Medicinal plants: Treasure for antiviral drug discovery

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The pandemic of viral diseases like novel coronavirus (2019-nCoV) prompted the scientific world to examine antiviral bioactive compounds rather than nucleic acid analogous, protease inhibitors, or other toxic synthetic molecules. The emerging viral infections significantly associated with 2019-nCoV have challenged humanity's survival. Further, there is a constant emergence of new resistant viral strains that demand novel antiviral agents with fewer side effects and cell toxicity. Despite significant progress made in immunization and regenerative medicine, numerous viruses still lack prophylactic vaccines and specific antiviral treatments that are so often influenced by the generation of viral escape mutants. Of importance, medicinal herbs offer a wide variety of therapeutic antiviral chemotypes that can inhibit viral replication by preventing viral adsorption, adhering to cell receptors, inhibiting virus penetration in the host cell, and competing for pathways of activation of intracellular signals. The present review will comprehensively summarize the promising antiviral activities of medicinal plants and their bioactive molecules. Furthermore, it will elucidate their mechanism of action and possible implications in the treatment/prevention of viral diseases even when their mechanism of action is not fully understood, which could serve as the base for the future development of novel or complementary antiviral treatments.

KEYWORDS
2019-nCoV, antiviral chemotypes, medicinal plants, phytomolecules, viral infections

1 INTRODUCTION

Among all the numerous outbreaks of infectious diseases confronted by humankind, it's indeed the viral infections that are undoubtedly the biggest pandemic threat in the recent era. The replication patterns and viral modes of transmission are the main determinants underpinning this assault. A wide-spectrum antiviral agent's inadequacy plays a pivotal role (Center for Health Security, 2019). Viruses need to use host cell machines for several functions. Therefore, their obligatory parasitic nature and antiviral approaches must be applied directly to a virus to minimize interference with the host cell functions (Adalja & Inglesby, 2019).

Further, the virus acts as barriers to broad-spectrum antiviral agents, including distinctions among RNA and DNA viruses, completely distinct virally encoded proteins, single or double genomic structure, cycles of cytoplasmic or nuclear replication, and degree of dependence on host proteins (Schoeneman & Fielding, 2019). The global antiviral drug armamentarium is expanding exponentially and is now covering many viral families. Nonetheless, very few known antiviral agents have activity spectrums that even marginally match up to the penicillin or sulfa range, the very first antibacterial agents identified.

The Earth's planet constitutes approximately 1,031 viruses, and their pervasiveness has colonized the marine ecosystem, where about 5,000 viral genomes seem to be prevalent in every 200 L of water (Breitbart & Rohwer, 2005). Also, viruses continue moving between the environments. They are available worldwide, for example, in deep Ocean, polar ices, alkaline, hot, and salt waters, and are about 2,000 m deep in the terrestrial ecosystem. There have been nearly 20 families
of viruses that certainly infect humans (Harvey, Champe, Fisher, & Strohl, 2006), and many of them also trigger diseases in animals (Mahzounieh, Mohtadai, & Zahraei Salehi, 2006). Virus particles contact the living system, and if they inundate the human immune response, then preventing their expansion in the body would be almost unfeasible. For the sake of their frequent replication, they control the host biochemical pathway/metabolic processes and make their treatment almost tricky. However, it is now well comprehended that viruses are specific in their replication mode that could be effectively approached (Syed, Amako, & Siddiqui, 2010). For instance, the proteolytic enzyme enhances viral maturation by distinguishing the viral polyprotein predecessor, whose obstruction would prevent its growth (Wapling, Srivastava, Shehu-Xhila, & Tachedjian, 2007). The epidemic outbreaks caused by emerging and re-emerging viruses represent a critical threat to public health, mainly when preventive vaccines and antiviral therapies are unavailable. Several hard-to-cure diseases and complex syndromes, including Alzheimer’s disease, type 1 diabetes, and hepatocellular carcinoma (HCC), have also been associated with viral infection (M. J. Ball, Lukiw, Kammerman, & Hill, 2013; Hober et al., 2012; Morgan et al., 2013). However, many viruses remain without adequate immunization and, only a few antiviral drugs are licensed for clinical practice. The situation is further exacerbated by drug-resistant mutants’ especially when using viral enzyme-specific inhibitors, which significantly hampers drug efficacy (Geretti, Armenia, & Cecherini, 2012; Locarnini & Yuen, 2010). Hence, there is an urgent need to discover novel antivirals that are highly productive and cost-effective for managing and controlling viral infections when vaccines and standard therapies lack.

New viral infections needed quite advanced drug molecules; however, the process of establishing such approaches toward this moment seems to have been sluggish and filled with impediments (Desselberg, 2000). Antiviral chemotherapy has proceeded at a snail-like pace, unlike antibiotics that had attained a specific treatment level in three decades. Nevertheless, it ended up taking nearly 60 years for antiviral development to achieve its current prevalence position. The evolution of diagnosis for Hepatitis C is a prime illustration of how complicated the antiviral effect can be. However, cumulative and aimed antiviral therapy has proven to be an excellent strategy for treating viral infectious disease.

Viruses are amongst the substantial causes of mortality and morbidity globally (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; WHO, 2015). Antiviral drugs and vaccines are being used to control human viral infections (De Clercq & Li, 2016). Eventually, the main focus was on “one drug, one virus” dogma, which depends solely on targeting virus-specific factors. A counterstatement to this is “one drug multiple viruses” (BSAAs), as viruses utilize similar pathways and host factors to replicate within a cell (Bekerman & Einav, 2015; Bosl et al., 2019; de Clercq & Montgomery, 1983; De bing, Neyts, & Delang, 2015; Ianevski, Andersen, Merits, Bjoras, & Kainov, 2019; Rada & Dragan, 1977; Sidwell et al., 1972). Though the concept of BSAAs was about 50 years ago, due to the recent outbreaks of a novel coronavirus (2019-nCoV) and several other viral infections, the field has acquired new urgency for the discovery of novel host-directed agents and the expansion of a drug repositioning methodology (Paraskevis et al., 2020).

Drug repurposing, also known as repositioning, redirecting, repurposing, is a strategic approach for accumulating additional benefits from an approved drug by approaching a disease apart from that it was initially envisioned (Nishimura & Hara, 2018; Pushpakom et al., 2019). It has distinct advantages over new drug discovery since chemical synthesis, manufacturing processes, reliable safety, and pharmacokinetic properties are accessible in pre-clinical and early clinical development phases. Consequently, the repositioning of launched or perhaps failed viral drugs offer incredible translational opportunities, such as a substantially higher probability of commercial success in comparison to the implementation of novel virus-specific medicines and vaccines and a substantially decreased cost and timeframe for clinical accessibility (Ianevski et al., 2019; Pizzorno, Padey, Terrier, & Rosa-Calatrava, 2019; Zheng, Sun, & Simeonov, 2018).

Antivirals are antimicrobial compounds derived from living organisms or generated by chemical synthesis, mostly hindering viral replication. Antivirals tamper with one or more phases of the viral life cycle, which include: cell attachment, cell penetration, viral uncoating, copy of the viral genome (DNA/RNA), maturation, and reveal of viral progeny and, are an essential tool to facilitate vaccine action (Veiga-Crespo, Viñas, & Villa, 2015). The synthesized antiviral drugs such as moxoxydine, ganciclovir, valganciclovir, and valaciclovir were used to inhibit virus replication through various mechanisms (Biron, 2006). However, due to their low efficacy, cytotoxicity, and the development of viral resistance, difficulties in treating drugs arise. A further antiviral therapy, vaccination, may be used but is still under advancement because it often provides inadequate virus protection, and its validity needs further investigation (Subbarao & Joseph, 2007). Thus, more scientific research is required in the treatment of antiviral synthetic drugs and vaccines.

Nature has provided yet another credible source of antiviral agents, and almost 40% of the drugs available at the moment are directly or indirectly plant derivatives. A range of ethnobotanical studies focused on identifying possible therapeutic plants for even more effective management of healthcare issues, demonstrating the significance of medicinal plants in the healthcare delivery system (Ansari & Inamdar, 2010; Appidi, Grierson, & Afolayan, 2008; Heneidy & Bidak, 2004; Ky et al., 2009; Makambila-Koubamba, Mbatchi, Ardid, Gelot, & Henrion, 2011; Shinwari & Khan, 2000). Herbal remedies and extracted natural products often provide a significant source of novel antiviral developing drugs. Antiviral medications’ characterization from such natural sources sheds light on where they interrelate with the viral replication cycle, like viral entry, replication, assembly, and release, and the targeting of precise virus-host interactions. Here, we enumerate the antiviral activities of a range of natural products and herbal medicines against specific critical viral pathogens. This study aims to assess previously published antiviral plants and spot possible action mechanisms and substances accountable for their antiviral activity. A deeper understanding of the mode of action and evaluating the concerned compounds will provide a unique insight into the concept of new antiviral drugs for even more effective viral co-operation.
2 | METHODOLOGY

An extensive review of the literature was carried out on antiviral medicinal plants and their associated bioactive compounds between 2019 and 2020 via electronic search Pubmed, Scopus, Web of Science, Science Direct, J-Gate, Google Scholar, and a library search for articles published in peer-reviewed journals. The unpublished materials have been excluded from this review. The review process was further continued by the refining of the search results using the keywords namely viral medicinal plants, antiviral bioactive compounds, emerging viral infections, novel coronavirus, coxsackievirus (CV), dengue virus (DENV), enterovirus 71, human herpes viruses, hepatitis virus, human immunodeficiency virus, influenza virus, measles virus (MV), respiratory syncytial virus (RSV), and rotavirus. The literature cited in the review dated from 1950 to 2020 and limited to the English language. The final data collected through the authors’ discussions were then compiled, evaluated, compared, and drawn accordingly.

3 | BASIC VIRAL STRUCTURE AND ITS PATHOBIOLOGY

Viruses are organic artifacts that are metabolically inactive outside the host and after accessing the host cell becomes activated (Dupre & O’Malley, 2009). They are comprised primarily of proteins and nucleic acid; the proteins contribute to their unique shape by forming a capsid (Andersson, 2010). Therefore, viruses are of different forms, like superficial, helical, icosahedral, or complex, and perhaps some viruses are accompanied by a lipid bilayer extrapolated from a host membrane called an envelope (Geng et al., 2007). Besides, capsid proteins associated with nucleic acids form nucleocapsids. Proteins related to viral nucleic acids are called nucleoproteins. Virus nucleic acid is either DNA or RNA and has been the elementary source of knowledge required to monitor its metabolic functions. This DNA and RNA are categorized based on the number of strands into single or double-stranded DNA/RNA (Firth et al., 2010; Pichlmair et al., 2006). The sense of strand can further differentiate single-stranded RNA viruses stranding DNA/RNA (Firth et al., 2010; Pichlmair et al., 2006). The categorized based on the number of strands into single or double-stranded DNA/RNA (Firth et al., 2010; Pichlmair et al., 2006). The sense of strand can further differentiate single-stranded RNA viruses stranding DNA/RNA.

The multiplication of all viruses results from several sequential processes: adhesion of the virus to the cell surface, virus adsorption and entry into the cell, replication of viral nucleic acids, and expression of viral proteins, and release of virus particles from the cell. For example, the virus entrance process is often carried out by cell surface proteins; Hepatitis C virus (HCV) entry involves claudin-1, occludin, and tetraspanins as the primary receptor proteins (Burlone & Budkowska, 2009). The latter's accession is influenced by other lipoproteins and the enzyme lipoprotein lipase. Moreover, infection with the influenza virus is modulated by a protease enzyme that triggers the viral surface protein hemagglutinin (Zambon, 2001). The protease enzyme is pertinent for illustrating viral proteins; it categorizes proteins into groups based on everyone's structural and non-structural features (Appel, Schaller, Penin, & Bartenschlager, 2006). But RNA viruses require two powerful enzymes to sustain; reverse transcriptase and integrase, former transcribed viral RNA to DNA at the moment of replication (Briones, Dobard, & Chow, 2010; Sluis-Cremer & Tachedjian, 2008). In contrast, the second enzyme integrates viral DNA into the host genome and is required for the effective uncoating of virus-core proteins. As a result, the virus needs enzymatic and non-enzymatic proteins to stop its replication and infection.

4 | ANTIVIRAL MOLECULES OF PLANT ORIGIN

Conventional medicine is indeed a worthwhile line of study for analyzing, extracting, and developing medicinal benefits. Conversely, a relatively small proportion of bioactive compounds were studied systematically for their therapeutic uses. Natural products include an unusual approach to exploring antiviral agents with remarkable pharmacological properties (Cragg & Newman, 2013; Atanasov et al., 2015). Herbal therapists have been using traditional plants since prehistoric days to cure diseases in humans and animals, particularly in the Asia-Pacific region. People continue to rely on medicinal herbs and their products for their wellness and primary medical care throughout the globe (Ekor, 2014). About 2,500 natural plant species are listed globally to diagnose many diseases and illnesses (Kapoor, Sharma, & Kanwar, 2017).

Collecting traditional data from local or indigenous communities or even using important ethnopharmacology plant(s) to extract bioactive molecules/phytochemicals is a very demanding approach for diagnosing different ailments (Altemimi, Lakhsassi, Baharlouei, Watson, & Lightfoot, 2017). Numerous aspects, including the various solvents (polar, non-polar) used during the extraction of bioactive constituents and the selection of plant parts/tissue for their extraction from plants, commonly play a crucial role (Ben-Shabat, Yarmolinsky, Porat, & Dahan, 2020). A holistic approach for isolating and characterizing bioactive molecules and virus replication inhibitory experiments in animal cell systems is required when such bioactive molecules could be used to cure a viral infection (Kapoor et al., 2017). The eternal objective of establishing high throughput screening assays is just the way to recognize bioactive molecules/phytochemicals from large chemical libraries quickly and accurately. In vivo experiments and consequent clinical studies are necessary to identify the antiviral activity and severe complications like reactogenicity or toxicity of purified bioactive molecules.

4.1 | Coronavirus and medicinal plants

Coronavirus (CoV) is a single-stranded, positive-sense envelope (ss-RNA) virus (Family: coronaviridae). The CoV family comprises many
species responsible for causing respiratory and gastrointestinal infections in mammals and birds. It mostly leads to cold or flu in human beings, yet complications could emerge, such as pneumonia and severe acute respiratory syndrome (SARS) (Van-der Hoek, 2007). The documented CoV (HCoV) comprises HCoV-229E, -OC43, -NL63, -HKU1, and the universally recognized severe acute respiratory coronavirus syndrome (SARS-CoV), which triggered a high mortality threat to the world in 2003 (Geller, Varbanov, & Duval, 2012). In 2012, the World Health Organization (WHO) reported a sixth highly lethal form of HCoV infection known as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (WHO, 2013).

The severe acute coronavirus 2 respiratory syndromes (SARS-CoV-2) was first reported in December 2019 in Wuhan, Hubei, China, and declared by the World Health Organization (WHO) as a pandemic on March 11, 2020 (WHO, 2020). The tentative name 2019-nCoV was given by the World Health Organization, later by the International Committee on Taxonomy of Viruses renamed it as SARS-CoV-2 (Coronavirus disease 2019). The Wuhan strain was recognized as a new strain of Group 2B Betacoronavirus with nearly 70% genetic ancestry to SARS-CoV (Hu, Azhar, Madani, & Ntoumi, 2020). The virus seems to have a 96% resemblance to the coronavirus bat, and therefore it is generally believed to emanate from bats. There seem to be no precise medications or treatment options for COVID-19; however, numerous clinical trials assessing possible treatments are continuing during this period (WHO, 2020).

Coronaviruses are large pleomorphic spherical particles with a bulbous surface projection. The diameter of the virus particle is approximately 120 nm (Fehr, Perlman, Maier, Bickerton, & Britton, 2015). The virus membrane in electron micrographs did appear as a unique pair of thick electron shells. The viral envelope consists of a lipid bilayer under which the membrane, envelope, and spike structural proteins are situated. A beta coronavirus subgroup A have a shortened spike-like surface protein called hemagglutinin esterase (HE) (Neuman, Kiss, Kunding, Bhella, & Baksh, 2011).

Moreover, nucleocapsid develops copies of the nucleocapsid protein attached to the positive-sense single-stranded RNA genome (Fehr et al., 2015). The genome size for coronaviruses ranges from 27 to 34 kilobases, the largest among documented RNA viruses. The lipid bilayer envelope, membrane protein, and nucleocapsid safeguard the virus outside the host cell (Neuman et al., 2011). There is only one amino acid variation in specific genome sequences among viruses discovered in pangolins and viruses found in humans.

Interestingly, about 92% of the genetic material accessed between pangolin coronavirus and SARS-CoV-2 has been identified as a complete genome comparison to date that is grossly inadequate to demonstrate that pangolins are intermediate hosts (Cyranoński, 2020). The virus does have a 96% resemblance to the coronavirus bat, and therefore it is generally believed that it emanates from bats (Cohen, 2020). The name coronavirus is derived from the Latin word corona, which means “crown” or “halo,” which pertains to the characteristic appearance of the crown or solar corona around the virions (virus particles) under two-dimensional electron microscopy, due to the surface covering of the club-shaped protein spikes.

There have been no specific treatments for CoV infection, and preventive vaccines are still under examination. It illustrates the need to implement new antivirals for prophylaxis and treatment of CoV infection. The complete list of the potent plant extracts and their bioactive compounds that inhibit coronavirus are depicted in Table 1. Ginsenoside Rb1 (Gynosaponin C), one of the bioactive ginsenosides extrapolated from Panax ginseng, displayed antiviral activity (Wu et al., 2004). Tetra-O-galloyl-beta-o-glucose, luteolin, and tetra-O-galloyl-beta-o-glucose, blocked the SARS-CoV host cell entry (Yi et al., 2004). Chinese herbs have long been known for their antiviral effects and therefore examined for SARS-CoV’s potential role. Of the 200 herbal extracts analyzed, Lycoris radiata, Artemisia annua, Pyrosia lingua, and Lindera aggregata seemed to have an anti-SARS-CoV impact with a 50% effective aa(EC50) of 2.4–88.2 μg/ml (Li et al., 2005a). Additionally, tannic acid, 3-isothioflavin-3-gallate, and theaflavin-3,3’-digallate, three black tea phenolics, collectively, exhibited inhibitory effects SARS-CoV 3CLpro with IC50 values of 3, 7, and 9, 5 μM, respectively (Chen et al., 2005). On the other hand, phenolic compounds from Isatis indigotica showed an inhibitory effect against SARS-CoV 3CLpro with IC50 values of 217, 752, 8.3, 365, and 1,210 μM, respectively for sinigrine, indigo, aloem emodin, hesperetine, and β-sitosterol (Lin et al., 2005).

Saikosaponins (A, B2, C, and D), naturally occurring triterpene glycosides obtained from Bupleurum spp., Heteromorpha spp., and Scrophularia scorodonia, exhibited antiviral activity against HCoV-229E. Saikosaponin A, B2, C, and D have efficacy toward human CoV-229E, with EC50 values of 8.6, 1.7, 19.9, and 13.2 μM, respectively; saikosaponin B2 subdued viral attachment and penetration stages (Cheng et al., 2006a). These natural compounds effectively avoid the initial stage of HCoV-229E infection, like viral attachment and penetration, following co-challenge with the virus. In contrast, Rheum officinale, Polygonum multiflorum, and emodin have been investigated and proven to suppress SARS-CoV (S) protein and ACE2 interaction with IC50 valuesHo et al., 2007). Among 221 phytochemicals studied against SARS-CoV, 10 diterpenes, two sesquiterpenes, two triterpenes, and five lignans curcumin exhibited inhibitory effects at 3–10 μM concentration (Wen et al., 2007).

Interestingly, psoralidin showed a strong protease inhibitor influence on SARS-CoV with an IC50 value of 4.2 μM. Simultaneously, emodin, rhein, and chrysirin hindered SARS-CoV (S) and ACE2 protein-protein interaction at 0–400 μM (T. Y. Ho et al., 2007; Kim et al., 2007). Conversely, ferruginol, 8β-hydroxyxabiota-9(11),13-dien-12-one, 3β,12-diacetoxyabiota-6,8,11,13-tetraene, betulonic acid, betulinic acid, hinokin, savinine, and curcumin inhibits replication of SARS-CoV at 0–80 μM (Wen et al., 2007). Other natural anti-CoV molecules include water extract from Houttuynia cordata, which displayed antiviral mechanisms against SARS-CoV, such as viral 3CL pro tease inhibition and viral RNA-dependent polymerase activity blockade (Lau et al., 2008). In the same way, Toona sinensis aqueous leaf extract inhibited SARS-CoV replication with EC50 values ranging from 30 to 40 μg/ml and SI values ranging from 12 to 17 (Chen et al., 2008). Procyandin A2, procyandin B1, and cinnamon tannin B1, extracted from Cinnamomi cortex, also hindered SARS-CoV infection at 0–500 μM (Zhuang et al., 2009).
**Table 1** List of the potent extracts bioactive compounds that inhibit Coronavirus

| Natural product(s) evaluated | Test system | Test dose | Proposed mechanism(s) | References |
|------------------------------|-------------|-----------|-----------------------|------------|
| Lycoris radiate              | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Artemisia annua              | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Pyrois lingua                | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Lindera aggregata            | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Isatis indigotica            | SARS-CoV    | 1–500 μg/ml | 3CL protease inhibition | Li et al., 2005a |
| Extract (Rheum officinale Baill., Polygonum multiflorum Thunb.) | SARS-CoV spike (S) Protein | 0–100 μg/ml | Inhibits the interaction of SARS-CoV S protein and ACE2 | Ho, Wu, Chen, Li, & Hsiang, 2007 |
| Houttuynia cordata Aq. Extract | SARS-CoV | 0–400 μg/ml | 3CL protease and viral polymerase inhibition | Lau et al., 2008 |
| Herbal extracts (Gentiana scabra, Dioscorea batatas, Cassia tora, Taxillus chinensis, Cibotium barometz) | SARS-CoV | 25–200 μg/ml | 3CL protease inhibition | Wen et al., 2011 |
| Anthemis hyalina, Nigella sativa, and Citrus sinensis Extracts | SARS-CoV | 1/50 and 1/100 dilution of ethanolic (100 g/200 ml) | Increased IL-8 level. Significantly changed the expression of TRPA1, TRPC4, TRPM6, TRPM7, TRPM8, and TRPV4 genes | Ulasli et al., 2014 |

| Natural product(s) evaluated | Test system | Dose/concentration | Proposed mechanism(s) | References |
|------------------------------|-------------|--------------------|-----------------------|------------|
| Lycoris radiate              | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Artemisia annua              | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Pyrois lingua                | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Lindera aggregata            | SARS-CoV    | $10^{-1}$–$10^{-4}$ mg/ml | Undefined             | Li et al., 2005a |
| Isatis indigotica            | SARS-CoV    | 1–500 μg/ml | 3CL protease inhibition | Li et al., 2005a |
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| Aloe emodin, Beta-sitosterol, Hesperetin, Indigo and Sinigrin (Isatis indigotica) | SARS-CoV | 1–100 μg/ml | 3CL protease inhibition | Lin et al., 2005 |
| Amentoflavone (Torreya nucifera) | SARS-CoV | 1–1,000 μM | 3CL protease inhibition | Ryu et al., 2010 |
| Apigenin (Torreya nucifera) | SARS-CoV | 1–1,000 μM | 3CL protease inhibition | Ryu et al., 2010 |
| Bavachinin (Psoralea corylifolia) | SARS-CoV | 1–150 μM | Inhibitors of papain-like protease (PLpro) | Kim et al., 2014a |
| Rosmariquinone and Tanshinone I (Salvia miltiorrhiza) | SARS-CoV | 1–1,000 μM | Inhibition of SARS-CoV viral infection and replication | Park et al., 2012 |
| Natural product(s) evaluated | Test system | Dose/concentration | Proposed mechanism(s) | References |
|-----------------------------|-------------|--------------------|-----------------------|------------|
| Cinanserin (1 dpi) and Cinanserin (2 dpi) (Houttuynia cordata) | Murine CoV | 15.63–500 μg/ml | Undefined | Chiow et al., 2016 |
| Cinnamtannin B, Procyanidin A2 and B1 (Cinnamomi cortex) | SARS-CoV | 0–500 μM | Inhibition of pseudovirus infection | Zhuang et al., 2009 |
| Corylifol and Psoralidi (Psoralea corylifolia) | SARS-CoV | 1–150 μM | Inhibitors of papain-like protease (PLpro) | Kim et al., 2014a |
| Dieckol, 7-Phloroeckol, Phlorofucofuroeckoln and Eckol (Ecklonia cava) | Porcine epidemic diarrhea CoV | 1–200 μM | Inhibition of viral replication/Blockage of the binding of virus to cell | Kwon et al., 2013 |
| Diplacone, Tomentin A, B, C, D, E (Paulownia tomentosa) | SARS-CoV | 0–100 μM | Inhibition of papain-like protease | Cho et al., 2013 |
| Broussochalcone A and B, 4-Hydroxyisolonchocarpin, Papyriflavonol A, Kazinol A, B, F, J and 3-(3-methylbut-2-enyl)-3,4,7-trihydroxyflavan (Broussonetia papyrifera) | | 0–200 μM | Protease inhibition | Park et al., 2017 |
| Isobavachalcone (Psoralea corylifolia) | SARS-CoV | 1–150 μM | Inhibitors of papain-like protease (PLpro) | Kim et al., 2014 |
| 3-Isotheaflavin-3-gallate and tannic acid (black tea) | SARS-CoV | 4–20 μM | Inhibition of 3C-like protease (3CLPro) | Chen et al., 2005 |
| Luteolin and Quercetin (Torreya nucifera) | SARS-CoV | 1–1,000 μM | 3CL protease inhibition | Ryu et al., 2010 |
| Lycorine (Lycoris radiata) | SARS-CoV | 10⁻¹–10⁻⁴ | Undefined | Li et al., 2005a |
| Quercetin and Rutin (Houttuynia cordata) | Murine CoV | 500–15.63 μg/ml | Undefined | Chiow et al., 2016 |
| Glycoside juglanin (Quercus ilex) | SARS-CoV | 10–40 μM | Blocks the 3a channel | Schwarz et al., 2014 |
| 4'-O-methylbavachalcone and Neobavaisoflavone (Psoralea corylifolia) | SARS-CoV | 1–150 μM | Inhibitors of papain-like protease (PLpro) | Kim et al., 2014a |
| Mimulone, 3'-O-methylidiplacol, 4'-O-methylidiplacol, 3'-O-methylidiplacone, 4'-O-methylidiplacone (Paulownia Tomentosa) | SARS-CoV | 0–100 μM | Inhibition of papain-like protease | Cho et al., 2013 |
| 7-Methoxycryptopleurine and Tylophorine (Tylophora indica) | CoV-infected swine testicular cells | - | Inhibition of viral replication | Yang et al., 2010 |
| Saikosaponins A, B2, C, D | HCoV-22E9 | 5–25 μM/L | Saikosaponin B₂ inhibits viral attachment and penetration stages | Cheng et al., 2006 |
| Tylophorin | CoV | 0–100 μM | Targeting viral RNA replication and Cellular JAK2 mediated dominant NF-κB activation | Yang et al., 2017 |
| Natural product(s) evaluated | Test system | Dose/concentration | Proposed mechanism(s) | References |
|-----------------------------|-------------|--------------------|-----------------------|------------|
| Scutellarein                | SARS-CoV    | 0.01-10 μM         | 3CL protease inhibition | Yu et al., 2012 |
| Savinin                     | HCoV-229E   | 8-80 μM            | Inhibition of cap-dependent viral mRNA translation | Muller et al., 2019 |
| Silvestrol                  | HCoV-OC43   | 0.6-2 μM           | Inhibition of cell division | Shen et al., 2019 |
| Tetrandrine                 | HCoV-OC43, HCoV-NL63, HCoV-OC43-infected MRC-5 infected human lung cells | 2-20 μM | Undefined | Kim et al., 2019 |
| Phenazopyridine             | HCoV-OC43, HCoV-NL63, HCoV-OC43-infected MRC-5 infected human lung cells | 0-5 μM | Undefined | Shen et al., 2019 |
| Mycophenolatefomi          | HCoV-OC43, HCoV-NL63, HCoV-OC43-infected MRC-5 infected human lung cells | 0-5 μM | Inhibited RNA, DNA, and protein synthesis | Shen et al., 2019 |
| Lycorine                    | HCoV-OC43, HCoV-NL63, HCoV-OC43-infected MRC-5 infected human lung cells | 0-5 μM | Inhibited cell division | Shen et al., 2019 |
| Emetine                     | HCoV-OC43, HCoV-NL63, HCoV-OC43-infected MRC-5 infected human lung cells | 0-5 μM | Undefined | Shen et al., 2019 |
| Berbamine                   | HCoV-NL63   | 0-20 μM            | Undefined | Kim et al., 2019 |
| Fangchinoline               | HCoV-OC43, HCoV-NL63, HCoV-OC43-infected MRC-5 infected human lung cells | 0-20 μM | Undefined | Kim et al., 2019 |

Flavonoids and biflavones isolated from *Torreya nucifera* exude cytotoxic effect on SARS-CoV 3CLpro (Ryu et al., 2010), and Tylophorine and 7-methoxycytoterpene isolated from *Tylophora indica* inhibit both N and S protein function and viral replication of enteropathogenic coronavirus transmissible gastroenteritis virus (Yang et al., 2010). Such molecules showed incredible antiviral activity with IC<sub>50</sub> values of 0.018 and <0.005 μM, respectively. Tylophorine and 7-methoxycytoterpene separated from *T. indica* have been shown to impede viral replication in CoV-infected swine testicular cells (Yang et al., 2010). Six plant extracts (Gentiana scabra, Dioscorea batatas, Cassia tora, Taxillus chinensis, Cibotium barometz) asserted inhibitory effect against SARS-CoV 3CLpro with IC<sub>50</sub> values of 39 and 44 μg/ml, respectively (Wen et al., 2011). Besides, diterpenoid, 8b-hydroxyabieta-9 (11), 13-dien-12-one, and lignin, savinin were reported to prevent SARS-CoV 3CLpro activity with a SI >667. In comparison, betulinic acid and savinin were found competitive inhibitors of SARS-CoV 3CLpro with Ki values of 8.2 and 9.1 μM, respectively. Tanshinones (e.g., tanshinone I, rosmarinquinone) derived from *Salvia miltiorrhiza* also hindered infection and replication of SARS-CoV 3CLpro and PLpro at 1–1000 μM (Park et al., 2012). Further, myricetine and scutellarein exert an inhibitory effect of 0.01–10 μM for SARS-CoV 3CLpro (Yu et al., 2012). Likewise, (-)-catechin gallate and (-)-gallocatechin gallate at 0.001-1 μg/ml prevented SARS-CoV nanoparticle RNA oligonucleotide (Roh, 2012).

Further, Eckol, 7-phloroeckol, phlorofucofuroeckol, and dieckol segregated from *Ecklonia cava* obstructed virus adhesion to porcine epidemic cells at 1–200 μM with IC<sub>50</sub> values of 22.5, 18.6, 12.2, and 14.6 μM, respectively (Kwon et al., 2013). Similarly, tomentine A, B, C, D, and E, 3′-O-methylidiplacol, 4′-O-methylidiplacol, 3′-O-methylidiplacol, 4′-O-methylidiplacol, mimulone, diplacol, and 6-geranyl-4,5,7-trihydroxy-3′,5′-dimethoxyflavanone isolated from *Paulownia tomentosa* have been reported to suppress SARS-CoV PLpro at 0–100 μM (Cho et al., 2013). *Anthemis hyalina*, *Nigella sativa*, and *Citrus sinensis* extracts significantly reduced viral infection after HeLa-CEACAM1a (HeLa-epithelial carcinoembryonic antigen-related cell adhesion molecule 1a) has been afflicted with MHV-A59 (Mous Hepatitis Virus A59) CoV, with A. hyalina being the most effective of the three plants assessed. Even though TRP gene expression was reduced upon diagnosis with these extracts, a rise in calcium ion level made it unconvincing to equate this impact with reduced viral replication (Ulasli et al., 2014). In another report, bavachinin, neobavaisoflavone, isobavachalcone, 4′-O-methylbavachalcone, psoraladin, and coumefol isolated from *Psoralea corylifolia* suppressed papain-like protease (Kim et al., 2014a). The investigation by Schwarz et al. (2014) noticed that juglalin prevents the SARS-CoV 3a channel with an IC<sub>50</sub> value of 2.3 μM. Among the NIH clinical collection of 727 tested antiviral activity compounds against both murine and human coronavirus, alkaloid macetaxine (homoharringtonine) was perhaps the most effective (Cao, Forrest, & Zhang, 2015). On the other side, Quercetin, Quercetin, Rutin, Cinanserin (1 and 2 dpi) isolated from *H. cordata* reported showed significant against CoV murine at 15.63–500 μg/ml (Chiow et al.,
2016). Note that the SARS-CoV spike protein (S) uses ACE2 as a responsive binding site to invade host cells (Li, 2016).

In contrast, broussonetol A, broussonetol C, 4-hydroxyisolonchocarpine, papyriflavonol A, 3’-(3-methylbut-2-enyl)-3’,4,7-trihydroxyflavane, kazinol A, broussonetol A, kazinol F, and kazinol J extracted from Broussonetia papyrifera suppressed both SARS-CoV 3CLpro and PLpro, during which papyriflavonol A had the highest inhibition toward PLpro with an IC50 value of 3.7 μM (Park et al., 2017). Likewise, 7-methoxycryptopleurine (IC50: 20 nM) was much more efficient than tylophorine (IC50: 58 nM). In another investigation, tylophorine was also identified to approach viral replication of RNA and cellular JAK2-mediated dominant NF-B activation in CoV at 0–1000 nM (Yang et al., 2017). In comparison, silvestrol impeded cap-dependent viral mRNA translation of HCoV-229E with an IC50 of 40 nM at 0.6–2 μM, and ouabain decreased both viral titers and viral yields and decreased the incidence of viral RNA copies at 0–3000 nM (Muller et al., 2018; Yang et al., 2020). New reports have shown that tetrandrin, fangchinoline, and cepharanthin, significantly inhibit initial phase viral-induced cell death in HCoV-OC43-infected human MRC-5 lung cells with IC50 values of 0.33, 1.01, and 0.83 μM, respectively (Kim et al., 2019). Also, lycorin, berbamine, emetine and mycophenolate mofetil were shown to intervene against HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59 at 0–5 μM. Lycorin and emetine suppressed cell division and hindered RNA, DNA, and protein synthesis, respectively while mycophenolate mofetil conferred an immune suppression effect on CoV species (Shen et al., 2019).

The docking studies analysis was used to examine the binding affinity and type of interaction among all compounds (67 natural molecules) and the target (Coronavirus (2019-nCoV) main protease). The outcomes of molecular modeling shown that among 67 molecules of biological origin crocin, digitoxigenin, and b-eudesmol act as inhibitors against the Coronavirus based on the energy types of interaction molecules (Aanouz et al., 2020). Also, 3CLpro sequence SARS-CoV-2 was assessed; its 3D homology model was developed and examined against a medicinal plant library containing 32,297 potential antiviral phytochemicals/Chinese traditional therapeutic molecules. Further, 5, 7, 3’, 4’-tetrahydroxy-2’-(3,3-dimethylallyl) isoflavone, myricitrin, methyl rosmarinate, (2S)-eriodictyol7-O-(600-Ogalloyl)-beta-D-glucopyranoside and calceolarioside B isolated from Psorothamnus arborescens, Myrica cerifera, Hyptis atrorubens Poit. Phyllanthus emblica and Fraxinus sieboldiana may act as anti-SARS-CoV-2 active compounds for more prioritization (Ul Qamar, Alqahtani, Alamri, & Chen, 2020).

4.2 | Human herpes viruses and medicinal plants

Numerous members of the human herpesvirus (HHV) family are mostly causative factors for various human diseases. In contrast, many HHV infections are associated with Herpes Simplex Virus (HSV-1 and HSV-2). Other members of herpes viruses that cause multiple conditions are HHV-3 (Varicella-Zoster Virus), HHV-4 (Epstein Barr virus), HHV-5 (Cytomegalovirus), HHV-6, HHV-7, and HHV-8. HSV-1 and HSV-2 have encapsulated dsDNA viruses of the family Herpesviridae. HSV infection causes mucosal lesions in the ocular/perioral (usually HSV-1) and genital (usually HSV-2) areas and many other body sites. HSV tends to cause lifetime infection by developing itself on the sensory neurons and thus can be reactivated by different stimuli, like sun exposure, sore throat, immune suppression, menstrual cycles, or anxiety (Fatahzadeh & Schwartz, 2007). The transmission of HSV results from direct contact with infected lesions and could occur via vertical transmission from infected mother to fetus. However, the disease is typically self-limited and can be handled with antiviral drugs. However, consequences could develop in neonates, and immuno-suppressed persons lead keratoconjunctivitis and life-threatening meningitis (Arduino et al., 2008; Chentoufi & Benmohamed, 2012).

Hardly any vaccine is recommended against HSV, even though there are no effective drugs that could neutralize innate HSV infection. A few primary and metastatic conditions could be monitored by analogous like acyclovir, penciclovir, and produgs. Moreover, the expansion of resistance to antibiotics virus is becoming a severe problem, especially in immune-compromised patients (Morfín & Thouvenot, 2003). Therefore, the discovery of new anti-HSV agents with diverse mechanisms is significant to HSV’s clinical management. Plant extracts attracted substantial attention while looking for alternative compounds with anti-herpetic activity. Intriguingly, innumerable plant-derived extracts and molecules were already known to prevent HSV replication (Table 2) (Akram et al., 2018; Li et al., 2017).

Licorice roots of Glycyrrhiza glabra were used to prepare a 2% topical acid cream, which contains carbenoxolone sodium. The cream was used to cure12 patients having acute oral herpetic (HSV) infections. The disease symptoms such as pain and dysphagia were resolved after applying the cream six times a day within a short span of 24–48 hr. In contrast, ulceration and lymphadenopathy were shown to cure steadily within 24–72 hr (Partridge & Poswillo, 1984). Samarangenin B extracted from the leaves of Limonium sinense observed suppression of HSV-1 g gene expression (Kuo et al., 2002). Further, Artocarpus lakoocha containing oxyresveratrol was reported to prevent early and late HSV-1 and HSV-2 viral replication phases, respectively (Chuanasa et al., 2008). Pterocarpan A compound isolated from Pterocarya stenoptera impeded HSV-2 from adhesion and infiltration to host cells (Cheng et al., 2004). Yatein extracted from Chamaecyparis obtuse substantially inhibits HSV-1 replication in HeLa cells without noticeable cytotoxic effects (Kuo et al., 2006).

In comparison, several H. cordata flavonoids were assessed to determine their capability to obstruct the HSV-2 replication cycle. The principal flavonoids quercetine, quercitrine, and isoquercitrine showed significant HSV-2 activity (Chen et al., 2011). Subsequent investigation assessed that the mode of action could be behind the anti-herpetic activity of H. cordata, like adsorption, entry, post-infection by NF-kB, and virucidal activity (Hung et al., 2015). Also, meliacin obtained from Melia azedarach was shown to induce TNF-α and IFN-α production and reduce HSV-2 by improving virus-induced pathogenesis in the mouse genital model of herpetic inflammation (Petra & Coto, 2009).

Comparably, the aqueous extract from Rhododendron ferrugineum blackberry extract and the extract from Myrothamnus flabellifolia
enriched with proanthocyanidin prevented the HSV-1 infection (Danaher et al., 2011; Gescher, Kuhn, Hafezi, et al., 2011; Gescher, Kuhn, Lorentzen, et al., 2011). Glucoevatromonoside, a cardenolide from Digitalis lanata, alter the cellular electrochemical gradient and hinder the proliferation of HSV-1 and HSV-2 in cells (Bertol et al., 2011). The natural products from the marine ecosystem such as algae and sponges produce active metabolites with anti-HSV activity (Sagar et al., 2010; Vo et al., 2011). Houttuynoids A-E extracted from H. cordata, showed effective anti-HSV-1 activity (Chen et al., 2012a). Another resveratrol compound isolated from the Veratrum grandiflorum inhibited NF-κB activation, the primary bioactive substance present in grapes, peanuts, legumes, or other plant-derived matrices and perhaps in red wine (Chen et al., 2012b).

Numerous studies documented the antibacterial activity of resveratrol against the ACV-resistant and wild-type HSV-1 and HSV-2 replication cycles in cell lines and animal studies (Faith et al., 2006; Leyton et al., 2015). Compounds like spiroketalenol ether derivatives extracted from Tanacetum vulgare rhizome extract served as cell entry inhibitors and apprehend HSV-1 gC and HSV-2 gG glycoproteins production (Alvarez et al., 2015). Essential oils derived from Glechon spathulata and Glechon marifolia noted antiviral activity against HSV-1, which became effective after infecting Vero cells (Venturi et al., 2015). Furthermore, essential oils derived from plants of the families Labiatae and Verbenaceae have an antiviral effect on HSV. Vero cells after incubation with HSV and essential oils for 48–72 hr dramatically lowered viral titers of HSV-1 and HSV-2. It is important to note that their modes of action were related to the pre-infective stages (Brand et al., 2016). An analysis showed that the leaves of Morus alba L. exhibited antiviral properties against HSV-1 and HSV-2. Kuwanon X, a stilbene polyphenol derivative active compound found in this plant, reported antiviral activity against HSV at different phases of the infection process, preventing adsorption and penetration, and instant early and late gene expression of HSV-1, and replication of HSV-1 DNA (Ma et al., 2016).

Ethanic extract from the Eucalyptus camaldulensis leaves prevents HSV-1 and HSV-2 infection during and after illness to Vero cells. Synergism was observed in cultured cells among acyclovir and ethanol extracts (Abu-Jafar & Mahmoud, 2017). Similarly, the antiviral activity of 24 new metabolites from the leaves of Eucalyptus sideroxylon and four new metabolites from genus Eucalyptus were reported. In contrast to HSV-1 and HSV-2 these compounds suppressed hepatitis A, coxsackie, and adenoviruses. Notably, antiviral activity against HSV-2 was exhibited by inhibiting the entrance of viruses and consequent infection processes (Okba et al., 2017). Xanthotoxin, bergapten, imperatorin, phellopterin, isoimperatorin, imperatorin, and phellopterin isolated from dichloromethane fruit extract of Angelica archangelica were explored as the practicable antiviral agents toward HSV I. Imperatorin and phellopterin showed the highest effect, minimizing replication of HSV-1 by 5.61 logs and 4.7 logs, respectively. The extract resulted in a decrease in the titer of the virus controlling the control of the virus. The findings demonstrate that coumarins of A. archangelica may be an excellent material for the formation of an alternative natural anti-HSV-1 compound (Rajtar et al., 2017).

Further, 12 compounds isolated from Eucalyptus globulus leaves and twigs were noticed to have antiviral efficacy against HSV-1 and HSV-2. Tereticornate A has been assessed to holds the most incredible action against HSV-1, relatively high than acyclovir. Cypellocarpin C showed significant antiviral activity against HSV-2, higher than that offered by acyclovir (Brezná et al., 2018). Organic extracts relating to the Peganum harmala species showed antiviral activity against HSV-2 by disrupting virus entry (Benzekri et al., 2018). Besides, Yatein separated from C. obtuse prevents HSV-1 alpha gene expression, along with ICPO and ICPO4 expression of genes, by halting HSV-1 DNA replication and structural protein expression in HeLa cells (Wang et al., 2019). Natural anti-HSV substances’ availability should provide novel pharmaceutical properties against the virus for future use in monitoring HSV infections.

4.3 Medicinal plants in viral hepatitis

Viral hepatitis or inflammation of the liver is associated with several different viruses called hepatitis A, B, C, D, and E. Since exposure to any of these viruses results in acute infection, type B and C are distinctive in inducing chronic conditions.

4.3.1 Hepatitis B virus

Hepatitis B virus (HBV) a prototype virus belonging to Hepadnaviridae family, is an enveloped virus with a relaxed circular and partly double-stranded DNA genetic structure (dsDNA) (Liang, 2009). HBV induces hepatitis B and is transmitted by contact with the virus-containing blood or other body fluids. Though some spontaneous recovery following acute hepatitis B is prevalent, due to the extreme risk of cirrhosis, HCC therapy is advised for chronic infection. The HBV vaccine design and the national vaccination policy against hepatitis B in endemic regions like Taiwan have helped to alleviate HBV infection and decreased the prevalence of HCC in the childhood stage (Ni & Chen, 2010).

Given the availability of effective vaccinations, the existing HBV compromised population remains at the threat of end-stage liver diseases, mostly in areas where vaccine schedules are inaccessible. Nucleotide/nucleoside analogs like lamivudine, adefovir, tenofovir, telbivudine, entecavir, and the immune modulator pegylated interferon-α (Peg-IFN-α) were used for the treatment of HBV infections (Kwon & Lok, 2011). Nevertheless, it is difficult to eradicate HBV from the body once a prolonged inflammation occurs. The condition gets exacerbated by threats of selecting drug-resistant viral mutants, failure of diagnosis in non-responders, and possible future viral recurrence. Thus, anti-HBV drugs’ development will always be of significance for the scientific attention and hepatitis B management system’s assistance to diagnose about 300–400 million carriers globally (Franco et al., 2012).

Phyllanthus species are considered an essential source of antiviral bioactive metabolites such as lignans, including hypophyllanthine and...
| Plant name                          | Natural product(s) evaluated | Virus assessed                  | Culture / Animal model assessed | Proposed mechanism                                      | References                       |
|------------------------------------|------------------------------|--------------------------------|---------------------------------|---------------------------------------------------------|----------------------------------|
| *Peganum harmala* (Wild rue)       | Harmine                      | HSV-2                          | In vitro                        | Inhibition of viral entry                                | Benzekri et al., 2018            |
| *Melia azedarach* (Chinaberry tree)| Meliacine (Glycopeptide)     | HSV-1 and HSV-2                | In vitro and in vivo            | Inhibiting replication of HSV after entry               | Petrera & Coto, 2009; Barquero et al., 1997 |
| *Avicennia marina*                  | Polyphenol                   | HSV-1                          | In vitro                        | Inhibit replication of HSV after entry                  | Namazi et al., 2014              |
| *Glechon spathulata*                | Bicyclogermacrene           | HSV-1                          | In vitro                        | Inhibition after viral attachment                       | Venturi et al., 2015             |
| *Glechon marifolia*                 | Bicyclogermacrene           | HSV-1                          | In vitro                        | Inhibition after viral attachment                       | Venturi et al., 2015             |
| *Aglaia odorata*                    | Moringa oleifera and *Ventilago denticulata* | HSV-1 and HSV-2 | In vitro and in vivo | Virucidal, inhibition of viral binding, inhibition of viral entry | Lipun et al., 2003; Brand et al., 2016 |
| *Morus alba* (white mulberry)      | Kuwanon X                    | HSV-1 and HSV-2                | In vitro                        | Inhibition of early stages of viral infection           | Ma et al., 2016                  |
| *Houttuynia cordata*                | Quercitin, Isoquercitrin, and Quercitrin | HSV-1 and HSV-2 | In vitro                        | Inhibition of NF-kB activation, inhibition of viral binding, inhibition of viral entry | Chen et al., 2011; Hung et al., 2014; Leyton et al., 2015 |
| *Veratum grandiflorum*              | Resveratrol                   | HSV-1 and HSV-2                | In vitro                        | Inhibition of viral replication                          | Pacheco et al., 1993             |
| *Eucalyptus camaldulensis* (River Red Gum) | Tereticornate A, Cypellocarpin C | HSV-1 and HSV-2 | In vitro                        | Inhibition of virus binding, post-infection antiviral effects | Abu’l-Fulah & Mahmoud, 2017 |
| *Cassia stipulacea* (Quebracho) and *Escallonia illinita* (Ñipa) | Chikusetsusaponin IV | HSV-1 and HSV-2 | In vitro and in vivo | Virucidal, inhibition of virus binding, inhibition of virus entry | Rotori et al., 2007 |
| *Alternanthera philoxeroides* (Alligator weed) | Chikusetsusaponin IV | HSV-1 and HSV-2 | In vitro and in vivo | Inhibition of virus binding, inhibition of virus entry | Abu’l-Fulah et al., 1995 |
| *Melissa officinalis* (Balm Mint)   | Unknown                      | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Alshnaibi et al., 2007            |
| *Alpinia officinarum* (Lesser Galangal) and *Geum japonicum* (Asian Herb Bennet) | Unknown | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Kurokawa et al., 1995             |
| *Melaleuca alternifolia* (tea tree) | Unknown                      | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Garozzo et al., 2009; Rattanachangklin et al., 2009 |
| *Quillaja saponaria* (soap bark tree) | Unknown                      | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Roner et al., 2007; Garozzo et al., 2009 |
| *Melissa officinalis* (Balm Mint)   | Unknown                      | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Alshnaibi et al., 1995            |
| *Alpinia officinarum* (Lesser Galangal) and *Geum japonicum* (Asian Herb Bennet) | Unknown | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Kurokawa et al., 1995             |
| *Melissa officinalis* (Balm Mint)   | Unknown                      | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Alshnaibi et al., 1995            |
| *Alpinia officinarum* (Lesser Galangal) and *Geum japonicum* (Asian Herb Bennet) | Unknown | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Kurokawa et al., 1995             |
| *Melissa officinalis* (Balm Mint)   | Unknown                      | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Alshnaibi et al., 1995            |
| *Alpinia officinarum* (Lesser Galangal) and *Geum japonicum* (Asian Herb Bennet) | Unknown | HSV-1                          | In vitro                        | Virucidal, inhibition of virus binding, inhibition of virus entry | Kurokawa et al., 1995             |
| Plant name | Natural product(s) evaluated | Virus assessed | Culture / Animal model assessed | Proposed mechanism | References |
|------------|----------------------------|----------------|---------------------------------|--------------------|------------|
| Carissa edulis Vahl. | Unknown | HSV-1 and HSV-2 | In vitro and in vivo | Delayed the onset of HSV infections | Tolo et al., 2006 |
| Paeonia suffruticosa (Mudan), Phellodendron amurense (Amur Cork tree), Polygonum tenuifolia (Yuan Zhi), Polygonum cuspidatum (Asian Knotweed), Rhus javanica (Java Brucea), Syzygium aromaticum (clove), Terminalia arjuna (Arjun tree) and Terminalia chebula (Black Myrobalan) | Unknown | HSV-1 | In vitro and in vivo | Inhibition after virus adsorption | Kurokawa et al., 1995 |
| Phyllanthus urinaria L. | 1346TOGDG and geraniin | HSV-1 and HSV-2 | In vitro | Undefined | Yang et al., 2007 |
| Rheum palmatum | Aloe-emodin | HSV-1 and HSV-2 | In vitro | Prevention of virus adsorption and subsequent replication | Sydiskis et al., 1991 |
| Terminalia arjuna (Arjun tree) and Terminalia chebula (Black Myrobalan) | Oxyresveratrol | HSV-1 and HSV-2 | In vitro | Inhibition of viral replication and late protein synthesis | Chuanasa et al., 2008 |
| Melia azedarach L. | Tetranortriterpenoid 1-cinnamoyl-3,11-dihydroxymeliacarpin (CDM) | VSV HSV-1 | In vitro | CDM modulates the NF-κB signaling pathway by lowering down its activation in HSV-1-infected conjunctival cells | Zhang et al., 2007 |
| Limonium sinense | Samarangenin B | HSV-1 | In vitro | Inhibit HSV-1 α gene expression and by arresting HSV-1 DNA synthesis and structural protein expression in Vero cells | Kuo et al., 2002 |
| Prunella vulgaris | Lignin–carbohydrate complex (PPS-2b) | HSV-1 and HSV-2 | In vitro and in vivo | Block HSV-1 binding and inhibiting penetration into Vero cells | Zhang et al., 2007 |
| Scoparia dulcis L. | Scopadulcic acid B | HSV-1 | In vitro and in vivo | Inhibit the viral replication | Hayashi et al., 1988 |
| Tanacetum vulgare | Spiroketalenol ether derivative | HSV-1 and HSV-2 | In vitro | | Alvarez et al., 2015 |
| Rhus aromatic | Unknown | HSV-1 and HSV-2 | In vitro | Undefined | Reichling et al., 2009 |
| Arisaema tortuosum | Apigenin and luteolin | HSV-1 and HSV-2 | In vitro | Inhibition of both early and late events of the HSV-2 replicative cycle | Rittà et al., 2020 |
| Pterocarya stenoptera | Pterocarnin A | HSV-2 | In vitro | Inhibits adsorption, penetration and multiplication of HSV2 into cells | Cheng et al., 2014 |
| Cassia javanica | ent-Epiafzelechin-(4α → 8)-epiafzelechin | HSV-2 | In vitro | Inhibits viral replication | Cheng et al., 2006c |
| Phyllanthus urinaria | Hippomanin A | HSV-2 | In vitro | Prevented HSV-2 from penetrating the cell and also interfered with HSV-2 replication at the late stage of its life cycle | Yang et al., 2007 |
| Plant name                  | Natural product(s) evaluated | Virus assessed | Culture /Animal model assessed | Proposed mechanism                                                                                       | References                        |
|----------------------------|------------------------------|----------------|-------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------|
| *Phyllanthus urinaria*     | Excoecarianin                | HSV-2          | In vitro                      | Inactivation of virus particles                                                                        | Cheng et al., 2011                |
| *Terminalia chebula*       | Chebulagic acid and punicalagin | HSV-1          | In vitro                      | Cell surface GAG competitors; inhibit viral entry (binding and fusion) and post-infection cell-to-cell spread | Lin et al., 2011                  |
| *Melia azedarach*          | Meliacine                    | HSV-2          | In vivo                       | Induces TNF-α and IFN-γ production                                                                      | Petrera et al., 2009              |
| *Houttuynia cordata*       | Houttuynoids A-E             | HSV-1          | In vitro                      | Undefined                                                                                              | Chen et al., 2012a                |
| *Rhododendron ferrugineum* | Unknown                      | HSV-1          | In vitro                      | Inhibits viral adsorption and penetration                                                              | Gescher et al., 2011a             |
| *Melia azedarach*          | Meliacine                    | HSV-2          | In vivo                       | Induces TNF-α and IFN-γ production                                                                      | Petrera et al., 2009              |
| *Houttuynia cordata*       | Houttuynoids A-E             | HSV-1          | In vitro                      | Undefined                                                                                              | Chen et al., 2012a                |
| *Rhododendron ferrugineum* | Unknown                      | HSV-1          | In vitro                      | Inhibits viral adsorption and penetration                                                              | Gescher et al., 2011a             |
| *Blackberry extract*       | Unknown                      | HSV-1          | In vitro                      | Inhibits viral replication and exhibits virucidal activity                                              | Danaher et al., 2011              |
| *Myrothamnus flabellifolia*| Proanthocyanidin-enriched extract | HSV-1          | In vitro                      | Inhibits viral adsorption and penetration steps                                                          | Gescher et al., 2011a             |
| *Digitalis lanata*         | Glucoevatromonoside          | HSV-1          | In vitro                      | Inhibits viral protein synthesis                                                                       | Bertol et al., 2011               |
| *Schinus terebinthifolia*  | Catechin                     | HSV-1          | In vitro                      | Effective in the attachment and penetration stages                                                      | Nocchi et al., 2017               |
| *Cornus canadensis*        | Tellimagrandin I             | HSV-1          | In vitro                      | Undefined                                                                                              | Lavoie et al., 2017               |
| *Hemidesmus indicus*       | 2-Hydroxy-4-methoxybenzaldehyde; 3-hydroxy-4-methoxybenzaldehyde | HSV-1 and HSV-2 | In vitro                      | Anti-ERα-glucosidase inhibitory activity                                                               | Bonvicini et al., 2018            |
| *Equisetum giganteum* and *Copaifera reticulate* | Unknown | HSV-2 | In vitro and in vivo | Interfering with viral cell attachment and entry                                                       | Churqui et al., 2018              |
| *Punica granatum*          | Punicalagin                  | HSV-2          | In vitro                      | Undefined                                                                                              | Arunkumar & Rajarajan, 2018       |
| *Peganum harmala*          | Harmine                      | HSV-2          | In vitro                      | Undefined                                                                                              | Benzekri et al., 2018             |
| *Erythrina speciosa*       | Vitexin                      | HSV-1          | In vitro                      | Undefined                                                                                              | Fahmy et al., 2020                |
phylanthine, flavonoids (ternatin), and alkaloids such as quercetin. They can block the endogenous DNA polymerase enzyme of HBV, which is crucial for viral replication (Venkateswaran et al., 1987). A variety of bioactive metabolites were extracted from Phyllanthus niruri and were also evaluated for their inhibitory potential, using sera containing HBsAg, collected from chronic HBV patients (Thyagarajan et al., 1982). Subsequent studies have revealed the in vivo efficacy of P. niruri extract in eliminating HBV in 3–6 weeks in mammals. A 90-day treatment with plant extracts successfully reduced the HBV antigen to undetectable levels among two-thirds of HBV-positive patients (Wang et al., 1995). Further, numerous studies were conducted in the last several years to recognize anti-HBV molecules from medicinal herbs (Cui et al., 2010; Qiu et al., 2013; Zhan et al., 2010; Zhang et al., 2010). For examples, the antiviral effects of the saikosaponins from Bupleurum species and the ethanol extract from Polygonum cuspidatum were reported against HBV in vitro (Chang et al., 2007; Chang et al., 2005). Further, curcumin showed to suppress the HBV gene’s replication and an appearance by controlling the peroxysome proliferator-activated gamma receptor co-activator 1-alpha (PGC-1α), the HBV transcription co-activator (Rechtman et al., 2010). Furthermore, Phyllanthus, Salvia miltiorrhiza, Rheum palmatum L., and Radix astragali and chemical compounds like oxymatrine, arteisinin, artesunate, and wogonin also reported promising anti-HBV activities (Cui et al., 2010). Other examples include isochlorogenic acid A, amide alkaloid, and dehydrocheilanthifoline from Laggera alata, Piper longum, and Corydalis saxicola experienced high anti-HBV activities (Hao et al., 2012; Jiang et al., 2013; Zeng et al., 2013). The LPRP-Et-97,543, isolated from the roots of Liriope platyphylla, hinders the mechanism of HBV’s action by regulating the gene expression and the DNA replication by viral proteins by interacting with the pathway of NF-κB nuclear factor (Huang et al., 2014).

There seems to be a lack of studies on bioactive components’ mode of action against HBV, while most natural compounds were proven to effectively suppress the HBV (Wu, 2016) (Table 3). For instance, Acanthus ilicifolius L. significantly decreases HBV-induced liver damage by lowering the transaminase (Wei et al., 2015). Gymnema sylvestre phytocconstituents prevent HBsAg binding and HBV DNA polymerase activity (Subashini and Rajendran, 2015). Further, the expression of intracellular HBV DNA in HBV WT-or mutant-transfected HepG2 cells declined following Phyllanthus extract treatment. Phyllanthus triggered interferon-beta, cyclooxygenase-2, and interleukin-6 mRNA expression in HBV WT-transfected HepG2 cells, probably by modulation of extracellular signal-regulated kinases and c-Jun N-terminal kinases and by induction of retinoic acid-inducible gene-I, toll-like receptor 3, myeloid distinctions of primary response gene, and tumor necrosis of fac (Jung et al., 2015). Two new major C-βorovinopranosyl flavones (luteolin-6-C-β-o-bovinopyranosyl 3’-O-β-o-glucopyranoside and chrysosyerol-6-C-β-bovinopyranosyl 4’-O-β-o-glucopyranoside) isolated from Alternanthera philoxeroids showed substantial anti-HBV activity by reducing HBsAg secretion in HepG2.15 cells (Li et al., 2016).

Consequently, ethanol extract of Sanguisorba officinalis and its significant compounds (ziyuglycoside I and II) against HBV in HepG2.2.15 cells inhibit replication and antigen secretion of HBV. Hence, describing the plant’s tendency as novel candidates for the treatment of HBV-related diseases (Jang et al., 2018). The anti-HBV effect of Abrus cantoniensis was explored both in vitro and in vivo studies. Treatment of A. cantoniensis strongly suppressed the development of HBV DNA, Hepatitis Be Antigen (HBeAg), and Hepatitis B surface antigen (HBsAg) in HepG2.2.15 cells and rAAV8-1.3HBV transfected mice, which provides a base for its possible clinical usage (Yao et al., 2020). Quercetin and myricetin-3-O-rhamnoside extracted from Guiera senegalensis leaves showed antiviral activity (HBsAg and HBeAg assay) in HepG2.2.2.15 HBV-reporter cells. Quercetin notably repressed HBsAg and HBeAg synthesis by approximately 60 and 62%, respectively, compared to myricetin-3-O-rhamnoside by 44 and 35%. Their probable anti-HBV mode of action was expected by the ability to bind with viral Pol/RT and core as well as host NTCP proteins (Parvez et al., 2020).

Furthermore, the HBV inhibition activities of polysaccharide from Radix isatidis were mediated by the stimulation of the IFN-α-dependent JAK/STAT signal pathway and the initiation of protein expression against HBV (Wang et al., 2020). Swertisin obtained from Iris tectorum displayed a significant inhibitory effect for HBV replication by inhibiting HBeAg and HBsAg and HBV DNA (Xu et al., 2020). Although novel anti-HBV inhibitors were developed, the combination of remedies with conventional nucleotide/nucleoside analogs or IFN-α-based hepatitis B therapy must also be assessed in future research.

### 4.3.2 | Hepatitis C virus

HCV is a flavivirus with a positive-sense ssRNA, usually transmits through blood-to-blood interactions, intravenous injections, blood transfusion, and varying exposures to blood toxic substances. Due to the overly abstract nature of HCV, a precautionary vaccine has not been available yet. Approximately 70% of infections are consistent, affecting an estimated 300 million carriers worldwide, among which 1–3% can proceed to end-stage liver diseases, such as cirrhosis and HCC (El-Serag, 2012). The recommended treatment comprises Peg-IFN-α plus oral ribavirin parenteral. Nevertheless, few challenges exist in the current method of HCV treatment. They have limited efficacy for specific viral genetic variants, unavoidable selection of drug-resistant mutants, adverse side effects, exorbitant prices of medication, patient adherence issues, and challenges in diagnosing communities such as non-responsive patients and patients with liver transplantation (Welsh et al., 2012). The rapid expansion of anti-HCV substances is indeed essential to address such deficiencies.

Table 3 summarizes the antiviral potential of different natural products determined against HCV infection. For instance, Silybum marianum and its flavonolignans showed significant anti-HCV activity in vitro (Polvak et al., 2007, 2010). Many clinical trials showed a viable impact on reducing the viral load (Marino et al., 2013; Neumann et al., 2010). Curcumin was reported as a critical inhibitor of HCV replication by conceivably restricting the sterol regulatory element-binding to protein-1 (SREBP-1)-Akt pathway Kim et al., 2010), and its
| Natural products/Extracts evaluated | Virus strain assessed | Culture/Animal model assessed | Proposed mechanism | References |
|-----------------------------------|-----------------------|------------------------------|--------------------|------------|
| Isochlorogenic acid A (Laggera alata) | HBV | HepG2.2.15 cells | Blocking the translation step of the HBV replication and reducing the stability of the HBV core protein and thus blocking the refill of nuclear HBV cccDNA | Hao et al., 2012 |
| Amide alkaloid (Piper longum) | HBV | HepG2.2.15 cells | Undefined | Jiang et al., 2013 |
| Dehydrocheilanthifoline (Corydalis saxicola) | HBV | HepG2.2.15 cells | Inhibits the replication of HBV | Zeng et al., 2013 |
| Saikosaponins (C, D) (Bupleurum species) | HBV | HepG2.2.15 cells | Saikosaponin C inhibits HBeAg expression and HBV DNA replication | Chiang et al., 2003 |
| Ethanol extract (Polygonum cuspidatum) | HBV | HepG2.2.15 cells | Inhibits the expression of HBeAg | Chiang et al., 2005 |
| Curcumin | HBV | HepG2.2.15 cells | Viral transcription suppressor via down regulation of the co-activator PGC-1α | Rechtman et al., 2010 |
| Glycyrrhizinic acid (Glycyrrhiza glabra) | HBV | HepG2.2.15 cells | Undefined | Pompei et al., 2009 |
| Artemisinin (Artemisia annua) | HBV | HepG2.2.15 cells | Inhibition of viral production | Efferth et al., 2008 |
| Root extract (Boehmeria nivea) | HBV | HepG2.2.15 cells | Inhibition of viral production | Huang et al., 2006 |
| Ethanol extract (Polygonum cuspidatum) | HBV | HepG2.2.15 cells | Inhibition of viral production | Chang et al., 2005 |
| LPRP-Et-97,543 (Liriope platyphylla) | HBV | HepG2.2.15 cells | Inhibit viral gene expression and replication. Inhibit viral promoter activity | Huanga et al., 2014 |
| 1,2,3,4,6-penta-O-galloyl-beta-D-glucoside (Saxifraga melanocentra Engl.& Irmsch) | HCV | COS-7 fibroblast-like cells | Inhibition against HCV NS3 serine protease | Zuo et al., 2005 |
| Standardized Silymarin extracts (Silybum marianum) | HCV | Human hepatoma-derived (Huh7 and Huh7.5.1) cells | Antiviral effect partly due to enhancement of the IFN-associated JAK–STAT pathway | Polyak et al., 2007 |
| Flavonolignans (Silybum marianum/silymarin) | HCV | Huh7 cells | Antiviral effect probably related to antioxidant functions of the flavonolignans | Polyak et al., 2010 |
| Curcumin | HCV | Huh7 cells | HCV replication inhibitor via suppressing Akt-SREBP-1 pathway | Kim et al., 2010 |
| Epigallocatechin-3-gallate | HCV | Huh7 cells | Inhibits viral entry by affecting the fluidity of the HCV envelope; inhibits viral entry | Ciesek et al., 2011; Calland et al., 2012 |
| Griffithsin | HCV | Huh7 cells | Prevents infection and inhibits viral cell-to-cell transmission | Meuleman et al., 2011 |
| Ldanein | HCV | Primary human hepatocytes | Inhibits viral entry | Haid et al., 2012 |
| Tellimagrandin I (Rosae Rugosae) | HCV | Huh7 cells | HCV invasion inhibitor | Tamura et al., 2010 |
| Chebulagic acid and punicalagin (Terminalia chebula Retz.) | HCV | Huh-7 cell | Inactivate free virus particles; interfere with viral binding, fusion, and post-infection cell-to-cell spread | Lin et al., 2013 |
| Saikosaponin b2 (Bupleurum koi) | HCV | Huh-7 cells | Inhibiting early HCV entry, including neutralization of virus particles, preventing viral attachment | Lin et al., 2015 |
| Chalepin and pseudane IX (Ruta angustifolia) | HCV | Huh-7 cells | Inhibited HCV at the post-entry step and decreased the levels of | Wahyuni et al., 2014 |
| Natural products/Extracts evaluated | Virus strain assessed | Culture/Animal model assessed | Proposed mechanism | References |
|------------------------------------|-----------------------|------------------------------|--------------------|------------|
| Elderberry liquid extract (Sambucus nigra) | IFA and IFB | Madin–Darby canine kidney (MDCK) cells | HCV RNA replication and viral protein synthesis | Krawitz et al., 2011 |
| Eps® 7,630 (Umckaloabo®) Root extract (Pelargonium sidoides) | IFA | MDCK cells | Inhibits viral entry and release; inhibits viral hemagglutination and NA activity | Theisen et al., 2012 |
| Aqueous extract (Taraxacum officinale) | IFA | MDCK cells | Inhibits viral NP RNA levels and polymerase activity | He et al., 2011 |
| Spiroooliganone B (IlliciumOligandrum) | IFA | MDCK cells | Undefined | Ma et al., 2013 |
| Chalcones (Glycyrrhiza inflata) | IFA | MDCK cells | IFA NA inhibitors | Dao et al., 2011 |
| Xanthones (Polygala karensium) | IFA | MDCK cells | IFA NA inhibitors | Dao et al., 2011 |
| Homoioisoflavonoids (Caesalpinia sappan) | IFA | MDCK cells | IFA NA inhibitors | Jeong et al., 2012 |
| Quercetin 3rhamnoside (Houttuynia cordata) | IFA WS/33 virus | MDCK cells | Inhibit replication in the initial stage of virus infection by indirect interaction with virus particles | Choi et al., 2009 |
| Geranium sanguineum | IFA | MDCK cells/male and female (16-18 g), inbred ICR mice | Undefined | Pantev et al., 2006 |
| Elderberry extract | IFA and IFB | 60 adult influenza patients | Undefined | Zakay-Rones et al., 2004 |
| Taxodium distichum | IFA and IFB | MDCK cells | Inhibited viral entry and budding; blocked neuraminidase activity | Hsieh et al., 2016 |
| CYSTUS052 (Cistus incanus) | IFA (H7N7) | MDCK cells | Undefined | Droebner et al., 2007 |
| Water extract (Panax notoginseng) | IFA | MDCK, YAC-1, and RAW 264.7 cells | Undefined | Choi et al., 2017 |
| Aurantiamide acetate (Baphicacanthus cusia) | IFA | MDCK cells | Inhibition of the NF-κB pathway | Zhou et al., 2017 |
| Isocorilagin (Canarium album) | IFA | MDCK cells | Inhibited neuraminidase activity | Chen et al., 2020 |
| Jatropha multifida | IFA | MDCK cells | Undefined | Shoji et al., 2017 |
| Ethanol extract (Gerani Herba) | IFA | MDCK cells | Inhibited neuraminidase activity | Choi et al., 2019 |
| Polyphenols (Avicennia marina) | HIV-1 Human embryonic kidney cells (HEK293) | Undefined | Namazi et al., 2014 |
| Soulttrolid (Calophyllum teysmannii) | HIV-1 and HIV 2 | CEM-S5 cells | Undefined | Pengsuparp et al., 1996 |
| Phyllanthus amarus and Olive leaf extract | HIV-1 and HIV 2 | MT4 and MOLT3 cell lines | Inhibits HIV replication both in vitro and in vivo | Notka et al., 2004 |
| Artemisia annua and Artemisia afra | HIV-1 | HeLa cells | Undefined | Lubbe et al., 2012 |
| Tricyclic coumarin (Calophyllum brasiliense) | HIV-1 | U1 and Molt-4 cell lines | Inhibits viral replication in both acute and chronic infections by suppressing NF-κB | Kudo et al., 2013 |
| Patentiflorin A (Justicia gendarussa) | HIV-1 | Undefined | Inhibits NRTI (nucleoside reverse transcriptase inhibitor)-resistant isolate (HIV-11617-1) of the analog (AZT) as well as the NNRTI (non-nucleoside reverse transcriptase inhibitor)-resistant isolate (HIV-1N119) of the analog (nevaripine). | Zhang et al., 2017a, 2017b |
| HIV-1 | LC5-RIC cells | Helfer et al., 2014 | *(Continues)* |
| Natural products/Extracts evaluated | Virus strain assessed | Culture/Animal model assessed | Proposed mechanism | References |
|-----------------------------------|-----------------------|-------------------------------|--------------------|------------|
| Root extract (Pelargonium sidoides) | Interferes directly with viral infectivity and blocks the attachment of HIV-1 particles to target cells, protecting them from virus entry | | | |
| Aqueous extracts (Cistus incanus) | Preventing primary attachment of the virus to the cell surface and viral envelope proteins from binding to heparin | | | |
| Rhusflavanone (Rhus succedanea and Garcinia multiflora) as well as their methyl ethers and acetates | Inhibited MV replication, as indicated by the absence of CPE at higher extract concentrations | | | |
| Calcium spirulan (Spirulina platensis) | Inactivation of free virus particles; interfere with viral binding, fusion, and post-infection cell-to-cell spread | | | |
| Zanthoxylum chalybeum and Warburgia ugandensis | Inactivation of free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell | | | |
| Olina rochetiana and Warburgia ugandensis | Neutralize virus particles | | | |
| Stem and root extract (Cajanus cajan) | Inhibited MV replication, as indicated by the absence of CPE at higher extract concentrations | | | |
| Chebulagic acid and punicalagin (Terminalia chebula) | Inactivation of free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell | | | |
| Uncinoside A and B (Selaginella uncinata) | Undefine | | | |
| Dicafeoylquinic acids (Schefflera heptaphylla) | Inhibition of virus–cell fusion in the early stage and the inhibition of cell–cell fusion at the end of the RSV replication cycle | | | |
| Genkwanol B, genkwanol C, and stelleranol (Radix Wikstroemiae) | Undefine | | | |
| Flavones C-glycosides (Lophatherum gracile) | Inhibits viral attachment and internalization steps; stimulates IFN-β secretion | | | |
| Cimicifugin (Cimicifuga foetida) | Inhibits viral attachment and internalization steps; stimulates IFN-β secretion | | | |
| Cimicifuga foetida | Reduces virus-induced airway inflammation via down-regulation of IFN-γ levels during RSV infection | | | |
| Resveratrol | | | | |
| Chebulagic acid and punicalagin (Terminalia chebula Retz.) | | | | |
| Natural products/Extracts evaluated | Virus strain assessed | Culture/Animal model assessed | Proposed mechanism | References |
|-----------------------------------|-----------------------|------------------------------|--------------------|------------|
| Tangeretin and nobiletin (Polymethoxylated flavones) (Citrus reticulate) | RSV | HEp-2 cell line | down regulated the expression of RSV phosphoprotein (P protein) | Chen et al., 2019 |
| Ethanol extract (Lophatherum gracile) | | | Inhibit RSV infection and RSV-induced inflammation | Chen, 2019 |
| Aqueous and ethanolic extracts; linalool, apigenin, and ursolic acid (Ocimum basilicum) | CVB | BCC-1/KMC cells | Ursolic acid interferes with viral infection and replication | Chiang et al., 2012 |
| Raoulic acid (Raoulia australis) | CVB | Vero cells | Undefined | Choi et al., 2009 |
| Isatindolignanoside A (Isatis indigotica) | CVB3 | Vero cells | Undefined | Meng et al., 2018 |
| Aqueous leaf extract (Azidarachta indica) | DENV-2 | C6/36 cells | Undefined | Parida et al., 2000 |
| Petroleum ether, ethyl acetate, ethyl ether and coumarine (Alternanthera philoxeroides) | DENV | C6/36 cells | Undefined | Jiang et al., 2005 |
| Flavonoids and cyclohexenyl (Boesenbergia rotunda) | DENV-2 | C6/36 cells | Inhibition of dengue-2 virus NS3 protease | Kiat et al., 2006 |
| Narasin | DENV-2 | Huh-7 cells | Disrupts viral protein synthesis without affecting viral RNA replication | Low et al., 2011 |
| Quercetin | DENV-2 | Vero cells | Inhibits viral replication but not the viral attachment and entry processes | Zandi et al., 2011 |
| Polyphenol (Sambucus nigra) | DENV-2 | BHK-21 and VERO cells | Undefined | Castillo-Maldonado et al., 2017 |
| Ethanol extract of leaves (Senna argustifolia), ethanol extract of leaves (Tridax procumbers), and methanol extract of leaves (Vernonia cinerea) | DENV-2 | Vero cells | Undefined | Rothan et al., 2014 |
| Baicalein | DENV-2 | Vero cells | Virucidal activity against extracellular virus; impedes viral adsorption onto the host cell; inhibits viral replication post entry | Zandi et al., 2012 |
| Chebulagic acid and punicalagin (Terminalia chebula) | DENV-2 | Vero cells | Inactivate free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell transmission | Lin et al., 2013 |
| Schisandrin (Schisandra chinensis) | DENV | Vero cells | Inhibits DENV replication | Yu et al., 2017 |
| Epigallocatechin gallate (green tea) | EV 71 | Vero cells | Interferes with viral replication via modulation of the cellular redox environment | Ho et al., 2009 |
| Raoulic acid (Raoulia australis) | EV 71 | Vero cells | Undefined | Choi et al., 2009 |
| Gallic acid (Woodfordia fruticosa) | EV 71 | Vero cells | Inhibition of EV71 production | Choi et al., 2010 |
| Aqueous and ethanolic extracts; linalool, apigenin, and ursolic acid (Ocimum basilicum) | EV 71 | BCC-1/KMC cells | Ursolic acid interferes with viral infection and replication | Chiang et al., 2003 |
| Hederasaponin B (Hedera helix) | EV 71 | Vero cells | Inhibition of viral capsid protein synthesis | Song et al., 2014; Hong et al., 2015 |
| Rosmarinic acid (Melissa officinalis) | EV 71 | Vero cells | Suppresses eIF4G cleavage; removes ROS and inhibits | Chen et al., 2017 |

(Continues)
adverse impact on HCV entry (Anggakusuma et al., 2013). Many natural products deter HCV entry, including epigallocatechin-3-gallate, griffithsin, ladanein, and tellimagrandin I (Calland et al., 2012; Ciesek et al., 2011; Haid et al., 2012; Meuleman et al., 2011; Takebe et al., 2013). Similarly, chebulagic acid and punicalagin hydrolyzable tannins were found as competitive HCV intake inhibitors (Lin et al., 2013). Similarly, chebulagic acid and punicalagin hydrolyzable tannins were found as competitive HCV intake inhibitors (Lin et al., 2013). Both tannins inactivate free virus particles, inhibit viral adhesion and penetration of the host cell, and interrupt HCV cell-to-cell post-infection transfer. As the HCV immunization is unavailable, the identification of new anti-HCV entry inhibitors could help develop preventive hepatitis C therapy/medication.

Loliolide isolated from Phyllanthus urinaria inactivates the HCV virus and stops viral attachment and entry/fusion (Chung et al., 2016). Leaves extract and fractions of Ficus fistulosa using Huh7it-1 cells and HCV JFH1a inhibited HCV JFH1a with an ICs0 value of 20.43 ± 4.51 μg/ml (Hafid et al., 2016). The dichloromethane extract of Artocarpus heterophyllus demonstrated good anti-HCV activity using Huh7it-1 cells with an inhibitory concentration (ICs0) of (1.5 ± 0.6) μg/ml. A. heterophyllus impeded the viral entry process by direct virucidal activity and targeting host cells and HCV RNA replication. HCV protein expression was substantially decreased by elevated-concentration treatment (Hafid et al., 2017). Antiviral activity of methanol extract of Ajuga bracteosa, Ajuga parviflora, Berberis lyceum, and Citrus lemon against HCV infected HepG2 cells showed that 24-hour treatment with A. parviflora exhibited maximum antiviral activity, accompanied by A. bracteosa. The findings demonstrate these as a substitute standard therapy or in combination with conventional HCV therapies to treat HCV infections (Yousaf et al., 2018). Two fractions “N1” and “N8” isolated from acetone extract of Nymphaea alba suppressed HCV NS3 gene expression in transfected Huh-7 cells with an ECs0 value of 37 ± 0.03 and 20 ± 0.02 μg/ml, respectively. Besides, the combination of fractions with the standard antiviral drug showed stimulatory activity to suppress HCV replication. N. alba and its isolated compounds may offer a promising source regimen against HCV, alone or even in mixture with other prospective anti-HCV entities (Rehann et al., 2018).

### 4.4 HIV/AIDS and medicinal plants

Human immunodeficiency virus (HIV) is an encased lentivirus of the Retroviridae family. HIV attacks immune cells, reverses the ssRNA genome’s transcription, and incorporates into the host chromosome DNA (Sierra et al., 2005). It is transmitted through an interchange of viruses containing blood and fluids, like sexual intercourse, the sharing of infected needles/sharp objects, and breastfeeding (Shaw & Hunter, 2012). HIV is the principal cause of acquired immunodeficiency syndrome (AIDS), the gradual incompetence of the immune cells due to CD4+T lymphocyte deterioration, leading to life intimidating infectious disease and autoimmune disorders (Moss, 2013).

Amidst approximately 30 years of scientific research ever since its exploration, there’s still currently no specific preventative medicine or remedy for HIV infectious diseases. The high antigenic variability and myriad pathways used by the virus to undermine the immune system’s appreciation have made prophylactic/therapeutic management of HIV infection complicated (Burton et al., 2004). Interestingly, the development of highly active antiretroviral therapy (HAART), consisting of a cocktail of nucleoside analog/non-nucleoside reverse transcriptase inhibitors, has significantly decreased the mortality rates associated with HIV/AIDS (Ghosh et al., 2011). However, there is still an urgent need for adequate therapeutic approaches against HIV infection related to drug resistance development, accompanying toxicity treatment, patient adherence, and inadequate access in resource-poor areas (Piot & Quinn, 2013).
A comprehensive list of herbal ingredients for HIV infection was examined (Cos et al., 2008; Singh & Bodiwala, 2010) (Table 3). In contrast, marine products with anti-HIV activity were reported as potential anti-HIV treatment (Kim et al., 2011; X. Zhou et al., 2013). *Phytolacca americana* is a potent source of a set of plant proteins known as pokeweed antiviral protein (PAP). Three isoforms, specifically from spring leave PAP-I, early summer leaves PAP-II, and late summer leaves PAP-III was identified as a class of ribosome-inactivating proteins (RIPs) responsible for causing depurination of genomic HIV-1 RNA (Rajamohan et al., 1999). Similarly, *Momordica charantia* and *Gelonium multiform* are considered useful sources of an anti-HIV protein MAP30 and GAP31, similar to RIPs known for their anti-HIV potency (Schreiber et al., 1999).

Furthermore, the leaves of *P. americana* also contain an anti-HIV protein PAP29, having a prophylactic anti-HIV potential. P. Wang and Tumer (1999) reported that PAP isolation cleaves supercoiled DNA into linear and straightforward forms using the same active site required to remove rRNA purine. The RIPs are toxic N-glycosidases that purify the typically preserved α-sarcin loop of large RNAs. Thus, depurination disables the ribosome, consequently obstructing its further involvement in protein synthesis. Several studies have shown that RIP’s enzymatic activity is not only restricted to site-specific activity on ribosome rRNAs but also entails the depurination and nucleic acid scission of other targets (Barbieri et al., 2000; Horrix et al., 2011; Nicolas et al., 1998). Trichobacitin, a RIP, extracted from the roots of *Trichosanthes kirilowii* was reported to decline the appearance of the p24 HIV-1 antigen by reducing the number of antigens in HIV-positive cells in an acute in vitro assay but failed in cases of chronic infection (Zheng et al., 2000). Cyanovirin-N extracted from marine algae showed an inhibitory effect on HIV through aborting transmission and cell to cell fusion of HIV by interacting strongly with gp120 (De Clercq, 2000). Several sulfated polysaccharide groups extracted from seaweeds possess anti-HIV effects by interfering with viral adsorption (Duarte et al., 2001; Schaeffer & Krylov, 2000). Alkaloid extracts of *P. niruri* exhibited an inhibitory effect on HIV by monitoring the inhibition of HIV-induced cytopathogenicity in human MT-4 cells (Naik & Juvekar, 2003). Furthermore, coumarin-containing calophyllum species exhibited an inhibitory effect on HIV (Cesar et al., 2011; Huerta-Reyes et al., 2004). Similarly, the crude extracts of *A. annua* and *Artemisia afra* revealed promising anti-HIV efficacy (Lubbe et al., 2012). In regards, tricyclic coumarin reported from *Calophyllum brasiliense* stem bark suppressed HIV replication by repressing the activation of nuclear factor-kappa B (NF-κB) in vitro models (Kudo et al., 2013).

The root extract of *Pelargonium sidoides* displays potent anti-HIV-1 activity by protecting peripheral blood mononuclear cells and macrophages from infection with several X4 and R5 tropic HIV-1 strains. Thus, it is considered a novel herbal medicine for anti-HIV-1 therapy with different action mechanisms and complementary to current single-molecule drugs (Helfer et al., 2014). Furthermore, *Cistus incanus* inhibited clinical HIV-1 and HIV-2 isolates in vitro, and no resistant viruses appeared throughout 24 weeks of continuous propagation of the virus in the presence of *C. incanus* aqueous extract (Rebensburg et al., 2016). Methanol extracts of *Euphorbia spinidens Bornm* (Euphorbiaceae) possess significant antioxidant activity due to high phenolics terpenes and saponins and flavonoid compounds and have a strong antiviral effect on HSV-1 by inhibiting the replication of the virus (Karimi et al., 2016; Mohammadi et al., 2014). Patentiflorin A isolated from *Justicia gendarussa*, shows significant activity against various HIV strains by acting as a potential HIV-1 reverse transcription inhibitor with IC₅₀ values ranging from 15–21 nM (Zhang et al., 2017a, 2017b).

Besides this, a diverse range of medicinal plants such as *Withania somnifera* (Williams-Orlando, 2017), *Tinospora cordifolia* (Husain et al., 2017), *Moringa oleifera* (Monera-Penduka et al., 2017), *Hypericum perforatum* (Béjaoui et al., 2017), *Silybum marianum* (Lovelace et al., 2017), *Panax ginseng* (Cho & Kim, 2017), *Hypoxis hemerocallidea* (Jegede et al., 2017), *Sutherlandia frutescens* (Wilson et al., 2015), *Lobostemon trigonus* (Koffuor et al., 2014), and *Curcuma longa* (Kim et al., 2014b) were used in the diagnosis and treatment of AIDS. In comparison, four new lignans from the aerial parts of *Justicia procumbens* were examined for anti-HIV-1 activity. One of the new secoisolariciresinol dimethyl ether acetate showed significant anti-HIV-1 activity with an IC₅₀ of 5.27 μM in vitro (Xu et al., 2019). Promised on the scientific advances till now, rapid advances in identifying natural antivirals against HIV must produce novel therapeutic regimens that would play a critical role in combating the existing immediacy of anti-HIV/AIDS therapeutics.

### 4.5 Anti-influenza virus and medicinal plants

Influenza A, B, and C viruses (IFA, IFB, and IFC) are encapsulated negative-sense ssRNA viruses categorized in the Orthomyxoviridae family. Such viruses can cause respiratory infection with symptoms include fever, headache, sore throat, sneezing, and muscle and joint pain, which can lead to devastating and potentially lethal situations like pneumonia (Eccles, 2005; Rello & Pop-Vicas, 2009). IFA (most epidemics) has a broad array of hosts, such as birds, human beings, and other mammals. At the same time, IFB seems to harm people naturally, and IFCs could be separated from humans and pigs (Pleschka, 2013). The infection of influenza viruses has caused significant human morbidity, and approximately 250,000 to 500,000 fatalities happen yearly as a consequence of periodic epidemics. This figure was documented to rise to about 20–40 million deaths in major pandemics, as was the case with the Spanish flu of 1918 (Saunders-Hastings & Krewski, 2016).

Hemagglutinin (HA) and neuraminidase (NA) protein envelopes are developed by the IF vaccines through prior contact or immunization, thus, making any pre-existing antibody inefficient and susceptible to infection. Another concern is the pervasive growth of drug resistance, mostly M2 ion channel blockers of amantadine and rimantadine, in the first wave of anti-influenza drugs. Resistant strains of available neuraminidase inhibitors such as oseltamivir and zanamivir (which mainly prevent the release of mature influenza viruses) have also been identified (Samson et al., 2013). As a result of drug...
resistance development, the rapid evolution of influenza viruses, and the incidence of many recent outbreaks (e.g., H5N1, H1N1, H7N9), more advanced antiviral strategies are urgently needed to prevent and control potential pandemics with evolving influenza strains (Shao et al., 2017). Numerous natural products have been assessed for their adverse effects on influenza (Table 3).

*Pelargonium estides* root extract restricts IFA entry influences, viral hemagglutination, neuraminidase function, and improves influenza-infected mice (Theisen & Muller, 2012). Aqueous extract from *Taraxacum officinale* inhibits IFA infection and reduces the activity of polymerase and nucleoproteins (NP) RNA levels (He et al., 2011). Several plant secondary metabolites were also determined as possible inhibitors of NA influenza (Grienke et al., 2012) such as chalcones from *Glycyrrhiza inflata* (Dao et al., 2011), xanthones from *Polygala karensium* (Dao et al., 2012), homoisoflavonoids from *Caesalpinia sappan* (Jeong et al., 2012), and spiroooligonganone B from the roots of *Illicium oligandrum* (Ma et al., 2013). Lariciresinol-4-O-glcophyrosnoise isolated from the root of *Isatis indigotica* hindered the IAV-induced pro-inflammatory response. The underpinning coping mechanism against IAV infection derives from pharmacological actions on the immune system, signal transduction, cell cycle, and metabolism (Li et al., 2015; Zhou et al., 2017). The *Sambucus nigra* activities against influenza were investigated extensively, especially in the vicinity (Roschek et al., 2009; Ulbricht et al., 2014). Studies have shown the potency of *S. nigra* toward infectious disease, which may be caused by immune system stimulation (Ho et al., 2015; Ho et al., 2016). Immunomodulating peptic polysaccharides, polyphenolic, and flavonoid of *S. nigra* are responsible for suppressing the viruses. This plant's berries and flowers are documented from diverse cultures (Porter & Bode, 2017).

The double-blind trial was conducted among 40 adults and children in southern Israel confirmed to have influenza B. The fruit of *Sambucus nigra* (black elder) syrup or placebo 1 tbsp b.i.d. (for children) or 2 tbsp b.i.d. (for adults) was given. Symptom severity and duration (mean 1.3 days shorter with black elders) were appreciably lesser in the black elder group than placebo (Zakay-Rones et al., 1995). A similar double-blind trial of 60 adult Norwegians with influenza A or B was conducted. Again, symptom severity was significantly less with black elders than placebo, and in this case, recovery was on average 4 days quicker with black elders. The use of rescue medication was also notably less in the black elder group versus placebo. There were no adverse effects in either of these trials (Zakay-Rones et al., 2004).

Recently, a randomized trial of 312 Australian adults undertaking international travel by coach received black elder capsules 300 mg b.i.d. before travel and t.i.d. during travel and after arrival, or placebo. Each participant took their assigned medicine for a total of 14 days. There was no difference between the groups in terms of the incidence of clinical viral respiratory infections. However, these colds' duration was significantly shorter and severity substantially less in the black elder group than the placebo. There was no difference between the two groups' adverse effects, suggesting no significant danger from black elders (Tiralongo et al., 2020). The development of these natural anti-influenza agents for clinical use will further extend the portfolio of drugs for prophylactic treatment of severe flu epidemics or pandemic.

### 4.6 Enterovirus 71 and medicinal plants

Enterovirus 71 (EV71) is a pathogenic species of the Picornaviridae family. EV71 comprises a single positive RNA genome with approximately 7.5 kb. It was observed throughout a modest epidemic in California between 1969 and 1972 (Schmidt et al., 1974). EV71 became the most infective enterovirus serotypes, causing several global outbreaks. EV71 inflammation develops rashes, and vesicular lesions on the hands, legs, and oral mucosa. It sometimes develops fatal congenital abnormalities such as aseptic meningitis, encephalitis, acute respiratory disease, and pulmonary edema. A fecal-oral route mainly delivers EV71, but transfer by a respiratory droplet is indeed conceivable. It's among the most prominent reasons for hand-foot and mouth disease (HFMD) in young kids, often associated with severe neurological disorders that can be devastating (Tapparel et al., 2013). The risk of transmission in children below 5 years of age is reasonably high in endemic regions, and several epidemics had already happened during the last few millennia.

Preventive EV71 vaccines were currently developed, and palliative care is being used to improve the symptoms. However, many other natural products and herbal medicines exhibited inhibitory activity against EV71 infection (Table 3). The analysis revealed that *O. basilicum* extracts and isolated compounds effectively prevent EV71 disease and replication (Chiang et al., 2005). In contrast, raoulic acid recognized as a CVB inhibitor suppresses EV71 (Choi et al., 2009). Similarly, epigallocatechin gallate from green tea tamper with EV71 replication by modulating the redox cell environment (H. Y. Ho et al., 2009). Gallic acid from *Woodfordia fruticosa* flowers showed anti-EV71 activity (Choi et al., 2010). Anti-EV71 activity of chrysosplenetin and penduletin, two o-methylated flavonoids confined from the leaves of *Lageria pterodanta*, showed vigorous anti-EV71 activity with low cytotoxicity. Throughout the time-of-addition assay, all compounds impeded progeny virus development and RNA replication by almost 100% when incorporated within 4 hr post-infection (Zhu et al., 2011). In relation, there were studies undertaken to study the antiviral capabilities of various plant or algae-derived EV 71-containing compounds (Chiu et al., 2012; Lin et al., 2009; Wang et al., 2011a; Wang et al., 2012d; Wang et al., 2013; Yang et al., 2012).

Contrary, phytochemicals evaluated for EV71 antiviral activity showed low cytotoxicity. Some of them, such as aloe-emodin, (Lin et al., 2008) extract of *H. cordata*, kappa carrageenan (Chiu et al., 2012) extract of *Kalanchoe gracilis*, and extract of *Paris polyphylla* Smith (Wang et al., 2011b) have a precise molecular mechanism(s) of action. The research tries to evaluate 12 frequently used antiviral herbs preferred by Chinese government agencies for the HFMD. *H. cordata* found the only remedy with potent antiviral activity against both EV71. These study results may justify follow-up experiments to determine the precise molecular mechanisms of action and to analyze the plant's anti-EV71 capability in the animal study (Chen et al., 2013). Chebulagic acid, isolated from *Terminalia chebula* fruit, displayed...
antiviral activity against human enterovirus 71 in vitro and in vivo models. Its treatment significantly reduced the viral cytopathic effect on rhabdomyosarcoma cells with an IC₅₀ of 12.5 μg/ml. The use of chebulagic acid therapy in patients with enterovirus 71 effectively reduced mortality and alleviated clinical symptoms by inhibiting viral replication. Chebulagic acid may be a potent pharmacological entity to influence enterovirus 71 infections (Yang et al., 2013). Hederasaponin B and 30% ethanol extract of Hedera helix against EV71 subgenotypes C3 and C4a in Vero cells showed vigorous antiviral activity by lowering visible development CPE. It further impeded viral VP2 protein expression, implying the suppression of viral capsid protein synthesis (Hong et al., 2015; Song et al., 2014). Without appropriate medical care to prevent and treat EV71 infection, further studies are needed to explore novel enteroviral antivirals.

4.7 | Respiratory syncytial virus and medicinal plants

RSV is an enshrouded negative-stranded ssRNA virus belonging to the Paramyxoviridae family. RSV is a prevalent virus responsible for respiratory illness in infants and toddlers (Hall, 1994). Almost all children often get afflicted with RSV well before 2 years (Braciale, 2005). It develops mild symptoms and bronchiolitis or pneumonia in infants and immunocompromised patients (Sigurs et al., 2005). Even though RSV causes the most severe illness in premature children, it continues to haunt living beings throughout their lifespan. Immune response to RSV is usually not sufficient to provide protection, but instead, humans are susceptible to reiterated re-infections (Hall et al., 2009; Henderson et al., 1979), that may be life-threatening for older or immune-compromised patients (Falsey & Walsh, 2000). Presently, RSV immunotherapy is not applicable. The therapies available for diagnosing RSV infections like palivizumab (a monoclonal antibody against RSV fusion protein) and ribavirin (nucleoside analog) are slightly effective. Therefore, it is necessary to develop new antivirals to manage RSV infections, and numerous plant-derived natural products were shown to display anti-RSV activity (Table 3).

Uncinösode A and B, the two isolated chromone glycosides from Selaginella uncinata, effectively inhibit RSV inflammation and biflavonoids, namely genkwanol B, genkwanol C, and stelleneranol derived from Radix Wikstroemiae, are said to have antiviral activity against RSV (Huang et al., 2010; Ma et al., 2003). Further, flavonous 6-C-monoglycosides from Lophatherum gracile leaves reported curtailing RSV infection in the cytopathic impact reduction assay (Wang et al., 2012c). Numerous natural anti-RSV therapies such as the herbal prescription (Cimicifuga foetida L., and bioactive compound cimicifuga) relieve respiratory diseases (Wang et al., 2011; Wang, Ho, et al., 2012; Wang, Chen, et al., 2012). Furthermore, chebulagic acid and punicalagin hydroxylizable tannins possess antiviral activity toward RSV infection. The two tannins can explicitly inactivate RSV entities and obstruct viral entry aspects, like binding and fusion. They are inadequate against the transmission of RSV post-infection and could contravene the same event in MV, which is another paramyxovirus (Lin et al., 2013). Certain herbal products will help improve the respiratory tract symptoms induced by RSV, like inflammation of the respiratory system to target the viral infection. Resveratrol is one specific illustration documented to stabilize IFN-γ levels and prevent the trachea’s inflammation/hyperresponsiveness throughout RSV infection in mice, implying its suitability to minimize airway symptoms triggered by RSV (Zang et al., 2011). Tangeretin and nobiletin (poly-methoxylated flavones) obtained from Citrus reticulate (Pericarps) impaired RSV replication intracellularly. Tangeretin significantly suppressed RSV phosphoprotein (P protein) expression through virus-cell fusion inhibition at an early stage and cell fusion inhibition at the end of the replication process (Xu et al., 2014). Schefflera heptaphylla-derived dicaffeoylquinic acids also hindered RSV replication (Li et al., 2005b). The ethanol extract of Lophatherum gracile suppressed RSV infection and inflammation prompted in a dose-dependent manner (Chen et al., 2019).

4.8 | Rotavirus and medicinal plants

Rotavirus is the common cause of chronic gastroenteritis in infants and young children across the globe. It is a paramount public health concern in low-income countries and massive morbidity and mortality rates in advanced nations (Parashar et al., 2006). The genus of rotavirus consists of nine species (A to I), but the only rotavirus A tends to cause more than 90% of human rotavirus infections (Kirkwood, 2010). The rotavirus’s genetic material consists of 11 dsRNA segments that code for six structural and six nonstructural proteins. Structural proteins form the rotavirus particle called VP1, VP2, VP3, VP4, VP6, and VP7 premised on their molecular weight. Besides, nonstructural proteins are only produced during cell infection and are called NSP1, NSP2, NSP3, NSP4, NSP5, and NSP. Rotavirus affects intestinal cells and causes gastroenteritis; even so, the disease is not restricted to the gastrointestinal tract, and systemic viral transmission has been extensively illustrated (Ramig, 2007; Rivero-Calle et al., 2016).

While there is no particular antiviral drug for rotavirus, several other preventative actions like environmental hygiene and safe food and water can reduce the risk of rotavirus infection (Brown et al., 2013). The U.S. Food and Drug Administration (FDA) certified two subsequent oral attenuated vaccines as an efficient way to prevent rotavirus pandemics. The RotaTeq (Merck), a pentavalent human-bovine vaccine is comprising four rotavirus strains generated by recombination and Rotarix (GlaxoSmithKline), a monovalent human-bovine vaccine that included one G1P-specific rotavirus strain (Desai et al., 2012; Gurgel et al., 2011). Hence, alternative safe therapies for rotavirus infections have become the subject of ongoing research (Alfajarø et al., 2014). Pinus koraiensis, Lomatium dissectum, Artocarpus integrifolia, Myristica fragrans, Spondias lutea, Tylosea esculentum, Byrsonima verbascifolia, Myracrodruon urundeuva Allemão, Eugenia dysenterica, Hymenaea courbaril, and Achillea kallawensis were reported to hinder rotaviral strains (Cecilio et al. 2012; Chingwaru et al. 2011; Gandhi et al., 2016; Goncalves et al., 2005; Taherkhani et al., 2013) (Table 4). The active ingredients have not yet been
| Plant name/Active compounds | Virus strain assessed | Test dose | Culture/Animal model assessed | Proposed mechanism | References |
|-----------------------------|-----------------------|-----------|-------------------------------|--------------------|------------|
| *Pinus koraiensis* Zucc. (seed Shell) | Human rotavirus | 250 μg/ml | African rhesus monkey kidney (MA-104) epithelial cells | Seed shell interferes with virus adsorption by inhibiting CPE of rotavirus in cell cultures | Mukoyama et al., 1991a |
| Epigallocatechin gallate and theaflavin digallate (green tea) | Human rotavirus (Wa) | IC$_{50}$ 125 μg/ml to 250 μg/ml | MA-104 cells | Interfered with virus adsorption | Mukoyama et al., 1991b |
| *Lomatium dissectum* Nutt. | Bovine rotavirus | Dilutions ranging from $1 \times 10^{-4}$ through $1 \times 10^{-7}$ of 0.2 ml of extract | MA-104 cells | Inhibited virus induced CPE | McCutcheon et al., 1995 |
| *Theobroma cacao* Linn. (husk pigment) | Simian rotavirus (SA-11) strain, human rotavirus strains | 1 mg/ml | MA-104 cells | Interfered with rotavirus adsorption to cells, also inhibited rotavirus intracellular replications and lessened the infectious viral titer | Gu et al., 2000 |
| *Hesperidin and neohesperidin* (*Citrus aurantium* Linn.) | Human rotavirus (Wa) | IC$_{50}$ 0.05 mg/ml, 10 μM/ml and 25 μM/ml | MA-104 cells | Hesperidin and neohesperidin exhibited inhibitory effect on rotavirus infection | Kim et al., 2000 |
| *Stevia rebaudiana* Bertoni. | Human rotavirus strains and SA-11 | EC$_{50}$ 431–492 μg/ml | MA-104 cells | Inhibitory activity against the replication of four serotypes of human rotavirus (HRV) and inhibited the binding of VP7 to the infected cells | Takahashi et al., 2001 |
| *Stevia rebaudiana* Bertoni. | Human rotavirus and SA-11 | EC$_{50}$ 32–153 μg/ml | MA-104 cells | Inhibitory activity against the virus replication and binding of viral proteins VP7 not VP4 to the infected cells | Takahashi et al., 2001 |
| *Artocarpus integrifolia* Linn. *Myristica fragrans* Houtt. and *Spongias lutea* Linn. | SA-11 and Human (HCR3) rotaviruses in MA-104 cells | (480 μg/ml), (160 μg/ml) and (40 μg/ml) | MA-104 cells | Antiviral activity against both the viruses | Goncalves et al., 2005 |
| 280 natural compounds | Rotaviruses | IC$_{50}$ 7.5 μg/ml | MA-104 cells | 18-β-glycyrrhetinic acid, abietic acid, alltrans-retinoic acid, and mangostin reduced the virus replication as well induced the cell signaling pathways involved in antiviral and inflammatory gene expressions | Shaneyfelt et al., 2006 |
| *Vaccinium macrocarpon* Aiton, (Juice) | SA-11 | 1.3, 2.5, 5, 10, 12, 20, 33, and 50% in PBS | MA-104 cells | Inhibited the rotavirus induced hemagglutination reaction and mediated the anti-rotavirus activity | Lipson et al., 2007 |
| *Aegle marmelos* Linn. | SA-11 | 0.51 mg/ml ± 0.005 mg/ml, 2.55 mg/ml ± 0.025 mg/ml and 5.11 mg/ml ± 0.05 mg/ml | MA-104 cells | Significantly decreased therotoviral infectivity or virus inhibition | Brijes et al., 2009 |
| Plant name/Active compounds | Virus strain assessed | Test dose | Culture/Animal model assessed | Proposed mechanism | References |
|-----------------------------|-----------------------|-----------|-------------------------------|--------------------|------------|
| *Quillaja saponaria* Molina. | Rhesus rotavirus      | 1–1,000 μg/ml | MA-104 cells | Blocked rotavirus attachment and attenuate infection | Roner et al., 2007 |
| Pectic polysaccharides (*Panax ginseng* C.A. Mey) | IC_{50} (15 and 10) μg/ml | Human rotavirus (Wa) | MA-104 cells | Protecting cell viability from rotavirus-induced infection. It possibly alleviated virus proliferation in cells | Baek et al., 2010 |
| Polyphenols (*Glycyrrhiza uralensis* Fisch) | EC_{50} of polyphenols were 18.7–69.5 μM against G5P[7] and 14.7–88.1 μM against G8P[7] | Bovine rotavirus G8P[7] and porcine rotavirus G5P[7] | Fetal rhesus Monkey kidney (TF-104) cells | Licocoumarone, licoflavonol, glyasperin D and 2’-methoxyisoliquiritigenin showed inhibition viral absorption, viral replication, and viral RNA synthesis | Kwon et al., 2010 |
| *Tylosera esculentum* Burch. | Rotaviruses human (H4) | 0.01 to 0.001 mg/ml | MA-104 cells | Showed profound CPE and interfered with viral replication and strengthened the intestinal epithelial barrier function | Chingwaru et al., 2011 |
| *Quillaja saponaria* | Rhesus rotavirus | 0.015 and 0.0125 mg/mouse (p.o.) | Newborn Balb/c mice/MA104 cells | Alleviated rotavirus infection by coating target cells and hence reduce rotavirus induced diarrhea | Tam and Roner, 2011 |
| *Vaccinium macrocarpon* (juice) and *Vitis labrusca* Linn. (juice) | SA-11 | 50% concentration of juices in PBS | MA-104 cells | Showed associated loss of RNA integrity of viral capsid protein | Lipson et al., 2011 |
| *Psidium guajava* Linn. | SA-11 | 0.027 ± 0.001 mg/ml, 0.027 ± 0.013 mg/ml, 1.350 ± 0.063 mg/ml and 2.7 ± 0.125 mg/ml | MA-104 cells | Decreased the cell death in virus infected cells | Birdi et al., 2011 |
| *Nelumbo nucifera* Gaertn. *Aspalathus linearis*, *Urtica dioica* Linn. *Glycyrrhiza glabra* Linn. and *Olea europaea* Linn. | SA-11 and the Rhesus rotavirus Strain | IC_{50} < 300 μg/ml | MA-104 cells | Exerted antiviral activities and has no positive effect on the maintenance of trans-epithelial resistance | Knipping et al., 2012 |
| *Glycyrrhiza uralensis* | Porcine rotavirus K85 (G8P[7]) Strain | 50.00, 200, and 400 mg/ml (p.o.) | Colostrum deprived piglets/TF-104 cells | Cured rotavirus diarrhea and down-regulated proinflammatory cytokines and its related transcription factor and signaling molecules | Alfajaro et al., 2012 |
| *Proanthocyanidins* (*Vaccinium macrocarpon* and *Vitis labrusca*) | SA-11 | 1,000 μg/ml in PBS | MA-104 cells | Proanthocyanidins effectively blocked capsid protein (VP6) binding to host cells | Lipson et al., 2012 |
| *Vaccinium macrocarpon* and *Vitis labrusca* | SA-11 | 50% concentrations of juices in PBS | MA-104 cells | Cranberry juice was most effective at pH 2.7 and grape juice at a suspension pH of 6.7. | Cecillo et al., 2012 |
| *Alpinia katsumadai* | Bovine G8P[7] and porcine G5P[7]) rotaviruses | EC_{50} 0.7 ± 0.4 to 33.7 ± 6.5 μg/ml against G5P[7] strain EC_{50} 8.4 ± 2.2 μg/ml, 6.5 ± 0.8μg/ml, and 8.4 ± 5.0 μg/ml against G8P[7] strain | MA-104 cells | Blocked viral adsorption | Kim et al., 2012 |
| Plant/Active compounds | Virus strain assessed | Test dose | Culture/Animal model assessed | Proposed mechanism | References |
|------------------------|-----------------------|-----------|-------------------------------|--------------------|------------|
| **Achillea kellalensis** Boiss. | Bovine rotavirus | EC<sub>50</sub> 100 µg/ml | MA-104 cells | Prevented viral replication and inhibited the viral CPE | Taherkhani et al., 2013 |
| **Tannins (Diospyros kaki Linn.)** | Viral strains | 0.05%, 0.025% and 0.005% of tannins | MA-104 cells | Inhibited attachment of the virus to the cells | Ueda et al., 2013 |
| **Rice bran (Oryza sativa Linn.)** | Human rotavirus(VirHRV)Wa strain(G1P1A[8]) | 10% of the pigs total daily calorie | Neonatal gnotobotic pigs | Rice bran promoted the development of IFN-T cell responses, total IgM IgSCs in ileum and spleen, total IgA IgSCs in spleen and blood, and total serum IgM, IgA, and IgG antibody production | Yang et al., 2014 |
| **Achyrocline bogotensis** DC. | Rhesus rotavirus | Substances dissolved in DMSO to a 100 mg/ml; dilutions µg/ml 0–1.000 down | MA-104 cells | Exhibited antirotaviral activity characterized by a virucidal effect and by the reduction of the infectious particles produced post-infection | Taherkhani et al., 2015 |
| **Eucalyptus camaldulensis** Dehnh. (essential oils) | Human rotavirus (Wa) strain | 1/10 dilutions | MA-104 cells | Reduced viral titres against rotavirus | El-Baz et al., 2015 |
| **Achillea fragrantissima** Linn. **Nitraria retusa** (Forssk.) Asch | Human rotavirus (Wa) strain | IC<sub>50</sub> 1.0–1.2 mg/ml and IC<sub>50</sub> 0.9–1.4 mg/ml | MA-104 cells | Reduced viral titres against rotavirus | Mohamed et al., 2015 |
| α-Glucosyl hesperitin and epigallocatechin gallate | SA-11 | 100 × 10<sup>3</sup> µg/ml nd 80, 160, and 320 µg/ml | MA-104 cells | Loss of viral capsid protein | Huang et al., 2015 |
| Genistein | Human rotavirus (Wa) and SA-11 strain | >160 µM | MA-104 human epithelial colorectal (Caco2) cells | Genistein inhibited rotavirus replication by upregulating AQP4 expression via the cAMP/PKA/CREB signaling pathway | Lipson et al., 2015 |
| Resveratrol, Piceatannol, Trans-arachidin-1 and Transarachidin-3 | SA-11 | 10–20 µM | Human adenocarcinoma intestinal cell lines (HT29 FT8) and MA-104 cells | Two stilbenoids, trans-arachidin-1 and transarachidin-3 showed therapeutic potential against rotavirus replication via downregulating NSP4 protein levels | Ball et al., 2015 |
| **Myracrodruon urundeuva** | SA-11 | 50–500 µg/ml | MA-104 cells | Diminished the multiplication of the virus including inhibiting the CPE | Cecílio et al., 2016 |
isolated and characterized from the above-described plant species. Further, chemical investigations are needed to explore plant species’ chemical compounds in mass quantities and display more inhibitory effects toward rotavirus than that of the extract.

*Aegle marmelos*, *Quillaja saponaria*, *Psidium guajava*, *Nelumbo nucifera*, *Aspalathus linearis*, *Urtica dioica*, *G. glabra*, *Olea europaea*, *Achyrocline bogotensis*, *Eucalyptus camaldulensis*, *Achillea fragrantissima*, *Nitraria retusa*: *Rindera lanata*, and *Euphorbia hirta* were reported as novel antiviral candidates toward rotavirus infection. They interfere with virus absorption, inhibits virus replication, and reduces the levels of virus titers (Birdi et al., 2011; Brijesh et al., 2009; Civra et al., 2017; El-Baz et al., 2015; Knipping et al., 2012; Mohamed et al., 2015; Pilau et al., 2011; Roner et al., 2010; Téllez, Téllez, Vélez, & Ulloa, 2015). Besides, *Vaccinium macrocarpon*, *Vitis labrusca*, and *Myracrodruon urundeuva* (Cecilio et al., 2016; Lipson et al. 2007, 2011, 2012) decreases the level of external viral capsid proteins and influences the virulence of rotavirus. Similarly, bioactive compounds such as licocoumarin, licoflavonol, glyasperin D, and 2′-methoxyisoliquiritigenin, carvacrol, 18β-glycyrrhetinic acid, luteolin, vitexin, apigenin-7-O-glucoside, and tannins from *Diospyros kaki* (Ebenaceae) inhibits the rotavirus infection of MA-104. Similarly, epigallocatechin gallate, theaflavin digallate, genistein, hesperidin, neohesperidin, diosmin, pectic polysaccharides isolated from the above-described plant species.

Aqueous ethanol extract and bioactive compounds, such as linalool, apigenin, and ursolic acid from *Ocimum basilicum* (sweet basil) reported antiviral activity against CVB1. In particular, Ursolic acid interacts with post-infection replication of CVB1 (Chiang et al., 2005). Further, *Bupleurum kaoi* was known to inhibit CVB1 infection by activating type I interferon response (Cheng et al., 2006b; Cheng et al., 2007). Raoulic acid from *Raoulia australis* was determined as an antiviral informant against many CVB subtypes; however, the mechanism for its influence is uncertain (Choi et al., 2009). *Rheum palmatum* (Polygonaceae) against CV B3 in vitro and in vivo showed inhibitory effects on HEp-2 cells. Extract-treated mice showed improved survival rate, reduced clinical symptoms, and lowered viral titers. The whole study demonstrates that interferon inducers of type I could be useful in maintaining CVB infection and could be further analyzed as a therapeutic intervention (Xiong et al., 2012). Besides, extracts of *Dodonaea viscosa* leaves displayed a therapeutic efficacy ranging from 0.3 to 25 with a reduction in virus titer ranging from 0.25 to 5 log10 TCID 50/ml against coxackievirus B3 (CVB3) infections. Crude extract provided significant inhibition of CVB3 replication by attaching to the viral capsid of CVB3, and prevents the virus from accessing host cells (Shaheen et al., 2015). *Cornus officinalis*, *Acer triflorum*, *Pulsatilla koreana*, and *Clematis heracleifolia* var. *Davidiana Hems* extracts showed significant antiviral activity toward CVA16 (Song et al., 2015). *Isatindolignanoside A*, a glucosidic indole-lignan isolated from aqueous root extract of *Isatis indigotica* revealed antiviral activity against CVB3 CVB3, with IC50 and SI values of 25.9 µM and >3.9, respectively (Meng et al., 2018).

### 4.10 Dengue virus and medicinal plants

DENV is an encased positive sensory ssRNA virus of the Flaviviridae family. The DENV is transferred particularly by mosquito bites of *Aedes aegypti* and is an influential arbovirus in Southeast Asia (Black et al., 2002). However, most of the four virus serotypes (DENV 1–4), could trigger dengue fever (Back & Lundkvist, 2013). Clinical symptoms of DENV infection include evident/mild febrile exposure, contemporary dengue fever (fever, headache, myalgia, joint pain, nausea, vomiting, and skin rash), and life-threatening hemorrhage diseases.
explicitly dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) (Sam et al., 2013). Although this is an obsolete viral infection, current vaccination and treatment interventions accessible to prevent and control DENV infection are minimal. The management of dengue-related illnesses entails mosquito-controlled viral infection prevention and the alleviation of infected patients’ symptoms.

Developing preventative/pharmacological intervention for DENV infection with natural ingredients could resolve these practical limits. Quite a few natural compounds, like quercetin and narasin, and marine algae derivatives exhibit robust anti-DENV features (Zandi et al., 2011; Low et al., 2011; Koishi et al., 2012) (Table 3). For example, Flavone baicalin shows inhibitory activities against DENV adsorption to host and post-entry viral replication (Zandi et al., 2012). Also, chebulagic acid and punicalagin, extracted from Terminalia chebula, have a broad array of antiviral agents against the viruses (Lin et al., 2013). They will effectively inactivate free DENV particles and tamper with attachment and fusion incidents throughout the early viral entry. Nordihydroguaiaretic acid extracted from the leaves of Larrea tridentata (Zygophyllaceae) was found to hinder the replication of the linked DENV by approaching genome replication and viral assembly (Soto et al., 2014).

In contrast, flavonoids are the inhibitors of NS2B-NS3 serotype 2 and 3 DENV proteases with IC50 values ranging from 15 to 44 μM. Myricetin is non-competitive serotype 2 NS2B-NS3 protease inhibitor with Ki values of 11 and 4.7 μM, respectively (Sousa et al., 2015). Ethanol extracts of Cassia grandis leaves, and Tabernaemontana cymosa bark toward two DENV serotype 2 strains DENV-2/NG and DENV-2/16681 in VERO, and U937 cells hinders viral replication and significantly impact viral internalization (Hernández-Castroa, Diaz-Castillo, & Martínez-Gutierrez, 2015). The recognition of such natural viral inhibitors may help in building anti-DENV therapy and lower DHF/DSS risk. Schisandrin A extracted from Schisandra chinensis hinders DENV replication by up-regulation of antiviral interferon responses through STAT signaling pathway (Yu et al., 2017).

### 4.11  |  MV and medicinal plants

MV is an encased negative-sense ssRNA virus of the Morbillivirus gene (Family: Paramyxoviridae). MV induces measles (an acute respiratory infection characterized by fever, conjunctivitis, coughing, runny nose, and nausea), and a generalized red macular rash across the body resulting in pneumonia encephalitis (Sabella, 2010). Although extremely infectious by interaction with respiratory secretions or airborne particulates, immunotherapies toward measles were described as a three-part MMR vaccine (measles, mumps, and rubella). Despite an effective MV vaccine, the virus remains a vital assassin for children in the developing world (Clements & Cutts, 1995; Murray & Lopez, 1997). A severe further aspect is a resurgence of measles in vaccinated populations and non-immunized individuals (Mossong & Muller, 2003; Zandotti et al., 2004). Such problems highlight MV’s medical significance and the need to develop appropriate drug therapies.

Natural products from East and South-east Asian medicinal plants (Kurokawa et al., 1993), the herbal decoction (Huang et al., 1997), the Cherokee remedy spicebush (McWhorter, 1996), plant bioflavonoid isolated from Rhus succedanea and Garcinia multiflora (Lin et al., 1999), calcium spirulan from the blue-green alga Spirulina platensis (Hayashi et al., 1996) and several Rwandan and Ugandan medicinal plant extracts were reported to inhibit MV infection (Cos et al., 2002) (Table 3). In contrast, certain Olinia rochetiana (Olkirenny) and Warburgia ugandensis (Oskonoi) typical dietary herbal additives were demonstrated to suppress in vitro MV infection (Parker et al., 2007). Another example is the Cojanus cojan extracts recommended to have anti-MV activity, though their bioactive components remain unknown (Nwodo et al., 2011). The chebulagic acid and punicalagin tannins showed potent efficacy against MV infection, mainly by inhibiting the virus particles, disrupting the attachment and fusion stages throughout viral entry (Lin et al., 2013). Therefore, they could serve as potential entry inhibitors to MV.

### 5  |  CONCLUSION AND FUTURE PERSPECTIVES

Antiviral drug production is a concern, as enzymes do not behave like normal living cells and antiviral medications could only deter replication of viruses or inhibit deeper inflammation. Accordingly, plant extracts/botanically derived compounds were documented with potential antiviral activity in cell line and animal model studies. Intriguingly, different mechanisms were established for these compounds, among which virucidal behavior is the most prevalent. Other confirmed exercises include hindering virus entrance into target cells, inhibiting viral protein expressions like 3CLpro, PLpro, S, and ACE2, and interfering with viral DNA replication, all of which are essential prerequisites constructing individual viral particles. Besides, the introduction of high-throughput technologies and traditional medicines together might play a critical role in assessing potential plant-derived substances for innovative discovery in contemporary drug development. They compete against viral diseases but have a long way to go before final use in the clinic to compensate for exploration, isolation, and mechanistic studies. Given the broad diversity of bioactive molecules derived from plants, a reliable, relentless, and constant approach is necessary to pursue unidentified bioactive molecules with potent antiviral activity, particularly relative to the risk posed by pathogenic viruses to enhance resistance to antibiotics. Many natural products like lycorine, homoharringtonine, silvestrol, ouabain, tylophorine glycyrrhetinic acid, acetoxime, and caffeic acid chebulagic acid, punicalagine and 7-methoxycryptopleurine possess significant antiviral activity even in the nanomolar concentration and will be better candidates for novel drug discovery. However, it requires further research to demonstrate the mechanism of secondary metabolites’ action in an in vivo and invitro model.

In contrast, many natural products with good antiviral activity are the essential components of some traditional food additives that could strengthen the wider public’s immune system in inevitable
outbreaks. Further, research must entertain therapeutic agents' feasibility with several other natural sources or with existing drugs, as the multi-target treatment mitigating the chances of drug-resistant viruses being developed. Therefore, comprehensive research in the forthcoming could recognize the possible antiviral molecules and understand their mechanism of action to stabilize such fatal viruses more appropriately.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
No data are available to share.

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