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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 pharmalogic 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 μM, while the IC50 for berberine was 0.01 μM.

This alkaloid also suppressed the growth of a separate strain of H1N1 IAV in vitro, with an IC50 of 0.44 μM. 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-a (TNF-a) 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

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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

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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 to lerated, 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 μM 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 μM 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].

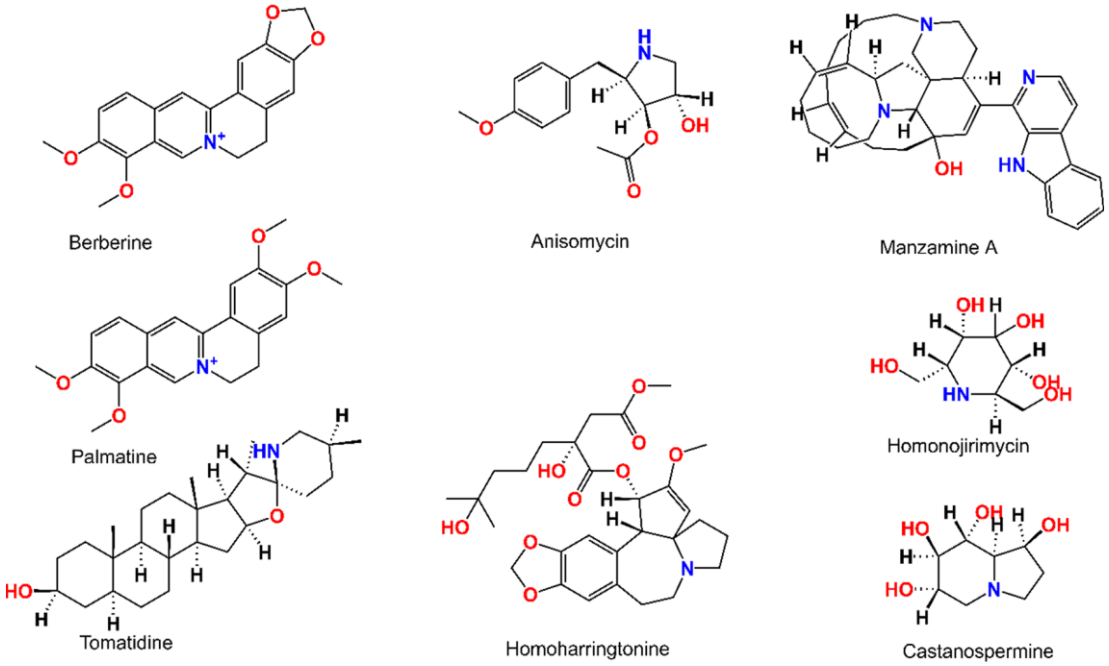

Fig. 1 Structures of some antiviral alkaloids

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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, aranotin, 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 μM, 1.5 μM, and 1.8 μM respectively. Other compounds like desethylamodiaquine, mefloquine, and quinine also showed good repressive activities with EC50 values of 0.52 μM, 1.8 μM, and 10.7 μM. 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 homorringtonine and emetine alkaloid can inhibit this virus with EC50 concentrations of 2.55 μM and 0.46 μM 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 μM and 6.25 μM. 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.

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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 μM and 47 μM 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 C3HlOTY1/2 (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 μg/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 μM 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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