      |
| 31  | *Ixeris Sonchifolia* | Compositae         | Whole plant | Methanol      | Inhibition of viral replication/HSV1     | [141]      |
| 32  | *Eucaicosa longifolia* | Simaroubaceae    | Stem       | Methanol      | Inhibition of viral replication/HSV1     | [142]      |
| 33  | *Garcinia mangostana* | Guttiferae       | Leaf       | Methanol      | Inhibition of viral replication/HSV1     | [143]      |
| 34  | *Peganum harmala*    | Nitrariaceae       | Seed       | Methanol      | Block virus entry/HSV2                  | [144]      |
| 35  | *Eura multi fora*    | Eriaceae           | Ariel      | Methanol      | Inhibition of viral replication/HSV1     | [145]      |
| 36  | *Toma sureni*        | Meliaceae          | Leaf       | Methanol      | Inhibition of viral replication/HSV1     | [146]      |
| No. | Plant                  | Family         | Part          | Extract       | Mode of Action/Virus                  | Ref.   |
|-----|------------------------|----------------|---------------|---------------|---------------------------------------|--------|
| 37  | Eucalyptus caesia      | Myrtaceae      | Aerial        | Hydro-distillation | Virucidal activity/HSV1               | [137]  |
| 38  | Vachellia nilotica     | Fabaceae       | Bark          | Methanol      | Block virus attachment/HSV2           | [138]  |
| 39  | Stephania cephalantha  | Menispermaceae | Root          | Methanol      | Virucidal effect/HSV1                 | [139]  |
| 40  | Zygophyllum album      | Zygophyllaceae | Whole plant   | Acetone       | Virucidal effect/HSV1                 | [136]  |
| 41  | Ficus religiosa        | Moraceae       | Bark          | Methanol      | Virucidal effect/HSV1                 | [140]  |
| 42  | Eucalyptus alba        | Myrtaceae      | Fruit         | Aqueous       | Virucidal effect/HSV1                 | [134]  |
| 43  | Swertia chirata        | Renunculaceae  | Leaf          | Aqueous       | Virucidal effect/HSV1                 | [141]  |
| 44  | Scoparia dulcis        | Plantaginaceae | Leaf          | Methanol      | Inhibit the viral replication/HSV1    | [142]  |
| 45  | Pedilanthus tithymaloides | Euphorbiaceae | Leaves       | Methanol      | Virucidal activity/HSV1               | [137]  |
| 46  | Melaleuca leucadendron | Myrtaceae      | Fruit         | Aqueous       | Virucidal effect/HSV1                 | [144]  |
| 47  | Andrographis paniculata | Acanthaceae  | Leaf          | Ethanol       | Virucidal effect/HSV1                 | [137]  |
| 48  | Artemisia kermes newest | Asteraceae     | Aerial        | Hydro-distillation | Virucidal activity/HSV1              | [145]  |
| 49  | Vigna radiata          | Fabaceae       | Spout         | Methanol      | Virucidal activity/HSV1               | [134]  |
| 50  | Schlechteroa oleosa    | Sapindaceae    | Fruit         | Aqueous       | Virucidal activity/HSV1               | [134]  |
| 51  | Quercus persicolor     | Fagaceae       | Fruit         | Hydro alcoholic | Viral attachment inhibition/HSV1     | [146]  |
| 52  | Pongamia pinnata       | Papilionaceae  | Seed          | Aqueous       | Virucidal activity/HSV1               | [147]  |
| 53  | Perocarya stenoptera   | Jujuyandaceae  | Bark          | Methanol      | Viral attachment and penetration inhibition/HSV2 | [148]  |
| 54  | Avicennia marina       | Avicenniaceae  | Leaf          | Methanol      | Viral replication inhibition/HSV1     | [149]  |
| 55  | Nepheleum lapicseum    | Sapindaceae    | Pericarp      | Water/methanol | Virucidal activity/HSV1               | [134]  |
| 56  | Zataria multiflora     | Labiatae       | Aerial        | Hydro-distillation | Virucidal activity/HSV1          | [137]  |
| 57  | Ocimum sanctum         | Lamiaceae      | Aerial        | Methanol      | Viral infection inhibition/HSV1       | [150]  |
| 58  | Artocarpus lakoocha    | Moraceae       | Wood          | Methanol      | Viral infection inhibition/HSV1       | [106]  |
| 59  | Scevola gaudichaudiana | Asteraceae     | Aerial        | Dichloromethane | Viral absorption inhibition/HSV1    | [151]  |
| 60  | Rosmarinus officinalis | Lamiaceae      | Aerial        | Hydro-distillation | Virucidal activity/HSV1         | [137]  |
| 61  | Limonium sinese        | Plumbaginaceae | Root          | Ethanol       | Virucidal activity/HSV1               | [152]  |
| 62  | Prunella vulgaris       | Lamiaceae      | Fruit spikes  | Aqueous       | Block HSV-1 binding                  | [153]  |
| 63  | Heterophylla pustulata | Rubiaceae      | Fruit         | Dried powder  | Viral absorption inhibition/HSV1     | [154]  |
| 64  | Filicium decipiens     | Sapindaceae    | Stem bark     | Water/methanol | Virucidal activity/HSV1              | [134]  |
| 65  | Punica granatum        | Punicaceae     | Pericarp      | Water/methanol | Virucidal activity/HSV1              | [134]  |
| 66  | Satureja hotensis      | Lamiaceae      | Aerial        | Hydrodistillation | Virucidal activity/HSV1       | [137]  |
Many herbal compounds have been investigated in the past for their effectiveness against HSV. The purification of new lead compounds from the plants and evaluating their targets and mechanism of action in HSV is also equally important. Many secondary metabolites have been proven to have anti-HSV effects such as lignans, tannins, saponins, terpenes, alkaloids, quinones, and glucosides [155–158]. In Table 4, we have mentioned the compounds that exhibited viral inhibition with inhibitory activity at the early phase and late phase of replication and HSV viral inhibition with IC₅₀ dose.
Table 4. Bioactive compounds derived from plants with anti-HSV activities.

| No. | Compound                                      | Activity                                      | Dose/IC$_{50}$   | Ref.  |
|-----|-----------------------------------------------|-----------------------------------------------|------------------|-------|
| 1   | 4E-jatrogrossidentadion                       | Viral inhibition/HSV 1                        | 2.05 µg/mL       | [159] |
| 2   | 7-galloyl catechin                            | Viral inhibition/HSV 1                        | 43.2 µg/mL       | [119] |
| 3   | Gallic acid                                   | Viral inhibition/HSV 1                        | 49.8 µg/mL       | [119] |
| 4   | Kaempferol 3-O-β-(6'-O-galloyl)-glucopyranoside| Viral inhibition/HSV 1                        | 124.1 µg/mL      | [119] |
| 5   | Quercetin 3-O-β-(6'-O-galloyl)-glucopyranoside| Viral inhibition/HSV 1                        | 175.6 µg/mL      | [119] |
| 6   | Curcumin                                      | Viral inhibition/HSV 1                        | 49.8 µg/mL       | [119] |
| 7   | Quercetin                                     | Viral inhibition/HSV 1                        | 78.1 µg/mL       | [119] |
| 8   | Kaempferol                                    | Viral inhibition/HSV 1                        | 76.1 µg/mL       | [119] |
| 9   | 3,4-Dehydrocycleanine                        | Viral inhibition/HSV 1                        | 43.2 µg/mL       | [139] |
| 10  | (−)-Cycleanine                                | Viral inhibition/HSV 1                        | 26.3 µg/mL       | [139] |
| 11  | (−)-Norcycleanine                             | Viral inhibition/HSV 1                        | 18.1 µg/mL       | [139] |
| 12  | 2-Norcepharanolinalne                         | Viral inhibition/HSV 1                        | 26.3 µg/mL       | [139] |
| 13  | Obaberine                                     | Viral inhibition/HSV 1                        | 14.8 µg/mL       | [139] |
| 14  | Homoaromoline                                 | Viral inhibition/HSV 1                        | 15.1 µg/mL       | [139] |
| 15  | Aromoline                                     | Viral inhibition/HSV 1                        | 20.4 µg/mL       | [139] |
| 16  | Isotetrandrine                                | Viral inhibition/HSV 1                        | 17.4 µg/mL       | [139] |
| 17  | Berbamine                                     | Viral inhibition/HSV 1                        | 17.4 µg/mL       | [139] |
| 18  | Thalrugosine                                  | Viral inhibition/HSV 1                        | 16.8 µg/mL       | [139] |
| 19  | Obamegine                                     | Viral inhibition/HSV 1                        | 23.5 µg/mL       | [139] |
| 20  | 2-Norberbamine                                | Viral inhibition/HSV 1                        | 16.8 µg/mL       | [139] |
| 21  | 3',4'-Dihydrostephasubine                     | Viral inhibition/HSV 1                        | 27.4 µg/mL       | [139] |
| 22  | Palmatine                                     | Viral inhibition/HSV 1                        | 34.0 µg/mL       | [139] |
| 23  | Cephakicine                                   | Viral inhibition/HSV 1                        | 44.5 µg/mL       | [139] |
| 24  | N-Methylcrotsparine                           | Viral inhibition/HSV 1                        | 8.3 µg/mL        | [139] |
| 25  | Andrographolide                               | Viral inhibition/HSV 1                        | 8.28 µg/mL       | [144] |
| 26  | Neoandrographolide                            | Viral inhibition/HSV 1                        | 7.97 µg/mL       | [144] |
| 27  | 14-Deoxy-11,12-didehydroandrographolide       | Viral inhibition/HSV 1                        | 11.1 µg/mL       | [144] |
| 28  | Oxyresveratrol                                | Inhibitory activity at the early phase and late phase of replication/HSV1 | 24 µg/mL         | [106] |
| 29  | Samaranegnin B                                | Inhibition of viral replication/HSV1          | 11.4 µg/mL       | [152] |
| 30  | (−)-epigallocatechin 3-O-gallate              | Viral inhibition/HSV 1                        | 38.6 µg/mL       | [152] |
| 31  | Pterocarnin A                                 | Viral attachment inhibition/HSV 1            | 5.4 µM           | [148] |
| 32  | Scopadulcic acid B                            | Viral attachment inhibition/HSV 1            | 0.012 µM         | [142] |
5. Influenza Virus

Pandemics are the mainly remarkable appearances of the influenza virus [160]. Three pandemics happened in the previous century: the H1N1 pandemic (1918), the H2N2 pandemic (1957), and the H3N2 pandemic (1968) [161,162]. Influenza is observed nationally and internationally through a multiparty system of surveillance systems distributed worldwide that eventually feeds into the WHO global influenza program [163,164]. The annual incidence is 3.5 million, with more than 250,000 deaths [165]. Alpha-influenzavirus is the primary cause of all the pandemics [166,167]. Various waves of beta-influenzavirus flu were observed in local settings around the world [168].

Influenza virus belongs to Orthomyxoviridae family (RNA viruses), which includes seven genera (Alpha, Beta, Delta, Gamma, Isavirus, Quaranjavirus, and Thogotovirus) [169,170]. Alpha, Beta, Delta, and Gamma caused mammalian flu. There are 18 various hemagglutinin (HA) subtypes and 11 various neuraminidase (NA) subtypes [171,172]. Subtypes are named by combining the H and N numbers—e.g., A(H1N1), A(H3N2). On the other hand, influenza B viruses are classified into two lineages: B/Yamagata and B/Victoria [173,174]. This genetic pattern imitates the altered nature of the antigenic properties of these viruses, and their following outbreak depends upon various factors [174,175]. Influenza B virus was supposed to have a weaker rate of antigenic progression than A and to cause milder sickness than A in the past [176,177].

Influenza virus mainly targets the columnar epithelial cells in the respiratory tract [178]. Firstly, the hemagglutinin (HA) present in the receptor binding site of virus attached to galactose bound sialic acid on the surface of the host. This receptor binding is the determining factor for turning part of an organism in a particular direction of infection in response to a virus stimulus. To achieve this receptor binding, the virus undergoes tremendous efforts to bypass host immune responses, mucociliary clearance, and genetic diversification of the host receptor. Then, after the binding, viron enters the host cell by an endocytosis mechanism with the protease cleavage of hemagglutinin. Then, the viron produces a vacuole membrane, which releases the viral RNA and proteins into the cytosol. These proteins and RNA form a complex (vRNA/RdRP), which reaches the nucleus [179,180]. Then, the viral RNA is translated into newly synthesized proteins, which are secreted via the Golgi apparatus to the nucleus to bind viral RNA to form a viral particle. Later, the RNA particle and viral proteins accumulate to form a new viron and buds off from the cell membrane (Figure 3).

![Figure 3](https://viralzone.expasy.org/)

**Figure 3.** Orthomyxovirus structure and replication mechanism. The Orthomyxovirus structure in this figure has been modified from the source [https://viralzone.expasy.org/](https://viralzone.expasy.org/).
In the contingency of a flu pandemic with a new strain, antiviral drugs symbolize the primary line of defense [181,182]. Research on the development of anti-influenza medications was started a long time ago [183,184]. This approach was based on the two mechanisms that induce viral replication in host immune reactions [185,186]. Viral replication has various cellular targets starting from the release of the new viruses from the host cells. Many drugs were scientifically proven to inhibit M2 Ion Channel and Neuraminidase on the virus itself [187,188], while other drugs work on some cell pathways evolving intracellular defense mechanisms [189]. This research on the development of anti-influenza medications also includes identifying traditional medicinal plant extracts and active compounds with anti-influenza activity [190]. These folk drugs were developed as an alternative to synthetic drugs. The exploration of plant-based antivirals against the influenza virus is hopeful, as several plants have been shown to have anti-influenza action. Therefore, the current review paper summarizes the previous findings and efforts of some studies on discovering anti-influenza medications from medicinal plants. A list of plant species with inhibition studies is summarized in Table 5.
Table 5. Review of the plants that have shown anti-flu virus activities with their prospective family, part, type of extract, and inhibition target.

| No. | Plant Family | Plant Name | Part | Type of Extract | Inhibition Target | Ref. |
|-----|--------------|------------|------|-----------------|-------------------|-----|
| 1   | Cistaceae    | Cistus incanus | Whole plant | Polyphenol-rich plant extract | MDCK cell-based assay | [191] |
| 2   | Cupressaceae | Thuja orientalis | Leaves | Methanol | Blockage of attachment to the host cells and inhibition of replication | [192] |
| 3   | Apiaceae     | Pimpeniella anisum | Seeds | Aqueous | Direct effect on replication | [193] |
| 4   | Xanthorrhoeaceae | Aloe sinana | Root and leaf latex | Methanol | Induced CPE and increased the cell viability of Vero cells | [194] |
| 5   | Lythraceae   | Punica granatum L. | Peel | Ethanol | Inhibit influenza A virus replication | [195] |
| 6   | Geraniaceae  | Geranium thunbergii | Dried aerial part | Ethanol | Neuraminidase (NA) inhibitors | [196] |
| 7   | Rubiaceae    | Mussaenda elmeri | Whole plant | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 8   | Euphorbiaceae | Trigonopleura malayana | Leaves | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 9   | Rubiaceae    | Mussaenda elmeri | Whole plant | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 10  | Burseraceae  | Santiria apiculata | Whole plant | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 11  | Anisophylleaceae | Anisophylla disticha | Stems | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 12  | Annonaceae   | Trivalvaria macrophylla | Roots | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 13  | Euphorbiaceae | Baccarea angulata | Stems | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 14  | Dilleniaceae | Tetracera macrophylla | Leaves | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 15  | Clusiaceae   | Calophyllum lanigerum | Whole plant | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 16  | Clusiaceae   | Calophyllum lanigerum | Stems | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 17  | Fabaceae     | Albizia corniculata | Stems | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 18  | Rubiaceae    | Mussaenda elmeri | Whole plant | Dichloromethane and methanol in a 1/1 (v/v) ratio | Inhibition of hemagglutination | [197] |
| 19  | Polygonaceae | Polygonum chinense | Whole plant | Methanol | Inhibited viral replication viral neuraminidase | [198] |
| 20  | Orchidaceae  | Bletilla striata | Rhizomes | Ethanol | Viability assay | [199] |
| No. | Plant                          | Family            | Part            | Extract           | Inhibition Target                                                                 | Ref. |
|-----|--------------------------------|-------------------|-----------------|-------------------|----------------------------------------------------------------------------------|------|
| 21  | *Jatropha multifida* Linn       | Euphorbiaceae     | Stems           | 70% aqueous ethanol | Virus-infected MDCK cells-based assay Inhibit polymerase activity and reduce virus nucleoprotein (NP) RNA level. | [200]|
| 22  | *Dandelion*                     | Asteraceae        | Whole plant     | Aqueous           | Inhibit replication                                                               | [201]|
| 23  | *Radix Paeoniae* Alba           | Paeoniaceae       | Roots           | Aqueous           | Inhibited the virus-induced hemagglutination of chicken RBCs                     | [202]|
| 24  | *Balanites aegyptiaca*          | Zygophyllaceae    | Leaves          | Aqueous or 70% methanol | Inhibited the virus-induced hemagglutination of chicken RBCs                     | [203]|
| 25  | *Cordia africana,*              | Boraginaceae      | Bark            | Aqueous or 70% methanol | Inhibited the virus-induced hemagglutination of chicken RBCs                     | [203]|
| 26  | *Aristolochia bracteolata*      | Aristolochiaceae  | Whole plant     | Aqueous or 70% methanol | Inhibited the virus-induced hemagglutination of chicken RBCs                     | [203]|
| 27  | *Bosica senegalensis*           | Capparaceae       | Leaves          | Aqueous or 70% methanol | Inhibited the virus-induced hemagglutination of chicken RBCs                     | [203]|
| 28  | *Leptadenia arboea*             | Apocynaceae       | Roots           | Aqueous or 70% methanol | Inhibited the virus-induced hemagglutination of chicken RBCs                     | [203]|
| 29  | *Punica granatum*L.             | Lythraceae        | Peel            | Ethyl alcohol extract | Inhibition of viral adsorption and viral RNA transcription                       | [204]|
| 30  | *Caesalpinia decapetala*        | Fabaceae          | Leaves          | 75% aqueous ethanol | Inhibit replication                                                               | [205]|
Among viral infections, the viruses of the influenza viral infection have the ability to mutate their genome and become resistant to drugs [206]. Thus, the discovery of phytochemicals against the influenza virus is more challenging compared to other viruses. Among the phytochemicals, alkaloids have shown superior activity against flu virus. It is believed that the alkaloids have the ability to kill virus by the induction of interferon of the immune system [207]. Some alkaloids can increase the phagocytosis by macrophages activity, whereas some can inhibit viral protein synthesis [208]. Besides, the inhibition of influenza by lignans [209] and terpenes [210] was well documented. In Table 6, we have mentioned the compounds that exhibited inhibitory activity on viral inhibition with an IC_{50} dose.

### Table 6. Bioactive compounds derived from plants with anti-flu activities.

| No. | Compound                        | Activity                                      | Dose/IC_{50}     | Ref.       |
|-----|---------------------------------|-----------------------------------------------|------------------|-----------|
| 1   | Pentagalloylglucose             | Inhibited the virus-induced hemagglutination of chicken RBCs | 11.3 µg/mL [211] |           |
| 2   | Quercetin                       | Inhibit the entry of the H5N1 virus           | 7.75 µg/mL [212] |           |
| 3   | Apigenin                        | Inhibited viral replication viral neuraminidase | 21.54 µM [213]   |           |
| 4   | Baicalein                       | Inhibited H5N1 viral replication viral neuraminidase | 18.79 µM [213]   |           |
| 5   | Biochanin A                     | Inhibited H5N1 viral replication viral neuraminidase | 8.92 µM [213]   |           |
| 6   | Hispidulin                      | Inhibition against H1N1 neuraminidase         | 11.18 µM [214]   |           |
| 7   | Nepetin                         | Inhibition against H1N1 neuraminidase         | 12.54 µM [214]   |           |
| 8   | Rosmarinic acid methyl ester    | Inhibition against H1N1 neuraminidase         | 15.47 µM [214]   |           |
| 9   | Luteolin                        | Inhibition against H1N1 neuraminidase         | 19.83 µM [214]   |           |
| 10  | Homonojirimycin                 | Inhibition against H1N1 neuraminidase         | 10.4 µg/mL [215] |           |
| 11  | Dendrobine                      | Inhibited early steps in the H1N1 viral replication cycle | 3.39 µg/mL [216] |           |

### 6. Hepatitis C Virus

Hepatitis C virus (HCV) infection is considered as a significant public health problem. It has infected around 180 million people worldwide [217]. In developed nations, the transmission is thought to be through sharing and the unsafe use of needles among drug users. In the meantime, in the other parts of the world, unsafe blood transfusion and unhealthy injection practices contribute to the development of HCV infection [218]. At present, no vaccine against HCV is available, and the presence of a high diversity of viral isolates will possibly make it very hard to develop a vaccine. Over the last five years, direct-acting antiviral agents (DAAs) have revolutionized the treatment of HCV infection with their specific mechanism of action [219]. DAAs were introduced in 2014, provided effective interferon-free therapy combinations for all HCV genotype, and have very few safety considerations. Serious adverse events are rare, but drug-drug interactions are considered a major issue regarding the choice of DAA regimen, which needs drug-drug interaction assessment before starting therapy [220].

Hepatitis C virus belongs to the Hepacivirus genus of the Flaviviridae family. It is a small enveloped virus with single-stranded genomic RNA with two embedded viral glycoproteins [221]. In the perisinusoidal space (between hepatocyte and a sinusoid), the lipo-viral particle is attached to the basolateral surface of the hepatocyte by virtue of a variety of receptors such as proteoglycans, LDL receptor, CD81, and claudin 1. After the endocytosis, the M2 proteins allow a pH-dependent fusion with the lysosome and the protons to move through the viral envelope, causing the uncoating and release of the viral RNA. Then, the viral replication proteins recruit membranes from the Endoplasmic Reticulum (ER) to form the closely ER-associated “Membranous web”, which is the site of viral replication. Afterward, the viral particles will remain in the nucleus or move to the cytosol, where they are translated into viral proteins via the Golgi apparatus. In addition, the viral proteins sometimes are brought back into the nucleus, where they bind with viral RNA and later form new viral genome particles [222,223]. The new virion buds off from the cell in a phospholipid sphere and is released from the cell (Figure 4).
Figure 4. Hepatitis C virus structure and replication mechanism. The Ortomyxovirus structure in this figure has been modified from the source https://www.gettyimages.ae/.

There are synthetic agents available now against HCV, but they have a lack of specific treatment for HCV therapy. Another concern in these cases is the presence of severe side effects and reported poor response rates. To manage and to get these problems under control for better treatment against HCV, new potential agents to be explored. As we see in the cases of other viruses discussed in the review, there are many promising natural products, which have led to the discovery of potent HCV inhibitors. A list of plant species with inhibition studies is summarized in Table 7.
Table 7. Review of the plants that have shown anti-HCV activities with their prospective family, part, type of extract, and inhibition target.

| No. | Plant                | Family         | Part     | Extract    | Inhibition Target               | Ref.       |
|-----|----------------------|----------------|----------|------------|---------------------------------|------------|
| 1   | *Ajuga bracteosa*    | Lamiaceae      | Leaves   | Methanol   | HCV infection                   | [224]      |
| 2   | *Ajuga parviflora*   | Lamiaceae      | Leaves   | Methanol   | HCV infection                   | [224]      |
| 3   | *Berberis lycium*    | Lamiaceae      | Roots    | Methanol   | HCV infection                   | [224]      |
| 4   | *Toona sureni*       | Meliaceae      | Leaves   | 80% Ethanol| HCV infection                   | [225]      |
| 5   | *Melicope latifolia* | Rutaceae       | Leaves   | 80% Ethanol| HCV infection                   | [225]      |
| 6   | *Melanolepis multiglandulosa* | Euphorbiaceae | Stems    | 80% Ethanol| HCV infection                   | [225]      |
| 7   | *Ficus fistulosa*    | Moraceae       | Leaves   | 80% Ethanol| HCV infection                   | [225]      |
| 8   | *Phyllanthus amarus* | Phyllanthaceae | Whole plant | Methanol | Inhibition of HCV RNA replication | [226]      |
| 9   | *Acacia nilotica*    | Mimosaceae     | Bark     | Methanol   | Hepatitis C virus (HCV) protease inhibition | [227]      |
| 10  | *Boswellia carterii* | Burseraceae    | Root     | Methanol   | Hepatitis C virus (HCV) protease inhibition | [227]      |
| 11  | *Embelia schimperi*  | Myrsinaceae    | Fruit    | Methanol   | Hepatitis C virus (HCV) protease inhibition | [227]      |
| 12  | *Piper cubeba*       | Piperaceae     | Fruit    | Aqueous    | Hepatitis C virus (HCV) protease inhibition | [227]      |
| 13  | *Quercus infectoria* | Fagaceae       | Gall     | Methanol   | Hepatitis C virus (HCV) protease inhibition | [227]      |
| 14  | *Syzygium aromaticum*| Myrtaceae      | Fruit    | Aqueous    | Hepatitis C virus (HCV) protease inhibition | [227]      |
| 15  | *Trachypermum amni*  | Apiceae        | Fruit    | Methanol   | Hepatitis C virus (HCV) protease inhibition | [227]      |
| 16  | *Morinda citrifolia* | Rubioideae     | Leaves   | Methanol   | Hepatitis C virus (HCV) protease inhibition | [228]      |
| 17  | *Silybum marianum*   | Asteraceae     | Flower   | Methanol   | Hepatitis C virus (HCV) protease inhibition | [229]      |
| 18  | *Limonium sinense*   | Plumbaginaceae | Flower   | Aqueous    | HCV infection                   | [230]      |
| 19  | *Bupleurum kaoi*     | Apiaceae       | Root     | Methanol   | Inhibit HCV entry               | [231]      |
| 20  | *Rhizoma ciptidis*   | Ranunculaceae  | Whole    | Methanol   | Inhibit HCV entry               | [232]      |
| 21  | *Schisandra sphenanthera* | Schisandraceae | Rhizome  | Methanol   | Inhibit HCV entry               | [232]      |
| 22  | *Solanum nigrum*     | Solanaceae     | Seed     | Chloroform | NS3 protease inhibition         | [233]      |
| 23  | *Terminalia arjuna*  | Combretaceae   | Bark     | Methanol   | NS3 protease inhibition         | [226]      |
| 24  | *Embelia ribes*      | Myrsinaceae    | Leaf     | Aqueous    | NS3 protease inhibition         | [234]      |
| No. | Plant                     | Family            | Part     | Extract  | Inhibition Target                                      | Ref.   |
|-----|--------------------------|-------------------|----------|----------|--------------------------------------------------------|--------|
| 25  | *Aeginetia indica*       | Orobanchaceae     | Whole    | Aqueous  | NS5B polymerase inhibition                              | [235]  |
| 26  | *Rhodiola kirilowii*     | Crassulaceae      | Flower   | Ethanol  | NS3 protease inhibition                                 | [236]  |
| 27  | *Schisandra sphenanthera* | Schisandraceae    | Fruit    | Ethanol  | Inhibition of HCV entry                                 | [237]  |
| 28  | *Spatholobus suberectus* | Fabaceae          | Leaf     | Ethanol  | NS3 protease inhibition                                 | [238]  |
| 29  | *Vitis vinifera*         | Vitaceae          | Root     | Ethanol  | NS3 helicase inhibition                                 | [239]  |
| 30  | *Cinnamomi cortex*       | Lauraceae         | Bark     | Methanol | Inhibition of HCV replication and RNA synthesis         | [240]  |
Developing an anti-HCV drug has become an important priority due to the complexity of the disease. Natural compounds always serve as a lead to create new drugs. There is a substantial increase in the reports on phytochemicals that show anti-HCV properties. Both primary and secondary metabolites have shown promising activities. For instance, alkaloids, flavonoids, polyphenols, coumarins, and peptides have been reported to possess anti-HCV activities [241]. We have identified such molecules and listed them in Table 8.

**Table 8. Bioactive compounds derived from plants with anti-HCV activities.**

| No. | Compound                        | Activity                                          | Dose/IC50       | Ref.     |
|-----|--------------------------------|---------------------------------------------------|-----------------|----------|
| 1   | Embelin                         | Hepatitis C virus (HCV) protease inhibition       | 21 µM [227]     |          |
| 2   | Silymarin                       | NS5B polymerase inhibition                        | 40 µM [242]     |          |
| 3   | 5-O-Methylembelin               | Hepatitis C virus (HCV) protease inhibition       | 46 µM [227]     |          |
| 4   | Phosphoribide a                 | Hepatitis C virus (HCV) protease inhibition       | 0.3 µg/mL [228] |          |
| 5   | Pentagalloylglucose              | Inhibit viral attachment                          | 2.2 µM [243]    |          |
| 6   | Quercetin                       | inhibitory effect of NS3 catalytic activity       | 10 µg/mL [234]  |          |
| 7   | Panthenolgenin                  | Hepatitis C virus (HCV) protease inhibition       | 200 µM [244]    |          |
| 8   | (+)-Epicatechin                 | Inhibition of HCV replication                     | 75 µM [245]     |          |
| 9   | (−)-Epicatechin                 | Inhibition of HCV replication                     | 75 µM [245]     |          |
| 10  | Ladanin                         | inhibition of the post attachment entry step of HCV| 2.5 µM [246]    |          |
| 11  | Luteolin                        | Inhibition of HCV infection                      | 7.9 µM [247]    |          |
| 12  | Honokiol                        | Replication in NS5B polymerase                    | 4.5 µM [248]    |          |
| 13  | 3-Hydroxy carulignan C          | Inhibition of HCV replication                     | 37.5 µM [249]   |          |
| 14  | Gallic acid                     | Inhibition of viral entry                         | 24.31 µM [230]  |          |
| 15  | Saikosaponin b2                 | Inhibition of viral entry                         | 16.13 µM [231]  |          |
| 16  | Delphinidin                     | Inhibition of viral entry                         | 3.7 µM [250]    |          |
| 17  | Amentoflavone                   | Inhibition of viral entry                         | 42 µM [251]     |          |
| 18  | 7,40-Dihydroxyflavanone         | Inhibition of viral entry                         | 42 µM [251]     |          |
| 19  | Orobol                          | Inhibition of viral entry                         | 42 µM [251]     |          |
| 20  | 3,3′-Digalloyloprodelphinidin    | NS5 protease inhibition                           | 0.77 µM [236]   |          |
| 21  | B2, 3,3′-Digalloyloprocyanidin   | NS5 protease inhibition                           | 0.91 µM [236]   |          |
| 22  | B2, (−)-Epigallocatechin-3-O-gallate, (−)-Epicatechin- | NS5 protease inhibition | 8.51 µM [236] |          |
| 23  | 3-O-gallate                     | NS5 protease inhibition                           | 18.55 µM [236]  |          |
| 24  | Schizandronic acid              | Inhibition of HCV entry                           | 5.27 µg/mL [237]|          |
| 25  | Vitisin B                       | NS3 helicase inhibition                           | 0.006 µM [239]  |          |
| 26  | Procyanidin B1                  | Inhibition of HCV replication and RNA synthesis   | 29 µM [240]     |          |
| 27  | Plumbagin                       | Inhibition of HCV infection                       | 0.57 µM [252]   |          |
| 28  | Caffeine                        | Replication in NS5B polymerase                    | 0.726 mM [253]  |          |
| 29  | Ursolic acid                    | Replication in NS5B polymerase                    | 16 µg/mL [254]  |          |

7. Conclusions

Viral infections and pandemic have been recorded as a potential risk for human survival. The lack of proper prophylactic vaccines and drugs for many viruses makes the situation worse in health management. There is a great need for novel antiviral compounds for drug development. This review provides in-depth and insightful information about different species of plants and their families with significant secondary metabolites with evidence-based antiviral properties. Based on the literature, we provided very promising drug candidates that have been investigated through in vitro screening, and cellular targets have been observed. In the current review, we have selected HIV, HSV, HCV and Influenza virus. Looking at the spectrum of plants and isolated compounds, we have seen that there is no significant selectivity among the plants and their compounds in inhibiting DNA or RNA virus. We have found that a similar class of phytochemicals can inhibit both types, but with the ability to inhibit different sites of mechanism. However, these compounds need a lot of further investigation to make them appropriate for clinical use. The pace of new antiviral drugs from natural origin has experienced a substantial upsurge in the last decade. Natural products directly or indirectly support the drug discovery against viruses. Many anti-viral drugs has been discovered from a synthetic source, but originally modeled on a natural product parent structure. Most of the plants we
have identified in this review hold other pharmacological benefits, proven long ago, together with their safety profile. This promotes the acceptance of these plants and their phytochemicals for antiviral drug discovery and development programs. Nevertheless, a thorough purification process for identifying new lead compounds and their preclinical and safety testing is a prerequisite. The current COVID-19 pandemic has taught us a more significant lesson: it is difficult to survive in this earth without accepting the probability of more pandemics in the future. Hence, taking the facts in a very comprehensive manner, a cohesive and focused drug discovery approach is warranted.

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