

Ethnopharmacological, Phytochemistry, and Antiviral Activity of Plants Belonging to Genus *Sida* - A Systematic Review

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Abstract

Viral infections are significant global health concerns, particularly in regions with limited healthcare infrastructure. The leading causes of viral-related mortality worldwide include influenza, COVID-19, Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS), and lower respiratory infections, such as pneumonia. Current antiviral therapies, such as protease and reverse transcriptase inhibitors, are effective but limited by high costs, side effects and drug resistance. This review aimed to provide an overview of the current landscape of viral infections, their impact, and available treatments. This review explores the antiviral potential of natural products, focusing on the genus *Sida*. A systematic literature search using database like PubMed, Science direct, Google Scholar and Wiley Online Library identified on *Sida* traditional uses, chemical composition and antiviral properties. This review outlined the the overview of *Sida* Genus as a promising source for new antiviral compounds due to its bioactive properties that may inhibit viral infection.

Keywords: Viral infections, Medicine, Genus *sida*, Natural products, Medicine plant

Introduction

Viruses responsible for the highest global mortality rates are primarily related to severe infectious diseases, particularly in regions with limited healthcare infrastructure. In this context, influenza viruses are among the leading causes, disproportionately affecting vulnerable populations such as the elderly and young children. The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus is the source of COVID-19, which has had a significant impact since its outbreak and is expected to kill over 8.7 million people by 2021, according to estimates from the World Health Organization (WHO) [1,2].

Acquired Immune Deficiency Syndrome (AIDS)/the Human Immunodeficiency Virus (HIV) are major worldwide health concerns, especially in low- and

middle-income nations. Despite advancements in antiretroviral therapy, the virus continues to claim approximately 700,000 to 1 million lives annually [3]. Recognizing that pneumonia and other lower respiratory infections are a leading cause of mortality, particularly in children under five, is crucial. These infections are often preventable with proper vaccination and healthcare but remain a significant burden in regions with limited access to medical care [2]. Other viruses of concern include those causing malaria, tuberculosis, and Ebola, which have high mortality rates in specific regions. For example, HIV is a major cause of mortality in tropical regions, particularly in Africa, where it claims hundreds of thousands of lives yearly. Tuberculosis, despite being treatable, remains a

significant public health concern due to its high prevalence and drug-resistant strains. Although less frequent, Ebola causes devastating epidemics throughout Africa and has a high case fatality rate [3,4].

In Indonesia, the number of deaths due to viruses is a significant public health concern, with various sources providing insights into the magnitude of this issue. Recognizing that COVID-19 has had a significant role in the nation's viral-related fatalities is crucial. According to Worldometer, as of April 13, 2024, Indonesia has reported a total of 162,063 deaths due to this disease [5]. Other viruses such as dengue fever and rabies also pose significant threats to public health. In Indonesia, illnesses including dengue fever, chikungunya, as well as Japanese encephalitis are prevalent, according to a review of earlier research on viral infections. The reports from the Indonesian Ministry of Health (MoH-RI) and WHO show a substantial increase in dengue infection incidence over the years, with severe cases potentially leading to hemorrhagic shock and organ failure [6].

These viruses disproportionately affect vulnerable populations and regions with limited healthcare resources, emphasizing the need for continued investment in public health infrastructure and vaccination programs. With many therapeutic classes now accessible to treat a variety of viral illnesses, such as influenza, HIV, hepatitis, as well as herpes viruses, the antiviral drug landscape has undergone tremendous change. By stopping the release of virus particles from infected cells, neuraminidase inhibitors, such as oseltamivir (Tamiflu) along with zanamivir (Relenza), are frequently used to treat influenza. In this context, protease inhibitors are crucial in the treatment of HIV and hepatitis C, inhibiting viral replication by blocking the protease enzyme necessary for maturation. Additionally, nucleoside analogs, such as acyclovir, are effective against herpes viruses, targeting viral DNA synthesis [7].

Despite the effectiveness of antiviral drugs, these medications present challenges of side effects which range from mild to severe, including nausea, diarrhea, and headaches. More severe adverse effects were cardiac issues or neuropsychiatric symptoms, particularly with certain HIV medications. Furthermore, the cost of antiviral treatments can be prohibitively high, specifically in nations with low and middle income,

limiting access for many patients. For example, antiretroviral therapy for HIV can be expensive, and despite the reduced costs of generics, the financial burden remains a significant barrier to treatment in many regions [8,9].

Another critical concern is antiviral resistance, which can develop when viruses mutate and become less susceptible to existing treatments. This phenomenon has been observed with influenza viruses, where mutations can render neuraminidase inhibitors ineffective. The formation of resistant strains complicates treatment protocols and necessitates ongoing study and development of new antiviral agents. Antiviral drugs play a vital role in managing viral infections. However, challenges such as side effects, costs, and resistance emphasize the need for continued innovation and accessibility in treatment options [10].

The search for alternative antiviral drugs has become increasingly urgent due to the rising costs, safety concerns, and effectiveness issues associated with current therapies [11]. Traditional antiviral drugs, including oseltamivir and zanamivir, are often expensive and may not be effective for all populations, particularly high-risk groups such as infants and pregnant women. For example, there is limited data on the efficacy and safety of oseltamivir for infants under 1 year of age, which raises concerns about its usage in vulnerable populations during influenza outbreaks [12].

A promising avenue for discovering new antiviral drugs is the exploration of plant-based sources. Our Previous study reported various medicinal plants possess potential activities for antiviral, such as hepatitis B, C and SAR Cov-2 viral. Medicinal plants have demonstrated significant potential in combating viral infections, including hepatitis C virus (HCV) and hepatitis B virus (HBV), through their bioactive compounds. The genus *Curcuma* has shown notable antiviral activity against HCV, with specific extracts exhibiting inhibitory effects on viral replication and IC_{50} values ranging from 1 to 5 $\mu\text{g/mL}$ [13]. Additionally, Indonesian medicinal plants have been recognized for their broad antiviral properties, including activity against HBV. Comprehensive studies have reported IC_{50} values below 50 $\mu\text{g/mL}$ for several plant extracts, highlighting their potency and therapeutic potential [14]. These findings underscore the importance of

traditional medicinal knowledge and biodiversity-rich regions in the discovery of new antiviral candidates.

Among the plants studied for their activity against HBV, *Phyllanthus niruri* exhibited significant efficacy due to its bioactive compounds, such as phyllanthin and hypophyllanthin, which inhibit HBV DNA polymerase and suppress viral replication. Similarly, *Curcuma* species, including *Curcuma longa* and *Curcuma xanthorrhiza*, displayed moderate to strong antiviral effects attributed to curcuminoids like curcumin, which interfere with HBV gene expression [15]. Furthermore, *Phyllanthus niruri* has also shown promise in addressing SAR Cov-2, as its isolated compounds have been found to inhibit viral protein interactions. Both computational and experimental studies have demonstrated that phyllanthin and hypophyllanthin possess notable antiviral activity against SAR Cov-2 proteases, with IC50 values ranging between 5 and 15 μM [16]. These findings emphasize the phytochemical potential of *P. niruri* and other medicinal plants in developing novel antiviral therapies for multiple viral infections.

Those antiviral activities are involved by various of metabolites in the plants. One of the important targets as antiviral is plant from the genus *Sida*. This genus contains promising metabolites which is a good target of its possible antiviral qualities [17]. The *Sida* compounds' antiviral effects may arise from the ability to interfere with viral replication and infectivity. Some studies have focused on the mechanistic insights of these bioactive metabolites, presenting their potential to inhibit key viral processes. The genus of *Sida* not only a source of traditional remedies but also a candidate for modern antiviral drug development. This study provided an overview of genus *Sida* in chemical compounds and their properties as antiviral agents.

Methods and discussion

The procedures include the identification of study questions, selection of relevant literature, applying inclusion and exclusion criteria, and organizing the collected data. Examining important scientific databases like Science Direct, PubMed, along with Wiley Online Library as well as search engines like Google Scholar allowed for the retrieval of pertinent literature. To find pertinent material, books as well as dissertations were also reviewed. Keywords like "Genus *Sida*" were used in the search. These publications were filtered based on

the review's criteria for "traditional uses," "chemical composition," "antiviral," as well as "Medicine plant" Primary sources were used for all investigation on pharmacological characteristics, phytochemistry, traditional usage, as well as bioapplication. Finally, a total of 50 articles were retrieved and analyzed.

Botanical aspects of plants from genus *Sida*

About 200 species of herbaceous plants with weed-like characteristics make up the genus *Sida*, which is a member of the Malvaceae family. Many species featured a low, much-branched, with a woody base and herbaceous tips. *Sida* plants can be annual, biennial, or perennial, with stems that are long and soft, often hairy, and bearing simple, alternately arranged leaves. The flowers, typically solitary in the leaf axils or form clusters on stem apices, measuring 10 - 20 mm in diameter, show colours, including shades of white, yellow, and orange. The fruit is a small capsule that splits apart at maturity into 5 to 12 segments called mericarps, each containing a seed. *Sida* species are commonly discovered in disturbed habitats, along roadsides, and in fields. *Sida* species show adaptability to a variety of soil types, including sandy and clay, and are often considered weeds in agricultural areas [18].

Genus has historically been a wastebasket taxon, with over 1000 names published. However, only about 150 to 250 valid names are currently accepted. In addition to being important for plant protection, the variety of trichomes which include conical, forked, stellate, capitate, uniseriate multicellular, as well as peltate types can help with taxonomic research. Aside to growing on open wastelands, the heliophilous weedy species may also be found as undergrowths in plantations, semi-deciduous and deciduous woods, as well as partially shaded areas. Genus *Sida* is derived from the Greek term for "pomegranate or water lily." Its traditional application in Ayurvedic, Siddha, Unani, as well as Homeopathic medicine underscores the importance of herbal remedies, particularly for treating rheumatism and various neurological disorders.

Ethnopharmacological claims

Sida species have been traditionally used in various cultures due to their medicinal properties. Commonly adopted species include *Sida cordifolia*, *acuta*, *rhombifolia*, and *spinosa*, used in folk remedies

for various ailments across Africa, Brazil, and India. The leaves and roots possessed anti-septic properties, treating fever, wounds, skin infections, conjunctivitis, as well as stomach and respiratory disorders. They also serve anti-inflammatory purposes for rheumatism, cancer, and leukemia [19]. For instance, *Sida acuta*, widely distributed in tropical regions, is recognized for its astringent and tonic qualities, effectively addressing urinary issues, blood disorders, and conditions affecting the liver and bile [2]. It has also historically been used to treat conditions like erectile dysfunction, elephantiasis, rheumatism, ulcers, rheumatism, bronchitis, malaria, gonorrhea, colds, gonorrhea, fever, bronchitis, diarrhea, headaches, and dysentery, as well as skin diseases, hemorrhoids, insect bites, erectile dysfunction, and breast cancer [20].

Phytochemical analyses illustrated the alkaloids, saponosides, coumarins, steroids, tannins, phenolic compounds, sesquiterpenes, as well as flavonoids presence in the plants, contributing to the diverse therapeutic profiles. For example, *Sida cordifolia*

features analgesic, anti-inflammatory, and antioxidant properties. Phytochemical screenings confirmed the reducing sugars, alkaloids, steroids, and saponins presence in the root extracts. This emphasized the potential as a natural remedy for various health disorders [21]. Similarly, the leaves of *Sida rhomboidal* showed significant antinociceptive as well as anti-inflammatory activities, reflecting the versatility of *Sida* species in addressing multiple health concerns [22].

Phytochemistry

Phytochemicals identified from various *Sida L.* species include alkaloids, flavonoids, ecdysteroids, terpenoids, lignans, coumarins, steroids, phenolics, aliphatics, phaeophytin, amino acids, and other compounds, as shown in **Table 1**. The most prevalent goals for plant research targeted at separating bioactive principles were mostly alkaloids, ecdysteroids, as well as flavonoids, which are the most prevalent indicators of this species, according to the separated phytochemicals.

Table 1 Compounds from *Sida* species.

Class of compounds	Compound	Species plants	References
Alkaloid	Quindoline	<i>Sida rhombifolia</i> , <i>Sida acuta</i> ,	[23]
	Cryptolepinone	<i>Sida acuta</i> ,	[23]
	Quinazoline	<i>Sida spinosa</i>	[24]
	Vasicine	<i>Sida spinosa</i>	[24]
	Vasicinone	<i>Sida spinosa</i>	[24]
	Cryptolepine	<i>Sida acuta</i> ,	[24]
	Vasicinol	<i>Sida rhombifolia</i>	[25]
	N-trans-feruloyltyramine	<i>Sida rhombifolia</i>	[25]
	Betaine	<i>Sida rhombifolia</i>	[25]
Flavonoid	Chrysin	<i>Sida acuta</i> ,	[23]
	Kaempferol	<i>Sida acuta</i> , <i>Sida rhombifolia</i>	[23,26]
	Luteolin	<i>Sida acuta</i> , <i>Sida cordifolia</i>	[23,26]
	Acacetin	<i>Sida acuta</i> , <i>Sida cordifolia</i>	[23,27]
	Tiliroside	<i>Sida rhombifolia</i>	[23]

Class of compounds	Compound	Species plants	References
	Flavonol C-Glycosides	<i>Sida cordifolia</i>	[28]
	Kampferol-3-O- α -L-rhamnopyranosyl- β -D-glucopyranoside	<i>Sida acuta</i> ,	[29]
	Kaempferol-3-O-Glucuronide	<i>Sida cordifolia</i>	[27]
	Kaempferol-3-O-arabinoside	<i>Sida cordifolia</i>	[27]
	Kaempferol-3-O-(p-coumaroyl) glucoside	<i>Sida cordifolia</i>	[27]
	Kaempferol-3-O-rhamnoside	<i>Sida cordifolia</i>	[27]
	Kaempferol dirhamnoside	<i>Sida cordifolia</i>	[27]
	Kaempferol-3-O- β -D-(6'' E-pcoumaroyl)glucopyranoside	<i>Sida tuberculata</i>	[30]
	Kaempferol-3-O-D-glucose-6''-D-rhamnose	<i>Sida rhombifolia</i>	[25]
	Quercetin	<i>Sida cordifolia</i> , <i>Sida rhombifolia</i>	[27,26]
	Quercetin hexoside	<i>Sida cordifolia</i>	[27]
	Quercetin 3-O-glucoside	<i>Sida cordifolia</i>	[27]
	Quercetin 3-O-rutinoside	<i>Sida cordifolia</i>	[27]
	Procyanidin B2	<i>Sida cordifolia</i>	[27]
	Procyanidin dimer 1	<i>Sida cordifolia</i>	[27]
	Rutin	<i>Sida cordifolia</i> , <i>Sida rhombifolia</i>	[27,26]
	Gallic acid	<i>Sida cordifolia</i>	[27]
	Apigenin	<i>Sida cordifolia</i>	[27]
	Naringin	<i>Sida cordifolia</i>	[27]
	Naringin 6'-malonate	<i>Sida cordifolia</i>	[27]
	3',4',7-Trihydroxyisoflavanone	<i>Sida cordifolia</i>	[27]
	Dihydromyricetin 3-O-rhamnoside	<i>Sida cordifolia</i>	[27]
	Rosmarinic acid	<i>Sida cordifolia</i>	[27]
	Ferulic acid 4-O-glucoside	<i>Sida cordifolia</i>	[27]
	Cinnamic acid	<i>Sida cordifolia</i>	[27]
	Isoquercetin	<i>Sida rhombifolia</i>	[26]
	Isorientin	<i>Sida rhombifolia</i>	[26]
	Epicatechin	<i>Sida rhombifolia</i>	[25]

Class of compounds	Compound	Species plants	References
	Glutinoside	<i>Sida rhombifolia</i>	[25]
Coumarin	Xanthyletin	<i>Sida acuta</i> ,	[23]
	Thamnosmonin	<i>Sida rhombifolia</i> , <i>Sida acuta</i> ,	[23]
	Scoparone	<i>Sida rhombifolia</i>	[23]
	Scopoletin	<i>Sida rhombifolia</i>	[26]
	Umbelliferone	<i>Sida rhombifolia</i>	[26]
Polyphenol	N-Feruloyltyramine	<i>Sida rhombifolia</i> , <i>Sida acuta</i> , <i>Sida tuberculata</i>	[23,30]
	Hydroxytyrosol 4-O-glucoside	<i>Sida cordifolia</i>	[23]
Steroid	20-Hydroxycdysone	<i>Sida rhombifolia</i> , <i>Sida tuberculata</i>	[23,30]
	20-Hydroxycdysone-3-O-b-D-glycopyranoside	<i>Sida tuberculata</i>	[23]
	20-Hydroxycdysone-3-O-b-D-xylose	<i>Sida tuberculata</i>	[30]
	Gamma-sitosterol	<i>Sida cordata</i>	[31]
Phenylpropanoid	Caffeic acid monohexoside derivative	<i>Sida cordifolia</i>	[27]
	Chlorogenic acid	<i>Sida cordifolia</i>	[27]
	Catechin	<i>Sida cordifolia</i>	[27]
	Caffeic acid-O- hexoside derivative	<i>Sida cordifolia</i>	[27]
	Cinnamaldehyde	<i>Sida cordifolia</i>	[27]
	Caffeic acid derivative	<i>Sida cordifolia</i>	[27]
	Caffeoyl glucose	<i>Sida cordifolia</i>	[27]
	Caffeoyl tartaric acid	<i>Sida cordifolia</i>	[27]
	Caffeic acid	<i>Sida cordifolia</i> , <i>Sida acuta</i> , <i>Sida rhombifolia</i>	[26,27,32]
	Dihydrosinapyl caffeoyl hexoside	<i>Sida cordifolia</i>	[27]
	3-p-Coumaroylquinic acid	<i>Sida cordifolia</i>	[27]
	Quinic acid derivative	<i>Sida cordifolia</i>	[27]
Phenolic Aldehydes	Coniferaldehyde	<i>Sida rhombifolia</i>	[26]
	Sinapaldehyde	<i>Sida rhombifolia</i>	[26]
	Syringaldehyde	<i>Sida rhombifolia</i>	[26]
	Vanillin	<i>Sida rhombifolia</i>	[26]
Tannin	Gallagic acid	<i>Sida cordifolia</i>	[27]

Class of compounds	Compound	Species plants	References
	Protocatechuic acid 4-O-glucoside	<i>Sida cordifolia</i>	[27]
Terpenoid	Vomifoliol	<i>Sida rhombifolia</i>	[25]
	Taraxasterone	<i>Sida rhombifolia</i>	[25]
	Stigmasterol	<i>Sida rhombifolia</i>	[33]
	Sitosterol	<i>Sida rhombifolia</i>	[33]
	Sitostenone	<i>Sida rhombifolia</i>	[33]
	Lupeol	<i>Sida rhombifolia</i>	[33]
	Lupenone	<i>Sida rhombifolia</i>	[33]
	Squalene	<i>Sida cordata</i>	[34]
	Vitamin D3	<i>Sida cordata</i>	[34]
	Vitamin E	<i>Sida cordata</i>	[34]
	3-Hexadecyloxy carbonyl-5-(2-hydroxyethyl)-4 methylimidazolium ion	<i>Sida cordata</i>	[34]
	1-Tetradecene	<i>Sida cordata</i>	[31]
	Neophytadiene	<i>Sida cordata</i>	[31]
Squalene	<i>Sida cordata</i>	[31]	

The genus *sida* for viral infections

The current treatments for various viral infections include different classes of antiviral drugs, each with distinct mechanisms of action. The following is short overview of the treatments for several common viral infections:

HIV Virus

Targeting and infecting cells of the human immune system, especially CD4-positive T-cells and macrophages, HIV is a sophisticated and extremely harmful retrovirus. Immune system deterioration brought on by this infection results in immunodeficiency, which can proceed to AIDS if treatment is not received [35]. HIV belongs to the Retroviridae family's Lentivirus genus [36]. When it enters a host cell, it has the capacity to reverse-transcribe a single-stranded RNA genome into double-stranded DNA. Reverse transcriptase, an enzyme encoded by the virus, is used in the process to convert the viral RNA

into DNA. With the aid of host co-factors, this molecule subsequently incorporates into the DNA of the host cell via an additional enzyme known as integrase [37].

HIV is treated with antiretroviral therapy (ART), which typically comprises drugs combination from various classes to prevent the virus from replicating. Protease inhibitors, such as ritonavir, atazanavir, and darunavir, function by blocking the enzyme required for duplicate. Aside from that, nucleoside reverse transcriptase inhibitors, including acyclovir, tenofovir, and valganciclovir, disrupt the reverse transcription process by incorporating it into the viral DNA, leading to chain termination. Additionally, integrase inhibitors, such as raltegravir, prevent the viral DNA integration into the host genome. Common side effects include gastrointestinal issues, fatigue, and increased risk of lipodystrophy and lactic acidosis, particularly with certain medications [9,35].

An important inspiration source for the antiviral medications development has been natural items. Many

derived plants and compounds such as alkaloids, flavonoids, and terpenoids, have shown significant antiviral properties, demonstrating their potential in combating viral infections like herpes, influenza, and HIV. have shown antiviral properties, but not all are directly used to treat viral infections. From the dried leaves and twigs of *Ostodes katharinae*, Chen *et al.* [37] extracted a new phorbol ester called Hop 8. In peripheral blood mononuclear cells (PBMCs), the isolate exhibits strong antiviral activity against drug-resistant strains of HIV-1 and HIV-2 as well as wild-type HIV-1 and HIV-2. Hop-8 outperformed Prostratin in the cytotoxicity test, with EC₅₀ values ranging from 0.396 to 6.915 M. Western blotting and cell transfection methods were employed to ascertain the mode of action. This analysis confirmed that Hop-8 uses a strategy to fend against HIV infection, which involves promoting A3G expression to stop Vif-mediated degradation [38]. A number of novel abietane-type diterpenoids were extracted by Zhao *et al.* from *Euphorbia neriifolia* leaves and twigs. In MT4 cells, these substances' anti-HIV properties were examined. The EC₅₀ values of Eurifoloids E (16) and F (17) were 3.58 μM and 7.40 μM, respectively, indicating substantial action [39].

Influenza

The enveloped virus influenza, which is a member of the Orthomyxoviridae family, has a divided negative-sense RNA genome which includes 11 viral genes. It has developed sophisticated ways to infiltrate host cells and interfere with the machinery that allows viruses to replicate [40]. Medication used to treat influenza targets the viral replication process. The neuraminidase enzyme is blocked by oseltamivir (Tamiflu), which functions as a neuraminidase inhibitor to stop the release of viral particles from infected cells. Another neuraminidase inhibitor that works similarly to oseltamivir is zanamivir (Relenza). A viral RNA polymerase inhibitor called favipiravir prevents influenza virus replication by blocking RNA-dependent RNA polymerase. Diarrhea, vomiting, and nausea were frequent adverse effects of these drugs [41].

Natural goods are a great resource for finding and creating novel medications, which are frequently found to be less costly and safer. Numerous research investigate the mechanisms of action and assess the potency of plant extracts. To assess the antiviral

qualities, Zhao *et al.* [41] separated fractions from *Forsythia suspensa* fruits. With IC₅₀ values ranging from 18.4 to 26.2 μM, 8 labdane diterpenoids demonstrated antiviral activity against influenza A (H1N1) virus *in vitro* [42]. Ha *et al.* [42] conducted a study to isolate ethanol extract from the leaves of *Cleistocalyx operculatus* using 8 compounds. Strong enzymatic inhibition of a variety of neuraminidases from several influenza viruses, such as H1N1, H9N2, novel H1N1, as well as oseltamivir-resistant novel H1N1 (H274Y mutation) produced in HEK293 cells, was demonstrated by compounds 6 and 8. According to the Cytopathic Effect (CPE) inhibition experiment, the drugs' respective IC₅₀ values varied from 5.07 ± 0.94 μM to 9.34 ± 2.52 μM [43].

Coronavirus

Coronavirus refers to a family of large, enveloped viruses known as Coronaviridae, which contain single-stranded RNA. These viruses were characterized by their crown-like appearance due to spike proteins on the surface [44] and can infect a variety of hosts, including birds and mammals. From the ordinary cold to more serious respiratory conditions like SARS, MERS (Middle East Respiratory Syndrome), as well as COVID-19, they are the cause of a number of human diseases. When the most latest coronavirus, SARS-CoV-2, emerged in late 2019, it sparked a worldwide epidemic that resulted in severe sickness and major public health issues. Based on observation, the ability to mutate resulted in the development of new variants and affected transmissibility and vaccine efficacy [45].

Numerous antiviral drugs that target distinct phases of the SARS-CoV-2 replication cycle are used to treat COVID-19. By blocking RNA-dependent RNA polymerase, Remdesivir (Veklury), a viral RNA polymerase inhibitor, prevents the replication process. Favipiravir is an effective inhibitor of viral RNA polymerase that combats COVID-19. Additionally, Lopinavir/Ritonavir is a combination of protease inhibitors that inhibit the enzyme necessary for viral replication. Common side effects associated with these treatments include gastrointestinal issues, headache, and increased risk of liver enzyme elevation [46].

The development of antiviral medications has been greatly aided by natural ingredients. These products, which come from microbes, plants, and

marine life, have been a significant source of lead chemicals for the development of new drugs. Natural ingredients have always played a key role in the creation of antiviral treatments. The first significant step in the creation of antiviral drugs was the 1963 approval of idoxuridine, an anti-herpes virus medication that was generated from a product parent. This highlighted how natural substances may be used to fight viral infections [47]. These findings highlight the phytochemical potential of *P. niruri* in addressing covid infections. Ryu and colleagues extracted amentoflavone, a biflavonoid, from *Torreya nucifera* leaves and found that it inhibited SARS-CoV 3CLpro by an IC_{50} value of $8.3 \pm 1.2 \mu\text{M}$. Replacing the apigenin motif at position C-3' may improve the inhibitory action against SARS-CoV-2, according to an analysis of the structure-activity connection with flavonoids [48]. After screening 122 Thai natural products, Kanjanasirirat *et al.* [48] found that the extract from *Boesenbergia rotunda* and its phytochemical component, panduratin A, had potent anti-virus properties (94). Compound 94 and *B. rotunda* extract, respectively, had IC_{50} s of $0.81 \mu\text{M}$ ($CC_{50} = 14.71 \mu\text{M}$) and $3.62 \mu\text{g/mL}$ ($CC_{50} = 28.06 \mu\text{g/mL}$) that inhibited SARS-CoV-2 infection *in vitro*. Both the pre-entry as well as post-infection stages were inhibited by panduratin A [49].

Herpes viruses

The extremely contagious illness known as herpes simplex virus (HSV) is brought on by HSV-1 and HSV-2. While HSV-2 is a major source of genital herpes, which affects the genitalia, buttocks, or anal region, HSV-1 is mostly linked to oral herpes, which causes cold sores surrounding the mouth or cheeks. Additionally, the virus may infect the skin, eyes, or other bodily parts. Direct touch is how HSV is transferred, and while some people may not show any symptoms, others may have painful blisters that go away over time. The virus established latency in neurons, allowing it to recur after various stimuli, leading to recurrent outbreaks. The immune system played a crucial role in controlling HSV infection but also contributed to chronic inflammatory characteristics of the lesions [50,51].

Herpes infections are treated with antiviral medications that target the viral replication process. Acyclovir, a nucleoside analog, inhibits viral DNA synthesis through incorporation, causing chain

termination. Valacyclovir is a prodrug of acyclovir, which was converted into acyclovir in the body and has a longer half-life, allowing for less frequent dosing. Another prodrug of ganciclovir, valganciclovir, was used to treat cytomegalovirus (CMV) infections. Common side effects experienced include gastrointestinal issues, headache, and fatigue [9]. Particularly in the battle against herpes viruses, natural materials have emerged as a viable source of antiviral medicines. These bioactive substances, which come from microbes, plants, and marine life, have distinct chemical structures and a range of modes of action that can stop the spread of infection and stop viruses from replicating. Numerous compounds, including alkaloids, terpenoids, and flavonoids, have been found in studies to have strong antiherpes properties [52].

According to a research by Donalisio *et al.* [53] leaf extract from *Arisaema tortuosum* shown strong antiviral activity towards HSV-2. The chloroform soluble fraction of the leaves had potent antiviral activity against it, with a selectivity index of 758, signifying high specificity and efficacy. Flavonoids, such as luteolin and apigenin, were shown to be the main active ingredients in the extract by HPLC-PDA-MS/MS analysis. With apigenin and luteolin exhibiting EC_{50} values of 0.05 and $0.41 \mu\text{g/mL}$, respectively, these substances demonstrated strong inhibitory efficacy. Using virus-specific inhibition tests, *Vachellia nilotica* bark extracts demonstrated considerable antiviral efficacy towards HSV-2 strains, an HIV-1IIIb strain, as well as HPV-16 pseudovirions *in vitro*. With effective concentrations (EC_{50} s) of $4.71 \mu\text{g/mL}$ against HSV-2 and $1.80 \mu\text{g/mL}$ against HPV-16, respectively, the methanolic extract of *Vachellia nilotica* exhibited the highest level of activity. Additionally, it demonstrated efficacy against an HSV-2 strain that was resistant to acyclovir, with an EC_{50} of $6.71 \mu\text{g/mL}$ [54]. Mangiferin, a polyphenol derived from mango tree (*Mangifera indica*), has been investigated for antiviral properties towards HSV-1, particularly acyclovir-resistant strains. *In vitro* study showed that mangiferin had significant antiviral activity, with IC_{50} values of $2.9 \mu\text{g/mL}$ and $3.5 \mu\text{g/mL}$ against the AR-29 as well as KOS strains. The substance showed a $CC_{50} > 500 \mu\text{g/mL}$, signifying low toxicity [55].

Hepatitis B and C

The hepatitis B virus (HBV) as well as the hepatitis C virus (HCV) are the infectious liver disorders known as viral hepatitis B and C, respectively. The liver is the primary target of both viruses, resulting in mild to severe inflammation and damage [56]. Hepatitis B is spread by coming into touch with contagious bodily fluids including blood, semen, or vaginal secretions, frequently through unprotected intercourse, sharing of needles, or mother-to-child contact after childbirth [57]. Meanwhile, Blood-to-blood contact is the main way that hepatitis C is transmitted, usually by sharing infected needles or receiving blood transfusions prior to the establishment of screening procedures [58]. While acute infections of both types may resolve without treatment, chronic infection can develop, leading to long-term liver damage, cirrhosis, liver failure, or cancer. Hepatitis B is preventable through a vaccine, but C has no vaccine and can be treated effectively with antiviral medications. Both forms of viral hepatitis represent significant global health challenges, requiring efforts in prevention, treatment, as well as diagnosis [59]. Hepatitis B and C are treated with antiviral medications that target the viral replication process. Entecavir, as a nucleoside analog, inhibits viral DNA synthesis and causes chain termination. Another nucleoside analog known as Tenofovir, is used to treat both hepatitis B and C. Ribavirin is an analog often used in combination with other medications to treat hepatitis C. Meanwhile, the common side effects experienced were gastrointestinal issues, fatigue, and increased risk of bone and kidney problems associated with long-term use [60]. These natural products often contain complex molecules such as alkaloids, chromones, furanocoumarins, flavonoids, lignans, phenolics, quinone/xanthenes, and phenylpropanoids, isolated and studied for antiviral properties [61].

The natural compounds were extensively investigated for their potential as anti-HCV agents,

offering good alternatives to traditional treatments. Various investigations have identified several phytochemicals with antiviral properties against HCV. Susiloningrum *et al.* [61] conducted an isolation study on *Melicope latifolia* using ethanol extract to purify and identify the active compound. A bioactivity-guided isolation approach was adopted, which causing the identification of the active fraction, designated as B1F D2H.3, containing the alkaloid N-methylflindersine. Against HCV genotype 2a (JFH1), this alkaloid fraction demonstrated strong anti-HCV activity *in vitro*, with an IC_{50} value of 6.21 $\mu\text{g/mL}$, a CC_{50} value of 82.64 $\mu\text{g/mL}$, as well as the 13.31 selectivity index [62].

From extracts of *Ruta angustifolia* leaves, Wahyuni *et al.* [62] identified 6 compounds: chalepin, scopoletin, γ -fagarine, arborinine, kokusaginine, and pseudane IX. The capacity of these substances to suppress HCV was examined. In particular, chalepin and pseudodane IX shown potent anti-HCV properties, with respective IC_{50} values of $1.7 \pm 0.5 \mu\text{g/mL}$ and $1.4 \pm 0.2 \mu\text{g/mL}$. This outperformed the widely used antiviral medication ribavirin, which has the $2.8 \pm 0.4 \mu\text{g/mL}$ IC_{50} value. With IC_{50} values of 6.4 ± 0.7 , 6.4 ± 1.6 , and $20.4 \pm 0.4 \mu\text{g/mL}$, respectively, arborinine, kokusaginine, and γ -fagarine exhibited considerable anti-HCV activities, although scopoletin exhibited no discernible action at 30 $\mu\text{g/mL}$ [63]. The HepG2.2.15 cell line was used in cell-based tests to assess the extracted sesquiterpenoids' anti-HBV efficacy. According to earlier research, several *Cyperus rotundus* sesquiterpenoids exhibited strong anti-HBV activity, with IC_{50} values ranging from $0.73 \pm 0.18 \mu\text{M}$ to $1.43 \pm 0.54 \mu\text{M}$, suggesting that they might be used as therapeutic agents [64]. **Table 2** provides a comprehensive list of natural products identified and studied for antiviral properties, outlining their potential as novel therapeutic agents against several viral infections.

Table 2 Antiviral from natural product.

Principal name	Family	Parts used	Extract used	Concentration range used	Assays used	Type of virus	Reference
<i>Ostodes katharinae</i>	Euphorbiaceae	Leaves, twigs	Methanol extract	0.106 - 7.987 μ M. (EC ₅₀)	<i>In vitro</i> cell anti-HIV assay	C8166 and PBMCs cell line with virus HIV-1 and HIV-2 strains	[38]
<i>Euphorbia nerifolia</i>	Euphorbiaceae	Leaves, twigs	Ethanol extract	EC ₅₀ values of 3.58 - 7.40 μ M	<i>In vitro</i> cell anti-HIV assay	MT-4 cell line, HIV-1 strain	[39]
<i>Forsythia suspensa</i>	Oleaceae	Fruits	Ethanol extract	18.4 - 26.2 μ M (IC ₅₀)	<i>In vitro</i> studies against influenza virus	influenza viruses	[42]
<i>Cleistocalyx operculata</i>	Myrtaceae	leaves	Ethanol extract	5.07 - 9.34 μ M (IC ₅₀)	<i>in vitro</i> Cytopathic effect (CPE) inhibition assay	influenza viruses	[43]
<i>Torreya nucifera</i>	Taxaceae	leaves	Ethanol extract	280.8, 20.2, and 23.8 μ M (IC ₅₀)	Fluorescence resonance energy transfer (FRET) assay	SARS-CoV 3CL	[48]
<i>Boesenbergia rotunda</i>	Zingiberaceae	Rhizomes	Ethanol extract	3.62 - 5.30 μ g/mL (IC ₅₀)	<i>In vitro</i> Plaque assay	Vero E6 cells, SARS-CoV-2	[49]
<i>Arisaema tortuosum</i>	Araceae	leaves	Ethanol extract	EC ₅₀ values of 0.05 and 0.41 μ g/mL	<i>In vitro</i> studies against HSV virus	HSV-1, HSV-2, HSV-2 ACV-r	[53]
<i>Vachellia nilotica</i>	Fabaceae	bark	chloroform, methanolic, and water bark extracts	EC ₅₀ 1.80 - 4.71 μ g/mL	<i>In vitro</i> assays using HSV-2	HSV-2 strains	[54]
<i>Mangifera indica</i>	Anacardiaceae	Plant extracts	Mangiferin constituents	2.9 - 3.5 μ g/mL (IC ₅₀)	<i>In vitro</i> studies against HSV-1 and other viruses	Vero cells, HSV-1 AR-29 strain, others	[55]
<i>Melicope latifolia</i>	Rutaceae	Leaves	Ethanol extract	6.21 μ g/mL (IC ₅₀)	<i>In vitro</i> cell-based, anti-HCV activities	Huh7it cells, JFH1a	[62].
<i>Ruta angustifolia</i>	Rutaceae	leaves	Ethanol extract	1.7 - 20.4 μ g/mL (IC ₅₀)	<i>In vitro</i> cell-based WST-1 assay for cytotoxicity, anti-HCV activities	Huh7.5 cells, JFH1a	[63]
<i>Cyperus rotundus</i>	Cyperaceae	Rhizomes	Ethanol extract	0.73 - 1.43 μ M (IC ₅₀)	<i>In vitro</i> studies against Assays of HBsAg, HBeAg and HBV	HepG2.2.15 cell line, HBV	[64]

Antiviral activity of *Sida* species

Studies on *Sida* species have revealed a broad spectrum of bioactive properties. Research on the chemical constituents of *Sida rhombifolia* and *Sida*

acuta demonstrates significant antiplasmodial activity, suggesting the plants' potential in treating parasitic infections [65]. Additionally, *Sida acuta* has been evaluated for its potent antioxidant and anticancer

effects, indicating its therapeutic relevance in oxidative stress-related diseases. Investigations into its antifungal properties further emphasize its effectiveness in combating fungal pathogens [66,67].

Furthermore, antiviral activity against various viruses has been demonstrated by several chemicals isolated from *Sida* species. **Table 3** presents the antiviral compounds, their sources, and experimental details.

Table 3 Antiviral compounds from *Sida* species.

Compound	Plant species	Part of the plant used	Type of extraction	Virus tested	Concentration used	IC50 value	Test used	Reference
(10E,12Z)-9-Hydroxyoctadeca-10,12-dienoic acid	<i>S. cordifolia</i>	Whole plant	Ethanol Extract	HIV	1 - 100 μ M	7.2 μ M	Viral inhibitory protein, NES antagonistic inhibitor assay	[68]
	<i>S. acuta</i>	Leaves	Ethanol Extract	HIV	25 μ g/mL	-	HIV Assay	[69]
	<i>S. acuta</i>	Whole plant	H2O extract	HIV	250 μ g/mL	-	HIV Assay	[69]
	<i>Sida acuta</i>	Leaves	Methanol extract	Herpes simplex virus (HSV-1)	0.1 mL from 500 μ g/mL	-	Virus induced cytopathic assay	[70]
	<i>Sida acuta</i>	Leaves	Methanol extract	Dengue virus	15 - 90 mg/L	LC50 of 38 - 48 mg/L	Larvicidal assay	[71]
	<i>Sida acuta</i>	Leaves	Methanol extract	Herpes simplex virus (HSV-1)	250 μ g/mL	-	The anti-HSV activity was considerably enhanced by light, especially UVA (long wavelength UV),	[72]

The global fight against viral infections remains a critical public health challenge, particularly in regions with limited healthcare resources. High mortality rates from viruses such as influenza, HIV, and SARS-CoV-2 underscore the urgent need for effective prevention and treatment strategies. Despite advancements in antiviral therapies, significant obstacles persist, including adverse side effects, high costs in low- and middle-income countries, and the emergence of drug-resistant strains. Exploring alternative antiviral sources, particularly plant-based compounds from the genus *Sida*, offers a promising avenue for future research. *Sida* species have shown potential antiviral properties, which could support the development of new treatments, particularly for vulnerable populations less responsive to conventional therapies [73].

The data presented in **Table 3** showed the potential of various *Sida* species as sources of compounds with antiviral activities. Empirical used of

the genus of *Sida* has been applied by various region among the world in several diseases without any toxic report. The compounds are the responsible substance that contribute for their bioactivities. Specifically, the isolated compounds had significant inhibitory effects against HIV, Herpes, and other viruses such as HSV-1 and dengue virus. Based on standard IC₅₀ values obtained ranged from < 1 to > 100 μ M for antiviral activity, most extracts and compounds tested in this study had moderate to strong activity. For example, the methanol extract of *Sida acuta* against the dengue virus showed IC₅₀ of 38 - 48 mg/L, placing it in the medium activity range. However, a few isolates from ethanol extract of *Sida cordifolia*, including compound of (10E,12Z)-9-Hydroxyoctadeca-10,12-dienoic acid, had considerable activity (1 - 20 μ M) with an IC₅₀ of 7.2 μ M. The results suggest that *Sida acuta* contained compounds with potential antiviral activity against several viruses, including HIV, herpes, and dengue fever

[72]. Moving forward, prioritizing interdisciplinary research that integrates traditional knowledge with modern pharmacological approaches is crucial. Continued exploration of bioactive compounds from *Sida* species holds the potential to develop novel, effective, and accessible antiviral agents. Addressing antiviral resistance through innovative drug design will be vital to ensuring the sustained efficacy of treatment options. Strengthening public health infrastructure and improving access to healthcare services will further enhance global capacity to manage viral infections. By focusing on these strategies, we can improve preparedness for future viral outbreaks and achieve better health outcomes for affected populations.

Further study is necessary to fully elucidate the mechanisms of action of the compounds as antiviral agents. Moreover in further development as antiviral drugs, the information of safety and efficacy in animal and humans are necessary. Preclinical studies, including animal models, should be conducted to evaluate the pharmacokinetics, pharmacodynamics, and toxicity profiles of the compounds. Additionally, clinical trials were needed to determine the optimal dosage, administration route, and efficacy in patients. These chemicals may be developed into novel medications to treat HIV, herpes, along with other infectious illnesses after demonstrating encouraging outcomes in clinical and preclinical trials. In the regulatory procedure was essential in guaranteeing the quality, safety, and effectiveness of any novel pharmaceutical products made from *Sida* species [73].

Conclusions

In conclusion, genus *Sida* presented a promising avenue for the antiviral agents' development, supported by its extensive traditional use and diverse phytochemical profile. A study showed particularly *Sida acuta* and *Sida cordifolia*, possessed significant antiviral properties against a range of viral pathogens, including coronavirus and herpes simplex viruses. The bioactive compounds' presence such as alkaloids, ecdysteroids, as well as flavonoids contributed to these effects. Despite the promising nature of preliminary studies, further investigation was essential to elucidate the mechanisms of action, optimize extraction methods, and conduct clinical trials

to validate the efficacy as well as safety of *Sida* as an antiviral treatment. This comprehensive understanding facilitated the integration of *Sida* into modern therapies, addressing the urgent need for effective treatments in the face of developing viral threats.

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References

- [1] N Nathanson. *The human toll of viral diseases: Past plagues and pending pandemics*. Elsevier Science, Amsterdam, Netherlands, 2016.
- [2] C Bochen, S Gretchen, A Ho, M Jessica and D Fat. *WHO methods and data sources for country-level causes of death*. World Health Organisation, Geneva, Switzerland, 2020.
- [3] M Naghavi, T Mestrovic, A Gray, AG Hayoon, LR Swetschinski, GR Aguilar, ND Weaver, KS Ikuta, E Chung, EE Wool, C Han, DT Araki, SB Albertson, R Bender, G Bertolacci, AJ Browne, BS Cooper, MW Cunningham, C Dolecek, ... CJL Murray. Global burden associated with 85 pathogens in 2019: A systematic analysis for the global burden of disease study 2019. *The Lancet Infectious Diseases* 2024; **24(8)**, 868-895.
- [4] RE Baker, AS Mahmud, IF Miller, M Rajeev, F Rasambainarivo, BL Rice, S Takahashi, AJ Tatem, CE Wagner, L Wang, A Wesolowski and CJE Metcalf. Infectious disease in an era of global change. *Nature Reviews Microbiology* 2022; **20(4)**, 193-205.
- [5] N Mboi, R Syailendrawati, SM Ostroff, IRF Elyazar, SD Glenn, T Rachmawati, WP Nugraheni, PB Ali, L Trisnantoro, QES Adnani, RI Agustiya, AD Laksono, B Aji, L Amalia, A Ansariadi, E Antriyandarti, I Ardani, R Ariningrum, NK Aryastami, ..., AH Mokdad. The state of health in Indonesia's provinces, 1990 - 2019: A systematic analysis for the global burden of disease study 2019. *The Lancet Global Health* 2022; **10(11)**, E1632-E1645.
- [6] WD Jong, M Rusli, S Bhoelan, FA Rantam, PA Noeryoto, U Hadi, ECMV Gorp and M

- Goeijenbier. Endemic and emerging acute virus infections in Indonesia: An overview of the past decade and implications for the future. *Critical Reviews in Microbiology* 2018; **44(4)**, 487-503.
- [7] D. R., Tompa, Immanuel, A., Srikanth, S., & Kadirvel, S. (2021). Trends and strategies to combat viral infections: A review on FDA approved antiviral drugs. *International Journal of Biological Macromolecules*, 172, 524–541.
- [8] G Pantaleo, B Correia, C Fenwick, VS Joo and L Perez. Antibodies to combat viral infections: Development strategies and progress. *Nature Reviews Drug Discovery* 2022; **21(9)**, 676-696.
- [9] S Kausar, F Said Khan, M Ishaq Mujeeb Ur Rehman, M Akram, M Riaz, G Rasool, AH Khan, I Saleem, S Shamim and A Malik. A review: Mechanism of action of antiviral drugs. *International Journal of Immunopathology and Pharmacology* 2021; **35**, 1-12.
- [10] BC Goncalves, MG Lopes Barbosa, APS Olak, NB Terezo, L Nishi, MA Watanabe, P Marinello, DZ Rechenchoski, SPD Rocha and LC Fraccin-Galhardi. Antiviral therapies: Advances and perspectives. *Fundamental and Clinical Pharmacology* 2021; **35(2)**, 305-320.
- [11] SL Bermingham, R Hughes, SL Bermingham, R Hughes, E Fenu, LM Sawyer, E Boxall, PT Kennedy, G Dusheiko, G Hill-Cawthorne and H Thomas. Cost-effectiveness analysis of alternative antiviral strategies for the treatment of HBeAg-Positive and HBeAg-negative chronic hepatitis B in the United Kingdom. *Value in Health* 2015; **18(6)**, 800-809.
- [12] M Okusa. *Antivirals for pandemic influenza: Guidance on developing a distribution and dispensing program*. National Academy of Sciences, Nidwalden, Germany, 2008.
- [13] TS Wahyuni, AA Permatasari, T Wdiandani, A Fuad, A Widyawaruyanti, C Aoki-Utsubo and H Hotta. Antiviral activities of curcuma genus against hepatitis C virus. *Natural Product Communications* 2018; **13(12)**, 1579-1582.
- [14] TS Wahyuni, L Tumewu, AA Permanasari, E Apriani, M Adianti, A Rahman, A Widyawaruyanti, MI Lusida, A Fuad, Soetjipto, Nasronudin, H Fuchino, N Kawahara, I Shoji, L Deng, C Aoki and H Hotta. Antiviral activities of Indonesian medicinal plants in the East Java region against hepatitis C virus. *Virology Journal* 2013; **10**, 259.
- [15] TS Wahyuni, AA Permanasari, A Widyawaruyanti, H Hotta, C Aoki-Utsubo and AF Hafid. Antiviral activity of indonesian medicinal plants against hepatitis B virus. *Pharmacognosy Journal* 2020; **12(5)**, 1108-1114.
- [16] HD Marhaeny, A Widyawaruyanti, T Widiandani, AF Hafid and TS Wahyuni. Phyllanthin and hypophyllanthin, the isolated compounds of Phyllanthus niruri inhibit protein receptor of corona virus (COVID-19) through *in silico* approach. *Journal of Basic and Clinical Physiology and Pharmacology* 2021; **32(4)**, 809-815.
- [17] FC Rodrigues and AFMD Oliveira. The genus Sida L. (Malvaceae): An update of its ethnomedicinal use, pharmacology and phytochemistry. *South African Journal of Botany* 2020; **132**, 432-462.
- [18] VV Sivaraajan and AK Pradeep. *Taxonomy of the sida rhombifolia (malvaceae) complex in india*. The Botanical Research Institute of Texas, Texas, 1994.
- [19] DM Benjumea, IC Gomez-Betancur, J Vasquez, F Alzate, A Garcia-Silva and JA Fontenla. Neuropharmacological effects of the ethanolic extract of Sida acuta. *Revista Brasileira de Farmacognosia* 2016; **26(2)**, 209-215.
- [20] MAM Momin, SF Bellah, SMR Rahman, AA Rahman, GMM Murshid and TB Emran. Phytopharmacological evaluation of ethanol extract of Sida cordifolia L. roots. *Asian Pacific Journal of Tropical Biomedicine* 2014; **4(1)**, 18-24.
- [21] S Venkatesh, YS Reddy, B Suresh, BM Reddy and M Ramesh. Antinociceptive and anti-inflammatory activity of Sida rhomboidea leaves. *Journal of Ethnopharmacology* 1999; **67(2)**, 229-232.
- [22] UM Femoe, JBK Fassi, HB Jatsa, YL Tchoffo, DCA Nna, BC Kamdoum, SCN Wouamba, BT Tchegnitegni, Bonaventure T Ngadjui, N Sewald, BN Lenta, LT Tchuenta, T Dimo. *In vitro* assessment of the cercaricidal activity of sida acuta burm . F . and sida rhombifolia Linn .

- (Malvaceae) hydroethanolic extracts, cytotoxicity, and phytochemical studies. 2022; **2022(1)**, 7281144.
- [23] D Sharma, R Mishra and MS Saluja. A brief overview of the ethnomedical, pharmacological, and phytochemical uses of *Sida spinosa*. *International Journal of Medical, Pharmacy and Drug Research* 2023; **7(5)**, 15-19.
- [24] AH Karomah, M Rafi, DA Septaningsih, A Ilmiawati, UD Syafitri, NS Aminah, M Insanu and A rohman. UHPLC-Q-Orbitrap HRMS-based untargeted metabolomics of *sida rhombifolia* leaves and stem extracts. *HAYATI Journal of Biosciences* 2023; **30(4)**, 770-778.
- [25] DM Ferro, S Mazzutti, L Vitali, CM Oliveira Muller and SRS Ferreira. Integrated extraction approach to increase the recovery of antioxidant compounds from *Sida rhombifolia* leaves. *Journal of Supercritical Fluids* 2019; **149**, 10-19.
- [26] D Padmanabhan, P Natarajan and S Palanisamy. Integrated metabolite and transcriptome profiling-mediated gene mining of *sida cordifolia* reveals medicinally important genes. *Genes* 2022; **13(10)**, 1909.
- [27] RK Sutradhar, AKMM Rahman and MU Ahmad. Iranian chemical society three new flavonol C-glycosides from *sida cordifolia* linn. *Journal of the Iraanian chemical Society* 2007; **4(2)**, 175-181.
- [28] N Srinivasan and R Murali. An overview of the traditional importance, phytochemistry, and pharmacological properties of *Sida acuta* Burm.f. *Annals of Phytomedicine: An International Journal* 2022; **11(2)**, 245-254.
- [29] HSD Rosa, VBD Camargo, G Camargo, CV Garcia, AM Fuentefria and ASL Mendez. Ecdysteroids in *sida tuberculata* R.E. fries (Malvaceae): Chemical composition by LC-ESI-MS and selective anti-*Candida krusei* activity. *Food Chemistry* 2015; **182**, 193-199.
- [30] M Banni and M Jayaraj. Identification of bioactive compounds of leaf extracts of *sida cordata* (Burm.f.) borss.waalk. by GC/MS analysis. *Applied Biochemistry and Biotechnology* 2023; **195(1)**, 556-572.
- [31] S Uysal, R Gevrenova, KI Sinan, AU Bayarslan, YC Altunoglu, D Zheleva-Dimitrova, G Ak, MC Baloglu, OK Etienne, D lobine, MF Mohomoodally and G Zengin. New perspectives into the chemical characterization of *Sida acuta* Burm. f. extracts with respect to its anti-cancer, antioxidant and enzyme inhibitory effects. *Process Biochemistry* 2021; **105**, 91-101.
- [32] SH Mah, SS Teh and GCL Ee. Anti-inflammatory, anti-cholinergic and cytotoxic effects of *Sida rhombifolia*. *Pharmaceutical Biology* 2017; **55(1)**, 920-928.
- [33] M Ganesh and M Mohankumar. Extraction and identification of bioactive components in *Sida cordata* (Burm.f.) using gas chromatography-mass spectrometry. *Journal of Food Science and Technology* 2017; **54(10)**, 3082-3091.
- [34] V Simon, DD Ho and QA Karim. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006; **368(9534)**, 489-504.
- [35] YV Heuvel, S Schatz, JF Rosengarten and J Stitz. Infectious RNA: Human immunodeficiency virus (HIV) biology, therapeutic intervention, and the quest for a vaccine. *Toxins* 2022; **14(2)**, 138.
- [36] S Suryono and N Nasronudin. Clinical description and diagnosis of HIV/AIDS. *Indonesian Journal of Tropical and Infectious Disease* 2015; **5(1)**, 23.
- [37] H Chen, R Zhang, R Luo, L Yang, R Wang, X Hao and Y Zheng. Anti-HIV activities and mechanism of 12-O-tricosanoylphorbol-20-acetate, a novel phorbol ester from *Ostodes katharinae*. *Molecules* 2017; **22(9)**, 1498.
- [38] J Zhao, C Liu, W Qi, M Han, Y Han, MA Wainberg and J Yue. Eurifoloids A-R, structurally diverse diterpenoids from *euphorbia neriifolia*. *Journal of Natural Products* 2014; **77(10)**, 2224-2233.
- [39] T Samji. Influenza A: Understanding the viral life cycle. *Yale Journal of Biology and Medicine* 2009; **82(4)**, 153-159.
- [40] Y Kang, Y Shi and S Xu. Arbidol: The current demand, strategies, and antiviral mechanisms. *Immunity, Inflammation and Disease* 2023; **11(8)**, e984.
- [41] L Zhao, K Xiang, R Liu, Z Xie, S Zhang and S Dai. Anti-inflammatory and anti-viral labdane diterpenoids from the fruits of *Forsythia suspensa*. *Bioorganic Chemistry* 2020; **96**, 103651.
- [42] TKQ Ha, TT Dao, NH Nguyen, J Kim, E Kim, TO Cho and WK Oh. Antiviral phenolics from the

- leaves of *Cleistocalyx operculatus*. *Fitoterapia* 2016; **110**, 135-141.
- [43] I Zanella, D Zizioli, F Castelli and E Quiros-Roldan. Correction to: Zanella et al. tenofovir, another inexpensive, well known and widely available old drug repurposed for sars-cov-2 infection. *pharmaceuticals* 2021, *14*, 454. *Pharmaceuticals* 2021; **14(8)**, 454.
- [44] P V'kovski, A Kratzel, S Steiner, H Stalder and V Thiel. Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews Microbiology* 2021; **19(3)**, 155-170.
- [45] Z Zuo, T Wu, L Pan, C Zuo, Y Hu, X Luo, L Jiang, Z Xia, X Xiao, J Liu, M Ye and M Deng. Modalities and mechanisms of treatment for coronavirus disease 2019. *Frontiers in Pharmacology* 2021; **11**, 583914.
- [46] JH Zhao, YW Wang, J Yang, Z Tong, J Wu, Y Wang, Q Wang, Q Li, Y Yu, X Leng, L Chang, X Xue, S Sun, H Li, N Ding, J Duan, N Li and Z Shi. Natural products as potential lead compounds to develop new antiviral drugs over the past decade. *European Journal of Medicinal Chemistry* 2023; **260**, 115726.
- [47] YB Ryu, HJ Jeong, JH Kim, YM Kim, J Park, D kim, TTH Nguyen, S Park, JS Chang, KH Park, M Rho and WS Lee. Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition. *Bioorganic and Medicinal Chemistry* 2010; **18(22)**, 7940-7947.
- [48] P Kanjanasirirat, A Suksatu, S Manopwisedjaroen, B Munyoo, P Tuchinda, K Jearawuttanakul, S Seemakhan, S Charoensutthivarakul, P Wongtrakoongate, N Rangkasenee, S Pitiporn, N Waranuch, N Chabang, P Khemawoot, K Sangiamsuntorn, Y Pewkliang, P Thongsri, S Chutipongtanate, S Hongeng, ..., A Thitithanyanont. High-content screening of Thai medicinal plants reveals *Boesenbergia rotunda* extract and its component panduratin A as anti-SARS-CoV-2 agents. *Scientific Reports* 2020; **10(1)**, 19963.
- [49] R Whitley and J Baines. Clinical management of herpes simplex virus infections: Past, present, and future. *F1000Research* 2018; **7**, 1726.
- [50] S Zhu and A Viejo-Borbolla. Pathogenesis and virulence of herpes simplex virus. *Virulence* 2021; **12(1)**, 2670-2702.
- [51] LVD Sand, M Bormann, Y Schmitz, CS Heilingloh, O Witzke and A Krawczyk. Antiviral active compounds derived from natural sources against herpes simplex viruses. *Viruses* 2021; **13(7)**, 1386.
- [52] M Rittà, A Marengo, A Civra, D lembo, C Cagliero, K Kant, UM Lal, P Rubolo, M Ghosh and M Donalisio. Antiviral activity of a arisaema tortuosum leaf extract and some of its constituents against herpes simplex virus type 2. *Planta Medica* 2020; **86(4)**, 267-275.
- [53] M Donalisio, V Cagno, A Civra, D Gibellini, G Musumeci, M Ritta, M Ghosh, D Lembo. The traditional use of *Vachellia nilotica* for sexually transmitted diseases is substantiated by the antiviral activity of its bark extract against sexually transmitted viruses. *Journal of Ethnopharmacology* 2018; **213**, 403-408.
- [54] DZ Rechenchoski, KF Agostinho, LC Faccin-Galhardi, AASG lonni, JVHD Silva, FGD Andrade, NMPS Ricardo, C Nozawa and REC Lnhares. Mangiferin: A promising natural xanthone from *Mangifera indica* for the control of acyclovir - resistant herpes simplex virus 1 infection. *Bioorganic and Medicinal Chemistry* 2020; **28(4)**, 115304.
- [55] U Saeed, Y Waheed and M Ashraf. Hepatitis B and hepatitis C viruses: A review of viral genomes, viral induced host immune responses, genotypic distributions and worldwide epidemiology. *Asian Pacific Journal of Tropical Disease* 2014; **4(2)**, 88-96.
- [56] World Health Organization. *Global Hepatitis Report 2024*. World Health Organization, Geneva, Switzerland, 2024.
- [57] A Petruzzello, S Marigliano, G Loquercio, A Cozzolino and C Cacciapuoti. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. *World Journal of Gastroenterology* 2016; **22(34)**, 7824-7840.
- [58] PH Almeida, CEL Matielo, LA Curvelo, RA Rocco, G Felga, BD Guardia and YL Boteon. Update on the management and treatment of viral

- hepatitis. *World Journal of Gastroenterology* 2021; **27(23)**, 3249-3261.
- [59] K Dyrka, M Miedziaszczyk, E Szalek and K Lacka. Drugs used in viral diseases - their mechanism of action, selected adverse effects and safety during pregnancy and lactation. *Postepy Higieny i Medycyny Doswiadczalnej* 2019; **73**, 491-507.
- [60] KAE Sayed. Natural products as antiviral agents. *Studies in Natural Products Chemistry* 2007; **24**, 473-572.
- [61] D Susiloningrum, AA Permanasari, M Adianti, L Tumewu, TS Wahyuni, M Tanjung, A Widyawaruyanti and AF Hafid. The alkaloid fraction from melicope latifolia leaves inhibits hepatitis C Virus. *Pharmacognosy Journal* 2020; **12(3)**, 535-540.
- [62] TS Wahyuni, A Widyawaruyanti, MI Lusida, A Fuad, Soetjipto, H Fuchino, N Kawahara, Y Hayashi, C Aoki and H Hotta. Inhibition of hepatitis C virus replication by chalepin and pseudane IX isolated from Ruta angustifolia leaves. *Fitoterapia* 2014; **99**, 276-283.
- [63] H Xu, Y Ma, X Huang, C Geng, H Wang, Y Zhao, T Yang, X Chen, C Yang, X Zhang and J Chen. Bioactivity-guided isolation of anti-hepatitis B virus active sesquiterpenoids from the traditional Chinese medicine: Rhizomes of cyperus rotundus. *Journal of Ethnopharmacology* 2015; **171**, 131-140.
- [64] S Tamura, M Kaneko, A Shiomi, G Yang, T Yamaura and N Murakami. Unprecedented NES non-antagonistic inhibitor for nuclear export of Rev from Sida cordifolia. *Bioorganic and Medicinal Chemistry Letters* 2010; **20(6)**, 1837-1839.
- [65] BC Kamdoun, I Simo, SCN Wouamba, BMT Tali, B Ngameni, GW Fotso, P Ammbassa, FB Fabrice, BN Lenta, N Sewald and BT Ngadjui. Bathelémy chemical constituents of two cameronian medicinal plants: Sida rhombifolia L. and Sida acuta Burm. f. (Malvaceae) and their antiplasmodial activity. *Natural Product Research* 2022; **36**, 5311-5318.
- [66] M Thondawada, S Mulukutla, KRS Raju, SP Dhanabal and AD Wadhvani. *In vitro* and *In vivo* evaluation of Sida Acuta burm.f. (Malvaceae) for its anti-oxidant and anti-cancer activity. *Der PharmaChemica* 2016; **8(19)**, 396-402.
- [67] TJ Ramesh, HNR Babu, N Rajeshwari, KY Prathibha and E keshmma. Determination of antifungal potential of Sida acuta. *Journal of Medicinal Plants Studies* 2022; **10(5)**, 21-25.
- [68] JP Essien, BS Antia and GA Ebong. Phytochemistry, antibacterial and anticoagulase activities of Sida acuta against clinical isolates of Staphylococcus aureus. *Journal of Applied and Natural Science* 2009; **1(1)**, 1-7.
- [69] K Anani, JB Hudson, CD Souza, K Akpagana, GHN Tower, JT Arnason and M Gbeassor. Investigation of medicinal plants of togo for antiviral and antimicrobial activities. *Pharmaceutical Biology* 2000; **38(1)**, 40-45.
- [70] M Govindarajan. Larvicidal and repellent activities of Sida acuta Burm. F. (Family: Malvaceae) against three important vector mosquitoes. *Asian Pacific Journal of Tropical Medicine* 2010; **3(9)**, 691-695.
- [71] G Indrayanto, GS Putra and F Suhud. Validation of *in-vitro* bioassay methods: Application in herbal drug research. *Profiles of Drug Substances, Excipients and Related Methodology* 2021; **46**, 273-307.
- [72] JB Hudson, K Anani, MK Lee, CD Souza, JT Arnason and M Gbeassor. Further investigations on the antiviral activities of medicinal plants of togo. *Pharmaceutical Biology* 200; **38(1)**, 46-50.
- [73] Center for Drug Evaluation and Research. *Guidance for industry antiviral product development - conducting and submitting virology studies to the agency*. Center for Drug Evaluation and Research, Maryland, 2006.