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# Antiviral Effects of Plant Extracts Used in the Treatment of Important Animal Viral Diseases

**Gamil Sayed Gamil Zeedan and Abeer Mostafa Abdalhamed**

*Department of Parasitology and Animal Diseases, National Research Centre, 33 Bohouth Street, Dokki, 12622, Egypt*

*Corresponding author's E-mail: gamilzee@yahoo.com; ORCID: 0000-0002-2723-542X

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**ABSTRACT**

The goal of this review was to highlight some plant species that have significant antiviral activity against DNA and RNA viruses *in vitro* and *in vivo* although more research is needed to address safety issues, drug interactions, and the possibility of using them in combination with other natural products. Viral infection plays an important role in human and animal diseases. Although there have been advances in immunization and antiviral drugs, there is still a lack of protective vaccines and effective antiviral drugs in human and veterinary medicine. The lack of effective antivirals necessitates the search for new effective antiviral compounds. Plants are naturally gifted at synthesizing antiviral compounds. They are rich sources of phytochemicals with different biological activities, including antiviral activities as a result of advanced analytical chemistry, standard virus assays, and development of standardization and extraction methods. Plant extracts have a wide variety of active compounds, including flavonoids, terpenoids, lignans, sulphides, polyphenolics, coumarins, saponins, furyl compounds, alkaloids, polyines, thiophenes, proteins, and peptides. Moreover, certain volatile oils have indicated a high level of antiviral activity. Replication, assembly, and release, as well as targeting virus host-specific interactions capable of inhibiting several viruses, could help the development of broad-spectrum antivirals for the prevention and control of viral pathogens. The *in vitro* antiviral activities of *Erythroxylum deciduum*, *Lacistema hasslerianum* (*chodat*), *Xylopia aromatica*, *Heteropteris aphrodisiaca*, *Acacia nilotica* (*gum arabic tree*), *Lippia graveolens* (*Guettarda angelica* (Velvetseed), *Prunus myrtifolia*, and *Symphyopappus* plant extracts can inhibit viral replication, and interfer with the early stages of viral adsorption of DNA viruses. However, *Boesenbergia rotunda* plant extracts have inhibited RNA viruses. A potent anti-SARS-CoV-2 inhibitor with *B. rotunda* extract and *panduratin A* after viral infection drastically suppresses SARS-CoV-2 infectivity in Vero E6 cells.

**Keywords:** Bovine herpes virus type-1, Bovine infectious, Bovine infectious cell protein 4, Buffalo pox virus, Foot-and-mouth disease, Plant extracts, Rotaviruses

## INTRODUCTION

Viral diseases are responsible for considerable rates of morbidity and mortality worldwide. Infectious viral diseases are still a major threat to public health and remain an important problem all over the world for humans and animals (Mani et al., 2012; Sarma 2017; Alakunle et al., 2020). Antivirals are medications or substances that have a protective or therapeutic effect on the virus-infected host (Abdalhamed et al., 2021; Dakum et al., 2021; Gakhar, 2021). Propolis has valuable properties, such as immunomodulatory, anti-inflammatory, hepatoprotective, anti-oxidative, antiviral, antibacterial, and antitumor that have potential health-promoting effects on humans, livestock animals, and poultry (Saeed et al., 2017).

The use of antiviral drugs in treating human and veterinary medicine is limited, compared to the use of antimicrobial agents due to viral mutant resistance to existing antivirals, emerging new viral pathogens, side toxic effects, high costs (Cos et al., 2006; Zeedan et al., 2019; Mahmud et al., 2021), the severity of viral diseases, and the ability of the virus to survive intracellularly (Varijakzhan et al., 2021). However, according to (WHO, 2010) at least 80% of people in African people still rely on medicinal plants for their health care.

In developing countries, approximately 80% of people and domestic animals use traditional and medicinal plants to maintain their health (Ozioma and Chinwe, 2019). Apart from being a primary food source, plants also serve as a very important source of medicine. From using the raw plant to extracting important compounds, medicinal plants are centuries-old sources of medicine in the various traditional herbal medicine systems. Their importance lies in the fact that the WHO concludes that 80% of the world population relies on them for treatment. It has been seen that there are medicinal plants already in use against respiratory viruses. *Cinnamon* bark extract and nanoparticles were examined for antiviral activity against H7N3 influenza A virus in Vero cells, and cell viability was measured using a tetrazolium dye (MTT) assay. When incubated with the virus prior to infection and delivered to cells after infection, silver nanoparticles generated from *Cinnamon* extract improved antiviral activity and were found to be efficient in both treatments. Cinnamon and its related nanoparticles were examined in Vero cells for their cytotoxic effects to determine the safety



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profile inVero cells were shown to be unaffected by the extract and nanoparticle at concentrations (up to 500 g/ml) (Fatima et al., 2016). Due to multi-targeting therapy of cinnamon and its components can be advised for SARS-CoV2 control (Yakhchali et al., 2021). The molecular level to understand the processes underpinning cinnamon's potential as a feed additive in poultry despite its promising effects remains limited (Saeed et al., 2018). In cell culture studies, Echinacea purpurea extract inactivated human highly pathogenic avian influenza virus (H5N1) and swine-origin H1N1 (S-OIV) H1N1-type IV (Pleschka et al., 2009).

Extracts from the dried fruit of Forsythiae fructus, are ongoing as a part of the world's race to develop an effective treatment for COVID-19. Therefore, it is no wonder that medicinal plants could be employed as a potent weapon against COVID-19. Traditional herbal medicine coming from these medicinal plants could serve different purposes, including alleviation of symptoms of COVID-19 in patients, as well as providing raw material for potent antiviral drugs (Ozioma and Chinwe, 2019).

Medicinal plants have become a new source of drug discovery due to the advent of today's advanced analytical chemistry, developed standardized and extraction procedures, as well as standard assays (Dilbato et al., 2019; Mbuni et al., 2020). Plants are responsible for around a quarter of all medications in use, and there are over 42,000 species of flowering plants, about 5000 of which are employed for therapeutic purposes (Mbuni et al., 2020). Medicinal plants with substantial antiviral activity, as well as those containing new plant-derived antiviral compounds, have been found to treat viral infections in people and animals (Abdalhamed et al., 2018; Chauhan et al., 2019). Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development (Mehrbod et al., 2018). Propolis's natural product has immunomodulatory and anti-inflammatory properties, and its effects on COVID-19 should be explored directly on the virus *in vitro* or on infected persons alone or in conjunction with antiviral medications. Because of its adjuvant qualities, propolis should be used in conjunction with vaccinations to improve the immunological response of individuals. Flavonoids produced from propolis have antiviral properties against the herpes virus, adenovirus, rotavirus, and coronavirus strains. More crucially, propolis has been proven to have antiviral activity against SARS-CoV-2 (Refaat et al., 2021). Propolis administered in a liposomal encapsulation was as effective as remdesivir in neutralizing SARS-CoV-2 *in vitro* (Refaat et al., 2021). Many computational and molecular docking investigations have suggested that propolis and its phenolic components are effective at interfering with a variety of SARS-CoV-2 proteins, including proteases and the spike protein. In addition, propolis is an effective antiviral agent. Propolis-derived phenolics, according to Kai et al. (2014).

It has been shown that the antiviral mechanisms of natural agents that interact with the viral life cycle, such as viral entrance, replication, assembly, and release, have been identified as targeting virus host-specific interactions (Mpiana et al., 2020).

**Viral infection control**

Unlike bacterial and fungal infections, the virus is not an autonomous organism, therefore, requires living cells to replicate, and difficulty to control, the fact that virus is functionally and physically integrated into the host cells, it is extremely difficult to distinguish, another problem that certain virus persists as latent infection (Jassim and Naji, 2003; Nazarov et al., 2020). The most alarming is the lack of effective treatment for many viral infections coupled with cross-resistant mutants as well as the potential toxic effect of antiviral drugs. Therefore, uses of plant extract and phytochemical of antivirals continue to receive the attention of scientists, as an alternative approach to the control of contagious diseases in livestock (Salazar et al., 2020; Giacometti et al., 2021).

**Antiviral drugs and their clinical limitations**

The antiviral drug is limited in comparison with an antimicrobial agent due to difficulty in the identification of specific viral targets with increased selectivity and reduced side effects. However, in recent years more rational approach characterized by new antiviral drugs. At the present, only one antiviral compound feline interferon-omega (IFN-ω) has been licensed for use in veterinary medicine, that undefined mechanism (Geraghty et al., 2021). Although several antivirals drugs are licensed idoxuridine, trifluoridine, and aciclovir in cats with feline herpes virus-1(FeHV-1), or zidovudine against feline immunodeficiency virus (FIV) but many reasons that lower using of antivirals agents in veterinary medicine as high cost, particularly for use in food species, animals species with lower cytotoxicity and absent rapid diagnostic techniques (Bule et al., 2019). Regardless of these arguments, animal viruses were used as models for developing antivirals drugs for humans include bovine viral diarrhea (BVD) considered a valuable surrogate for the hepatitis C virus (Dhama et al., 2018).

**Source of antiviral agents.**

Plants are naturally endowed with the ability to synthesize medicinal compounds, which has resulted in the discovery of new drugs with high therapeutic efficacy. Since nearly 80% of people rely on traditional medicine, plants and plant products have been used in the treatment of diseases for many centuries before the active principles in these products could be elucidated. About 50% of prescribed drugs are either plant-produced or their derivatives (Ungogo et al., 2020). Combination therapy using medicinal plants has effectiveness against a number of viruses, including herpes and influenza viruses. Also, *Agrimonia pilosa* and *Ocimum basilicum*, for example, exhibit antiviral properties against a wide spectrum of DNA and RNA viruses. (Nadjib, 2020).



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**Plant extracts targets of antiviral agent activity.**

The common antiviral compounds in medicinal plants are possible inhibited viral targets, and cellular attachment, one or more steps of virus replication, virus-specific enzymes, egress of progeny virus from infected cells. Also, it has an inhibitory effect on the virus itself. Another issue with the specific antiviral target method is the generation of virus-resistant mutants, particularly in the case of medicines aimed at specific viral genes or their products. (Mohammadi Pour et al., 2019). Combinations of two or more antiviral medications have been used to solve the problem. However, there is an alternate approach that can suppress a wide range of respiratory viruses (Ali et al., 2021b). Plaque formation was decreased by 98.8% for HSV-1 and 97.2% for HSV-2 at noncytotoxic doses of the oil, meaning that higher concentrations of the oil virtually eliminated viral infectivity. Time-on-addition tests were used to test the essential oil's antiviral activity. Pretreatment with balm oil before infection of cells greatly suppressed both herpesviruses. These findings show that Melissa oil has an antiviral impact on herpesviruses before adsorption but not after penetration into the host cell, implying that lemon balm oil has a direct antiviral effect on herpesviruses. Given the lipophilic characteristic of lemon balm essential oil, which allows it to penetrate deep into the skin (Schnitzler et al., 2008). These targets include virus attachment, entry inhibitors, modifiers of the viral genome, protein processing, virus assembly, release inhibitors, and immunomodulator as shown in Figure 1.

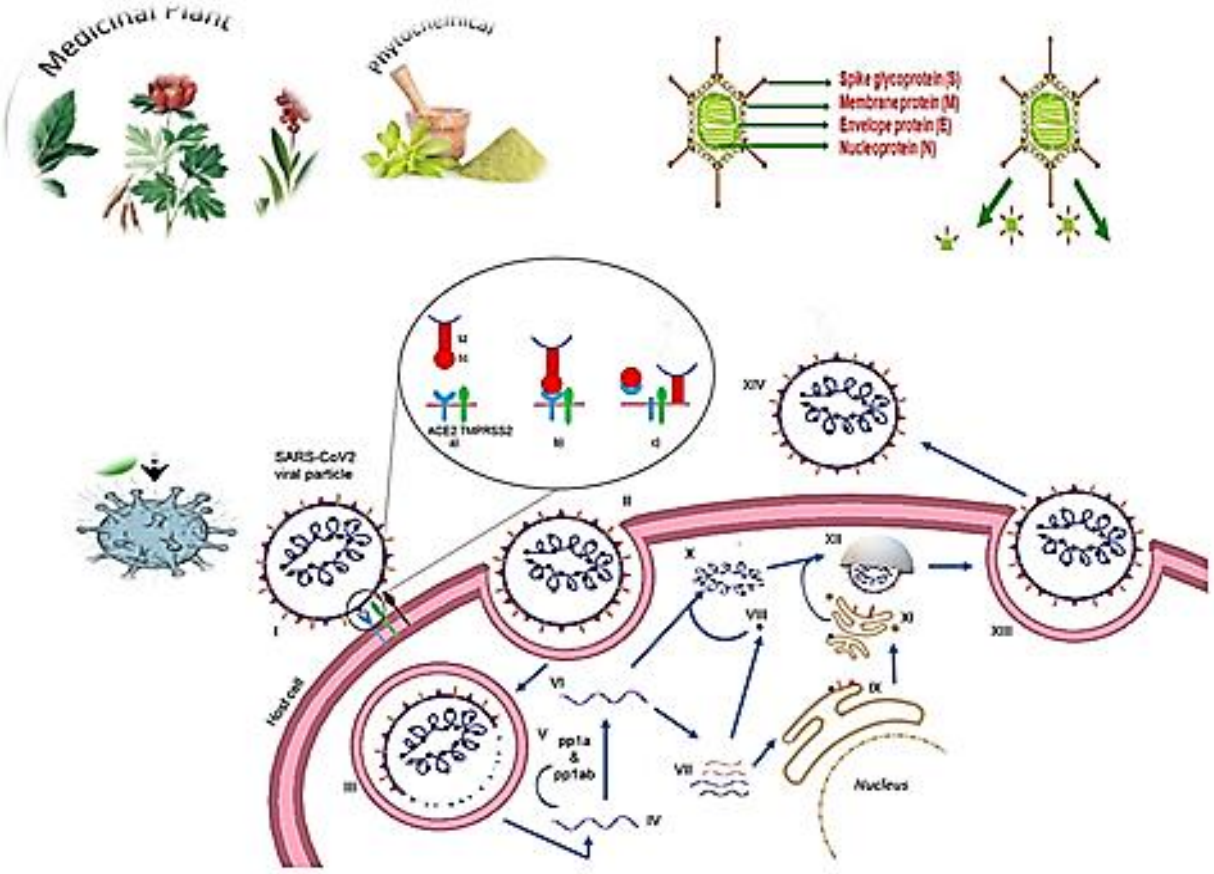


**Figure 1.** Virus life cycle and possible antivirus targets. I: The spike protein (S) on SARS-CoV-2 facilitates attachment to the host cell through the ACE2, TMPRSS2, II and III: Alternatively, the viral entry can also occur via endocytosis. IV: Release of the viral genome (+ strand) after entry. V: Translation of the strand leads to the formation of polyproteins (pp1a and pp1ab), VI: RdRp, VII: The transcription of the genome gives the subgenomic transcripts which encode the structural proteins, VIII: The nucleocapsid is translated in the cytoplasm. (IX) The other structural proteins are translated in the endoplasmic reticulum (ER), IX: The nucleocapsid and the genomic strand from the genomic RNA, X: The structural proteins are glycosylated in the golgi bodies, XI: A budding vesicle forms with the virion particles assembling, XII: Exocytosis of the assembled viral particle, XIII: The newly released viral particles can now infect other host cells.

**Virus attachment and entry inhibitors**

The attachment of the virus to the host cell and its entry is targeted by antiviral therapy. The virus enters the host cell by interacting with surface receptors or co-receptors to fuse the viral envelope to the host cell membrane, then uncoating to release the viral genome. Different antiviral plant products have indicated similar mechanisms for inhibiting viral replication. Specific plant lectins derived from the genera *Galanthus* and *Hippeastrum* can inhibit viral envelope glycoproteins, which inhibit viral entry into the cell. These agents also tend to interrupt the cell virus attachment, as in Figure 2. Also, extracts from seaweed, carrageenans, and seaweed-derived heparin sulphate molecules have an antiviral inhibitory effect against the dengue virus by preventing the un-coating of the virus. Antiviral medications can target the viral envelope while herpes *viruses*, *orthomyxoviruses*, *paramyxoviruses*, *rhabdoviruses*, *coronaviruses*, *retroviruses*, *arenaviruses*, *togaviruses*, *flaviviruses*, and *bunyaviruses* are non-enveloped viruses that are less affected by antiviral drugs (Frederico et al., 2017; Zheng et al., 2019).



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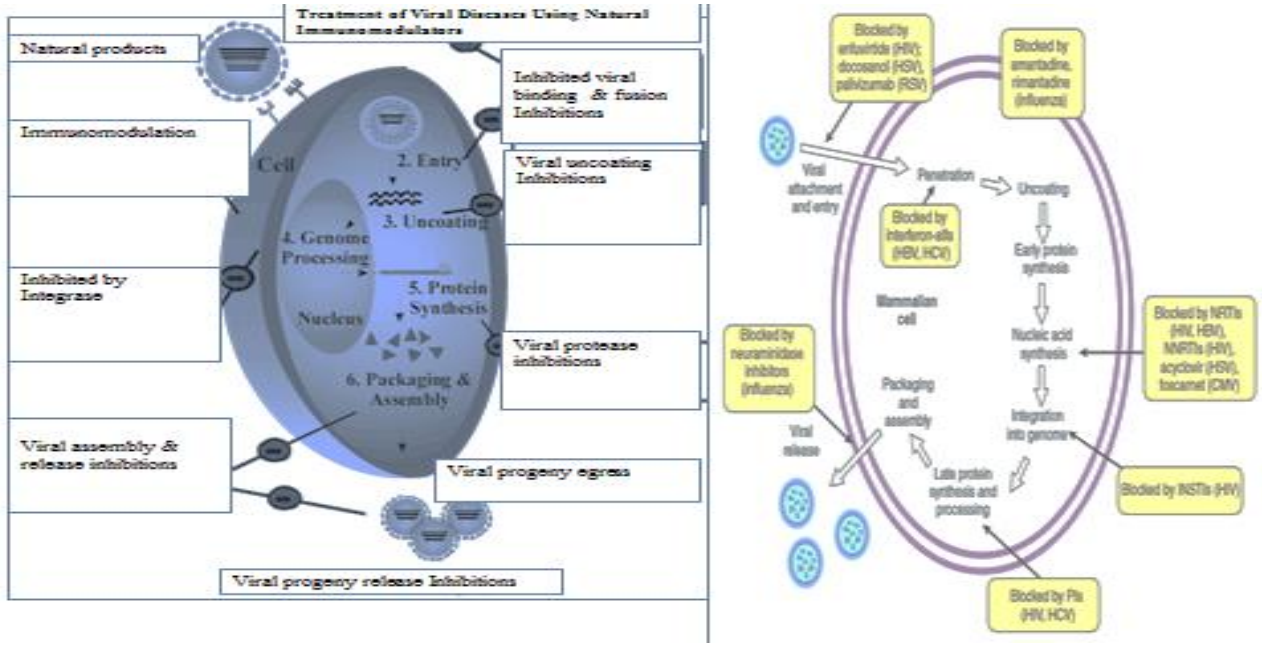


**Figure 2.** Targets of antiviral agents' therapy

**Modifiers of viral genome and protein processing**

The next target for an antiviral strategy that addresses viral transcription and translation processes is the genome of the DNA virus which is directly integrated into the genome of the host The antiviral agents can inhibit reverse transcription, integration, replication, transcription, and translation that provide potential targets (Meganck and Baric, 2021; Taliansky et al., 2021). Chemotherapy and medicinal plant targets viral nucleic acids lead to overlap and inhibit the viral protein synthesis as *Calophyllum lanigerum* they're binding to the enzyme's active site of reverse transcriptase enzyme by irreversibly manure (Alamgir, 2017; Mohan et al., 2020).

**Virus assembly and release inhibitors**

Antiviral drugs inhibit the arrangement of newly synthesized viral proteins and inhibit their release from the host cell like protease inhibitors prevent the cleavage of poly-protein, neuraminidase inhibitors blocking influenza virus release from infected cells, prevent virus transmission from cell-to-cell as oseltamivir and zanamivir. More than 30 different kinds of protease inhibitors have been isolated from plants with antiviral properties so far. For this objective, compounds from various botanical and chemical sources have been investigated. *Zingiber zerumbet, Orostachys japonicus, Boesenbergia pandurata, Alpinia galanga,*

**Immunomodulators**

One of the most significant mechanisms of antiviral medication is the stimulation of the defensive immune response. Many of the recently approved medications are designed to improve protection against viral infections. The most well-known immunostimulants include interleukin, colony-stimulating factors, and interferons. Interferons, which are polypeptides and glycoproteins that may be derived, operate as a catalyst to speed up the synthesis of certain enzymes that govern viral rebuilding in the cell (Zeedan et al., 2019). Interleukin is involved in the stimulation, growth, differentiation, maturation, and regulation of immune cells that can help in the neutralization of viruses (Andersen et al., 2020). The-sitosterol, which is derived mostly from Nigella plants, boosts the cellular immune response by increasing the activity of natural killer (NK) cells, CTLs, and cytokine release (Ali et al., 2021a).

**The immunomodulatory properties of several natural materials**

Examples of medications that might be employed as immunomodulators include carbohydrates, stilbenoids, alkaloids, polyphenols, lectins, and peptides derived from plants. The flowering tips of *Echinacea purpurea* have been utilized for immunological stimulation; the *Asteraceae* family is thought to be the biggest plant family with immunomodulatory activities. Allium sativum proteins have potent mitogenic activity against human lymphocytes, splenocytes, and thymocytes (El-Sherbiny et al., 2021).

**Bioactive compounds in medicinal plants are a source of antiviral agents.**

Plants are known for their capacity to create secondary metabolites that protect them during the growth and development process. Polyphenols, which comprise phenolic acids, tannins, flavonoids, and other chemicals found in vegetables, fruits, seeds, and their related products, constitute a large family of substances (Lin et al., 2016). Since 1938, when Szent-Gyorgyi demonstrated the action of citrus peel flavonoids in the prevention of capillary bleeding, polyphenols have been recognized as having potential biological benefits for human health. Over the years, more than 8000 polyphenol compounds have been discovered, with a wide range of biological activity (Zeedan et al., 2020). The rise of viral resistance to antiviral medicines has increased the demand for more efficient antiviral drugs. Compounds from natural sources are of interest as prospective sources to regulate viral infection. Medicinal plants offer a range of chemical ingredients that can suppress the replication cycle of many types of DNA or RNA viruses (Ghildiyal et al., 2020), as in Figure 3, and Table 1).



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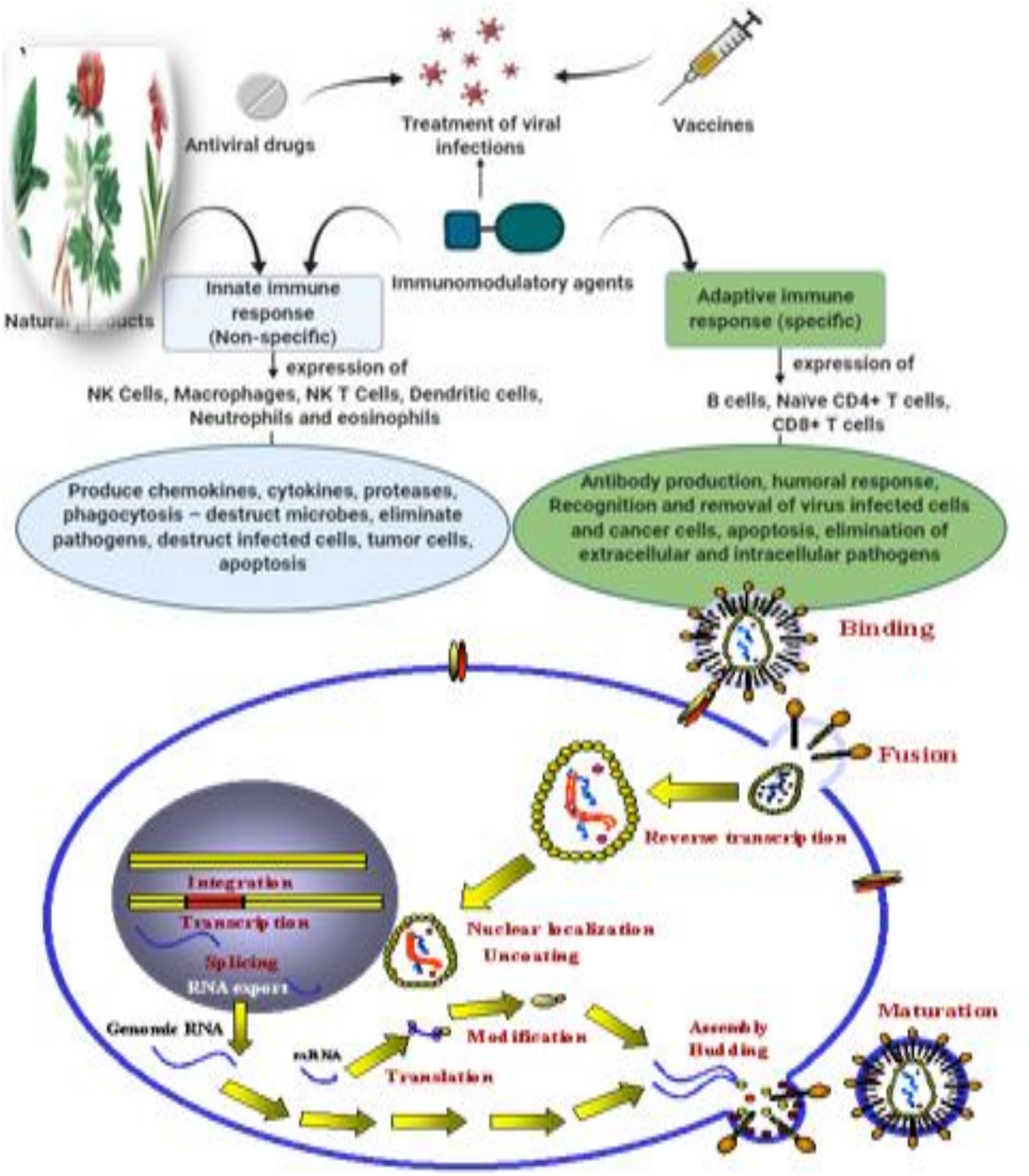


**Figure 3.** The various receptors via which the subtypes of virus enter the target cells. The presence of medicinal plant



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**Table 1.** Mechanism of the active antiviral compound from medicinal plants extracts

| Active of plant compound | Mechanism virus target | Example of plant source | References |
|---|---|---|---|
| Flavonoids: Amentoflavone, theaflavin, iridoids, phenylpropanoid glycosides, agathisflavone, robustaflavone, rhusflavanone, succedaneflavanone, chrysosplenol C, morin, coumarins, galangin (3,5,7-trihydroxyflavone), baicalin | disrupt viral enveloped Blocking RNA synthesis. Exhibited HIV-inhibitory activity | These active component isolated from the ethanol extract of Selaginella sinensis. Scutellaria baicalensiAgastacherugosa, Euphorbiagrantii, Barleriaprionitis, Calophyllumcerasiferum, Cal.inophyllum, Cal.teysmannii, Garciniamultiflora, Helichrysum ureonitens, Macluracochinchinensis, Markhamialutea, Monotesafricanus, Pterocaulon sphacelatum, Rhussuccedanea, Scutellariabaicalensis, Selaginellasinensis, Sophora moorcroftiana, Sophora tomentosa, Tephrosi sp. | Naithani et al. (2008), and Ngoci et al. (2011) |
| Tannins | Inhibition of viral RNA and DNA replication by inhibition of prooxidative enzymes | *Prunella vulgaris* L. (Lamiaceae) and *Rhizoma cibotte* | Ngoci et al. (2011) |
| Apigenin, Linalool, and Urolic Acid | Blocking virus replication have a broad spectrum of anti-DNA and anti-RNA virus activities | *Elsholtzia rugulosa* Hemsl. (Lamiaceae), a common Chinese herb | De Clercq (1988). Moreno-Altamirano et al. (2019) |
| Polysaccharides | Blocking virus binding | *Achyrocline flaccida*, *Bostrychia montagnei*, *Cedrela tubiflora*,*Prunella vulgaris*, *Sclerotium glucanicum*, *Stevia rebaudiana*,*Rhizophora mucronata* | Ogunwenmo et al. (2007) |
| Alkaloids | DNA and other polynucleotides and virions proteins. | Rutaceae, *Camptotheca acuminate*, *Atropa belladona* (L.),*Swainsona canescens*, *Astragalus lentiginosus*, *Castanospermum australe*, *Aglaia roxburghiana* | Ngoci et al. (2011) |
| Terpenoids<br>Terpenoids: sesquiterpene, triterpenoids (moronic acid, ursolic acid, maslinic acid and saponin) | Membrane-mediated mechanisms. Inhibition of viral DNA synthesis | *cokanthera sp.*, *Anagallis arvensis* (Primulaceae), *Cannabis sativa*,*Geum japonicum*, *Glycyrrhiza glabra*, *Glycyrrhiza radix*,*Glyptopetalum sclerocarpum*, *Gymnema sylvestre*, *Maesa lanceolata*,*Olea europa*, *Quillaja saponaria*, *Rhus javanica*, *Strophanthus gratus* | Yoong et al. (2014). |
| Miscellaneous phenolic compounds: anthraquinone chrysophanic acid, caffic acid, eugeniin, hypericin, tannins (condensed polymers), proanthocyanidins, salicylates and quinines (naphthoquinones, naphthoquinones and anthraquinones in particular aloe emodin) | Inhibition of viral RNA and DNA replication | *Aloe barbadensis*, *Aster scaber*, *Cassia angustifolia*, *Dianella longifolia*, *Euodia roxburghiana*, *Geum japonicum*, *Hamamelis virginiana*, *Hypericum* sp., *Melissa officinalis*, *Phyllanthus myrtifolius*,*Phyllanthus urinaria*, *Punica granatum*, *Rhamnus frangula*, *Rhamnus purshianus*, *Rheum officinale*, *Rhinacanthus nasutus*, *Shepherdia argentea*, *Syzgium aromatica*, St. John's wort | Jassim and Naji (2003). Naithani et al. (2010) |
| Thiophenes | Membrane interaction. Phototoxic activity | *Aspilia*, *Chenactis douglasii*, *Dyssodia anthemidifolia*, *Eclipta alba*,*Eriophyllum lanatum* | Parvez et al. (2020). |
| Lectins | Viral membrane interactions | *Canavalia ensiformis*, *Lens culinaris*, *Phaseolus vulgaris*, *Triticum vulgaris* | Lagarda-Diaz et al. (2017). |
| Antiviral factor | Mechanism of action is not known | *Nicotiana glutinosa* | Wani et al. (2021). |

*Coccinia grandis*, *Cassia garretiana*, and *Eclipta prostrata* extracts have demonstrated their antiviral activity by inhibiting proteases. (Menéndez-Arias and Gago, 2013; Zeedan et al., 2020), and *pandurata*, *Cassia garretiana* and *Orostachys japonicus* have antiretroviral efficacy (Menéndez-Arias and Gago, 2013; Lou et al., 2014; Singh et al., 2020).



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**Table 2.** Antiviral effects from several plant extracts against specific DNA viruses

| DNA Viruses | Mode of action | Plant extracts | References |
|---|---|---|---|
| 1. *Herpesviridae*<br>2. *Bovine herpes virus*<br>3. *Bovine herpesvirus type 1* (BHV-1)<br>4. *Equine herpesvirus 1*<br>5. *Feline herpesvirus-1* (FHV-1)<br>6. *Pesudorabies virus* | Inhibited viral replication by interfering with the early stages of viral adsorption and replication of | 1. *Erythroxylum deciduum,*<br>2. *Lacistema hasslerianum (chodat),*<br>3. *Xylopia aromatica ,*<br>4. *Heteropteris aphrodisiaca ,*<br>5. *Acacia nilotica (gum arabic tree),*<br>6. *Lippia graveolens (Mexican oregano or redbrush lippia),*<br>7. *Guettarda angelica (Velvetseed),*<br>8. *Prunus myrtifolia (West Indian cherry),*<br>9. *Symphyopappus compressus*<br>10. *Pimpinella anisum (Anise) T*<br>11. *Thymus capitata* | Rollinson (1992)<br>Ahmad et al. (1996)<br>Field et al. (2006)<br>Schnitzler et al. (2008) |
| Poxviridae<br>1. *Cowpox virus*<br>2. *Buffalopox virus*<br>3. *Parapoxvirus*<br>4. *Lumpy skin disease virus (LSDV* | Unknown | 1. *Podocarpus henkelii*<br>2. *Achillea fragrantissima*<br>3. *Artemisia herba alba plant is known as*<br>4. *Jasiona Montana*<br>5. *Egyptian propolis against parapox viruses* | Barnard et al. (1993) |
| **DNA Viruses** | **Mode of action** | **Plant extracts** | **References** |
| 7. *Herpesviridae*<br>8. *Bovine herpes virus*<br>9. *Bovine herpesvirus type 1* (BHV-1)<br>10. *Equine herpesvirus 1*<br>11. *Feline herpesvirus-1* (FHV-1)<br>12. *Pesudorabies virus* | Inhibited viral replication by interfering with the early stages of viral adsorption and replication of | 12. *Erythroxylum deciduum,*<br>13. *Lacistema hasslerianum (chodat),*<br>14. *Xylopia aromatica,*<br>15. *Heteropteris aphrodisiaca,*<br>16. *Acacia nilotica (gum arabic tree),*<br>17. *Lippia graveolens (Mexican oregano or redbrush lippia),*<br>18. *Guettarda angelica (Velvetseed),*<br>19. *Prunus myrtifolia (West Indian cherry),*<br>20. *Symphyopappus compressus*<br>21. *Pimpinella anisum (Anise) T*<br>22. *Thymus capitata* | Rollinson (1992)<br>Ahmad et al. (1996)<br>Field et al. (2006)<br>Schnitzler et al. (2008) |
| Poxviridae<br>5. *Cowpox virus*<br>6. *Buffalopox virus*<br>7. *Parapoxvirus*<br>8. *Lumpy skin disease virus (LSDV* | Unknown | 6. *Podocarpus henkelii*<br>7. *Achillea fragrantissima*<br>8. *Artemisia herba alba plant is known as*<br>9. *Jasiona Montana* | Barnard et al. (1993)<br>Zeedan et al. (2014) |



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**Effect of antiviral plant extracts on some animal viruses**

Many traditional medicinal herbs have been shown to have potent antiviral properties, and some of them have previously been utilized to treat viral infections in animals and humans. The most commonly mentioned medicinal plant species used to treat rabies in Ethiopia were Phytolacca dodecandra, Justicia schimperiana, Ricinus communis, Brucea antidysenterica, Croton macrostachyus, and Cucumis ficifolius. As a result, testing the antirabies efficacy of such therapeutic plant extracts is both required and beneficial. The antiviral effects of herbal plants on some DNA virus, such as Herpesviridae (*bovine herpesvirus type- 1* (BHV-1), *pesudorabies virus, equine herpesvirus-1* (EHV-1), *Poxviridae* (*poxvirus, parapoxvirus* (PPV), *lumpy skin disease virus* (LSDV), and Parvoviridae (*canine parvovirus type 2* (CPV-2) and RNA viruses as *Picornaviridae* (*foot-and-mouth disease* (FMD), Flaviviridae (*Bovine viral diarrhoea virus* (BVDV), *classical swine fever virus* (CSFV), Reoviridae (*Rotaviruses*), Orthmyxoviridae (*Influenza A*) Paramyxoviridae, *peste des petits ruminants* (PPR), *canine distemper virus* (CDV), *canine parainfluenza virus-2* (CPIV-2), Retroviridae (*Feline retrovirus, Feline leukaemia virus* (*FeLV*), (Vallbracht et al., 2019). Antivirals of natural origin have a broad spectrum of antiviral activity against a wide range of DNA and RNA viruses as shown in Tables 2 and 3.

**Table 3.** Antiviral effects from several plant extracts against specific RNA viruses

| RNA viruses | Mode of action | Plant extracts | References |
|---|---|---|---|
| Picornaviridae<br>Foot-and-mouth disease (FMD) | combined effects of polyherbal drug phytochemicals against FMDV and individual plant extracts against FMDV | *Ashwagandha, Tulsi, Turmeric Morinda elliptica L.M. citrifolia L.* | Younus et al. (2019) |
| Flaviviridae:<br>Bovine viral diarrhoea virus (BVDV)<br>Classical swine fever virus. | Antiviral activity as on HCV. Antiviral effect partly due to enhancement of the IFN‐associated JAK‐STAT pathway. inhibitors of viral replication | *Phylantus orbicularis, Melia azedarach, Perseaamericana , Acanthospermum hispidum Guazuma ulmifolia Stryphnodendron adstringes* | Backer et al. (2013) |
| Reoviridae<br>Rotaviruses,<br>Bluetongue virus | Saikosaponin B2 inhibits viral attachment and penetration stages | *Black tea, Citrus aurantium, Marine sponges, Stevia rebaudiana Alpinia katsumadai (AK), Zingiberaceae* | Kim et al. (2012). |
| Orthmyxoviridae<br>Influenza A. | Inhibits viral entry and release; inhibits viral hem-agglutination and NA activity. Inhibits viral NP RNA levels and polymerase activity | *H. erectum, T. chebula M. cochinchinensis* | Dhama et al. (2018) |

**Antiviral plant compounds**

Because microbial infections are becoming more resistant to pharmaceuticals, researchers are turning to natural resources, particularly plant metabolites, to develop lead molecules to combat human and animal illnesses. Furthermore, therapeutic made from natural plants or herbs account for around 35% of the worldwide medicine market. To combat this microbial resistance, researchers are looking for new and sophisticated medications made from a variety of herbal formulations. SARS CoV belongs to the beta family with a lot of similarities (Dilbato et al., 2019). Tropanes, pyrrolidines, isoquinoline purines, imidazoles, quinolizidines, indoles, piperidines, and pyrrolizidines are examples of alkaloids, which are categorized into numerous classes based on their heterocyclic ring Alkaloids have shown to be effective against HIV-1, HSV-1, HSV-2, DNV, VSV, influenza, and Newcastle disease virus (NDV), Emetine, Ipecac, Macetaxime, tylophorine, and 7-methoxy cryptopleurine are examples of alkaloids that have anti-SARS efficacy by inhibiting protease enzyme, RNA synthesis, and protein synthesis. Furthermore, certain alkaloids serve as a nucleic acid intercalator against SARS CoV (Dey et al., 2020).

The antiviral potency of Azadirachta indica (Neem), an indigenous Indian medicinal plant used in Traditional Indian Medicine, has been reported against avian influenza virus, bursal disease virus, Newcastle disease virus, group B coxsackievirus, dengue virus type-2, duck plague virus, poliovirus type-1, and bovine herpesvirus type-1. In the Ayurvedic system of medicine, neem is commonly used to treat asthma, cough, fever, and diarrhea which are the most common symptoms of SARS-CoV-2 infection. When the body is attacked by a virus, ingesting Neem boosts the immune system's cell and humoral responses. As a result of Neem's multifaceted antiviral therapeutic effectiveness, researchers hypothesized that it may be used to treat HIV (Sharma, 2021).

**Medicinal plants with antiviral and immune stimulant activities**

Medicinal plants have immunomodulating properties to combat infectious diseases specifically viral infections. A number of plants are already in use in traditional medicine for the treatment and prevention of viral infections by directly affecting the pathogen or stimulating the defense mechanism of humans' or animals' bodies in many ways. Terpenoids



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present in medicinal plants with bioactive compounds have promising efficacies in inhibiting the SARS-CoV-2 replications. Moreover, alkaloid active ingredients have anti-coronaviral activities and other active ingredients as emodin, baicalin, cryptotanshinone, silvestrol, sotetsuflavone, and lguesterin showed inhibition of important viral replication enzymes. Medicinal plants have evidence-based promising immunomodulation and antiviral activities in *vitro* and *in vivo* (Yang et al., 2020).

*Echinacea purpurea L.* is one of the most well-known medicinal plants, and its preparations are offered commercially all over the world as a general health tonic and for cold and flu prevention . It has antioxidative, anti-inflammatory, hypoglycemic, and anti-proliferative properties . Extracts from the root and above-ground sections purportedly have indicated antiviral activity and influenced macrophages, dendritic cells, monocytes, and NK cells. Antiviral capabilities, as evidenced by their ability to inactivate herpes simplex virus (HSV) and influenza virus). However, they were not effective against rhinovirus (RV). And herpes simplex virus both have similar membrane structures, while RV does not which suggests the membrane-bound property of antiviral components. Indirect antiviral actions, such as immune-modulating activities, such drugs are beneficial in the prevention or treatment of colds and flu (Alhazmi et al., 2021). Propolis is made up of around half resin (polyphenolic fraction), half wax, 10% essential oils, 5% pollen, and 5% other organic and inorganic substances. Propolis has complicated chemicals. Over 200 compounds have been discovered from plant extracts components as the polyphenolic fraction, primarily flavonoids, are responsible for its biological activity, followed by aromatic acids, phenolic acid esters, triterpenes, and lignans. Bactericidal, fungicidal, antiviral, antiprotozoal, antioxidant, anti-inflammatory, and immunomodulatory properties have been identified for these families of chemicals. The important chemicals for estimating propolis are flavonoids, one of the primary categories of phenolic compounds in propolis (Šturm et al., 2019).

*Artemisia annua* L is the major active ingredient in A. annua L., a Chinese traditional medicine. Artemisinin is a sesquiterpene trioxane lactone antimalarial medication that works by affecting parasite mitochondrial activity and influencing host immunity. Artemisinin and its derivatives aid to restore immunological function by increasing immune reconstitution and promoting T cell activation. In addition to antimalarial efficacy, it has shown promise in cancer therapy and angiogenesis suppression. Its tea infusion has no toxicity and can be used to treat malaria and HIV (Martínez et al., 2012).

*Azadirachta indica* is immensely popular in many areas of the world. This plant has been utilized for centuries for its anti-infective, anti-inflammatory, immunomodulatory, antioxidant, antiulcer, antimutagenic, and anticancer effects. Non-isoprenoids (azadiractins, salanin, vilasinin, and nimbin) and isoprenoids (azadiractins, salanin, vilasinin, and nimbin) make up the majority of the chemical ingredients (polyphenolics, flavonoids, coumarins, and sulphurous compounds). Hyperoside, a chemical derived from leaves, exhibited great interactions with conserved nucleoprotein residues and might be a potential influenza virus medication (Mahmood et al., 2018).

*Zizania latifolia* is a bioactive chemical, including flavonoids, polysaccharides, and saponins, all of which have therapeutic potential, including immunomodulation and antioxidant properties, and is used to treat a variety of ailments. Water-extractable polysaccharides extracted from swollen culms reportedly induced strong immunostimulation in murine macrophages RAW 264.7 by boosting proliferation, phagocytosis, and NO generation. In the realm of medicine and functional foods, the plant has the potential to be a promising immunomodulator (Alhazmi et al., 2021).

*Moringa oleifera* is widely used as food and medication. These benefits are linked to a variety of bioactive components found in the plant's leaf, pod, seed, and bark, including vitamins, flavonoids, minerals, isothiocyanates, and polyphenols. Several investigations have indicated that the leaf extract boosted humoral and cell-mediated immunity, which can be used as an alternative treatment for immunosuppression, the extract increased lymphocyte, neutrophil, and WBC counts, as well as hemagglutination antibody titer levels (Abdull Razis et al., 2014).

*Allium sativum* is widely used as a spice and as a traditional medicine in China and India due to its numerous health advantages. The presence of a number of bioactive ingredients, including organosulfur, saponins, and polysaccharides, is thought to be responsible for the plant's medicinal properties. Garlic's high immunomodulatory properties are due to its polysaccharide content, which regulates interferon-, TNF-, IL-6, and IL-10 production in macrophages. Garlic extracts, for example, controlled immune-system homeostasis and sustained immunological responses by increasing the expression and proliferation of cytokine genes, diallyl trisulfide concentration in garlic increased the expression and proliferation of cytokine genes (Shang et al., 2019).

**Other Plants**

A variety of additional medicinal plants have demonstrated moderate to good immunomodulation and antiviral activity in diverse *in vitro* and *in vivo* settings. For example, rosemary (Salvia rosmarinus) contains oleanolic acid, which is effective against herpes, HIV, influenza, and hepatitis A viruses. Many laboratory investigations revealed that sambucus, licorice, ginger, ginseng, and dandelion had potent antiviral properties. Glycyrrhizin and lycorine from G. glabra and Lycoris radiate, respectively, were shown to have strong anti-SARS-CoV action. Glycyrrhizin has also shown



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promise against the COVID-19 virus SARS-CoV-2, and might become a viable therapy option (Ghorbani and Esmaeilizadeh, 2017).

**Some plant extract failed to fight against viral diseases**

Phytoconstituents possess their own physicochemical interactions and are eventually released according to the solvent and solvent concentration, contact surface between extractor liquid and RVM, extraction time, granulometry, saturation, metabolite stability, eluent polarity, and constituent oxidation. Thus, it is interesting to perform experiments with different sample preparations to identify different constituent profiles The limitations of cytotoxicity assays through cell viability are not fully elucidated. To reduce the odds of over- or underestimating toxicity and confirm the values obtained herein, two assays (with different target organelles), two exposure periods and two cell lines were chosen. Regarding different measurements to estimate the cytotoxic values of extracts, it is possible to infer the toxicity of these extracts for comparison. No reports of cytotoxicity for hydroethanolic extracts of the Cymbopogon species tested herein were reported, but it is possible to infer that the compounds extracted by hexane presented higher toxicity. However, all CC50 values determined in the present study are higher, Aqueous extract to assess cytotoxic concentration 50% (CC50) at 630 g/mL in hepatocarcinoma cells using the NR assay (HepG2). Prior to undertaking antiviral evaluations, cytotoxicity assessments are required to determine the concentration limits to be employed in the next stage, based on the premise that a beneficial drug should have minimum toxicity towards the host. Hyssopus officinalis had the least anti-IBV activity, followed by Salvia officinalis with the most cytotoxicity and anti-IBV activity, and Mentha piperita. With the most standard index**(** SI ) (Muñoz-Acevedo et al., 2020).

## CONCLUSION

Viral infections play an important role in inducing diseases in humans and animals. Although the advances developed in immunization and antiviral drugs are widespread, many viruses lack protective vaccines or efficient antiviral therapies as a result of viral escape mutants. Natural products and their bio-activity are the main plans for supporting health systems. Some volatile essential oils from common plants and herbal teas have also been shown to have potent antiviral properties against viral infections. Novel antiviral compounds have a potential role in viral treatment. Most of the plants have inhibitory effects on herpesviridae and *flaviviridae*, followed by *retroviridae* and *picornaviridae*. Exploration and characterization of bioactive ingredients and studying antiviral mechanisms as well as judging inhibitory effects *in vivo* help to develop effective antiviral drugs. Investigating the potential for combination therapy with natural plants may aid in reducing the risk of viral drug resistance. However, it still needs further and extensive studies for safety and drug interaction. Medicinal plants may be important sources of antiviral medicines for human and animal infections, but more research into the bioactive elements of medicinal plants is still a top global priority. Several studies have been conducted to improve the antiviral activity of plant extracts as well as their water solubility. Investigations of the efficiency of plant extracts *in vivo* are encouraged to aid in the development of efficient antiviral medications, as are studies of natural agents combined with chemical antiviral therapies as a multitarget therapy for lowering viral escape mutants.

## DECLARATIONS

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

Dr GZ and Dr. AMA designed the plan of work and participated in drafting the manuscript. All authors read and approved the final manuscript.

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