
ALKALOIDS AS POTENTIAL ANTIVIRAL: A COMPREHENSIVE REVIEW

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ABSTRACT

Alkaloids are a diverse group of natural phytochemicals. These phytochemicals in plants provide them protection against pests, and herbivorous organisms and also control their development. Numerous of these alkaloids have a variety of biological effects, and some have even been developed into medications with different medicinal properties. This review aims to provide a broad overview of the numerous naturally occurring alkaloids. These alkaloid compounds have significant antiviral properties against several infectious viruses. These alkaloids repressed and targeted various important stages of viral infection at nontoxic doses while some of the alkaloids reported here also exhibited comparable inhibitory activities to commercially used drugs.

Keywords: Alkaloid antivirals, Antiviral agents, Antiviral phytochemicals, In vitro, Spread, Inhibition

1. INTRODUCTION

An alkaloid is a group of chemicals that is made from plants. It contains nitrogen in them. Many alkaloids also have potent pharmacologic effects. Some of the examples of alkaloids are cocaine, nicotine, strychnine, caffeine, morphine, pilocarpine, atropine, methamphetamine, mescaline, ephedrine, and tryptamine.

Plant species that possess above 0.001% alkaloids are referred to as alkaloids sources. As a result, plant groups such as *Solanaceae*, *Fabaceae*, *Asteraceae*, *Papaveraceae*, *Amaryllidaceae*, *Rutaceae*, *Apocynaceae*, and *Rubiaceae* have the potential to be utilized in pharmaceuticals [4].

Alkaloids can also be classified by their botanical source. For example, papaver plants belong to the *Papaveraceae* family and contain (opium) alkaloid. Cinchona plants belong to the *Rubiaceae* family, famous for cinchona alkaloids. Other botanical sources include alkaloids from *Rauvolfia*, *Catharanthus*, *Strychnos*, *Ergot*, and cactus plants [3]. Alkaloids such as theobromine and caffeine, found in coffee, cacao seeds, and tea leaves, are consumed worldwide by humans daily [3]. In humans, many alkaloids have potent biological effect.

In contrast to their edible use, alkaloids have a long history in human medicine and are often used to treat neurological problems [5], cancer [6], metabolic disorders [7], and infectious diseases [8]. Alkaloid phytochemicals may also help with antiviral treatment. Existing antiviral medications, on the other hand, have limited antiviral activity and variable toxicity toward patients, limiting their effectiveness. Phytochemicals such as alkaloids have a variety of biological and physiological functions and can be utilized as medications on their own [9]. Another possibility is that we can synthesize new drugs based on natural alkaloids.

Antiviral activities of alkaloids against multiple viruses

Alkaloids against influenza virus (IAV) Influenza A viruses are single-stranded, negative-sense RNA viruses in the Orthomyxoviridae family. Seasonal influenza A strains generate major morbidity and economic losses around the world each year.

In most cases, influenza A (IAV) infects tracheal cells and as well the bronchial epithelial cells, causing localised cellular damage and inducing an acute inflammatory response within the host [17]. Berberine alkaloid was studied in vitro for their effect on IAV infections. Berberine can suppress IAV type A/ PR/8/34 in the RAW-264.7 cells at over 1 μ M, while the IC₅₀ for berberine was 0.01 μ M.

This alkaloid also suppressed the growth of a separate strain of H1N1 IAV in vitro, with an IC₅₀ of 0.44 μ M. Berberine's mode of action implies that it affects virus protein maturation as well as its transportation, which in turn slows virus development. Berberine was also found to inhibit the production of tumour necrosis factor- α (TNF- α) and prostaglandin E₂ (PGE₂) in H1N1 (PR8) infected cells [18]. Berberine was also studied by other researchers both in vitro and in a mouse model for its antiviral properties.

In this study, berberine attenuated the cytopathic effect (CPE) of IAV in infected MDCK cells and lowered viral protein neuraminidase (NA) activity with an IC₅₀ of 0.025 g/L. Berberine significantly reduced mortality, increased

mean survival time, and decreased viral titers in IAV-infected mice. Berberine significantly reduced the degenerative alterations in the lungs of mice and showed a direct repressive effect on IAV infection in vitro and in vivo [19]. Another research team isolated Homonojirimycin (HNJ), an alkaloid from the *Commelina communis* L., and tested its antiviral efficacy on the IAV/PR/8/34 (H1N1) strain. HNJ had a substantial antiviral efficacy against IAV, with an inhibitory concentration EC₅₀ of 10.4 µg/mL [20]. These findings demonstrated that HNJ protected the mice against IAV infection and elicited efficient immune responses in the In vivo studies [21].

Alkaloids derived from marine micro-organisms were also reported to have notable antiviral effects on the IAV. Oxoglyantrypine alkaloid derived from the marine mangrove plant-fungal strain *Cladosporium* sp. Was noted to have a repressive effect against the IAV with an IC₅₀ of 85 µM; other alkaloids derived from this fungal strain were Norquinadoline A, Deoxynortryptoquivaline, Deoxytryptoquivaline, Tryptoquivaline had also a reported inhibitory effect with an IC₅₀ of 82, 87, 85, 89 µM, respectively, against IAV [22].

Synthetic alkaloids prepared by a single-stage synthesis procedure based on the quinazoline alkaloid are also reported to have potent antiviral activity against IAV. An alkaloid prepared from the (+)-camphoric acid which is a Quinazoline alkaloid's synthetic analogue, had significant antiviral activity against the IAVA/Puerto Rico/8/34 (H1N1) strain with an IC₅₀ of 17.9 ± 2.0 µM. Its CC₅₀ concentration was > 1117.9 µM towards the cells in which the virus was inoculated. Further, this compound also showed stronger inhibition of other IAV strains "A/Aichi/2/68 (H3N2) and A/mallard/Pennsylvania (H5N2)" with IC₅₀ values of 27 ± 4 and 21 ± 3 µM respectively [23].

Alkaloids against herpes simplex virus-I and II (HSV-I and II)

HSV is classified into two serovars: HSV-I and II. HSV-I infections are usually accompanied by moderate to severe symptoms such as blisters and swelling of cells in the mouth and eyes, and in certain situations can cause more serious conditions such as blindness, hearing loss, and fatal encephalitis. HSV-2 infections, on the other hand, can cause minor genital sores while significantly increasing the chance of contracting and transferring (HIV) and other opportunistic infections [24]. These alkaloids had a maximum non-toxic concentration (MNTC) of < 3.2 µg/mL towards the MDBK culture cells.

Other alkaloids used in this study also had a good repressive effect on the reduction of the CPE caused by HSV-I; scopolamine, allantoin, octopamine, synephrine, colchicine, and trigonelline alkaloids at a concentration of 1.6 µg/mL showed significant inhibitory activity on HSV-I [25] Manzamine-A, another alkaloid, was tested for its repressive effect on the HSV-1 EGFP virus in rabbit corneal cells (SIRC). It was found that Manzamine-A exhibited an effective inhibitory activity on the HSV-I replication process at a 1 µM concentration in rabbit corneal cells (SIRC).

The current anti-HSV-I medication acyclovir was also tested, and it exhibited similar inhibitory activity at 50 µM concentration according to RTPCR tests.

The IC₅₀ of Manzamine-A was reported to be 5.6 µM against this virus. These findings point to manzamines as a promising lead for reducing viral infection in corneal cells and preventing eye infections including keratitis induced by HSV-I [26]. Manzamine-A diminished the discharge of infectious viruses by a factor of 1011 in plaque assays. Manzamine A treatment reduced HSV-1 virion host shutoff function and also its ICP0 transcription process, according to RTPCR tests. The IC₅₀ of Manzamine-A was reported to be 5.6 µM against this virus.

These findings point to manzamines as a promising lead for reducing viral infection in corneal cells and preventing eye infections including keratitis induced by HSV-I [26]. These down-regulatory actions of Tetrandine on the anti-herpes immune response imply that this alkaloid can be used to control an early exuberant inflammatory response without compromising virus clearance from the eye.

This could be a significant step forward in the treatment of herpes ocular infections [27]. In comparison to untreated controls, the viral load inside the brain tissue of mice who received treatment 2 days before infection was reduced by a factor of 100. The IC₅₀ of 6-*O*-butanoyl castanospermine against HSV-I was 15 ± 4.8 µM when given before infection and 37 ± 5.5 µM when given after [28].

Alkaloids against dengue virus (DENV)

Dengue virus (DENV) is a flavivirus. *Aedes aegypti* and *Aedes albopictus* mosquitoes spread DENV when people are bitten by these mosquitoes resulting in dengue fever. DENV has an 11-kb positive-sense RNA-genome that encodes structural proteins such as capsid (C), envelope (E), and membrane precursor (prM), as well as several nonstructural proteins [34]. Dengue hemorrhagic fever and dengue shock syndrome are induced by four DENV serovars (DENV1-4), all of which are potentially deadly [35, 36]. Cherylline The inhibitory activity of the alkaloid anisomycin was tested on DENV-2 in another research in multiple cell lines. Anisomycin exerted dose-dependent inhibition on DENV-2. The addition of anisomycin alkaloid to the infected cell culture showed 99.9% inhibition of DENV-2 when

added at 8 h p.i, but when added later at 18 h p.i no inhibition was observed which indicates anisomycin. exerts its inhibitory activity in the initial stages of the viral infection. [37].

Viral internalization was noted to remain unaffected, but the viral protein synthesis of DENV-2 was strongly inhibited by anisomycin. Immunofluorescence showed that anisomycin inhibited the expression of the viral E-glycoprotein of DENV-2. Furthermore, qRT-PCR analysis showed that anisomycin alkaloid had a substantial inhibitory effect on DENV2 RNA synthesis at an inhibitory concentration of 200 nM [38].

Alkaloids against human cytomegalovirus (HCMV)

Cytomegalovirus is a member of the Herpesvirales genus of the Herpesviridae family of viruses and is a beta herpes virus. It has a ds-DNA genome with a size of roughly 230 kbp and is enveloped. HCMV is an opportunistic virus that infects a host which has a compromised immune system, including AIDS patients and children, causing a variety of ailments. [39]. In a LOPAC library screen against HCMV, emetine alkaloid had good antiviral activity as an HCMV inhibitor. Studies in human foreskin fibroblasts showed that emetine can effectively inhibit HCMV virus cell entrance but before DNA synthesis, resulting in lower viral protein expression. When emetine was used with ganciclovir, it produced synergistic viral inhibition. Emetine was well tolerated, had a long half-life, was distributed preferentially to tissues over plasma, and successfully inhibited the mouse-adapted CMV. [40].

Alkaloids against Zika virus (ZIKV)

Zika virus (ZIKV) is a Flavivirus with a genome size of 10.7 kb. ZIKV is an enveloped virus with positive-senses sRNA as genetic material. *Aedes aegypti* and *albopictus* mosquitoes are the carriers of this virus. In young newborns, it causes disorders like brain microcephaly. ZIKV outbreaks have been documented all over the world[41–47].

A study with *C. jagus* J. Thomps (Liliaceae) alkaloid extracts showed a significant antiviral effect on the Zika virus. Upon further studies on the alkaloids present in this plant, it was found that Cherylline was the most active alkaloid with repressive activity on ZIKV.

An experiment on ZIKVR2A which has the Renilla luciferase reporter gene showed that Cherylline at EC₅₀ of 20.3 μ M inhibited the ZIKVR2A replication with a selectivity index of > 12.3. Furthermore, the wild-type Zika strain H/PF/2013 and Zika virus MR766 instead of luciferase reporter infectious systems were used to certify the repressive properties of cherylline on the Zika virus. Cherylline treatment potently reduced the viral titer of the pathogenic H/PF/2013 strain 100-fold and MR766 by 88 percent. Plaque-assay with wild-type viruses revealed that cherylline inhibits ZIKV life cycles efficiently.

Moreover, the lycorine alkaloid used in this experiment also showed potent inhibition of the Zika virus with an EC₅₀ concentration of 0.41 μ M with an SI of 35.4 against this virus [48] Anisomycin alkaloid was evaluated for its efficacy against ZIKV in multiple cell lines and an AG129 mouse model. Dose-dependent inhibition of ZIKV by anisomycin was observed. Anisomycin addition of up to 8 or 5 h p.i. caused a 99.99 percent reduction in Zika virus production, according to a time-course investigation. [49].

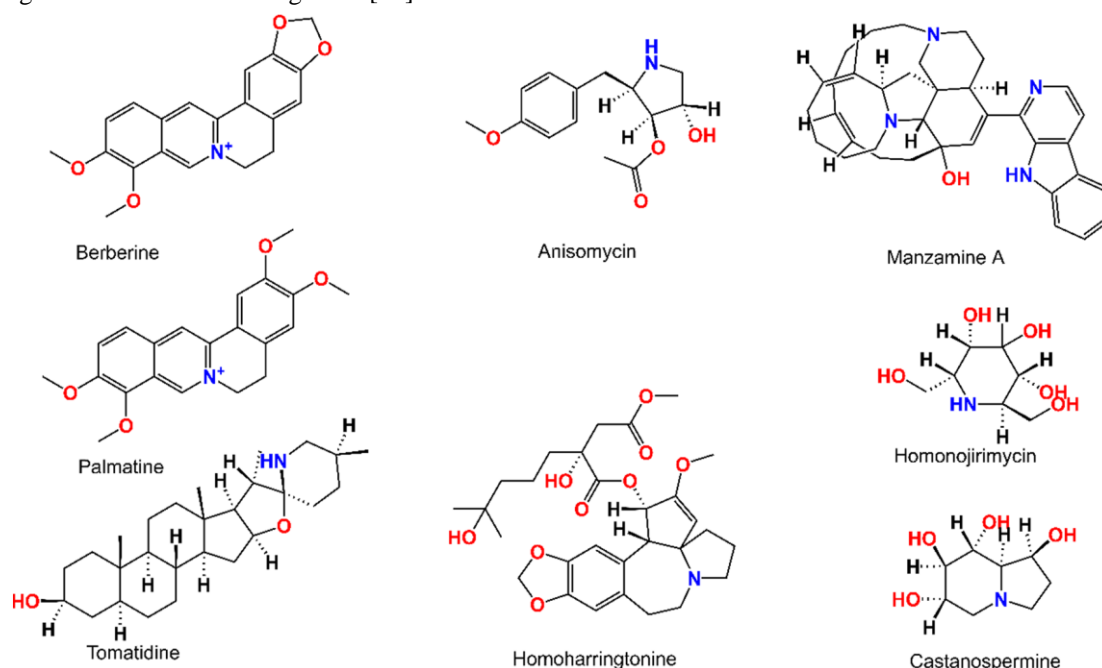


Fig. 1 Structures of some antiviral alkaloids

Alkaloids against SARS-CoV-2

Coronaviruses are also known as picornaviruses [50]. They carry a positive-sense RNA as genetic material and are commonly found in birds and other animals [51]. They cause a variety of disorders, the most prevalent of which are respiratory diseases including SARS-CoV-2 [52–55].

An in silico study involving molecular docking and MD simulation approaches identified several alkaloids which showed strong interactions with the SARS-CoV-2 Nsp-15 protein. Ajmalicine, arnottin, and piperine alkaloids were identified to be promising repressors of Nsp-15 of SARSCoV. The alkaloids in this computational investigation could potentially be promising leads against this virus by targeting replication. Nsp-15 is an important protein of SARS-CoV-2 and interfering with these alkaloid-based compounds may impede viral replication [56].

An in vitro screening of alkaloid compounds (mostly antimalarial inhibitors) against SARS-CoV-2 showed that alkaloids and alkaloid-based compounds have substantial repressive activity.

Chloroquine, hydroxy-chloroquine, and pyronaridine alkaloids-based drugs showed significant antiviral activities against SARS-CoV-2 having EC₅₀ concentrations of 2.1 μ M, 1.5 μ M, and 1.8 μ M respectively. Other compounds like desethylamodiaquine, mefloquine, and quinine also showed good repressive activities with EC₅₀ values of 0.52 μ M, 1.8 μ M, and 10.7 μ M. These results suggest that these compounds can be effective in inhibiting this rapidly mutating infectious virus [57].

Another bioinformatics study showed that two other alkaloids—sophaline D and thalimonine have been identified to have good binding energies towards the main-protease (MPRO) enzyme, suggesting that these alkaloids can be potential inhibitors of this virus [58].

An in vitro study in which the efficacy of certain antiviral drugs and alkaloids was evaluated against SARSCoV-2 in Vero E6 cells revealed that homoringtonine and emetine alkaloid can inhibit this virus with EC₅₀ concentrations of 2.55 μ M and 0.46 μ M respectively. Moreover, it was also noted that when emetine alkaloid and remdesivir are administered together, they inhibited the viral yield by 64.9 percent at doses of 0.195 μ M and 6.25 μ M. This study shows that the use of alkaloids in combinational therapy may result in better clinical outcomes [59].

Alkaloids against hepatitis B virus (HBV) and hepatitis C virus (HCV)

HBV is a major world health problem, and although a viable vaccine is available, it is still estimated that about 35 million people are continuously affected by this virus worldwide. HBV has a 3.2 kb relaxed circular-DNA genome. HCV affects about 3% of the world's populace and is the leading cause of chronic liver disease. HCV causes both acute and chronic hepatitis, with symptoms ranging from a brief illness to a serious, life-threatening condition [60, 64].

Alkaloids isolated from *Z. nitidum* (Roxb.) DC (Rutaceae) roots were evaluated for their anti-HBV activities in HepG2 2.2.15 cells. The cultured cells were first transfected with HBV DNA to produce HBV viral particles. It was reported that the tested alkaloids had potent inhibitory activities against HBV.

Alkaloids against human immunodeficiency virus (HIV)

HIV is a Lentivirus that causes AIDS, a condition in which the immune system gradually weakens, allowing lethal opportunistic infections and malignancies to grow and exacerbate the situation. It is an enclosed RNA virus with a single-stranded, positive-sense genome. Its viral RNA-genome is transformed to double-strand DNA in the infected host cell by reverse transcriptase once it enters the cell [65].

Several alkaloids have been reported to have significant anti-HIV activity. In an in vitro investigation, the bromoindole alkaloid dragmacidin-D obtained from the marine sponge *Halicortex* was tested against HIV. Dragmacidin-D was able to strongly repress the syncytia formation by HIV in the culture cells. These alkaloids also exhibited no cytotoxicity on the culture cells and were able to inhibit this [66].

Alkaloids against middle east respiratory syndrome coronavirus (MERS-CoV) and human coronavirus OC43 (HCoV-OC43)

MERS-CoV and HCoV-OC43 are enveloped coronaviruses (CoVs) with positive-sense ssRNA as genetic material. These viruses are zoonotic and jump from animals to human hosts.

They cause multiple respiratory infections. The most common subtype of HCoV, HCoV-OC43, is responsible for over 30% of respiratory infections and can cause re-infection for the rest of one's life [67]. An in vitro investigation found three alkaloids with anti-HCoV-OC43 potential in MRC-5 cells: tetrandrine (TET), fangchinoline (FAN), and cepharanthine (CEP).

In MRC-5 cell culture, treatment with these three alkaloids reduced the cytopathic effect of HCoV-OC43.

Alkaloids against bovine viral diarrhea virus (BVDV)

BVDV is a Pestivirus. It can be found in the majority of countries throughout the world [68], causing mucosal diseases, respiratory and GI-tract infections, and reproductive complications in cattle [69]. Alkaloid 6-*O*-butanoyl castanospermine (celgosivir), a derivative of castanospermine, was evaluated against the BVDV in different in vitro studies. Celgosivir exerted strong anti-BVDV activities and inhibited the release and mRNA production of this virus. Its inhibitory activity was measured in both plaque reduction and CPE assays. [70]. Celgosivir repressed BVDV growth at an IC₅₀ of 16 μ M and 47 μ M respectively. Mechanism of action studies revealed that celgosivir repressed the viral RNA and also reduced the quantity of the viral infectious units released from the infected cells. This alkaloid also repressed BVDV E2 viral protein expression levels. [71]. Moreover, the combination of this alkaloid separately each with Ribavirin and interferon- α showed a synergistic relationship in the inhibition of BVDV in plaque reduction assays [72].

Alkaloids against murine leukemia virus (MLV)

MLVs are Gammaretroviruses that cause malignancy in their murine (mouse) hosts. Other vertebrates may be infected by some MLVs. MLVs have a positive-sense ssRNA genome that replicates by reverse transcription via a DNA intermediary [73].

6-*O*-Butanoylcastanospermine (B-CAST) is a castanospermine alkaloid that was evaluated for its anti-MLV activities in chronically infected C3H10TY1/2 (clone 8) cells. This analog of castanospermine was more potent than the other analogues prepared in this study. [74].

As B-CAST is also a glucosidase inhibitor, this enzyme causes the misfolding of viral proteins and strongly represses the activity of the MLV in plaque reduction assay. MLV was inhibited by CAST-B with an IC₅₀ of 0.05 μ g/mL. [75].

Comparison of some antiviral alkaloids and standard drugs along with a brief overview of their toxicological effects and therapeutic uses

The alkaloids discussed here showed significant antiviral activities against different viruses, sometimes more potent than standard treatments. The dosage required for alkaloids to inhibit these viruses compared to the positive control drugs was also lower than the standard drugs. Confirming that alkaloids can be more potent in their repressive activities against different viruses.

Against HBV, different alkaloids demonstrated more potent activities than the standard drug lamivudine, with lower inhibitory concentrations and higher inhibitory rates. [76].

Harringtonine also showed better antiviral activities than the antiviral drugs Rottlerin and Ribavirin, and at much lower inhibitory concentrations. Similarly, Berberine was noted to have higher inhibitory activity with an IC₅₀ = 0.025 g/L compared to the Ribavirin IC₅₀ = 0.051 g/L concentration, capsaicin alkaloid also showed lower IC₅₀ values against the Para-influenza virus

compared to the Oseltamivir which is a standard antiviral drug, this similar trend of higher activity at lower IC₅₀ concentrations were also seen with a few other antiviral alkaloids against different viral targets. [77].

2. CONCLUSIONS

The alkaloid compounds and their synthetic analogues reviewed here exhibit robust antiviral activities against a wide range of infectious and deadly DNA/RNA viruses.

Some of these compounds have IC₅₀ concentrations lower than 5 μ M and may prevent viral infections by more than 90 percent. Some alkaloids have higher antiviral activities than some standard antiviral medications, at lower concentrations.

These reviewed alkaloids and their synthetic analogues were safe and nontoxic based on their cytotoxic concentration values and other assays that we reported here.

Alkaloid compounds that have not yet been evaluated in vivo could be investigated further to determine their efficaciousness against these viral infections.

We also found that the use of these alkaloids with other antiviral drugs in combination therapy can synergistically improve the efficacy of these standard medications and enhance antiviral activity to cure infections. However, before these alkaloids and their derivatives can be used as antivirals, a better understanding of their pharmacological properties and clinical outcomes is required.

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3. REFERENCES

- [1] Rosales PF, Bordin GS, Gower AE, Moura S. Indole alkaloids: 2012 until now, highlighting the new chemical structures and biological activities. *Fitoterapia*. 2020;143: 104558. [https:// doi. org/ 10. 1016/j. fitote. 2020. 104558](https://doi.org/10.1016/j.fitote.2020.104558).
- [2] Kurek J. Introductory Chapter: Alkaloids—their importance in nature and for human life. In: *Alkaloids—their importance in nature and human life*. London: InTech; 2019.
- [3] Dey P, Kundu A, Kumar A, Gupta M, Lee BM, Bhakta T, Dash S, Kim HS. Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). In: *Recent advances in natural products analysis*. Amsterdam: Elsevier; 2020. p. 505–67.
- [4] Yang L, Stockigt J. Trends for diverse production strategies of plant medicinal alkaloids. *Nat Prod Rep*. 2010;27:1469–79.
- [5] Howell G, Butler J, DeShazo RD, Farley JM, Liu HL, Nanayakkara NPD, Yates A, Yi GB, Rockhold RW. Cardiodepressant and neurologic actions of *Solenopsis invicta* (imported fire ant) venom alkaloids. *Ann Allergy Asthma Immunol*. 2005;94:380–6. [https:// doi. org/ 10. 1016/ S1081-1206\(10\) 60991-X](https://doi.org/10.1016/S1081-1206(10)60991-X).
- [6] Tao H, Zuo L, Xu H, Li C, Qiao G, Guo M, Lin X. Alkaloids as anticancer agents: a review of Chinese patents in recent 5 years. *Recent Pat Anticancer Drug Discov*. 2020;15:2–13. [https:// doi. org/ 10. 2174/ 15748 92815 66620 01311 20618](https://doi.org/10.2174/1574892815666200131120618).
- [7] Ajebli M, Khan H, Eddouks M. Natural alkaloids and diabetes mellitus: a review. *Endocr Metab Immune Disord Drug Targets*. 2020;21:111–30. [https:// doi. org/ 10. 2174/ 18715 30320 66620 08211 24817](https://doi.org/10.2174/1871530320666200821124817).
- [8] Ti H, Zhuang Z, Yu Q, Wang S. Progress of plant medicine derived extracts and alkaloids on modulating viral infections and inflammation. *Drug Des Dev Ther*. 2021;15:1385–408. [https:// doi. org/ 10. 2147/ DDDT. S2991 20](https://doi.org/10.2147/DDDT.S299120).
- [9] Patel A, Vanecha R, Patel J, Patel D, Shah U, Bambharoliya T. Development of natural bioactive alkaloids: anticancer perspective. *Mini-Rev Med Chem*. 2021;22:200–12. [https:// doi. org/ 10. 2174/ 13895 57521 66621 07121 11331](https://doi.org/10.2174/1389557521666210712111331).
- [10] Qing Z-X, Yang P, Tang Q, Cheng P, Liu X-B, Zheng Y, Liu Y-S, Zeng J-G. Isoquinoline alkaloids and their antiviral, antibacterial, and antifungal activities and structure–activity relationship. *Curr Org Chem*. 2017. [https:// doi. org/ 10. 2174/ 13852 72821 66617 02071 14214](https://doi.org/10.2174/1385272821666170207114214).
- [11] Zhang M-Z, Chen Q, Yang G-F. A review on recent developments of indole-containing antiviral agents. *Eur J Med Chem*. 2015;89:421–41. [https:// doi. org/ 10. 1016/j. ejmech. 2014. 10. 065](https://doi.org/10.1016/j.ejmech.2014.10.065).
- [12] Moradi M-T, Karimi A, Lorigooini Z. Alkaloids as the natural anti-influenza virus agents: a systematic review. *Toxin Rev*. 2018;37:11–8. <https://doi.org/10.1080/15569543.2017.1323338>.
- [13] Naithani R, Huma L, Holland L, Shukla D, McCormick D, Mehta R, Moriarty R. Antiviral activity of phytochemicals: a comprehensive review. *Mini-Rev Med Chem*. 2008;8:1106–33. [https:// doi. org/ 10. 2174/ 13895 57087 85909 943](https://doi.org/10.2174/138955708785909943).
- [14] Badshah SL, Ullah A, Syed S. The role of zinc-finger antiviral proteins in immunity against viruses. *Mol Genet Microbiol Virol*. 2020;35:78–84. [https:// doi. org/ 10. 3103/ S0891 41682 00200 20](https://doi.org/10.3103/S0891416820020020).
- [15] Fikatas A, Vervaeke P, Meyen E, Llor N, Ordeix S, Boonen I, Bletsa M, Kafetzopoulou LE, Lemey P, Amat M, et al. A novel series of indole alkaloid derivatives inhibit dengue and Zika virus infection by interference with the viral replication complex. *Antimicrob Agents Chemother*. 2021. [https:// doi. org/ 10. 1128/ AAC. 02349-20](https://doi.org/10.1128/AAC.02349-20).
- [16] Kaur P, Thiruchelvan M, Lee RCH, Chen H, Chen KC, Ng ML, Chu JH. Inhibition of Chikungunya virus replication by harringtonine, a novel antiviral that suppresses viral protein expression. *Antimicrob Agents Chemother*. 2013;57:155–67. [https:// doi. org/ 10. 1128/ AAC. 01467-12](https://doi.org/10.1128/AAC.01467-12).
- [17] Feng Y, Le X, Wu S. Pathogenesis and pathological changes of avian influenza in human. In: *Avian influenza in human*. Singapore: Springer Singapore; 2021. p. 29–40.
- [18] Cecil CE, Davis JM, Cech NB, Laster SM. Inhibition of H1N1 influenza A virus growth and induction of inflammatory mediators by the isoquinoline alkaloid berberine and extracts of goldenseal (*Hydrastis canadensis*). *Int Immunopharmacol*. 2011;11:1706–14. [https:// doi. org/ 10. 1016/j. intimp. 2011. 06. 002](https://doi.org/10.1016/j.intimp.2011.06.002).
- [19] Wu Y, Li JQ, Kim YJ, Wu J, Wang Q, Hao Y. In vivo and in vitro antiviral effects of berberine on influenza virus. *Chin J Integr Med*. 2011;17:444–52. [https:// doi. org/ 10. 1007/ s11655-011-0640-3](https://doi.org/10.1007/s11655-011-0640-3).
- [20] Zhang GB, Zhang B, Zhang XX, Bing FH. Homonojirimycin, an alkaloid from dayflower inhibits the growth of influenza A virus in vitro. *Acta Virol*. 2013;57:85–6.

- [21] Zhang GB, Tian LQ, Li YM, Liao YF, Li J, Bing FH. Protective effect of homonojirimycin from *Commelina communis* (dayflower) on influenza virus infection in mice. *Phytomedicine*. 2013;20:964–8. <https://doi.org/10.1016/j.phymed.2013.04.009>.
- [22] Peng J, Lin T, Wang W, Xin Z, Zhu T, Gu Q, Li D. Antiviral alkaloids produced by the mangrove-derived fungus *Cladosporium* sp. PJX-41. *J Nat Prod*. 2013;76:1133–40. <https://doi.org/10.1021/np400200k>.
- [23] Chernyshov VV, Yarovaya OI, Fadeev DS, Gatilov YV, Esaulkova YL, Muryleva AS, Sinogubova KO, Zarubaev VV, Salakhutdinov NF. Singlestage synthesis of heterocyclic alkaloid-like compounds from (+)-camphoric acid and their antiviral activity. *Mol Divers*. 2020;24:61–7. <https://doi.org/10.1007/s11030-019-09932-9>.
- [24] Madavaraju K, Koganti R, Volety I, Yadavalli T, Shukla D. Herpes simplex virus cell entry mechanisms: an update. *Front Cell Infect Microbiol*. 2021. <https://doi.org/10.3389/fcimb.2020.617578>.
- [25] Ozcelik B, Kartal M, Orhan I. Cytotoxicity, antiviral and antimicrobial activities of alkaloids, flavonoids, and phenolic acids. *Pharm Biol*. 2011;49:396–402. <https://doi.org/10.3109/13880209.2010.519390>.
- [26] Palem JR, Bedadala GR, El Sayed KA, Hsia SCV. Manzanine A as a novel inhibitor of herpes simplex virus type-1 replication in cultured corneal cells. *Planta Med*. 2011;77:46–51. <https://doi.org/10.1055/s-0030-1250093>.
- [27] Hu S, Dutt J, Zhao T, Foster CS. Tetrandrine potently inhibits herpes simplex virus type-1-induced keratitis in BALB/c mice. *Ocul Immunol Inflamm*. 1997;5:173–80. <https://doi.org/10.3109/09273949709116892>.
- [28] Bridges CG, Ahmed SP, Kang MS, Nash RJ, Porter EA, Tims AS. The effect of oral treatment with 6-*O*-butanoyl castanospermine (MDL 28,574) in the murine zosteriform model of HSV-1 infection. *Glycobiology*. 1995;5:249–53. <https://doi.org/10.1093/glycob/5.2.249>.
- [29] Amorim IS, Lach G, Gkogkas CG. The role of the eukaryotic translation initiation factor 4E (EIF4E) in neuropsychiatric disorders. *Front Genet*. 2018. <https://doi.org/10.3389/fgene.2018.00561>.
- [30] Dong HJ, Wang ZH, Meng W, Li CC, Hu YX, Zhou L, Wang XJ. The natural compound homoharringtonine presents broad antiviral activity in vitro and in vivo. *Viruses*. 2018. <https://doi.org/10.3390/v10110601>.
- [31] Tepaske MR, Gloer JB, Wicklow DT, Dowd PF. Tubingensin A: an antiviral carbazole alkaloid from the sclerotia of *Aspergillus tubingensis*. *J Org Chem*. 1989;54:4743–6. <https://doi.org/10.1021/jo00281a010>.
- [32] Chin LW, Cheng YW, Lin SS, Lai YY, Lin LY, Chou MY, Chou MC, Yang CC. Anti-herpes simplex virus effects of berberine from *Coptidis Rhizoma*, a major component of a Chinese herbal medicine, Ching-Wei-San. *Arch Virol*. 2010;155:1933–41. <https://doi.org/10.1007/s00705-010-0779-9>.
- [33] Wu ZN, Chen NH, Tang Q, Chen S, Zhan ZC, Zhang YB, Wang GC, Li YL, Ye WC. β -Carboline alkaloids from the seeds of *Peganum harmala* and their Anti-HSV-2 virus activities. *Org Lett*. 2020;22:7310–4. <https://doi.org/10.1021/acs.orglett.0c02650>.
- [34] Dwivedi VD, Tripathi IP, Tripathi RC, Bharadwaj S, Mishra SK. Genomics, proteomics and evolution of dengue virus. *Brief Funct Genom*. 2017;16:217–27. <https://doi.org/10.1093/bfpg/eltw040>.
- [35] Hsiung GD, Chang PW. Parainfluenza viral infection. In: *Handbook of zoonoses, second edition, section B: viral zoonoses*. Bosa Roca: CRC Press; 2017. p. 409–21. ISBN 978-1-35-144180-3.
- [36] Ramos-Castaneda J, Barreto dos Santos F, Martinez-Vega R, Galvao de Araujo JM, Joint G, Sarti E. Dengue in Latin America: systematic review of molecular epidemiological trends. *PLoS Negl Trop Dis*. 2017. <https://doi.org/10.1371/journal.pntd.0005224>.
- [37] Ka S, Merindol N, Sow AA, Singh A, Landelouci K, Plourde MB, Pepin G, Masi M, Di Lecce R, Evidente A, et al. Amaryllidaceae alkaloid cherylline inhibits the replication of dengue and zika viruses. *Antimicrob Agents Chemother*. 2021. <https://doi.org/10.1128/AAC.00398-21>.
- [38] Quintana VM, Selisko B, Brunetti JE, Eydoux C, Guillemot JC, Canard B, Damonte EB, Julander JG, Castilla V. Antiviral activity of the natural alkaloid anisomycin against dengue and zika viruses. *Antiviral Res*. 2020;176:104749. <https://doi.org/10.1016/j.antiviral.2020.104749>.
- [39] Whitby K, Pierson TC, Geiss B, Lane K, Engle M, Zhou Y, Doms RW, Diamond MS. Castanospermine, a potent inhibitor of dengue virus infection in vitro and in vivo. *J Virol*. 2005;79:8698–706. <https://doi.org/10.1128/jvi.79.14.8698-8706.2005>.
- [40] Diosa-Toro M, Troost B, van de Pol D, Heberle AM, Urcuqui-Inchima S, Thedieck K, Smit JM. Tomatidine, a novel antiviral compound toward dengue virus. *Antivir Res*. 2019;161:90–9. <https://doi.org/10.1016/j.antiviral.2018.11.011>.
- [41] Monsalve-Escudero LM, Loaiza-Cano V, Zapata-Cardona MI, Quintero-Gil DC, Hernandez-Mira E, Pajaro-Gonzalez Y, Oliveros-Diaz AF, Diaz-Castillo F, Quinones W, Robledo S, et al. The antiviral and virucidal

- activities of voacangine and structural analogs extracted from *Tabernaemontana cymosa* depend on the dengue virus strain. Plants. 2021. <https://doi.org/10.3390/plants10071280>.
- [42] Li Z, Wang J, Cheng X, Hu H, Guo C, Huang J, Chen Z, Lu J. The worldwide seroprevalence of DENV, CHIKV and ZIKV infection: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2021;15: e0009337. <https://doi.org/10.1371/journal.pntd.0009337>.
- [43] Varghese FS, Kaukinen P, Glasker S, Bepalov M, Hanski L, Wennerberg K, Kummerer BM, Ahola T. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antivir Res. 2016;126:117–24. <https://doi.org/10.1016/j.antiviral.2015.12.012>.
- [44] Troost B, Mulder LM, Diosa-Toro M, van de Pol D, Rodenhuis-Zybert IA, Smit JM. Tomatidine, a natural steroidal alkaloid shows antiviral activity towards chikungunya virus in vitro. Sci Rep. 2020. <https://doi.org/10.1038/s41598-020-63397-7>.
- [45] Farman A, Lal Badshah S, Khan K, Ahmad N, Naeem A. Ebola, the negative stranded RNA virus. In: Some RNA viruses. London: IntechOpen; 2021.
- [46] Ahmad N, Farman A, Badshah SL, ur Rahman A, Ur Rashid H, Khan K. Molecular modeling, simulation and docking study of Ebola virus glycoprotein. J Mol Graph Model. 2017;72:266–71. <https://doi.org/10.1016/j.jmgm.2016.12.010>.
- [47] Yang S, Xu M, Lee EM, Gorshkov K, Shiryayev SA, He S, Sun W, Cheng Y-S, Hu X, Tharappel AM, et al. Emetine inhibits zika and Ebola virus infections through two molecular mechanisms: inhibiting viral replication and decreasing viral entry. Cell Discov. 2018;4:31. <https://doi.org/10.1038/s41421-018-0034-1>.
- [48] Nag A, Chowdhury RR. Piperine, an alkaloid of black pepper seeds can effectively inhibit the antiviral enzymes of dengue and Ebola viruses, an in silico molecular docking study. VirusDisease. 2020;31:308–15. <https://doi.org/10.1007/s13337-020-00619-6>.
- [49] Mukhopadhyay R, Roy S, Venkatadri R, Su YP, Ye W, Barnaeva E, Mathews Griner L, Southall N, Hu X, Wang AQ, et al. Efficacy and mechanism of action of low dose emetine against human cytomegalovirus. PLoS Pathog. 2016. <https://doi.org/10.1371/journal.ppat.1005717>.
- [50] Hayashi K, Minoda K, Nagaoka Y, Hayashi T, Uesato S. Antiviral activity of berberine and related compounds against human cytomegalovirus. Bioorg Med Chem Lett. 2007;17:1562–4. <https://doi.org/10.1016/j.bmcl.2006.12.085>.
- [51] Teixeira SR, Elias J, Coutinho CM, Zotin MCZ, Yamamoto AY, De Moura Negrini SFB, Mussi-Pinhata MM. Cranial us in infants exposed to zika virus: the Natzig cohort. Radiology. 2021;300:690–8. <https://doi.org/10.1148/radiol.2021204150>.
- [52] Badshah SL, Mabkhot YN, Ahmad N, Syed S, Naeem A. Zika virus, microcephaly and its possible global spread. In: Current topics in zika. London: InTech; 2018.
- [53] Noreen, Ali R, Badshah SL, Faheem M, Abbasi SW, Ullah R, Bari A, Jamal SB, Mahmood HM, Haider A, et al. Identification of potential inhibitors of zika virus NS5 RNA-dependent RNA polymerase through virtual screening and molecular dynamic simulations. Saudi Pharm J. 2020;28:1580–91. <https://doi.org/10.1016/j.jsps.2020.10.005>.
- [54] Ahmad N, Badshah SL, Junaid M, Ur Rehman A, Muhammad A, Khan K. Structural insights into the zika virus NS1 protein inhibition using a computational approach. J Biomol Struct Dyn. 2021;39:3004–11. <https://doi.org/10.1080/07391102.2020.1759453>.
- [55] Badshah SL, Naeem A, Mabkhot Y. New high resolution crystal structure of NS2B-NS3 protease of zika virus. Viruses. 2017;9:7. <https://doi.org/10.3390/v9010007>.
- [56] Ahmad N, Rehman AU, Badshah SL, Ullah A, Mohammad A, Khan K. Molecular dynamics simulation of zika virus NS5 RNA dependent RNA polymerase with selected novel non nucleoside inhibitors. J Mol Struct. 2020. <https://doi.org/10.1016/j.molstruc.2019.127428>.
- [57] Badshah SL, Ahmad N, Rehman AU, Khan K, Ullah A, Alsayari A, Muhsinah AB, Mabkhot YN. Molecular docking and simulation of zika virus NS3 helicase. BMC Chem. 2019;13:67. <https://doi.org/10.1186/s13065-019-0582-y>.
- [58] Guo YW, Liu XJ, Yuan J, Li HJ, Mahmud T, Hong MJ, Yu JC, Lan WJ. l-Tryptophan induces a marine-derived *Fusarium* sp. to produce indole alkaloids with activity against the zika virus. J Nat Prod. 2020;83:3372–80. <https://doi.org/10.1021/acs.jnatprod.0c00717>.
- [59] Ho YJ, Lu JW, Huang YL, Lai ZZ. Palmatine inhibits zika virus infection by disrupting virus binding, entry, and stability. Biochem Biophys Res Commun. 2019;518:732–8. <https://doi.org/10.1016/j.bbrc.2019.08.120>.

- [60] Faisal S, Badshah SL, Kubra B, Sharaf M, Emwas AH, Jaremko, M, Abdalla M. Identification and Inhibition of the Druggable Allosteric Site of SARS-CoV-2 NSP10/NSP16 Methyltransferase through Computational Approaches. *Molecules* 2022;27. <https://doi.org/10.3390/molecules27165241>.
- [61] Kubra B, Badshah SL, Faisal S, Sharaf M, Emwas AH, Jaremko M, Abdalla M. Inhibition of the Predicted Allosteric Site of the SARS-CoV-2 Main Protease through Flavonoids. *J Biomol Struct Dyn.* 2022;0:1–18. <https://doi.org/10.1080/07391102.2022.2140201>.
- [62] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395:507–13. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7).
- [63] Badshah SL, Ullah A, Badshah SH, Ahmad I. Spread of novel coronavirus by returning pilgrims from Iran to Pakistan. *J Travel Med.* 2020. <https://doi.org/10.1093/jtm/taaa044>.
- [64] Badshah SL, Ullah A. Spread of coronavirus disease-19 among devotees during religious congregations. *Ann Thorac Med.* 2020;15:105–6. https://doi.org/10.4103/atm.ATM_162_20.
- [65] Faisal S, Lal Badshah S, Kubra B, Sharaf M, Emwas AH, Jaremko M, Abdalla M. Computational study of SARS-Cov-2 RNA dependent RNA polymerase allosteric site inhibition. *Molecules.* 2022;27:223.
- [66] Kumar S, Kashyap P, Chowdhury S, Kumar S, Panwar A, Kumar A. Identification of phytochemicals as potential therapeutic agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication. *Phytomedicine.* 2021;85: 153317. <https://doi.org/10.1016/j.phymed.2020.153317>.
- [67] Gendrot M, Andreani J, Boxberger M, Jardot P, Fonta I, Le Bideau M, Duflot I, Mosnier J, Rolland C, Bogreau H, et al. Antimalarial drugs inhibit the replication of SARS-CoV-2: an in vitro evaluation. *Travel Med Infect Dis.* 2020;37: 101873. <https://doi.org/10.1016/j.tmaid.2020.101873>.
- [68] Mamkulathil Devasia R, Altaf M, Fahad Alrefaei A, Manoharadas S Enhanced production of camptothecin by immobilized callus of *Ophiorrhiza mungos* and a bioinformatic insight into its potential antiviral effect against SARS-CoV-2. *J King Saud Univ Sci.* 2021;33: 101344. <https://doi.org/10.1016/j.jksus.2021.101344>.
- [69] Faisal S, Badshah SL, Kubra B, Sharaf M, Emwas AH, Jaremko M, Abdalla M. Identification and inhibition of the druggable allosteric site of SARS-CoV-2 NSP10/NSP16 methyltransferase through computational approaches. *Molecules.* 2022. <https://doi.org/10.3390/molecules27165241>.
- [70] Alfaro M, Alfaro I, Angel C. Identification of potential inhibitors of SARSCoV- 2 papain-like protease from tropane alkaloids from *Schizanthus porrigens*: a molecular docking study. *Chem Phys Lett.* 2020;761: 138068. <https://doi.org/10.1016/j.cplett.2020.138068>.
- [71] Garg S, Roy A. In silico analysis of selected alkaloids against main protease (Mpro) of SARS-CoV-2. *Chem Biol Interact.* 2020. <https://doi.org/10.1016/j.cbi.2020.109309>.
- [72] Choy K-T, Wong AY-L, Kaewpreedee P, Sia SF, Chen D, Hui KPY, Chu DKW, Chan MCW, Cheung PP-H, Huang X, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res.* 2020;178: 104786. <https://doi.org/10.1016/j.antiviral.2020.104786>.
- [73] Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci.* 2006;3:47–52.
- [74] Shahid F, Noreen, Ali R, Badshah SL, Jamal SB, Ullah R, Bari A, Mahmood HM, Sohaib M, Ansari SA. Identification of potential HCV inhibitors based on the interaction of epigallocatechin-3-gallate with viral envelope proteins. *Molecules.* 2021. <https://doi.org/10.3390/molecules26051257>.
- [75] Yang G, Chen D. Alkaloids from the roots of *Zanthoxylum nitidum* and their antiviral and antifungal effects. *Chem Biodivers.* 2008;5:1718–22. <https://doi.org/10.1002/cbdv.200890160>.
- [76] Zhang YB, Zhang XL, Chen NH, Wu ZN, Ye WC, Li YL, Wang GC. Four matrine-based alkaloids with antiviral activities against HBV from the seeds of *Sophora alopecuroides*. *Org Lett.* 2017;19:424–7. <https://doi.org/10.1021/acs.orglett.6b03685>.
- [77] Zhang YB, Yang L, Luo D, Chen NH, Wu ZN, Ye WC, Li YL, Wang GC. Sophalines E-I, five quinolizidine-based alkaloids with antiviral activities against the hepatitis B virus from the seeds of *Sophora alopecuroides*. *Org Lett.* 2018;20:5942–6. <https://doi.org/10.1021/acs.orglett.8b02637>.