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Plant-derived alkaloids as anti-viral agents

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Abstract

Humans are prone to many viral infections, most of them not causing diseases, and some will do. The new pandemic situation in global development and comfort to travel have highlighted their protection as a crucial problem in people's health and safety even though significant advancements are being made in the making of vaccines and drugs. The provenance of viral mutants generally threatens immunisation and effective anti-viral treatments. The discovery of novel anti-viral drugs is, therefore of paramount importance. The secondary metabolites from the plants with pharmacological activities are regarded as an exemplary repository for this diagnosis. An extensive study of phytochemicals and their mechanisms of action against the viruses might help in controlling harmful viruses. Many phytochemical entities, including terpenes, flavonoids, polyphenol, and phenolic compounds, have been studied for their anti-viral activity. Particularly in alkaloids, cutting edge study is making way to uncover innovative therapeutic strategies. Most of the alkaloids are being used as anti-viral agents, act against few prominent viral pathogens such as coronavirus (CoV), human immune deficiency virus (HIV), systemic acute respiratory syndrome (SARS) and respiratory virus (RSV). In this review, we intend to summarise the medicinal use of plant-derived alkaloids utilised to cure viral diseases in the past four decades.

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INTRODUCTION

Viruses are known for their deadly contagious diseases including human immunodeficiency virus (HIV), hepatitis B and C (HBV and HCV), coronaviruses (Middle Eastern respiratory syndrome MERS; extreme acute respiratory syndrome (SARS)), influenza (seasonal, pandemic), smallpox, viral haemorrhagic fevers (Ebola), dengue and chikungunya, etc. These viral diseases created severe social and economic effects all over the world. Most viruses seem to have RNA genomes and subsequently are capable of fast mutation and exhibit tolerance to the commercially available anti-viral drugs. The threat of resistance poses demanding challenges in clinical management to provide a novel drug to these viral infections. Nevertheless, ever from the emergence of acyclovir, a nucleoside analogue discovered in 1960, the area of anti-viral research has shown a stable flow in developments. Later, more than 60 anti-viral drugs of varied chemical classes were approved by the Food and Drug Administration, for the management of HIV, herpes, hepatitis B and C, influenza A and B viruses and there are several drugs at various phases of clinical trials. Despite the progress in the anti-viral agent development and their manage-

ment, there seems to be an urgent need for novel drugs that act through multiple mechanisms to tackle the viral drug resistance. Viruses are continuously developed and have adapted new ways of resisting drugs. However, these justify making the search for anti-viral therapy not clear because it is difficult to understand specific biochemical properties of viruses that could be suitable for targeted attacks without endangering the host cells. Most of the anti-viral drugs have been shown to be useful in in-vitro studies and less effective in clinical trials with animal models. This evidence proves how complicated is the action of an anti-viral drug on the virus-infected cells. The host cells naturally produce inflammatory compounds to suppress the infection, and these compounds interfere with the anti-viral effect of the drug. Hence, it is considered essential if these anti-viral agents possess both anti-inflammatory and anti-viral activity for effective treatment.

Plants are an important source of a large variety of bioactive compounds such as alkaloids, terpenoids, flavonoids, oils, phenolic derivatives, lignans and glycosides which exhibit pharmacological and toxicological properties. Plant-based medicines are a useful tool in the discovery of drugs from traditional practice. Only 25 % of phyto based drugs are currently available. Ethnopharmacological studies pose to be beneficial to discover promising drugs for the treatment of various diseases. *Allium sativum, Daucus maritimus, Helichrysum aureonitens, Pterocaulon sphacelatum* and *Quillaja Saponaria*, are shown to possess a comprehensive range of anti-viral activity. An extensive study of phytochemicals and their mechanisms of action against these viruses might help in controlling harmful viruses far more beneficially. Especially in alkaloids, cutting edge study is making way to uncover innovative therapeutic strategies. Plant alkaloids represent a highly diverse group of chemical compounds classified into different classes such as pyrrolizidines (known to be toxic), pyrrolidines, quinolizidines, indoles, tropanes, piperidine, purines, imidazole and isoquinolines (Thawabteh *et al.*, 2019). Literature survey implies that plant-derived alkaloids exhibit anti-nociceptive activity, anti-psychotic, anti-cholinergic, opioid analgesic,anti-malarial,anti-microbial,anti-oxidant,anti-viral,antifungal,analgesic, anti-diuretic, cerebellum stimulator, demulcent, hepatoprotective, antispasmodic, anti-inflammatory, anti-neoplastic, sympathomimetic activity and anti-hypertensive activities. This review intends to summarise the anti-viral potential of plant-derived alkaloids.

Anti-Viral Mechanism of Action of Alkaloids

Herbal and purified components provide a good source for the synthesis of novel anti-viral drugs. Characterisation of anti-viral mechanisms from such natural sources has highlighted the interaction with the cycle of viral life, such as viral entry, replication, assembly, and release, in addition to virus-host addressing specific interactions. Some of the commercially available anti-viral drugs are moroxydine, ganciclovir, valganciclovir, valaciclovir etc. which are used to control the viral replications. Due to their lower efficiency and cytotoxic effect to the host cell, their usage is being limited. Around 40% of the currently available drugs are derived from plants that block viral entry directly, inhibiting viral RNA replication (mostly targeting reverse transcriptase) and protein expression, viral helicase inhibition and competitors for SARS-CoV3CL protease. Some of these are peptide mimetics, and some up-regulate the expression of cytokines (IL-2, IFN-gamma and TNF-alpha) in different lymphoid tissues promote immune modulation by triggering phagocytic function and humoral immunity, increase antibody production and secretion of cytokine and inhibiting direct viral replication by stimulating immune defence function.

Leurocristine, periformyline, perivine and vincaleucoblastine are obtained from *Catharanthus roseus* and lanceus Pich (Apocycaceae). These compounds showed inhibitory activity against mengovirus extracellular virucidal, poliovirus and vaccinia, influenza virus. Cephalotaxus alkaloids were isolated from *Cephalotaxus drupacea*. Homoharringtonine and omacetaxine (HHT2) contain tetracyclic alkaloid backbone and act as potential tyrosine kinase inhibitor against SARS CoV and MERS-CoV infection. *Melissa officinalis* produces cytotoxic quinoline alkaloids, *Camptotheca acuminae* root and bark contain camptothecin compound potentially inhibiting DNA topoisomerase I. Some of the alkaloids fraction from *Narcissu*s are capable of viral modulation. A highly active anti-viral alkaloid cryptopleurine isolated from *Boehmeria cylindrical* (Urticaceae), potentially inhibits HSV-1. Roja and Heble (1995) reported the castanospermine alkaloid isolated from the seeds of *Castanospermum australe* against HIV. Wang and Ng (2001) described the gossypol and the *Corydalis yanhusuo* alkaloids, which are essential for the inhibition of HIV. Most of the compounds mainly targeted the reverse transcriptase activity of the virus and viral entry to the host cell.

Isoquinoline alkaloids such as lycorine, lycoricidine, narciclasine and cis-dihydronarciclasine, from

Amaryllidaceae (*Narcissus poeticus*) inhibit the activity of flavivirus, bunyaviruses and poliomyelitis 1mg/ml concentration at invitro. The alkaloids homonojirimycin and 1 deoxy manojirimycin were isolated from *Omphalea Diandra* (Euphorbiaceae). Homonojirimycin is an inhibitor of enzyme α-glucosidase I and I. Deoxymanojirimycin is interpreting the glycoprocessing of mannosidase. Castanospermine and australine, the alkaloids found in *Castanospermum austral*, *A. Cunn* and *C. Fraser* (Leguminosae) seeds, decrease HIV's potential to harm cultured cells and could treat AIDS. *Tripterygium hypoglaucum* and *Tripterygium wilfordii* (Celastraceae), alkaloids of sesquiterpene are reported to have anti-HIV activity.

Corydine and norisoboldine, isolated from the ethanol extract of *Croton Echinocereus* leaves inhibit the reverse transcriptase activity of HIV-1. Some of the other alkaloids including scopolamine (tropane type), vincamine (indole type), colchicine (tropolone type), allantoin (imidazolidine type), octopamine and synephrine (exocyclic amine type) have anti-viral activity against parainfluenza type 3 virus. A steroidal alkaloid cortistatin A and its analogue didehydro-cortistatin A isolated from Marine sponge *Corticium simplex* and are used as an antiretroviral agents to inhibit HIV1 and HIV2 replication by suppressing of Tat dependent HIV transcription at nanomolar level (Mousseau *et al.*, 2012).

Based on a recent study conducted, it was found that compounds present in commonly used organics could possibility be coronavirus protein inhibitors. Around 27 natural products, many of them remarkably familiar, used as spices and condiments or present in common vegetables were explored to view their binding capability to the active sites of COVID-19 proteases, 6LU7 and 6Y2E, critical for viral replication. The results showed that 15 were found to be effective in binding the viral protease and hence are likely to hinder viral replication. Besides the prevalent compounds, curcumin and coriandrin, that are used almost every day in the Indian cuisine, ursolic acid from apple peels, hederagenin in cucurbits, oleanolic acid in olive oil, rosemary and thyme or mint family plants (stagione), in red pepper (apigenin) to name a few are very promising. They could serve as potential candidates for further research (Sampangi-Ramaiah *et al.*, 2020).

A study was conducted to discover compounds for rapid and efficient clinical use, targeting COVID-19 virus main protease (M^{pro}) responsible for replication and transcription. Nearly 10,000 drug candidates were analysed by combining structure-based virtual assessment with high-power screening. Six compounds such as ebselen, disulfiram, Tideglusib, Carmofur, Shikonin, PX-12 which may inhibit M^{pro}, IC_{50} value ranging from 0.67-21.4μM. Cinanserin served as a robust enzymatic inhibitor, suggesting that it might have multi-drug targets in preventing viral infection. Ebselen and N3 showed most potent anti-viral activity, suggested for CoV treatment. The Cepharanthine, ergoloid and hypericin are also found to have high affinity with S protein. A report from Thailand showed that the combinations of influenza viral drugs and anti-HIV drugs, namely, oseltamivir, lopinavir, and ritonavir controlled COVID-19 within 48 hrs. Molecular docking studies of these three drugs agaist SARS CoV2 protease confirm the binding. (Muralidharan *et al.*, 2020).

Tropane type alkaloids

Scopolamine (L-hyoscine) which vary from atropine by incorporating a bridge of oxygen converts tropine into a base skeleton known as scopine. The action mechanism of anticholinergic drugs is perhaps the specific antagonism of acetylcholine at the muscarinic receptors, and these medications are categorised as antimuscarinic or muscarinic antagonists. Scopolamine and morphine are widely used for anaesthesia premedication for cardiac surgery: atropine is a synthetically produced source of extracted endogenous alkaloid from the herb *Atropa Belladonna*. Atropine acts as a definite, active antagonist of cholinergic muscarinic receptors and thereby reduces symptoms of parasympathetic stimulation. It has demonstrated prominent anti-viral activity against both HSV-1 and PI-3 assays (Rajput, 2014).

Tropolone type alkaloids

Colchicine is obtained from the *Colchicum autumnale* seeds and corms. Colchicine is a familiar antifibrotic and anti-inflammatory agent. In vitro studies imply that colchicine blocks the metaphase during mitosis and inhibits the synthesis of DNA, due to its anti-inflammatory properties, colchicine can be used in the treatment of acute gout and Hepatitis B virus (Floreani *et al.*, 1998).

Quinolizidine alkaloids

It has two fused six-membered rings that shared nitrogen, mostly found in the genus Lupinus. Matrine-type alkaloids have distinct tetracycloquinolizidine structures from the quinolizidine group, and more than ten types of matrine-type alkaloids are reported in Sophora species plants. Matrine, sophocarpine, sophoridine and their

N-oxides are the essential components of oxymatrine, oxysophocarpine and oxysophoridine. Pan *et al.* (2015) screened three new matrine-type alkaloids, [(+)-5a-hydroxyoxysophocarpine, 12b-hydroxyoxysophocarpine, and (+)-5a-hydroxylemannine. They have shown that compounds (+) -12a-hydroxysophocarpine, (-)12b-hydroxysophocarpine, and (+) -sophoramine are most powerful inhibitors against H3N2, with 40-60 mM IC_{50} values and above 3.1 therapeutic indexes. Their findings showed that the presence of an "a, b carbon double bond" in the compounds studied could make a positive contribution to anti-H3N2 activity (Pan *et al.*, 2015). Dang *et al.* (2014) reported inhibitory effect of pure alkaloids, isolated from the Sophora species, including aloperine, synthetic derivatives of aloperine and matrine, oxymatrine against a mouse-adapted influenza virus A/Puerto Rico/8/34 (H1N1) in vitro. Aloperine showed anti-influenza activity (Dang *et al.*, 2014). Sparteines exhibit activity against influenza A virus but the activity was twofold less potent than aloperine. The results showed that the small substitution of N12 in aloperine increased the efficacy significantly in comparison to aloperine (NH) and more significant N replacement demonstrated the most effective action against influenza A virus.

Pyridine alkaloids

Pyridine alkaloids contain the unsaturated heterocyclic ring. Trigonelline has major anti-viral as well as anti-inflammatory properties and is commonly found in seeds of Fenugreek (*Trigonella foenum graecum*). Capsaicin is a unique exocyclic amine type alkaloid found primarily in the fruit of the Capsicum genus and is what gives its spicy flavour. While capsaicin was reported to have no apparent anti-herpes effect, cis capsaicin (civamide) showed notable anti-viral activity of genital HSV (Bourne *et al.*, 1999).

Homonojirimycin (HNJ) is a leading compound which is an active agent used to treat alpha-galactosidase A deficiency leading to glycosphingolipid lysosomal storage induced Fabry disease. In a study by Zhang *et al.* (2013b), HNJ was isolated from total alkaloids of *Commelina communis* L., and the anti-viral activity against influenza A/PR/8/34 virus (H1N1) was measured. The findings revealed that HNJ had robust anti-viral activity against influenza virus A. Zhang *et al.* (2013a) investigated the effects of HNJ on protection against influenza virus infection in mice. Based on the analysis, HNJ was instrumental in increasing survival rate, and prolonging mean survival time and the virus yields in the lungs on Days 4 and 6 post-infection.

Imidazole alkaloids

Allantoin belongs to imidazole alkaloids derived from L-histidine. Allantoin, a new metabolite of the purine catabolism, frequently accumulates in plants under a stressed condition. Allantoin along with its cyclic metabolite allantoate are termed ureides and are found in the tropical legumes. They are used to store symbiotically fixed nitrogen as well as its transport through the xylem. The aqueous extract of comfrey root containing allantoin can be used in the treatment of skin irritation and has an anti-viral activity of herpes simplex 1 and parainfluenza type 3 (Özçelik *et al.*, 2011).

Quinoline and Isoquinoline alkaloids

Iwasa *et al.* (2001) studied the antimalarial, anti-HIV activities of 26 isoquinoline alkaloids, in which the compounds 1-ethyl-6,7-dihydroxy-2methylisoquinolin-2-ium and 6,7-dimethoxy-3,4-dihydro-isoquinoline-2-ium possess anti-HIV activity. The compounds 6,7,-bis(benzyloxy)-1,2-dimethyl isoquinoline-2-ium, 6,7-bis(benzyloxy)-1-ethyl-2-methylisoquinoline-2-ium,1-(1-(3,4-dimethoxy phenyl)ethyl)-6,7-dimethoxy-2-methylisoquinoline-2-ium and 1-ethyl-6,7-dihydroxy-2-methylisoquinoline-2-ium have antimalarial effects (recently it has been suggested that coronavirus can be treated antimalarial drug) ; compounds 2-benzyl-6,7-bis (benzyloxy)-1-propyl-3,4-dihydro isoquinoline-2-ium and 6,7,-bis(benzyloxy)-1,2-dimethyl isoquinoline-2-ium have cytotoxic and antimicrobial effects to the cells. The michellamines D and F naphthyl isoquinoline alkaloids, extracted from *Liana ancistrocladus korupensis* have HIV inhibitory activity.

Thalimonine, an alkaloid was extracted from *Thalictrum simplex* L plant in Mongolia in 1991 by Velcheva *et al.* (1992). Isoquinoline alkaloids are massively produced from the genus Thalictrum (Ranunculaceae). It was shown that (-)-Thalimonine permanently impeded proliferation of herpes simplex virus type 1 in cell culture systems, increased the multiplication of T-cell mytogens and repressed the functioning of B-cell mytogens in vitro. Serkedjieva and Velcheva (2003) explored impact of the pavine alkaloid (–) -thalimonin (3,4-methylene-deoxy-2,8,9-trimethoxypavinan) and (–) -thalimonin N-oxide on influenza virus reproduction A/Germany/27, str. Weybridge (H7N7) and A/Germany/34, str Rostock (H7N1) in vitro. Amaryllidaceae alkaloids constitute a broad group (more than 300 alkaloids) of isoquinoline-related alkaloids that occur in plants of this family. Experimental studies have proved that the alka-

loids, lycorine, hippeastrine, hemanthamine and 11-hydroxy vittatine showed anti-viral activities against influenza virus.

Indole alkaloids

Among the top 200 best selling drugs in the US retail sales in 2012, seven are indole containing commercial drugs. Indole derivatives offer enormous prospects for discovering new medicines with various modes of action. It has the special characteristics of imitating the peptide structure and reversibly binding to enzymes. It was reported that three known alkaloids (151-153) and three novel indole alkaloids (148-150) extracted from fungus *Cladosporium* sp. PJX-41 usually derived from mangrove showed their anti-viral property on influenza virus A (H1N1), and among them, significant activities were obtained from compound 150 as anti HINI drug. Seventeen new indole alkaloids and analogues of four known alkaloids were isolated from aqueous extract of the root of *Isatis indigotica* and arvelexin from *Brassica rapa*. Compounds 128-130 exhibited anti-viral activity against the influenza virus A/ Hanfang/359(H3N2). Epigoitrin alkaloid from roots of *Isatis indigotica* reduces influenza virus infection by mitochondrial signalling mechanism. A new study from Luo *et al.* (2019) reported about epigoitrin mechanism of inhibition in various ways against influenza virus by disturbing the viral replication, reducing the mitofusin 2 protein expression, and elevating the production of interferon-inducible transmembrane and INFβ. In *Isatis indigotica*, the enantiomers of epigoitrin and goitrin were efficiently separated by SFCMS within 6 minutes. It served as a biomarker to identify and authenticate the herb of Bei Ban Lan Gen in the market. The other Nan Ban Lan Gen does not have giotrin in their root extract.

Rinehart *et al.* (1984) isolated Eudistomin K and L, which contain unique oxathiazepine ring (C, E, F, K and L) from Caribbean tunicate *E.olivaceum*, which inhibits HSV-1 significantly. Seventeen *eudistomins* (A-Q) were divided into four groups(group1 contains β-carboline, including eudistomins D, J, N and O; group2 contains pyrrolyl-β-carbolineseudistomins A, B and M, group3 contains pyrrolinyl-β-carbolines, eudistomins G, H, P and Q and group4 contains tetrahydro-β-carbolines with an oxathiazepine ring of eudistomins C, E, F, K and L). The substituents Br and OH in β carboline ring significantly affect the anti-viral activity. Eudistomins C and E potentially inhibit RNA viruses such as Coxsachie A-21 and euine rhinovirus and DNA virus-like HSV1, HSV2 and Vaccinia virus. Lake *et al.* (1989) isolated eudistomins from Ascidian *Ritterella sigillinoides* from New Zealand, which showed inhibitory activity against Herpes simplex virus type 1 and polio vaccine type 1 viruses. Tsujii *et al.* (1988) isolated Toposentin and bromotopsentin from *S.ruetzleri* containing Bis (indolyl) imidazole structures, showing anti-viral activities against coronavirus A-59, HSV-1, Vesicular stomatitis virus(VSV) collected from the Bahamas. Some reverse transcriptase inhibiting compounds fascaplysin and homofascaplysin were isolated from *Fascaplysin opis reticulate*. The anti-HIV-1 activity of unprecedented polycyclic skeletons of three novel indole alkaloids trigonoliimines A-C (141-143) isolated from leaf extract of *Trigonostemin lii*. Compound 141 and 142 were tested with Zidovudine for syncytium formation infectivity assay as a positive control in microtiter assay. Compound 143, namely, Trigonoliimine A exhibits modest anti-HIV-1 activity.

Bisindole alkaloids

A bis Indole derived Dragmacidin D alkaloid obtained from *Spongosorites* sp showed inhibitory activity against HSV-1 (EC_{50}= 95.8μM) and HIV-1(EC_{50}=0.91μM). Anti-HIV compounds coscinamide A, B and C were obtained from the organic extract of *Coscinoderma* sp. from New Guinea. Hodgkinsine got from *C.milnei*, shows anti-viral activity against herpes simplex virus type 1 and vesicular stomatitis viruses. Borowski *et al.* (2003) reported tetrabromo benzotriazole (TBBt) and 5, 6-dichloro-1-(β-D-ribofuranosyl) benzotriazole (DRBt) as potential inhibitors of Hepatitis C virus replication. Meng *et al.* (2017) isolated indole alkaloids sulfonic acids such as Isatibisindosulfonicacid A3-O-β-D-glucopyranoside, Isatibisindosulfonic acid B, Isatindosulfonic acid A3-O-β-D-glucopyranoside, Isatinodosulfonic acid B, Isatindosulfonic acid C, Isatindosulfonic acid D, Isatindosulfonic acid E, Isatindosulfonic acid F from the aqueous root extract of *Isatis indidotica* (Cruciferae) showing anti-viral activity against Coxsackie Virus B3 and influenza virus A and H3N2. Liu *et al.* (2015) isolated the two enantiomers with novel bis indolyl acetamide skeleton, namely, 1a and 1b which showed promising anti-viral activity of coxsackievirus B3 CVB3, herpes simplex virus-1 and HIV1, by inhibiting protein tyrosine phosphatase and glucuronidase production. Some of the marine natural products belong to the category of bisindole alkaloids that exert development of novel potential drug leads. The unusual arrangement of 2-ketoenamide functionality in coscinamides (135-137) shows partial cycloprotein inhibitory activity of HIV in the NCI assay. The compounds 138-140 are chondriamides belonging to indolicenamides and show the

inhibitory activity of HSV II with 1μM of IC_{50} value. Due to this unique structure and functionality, bis and tri indole alkaloid leads are promising anti-viral drugs in the development of a new drug.

Indolizidine and quinolizidine alkaloids

Castanospermine is an indolizidine alkaloid initially extracted from the seeds of *Castanospermum austral*. It is a potent inhibitor of alpha-glucosidase enzymes and has in vitro anti-viral properties in mouse models. Aza sugars demonstrate anti-viral effects by restricting the development of incorrect viral envelope proteins folding by inhibiting the N-glycans synthesis. An analysis of anti-viral therapies based on endoplasmic reticulum α-glucosidases illustrated the use of multiple sugar inhibitors like celgosivir and castanospermine. The review was based on diseases such as HIV-1, Hep-C and dengue virus. It has been recorded based on the effects of Celgosivir on Herpes simplex virus, HCV, bovine viral diarrhoea virus (BVDV), and HIV-1. It was found to be non-toxic compared to castanospermine, as castanospermine had side effects such as inhibition of intestinal sucrases and osmotic diarrhoea recorded at the time of clinical trials. Many reviews conclude its prospective usage in anti-HCV treatment (Michael, 2008).

Castanospermine and minor products 6-epi-castanospermine, 6-7-di-epi-castanospermine, 7-deoxy -6-castanospermine were isolated from the seeds of *Castanospermum austral*e. The potent glucosidase inhibitors disturb the incorrect folding of viral envelope protein during N-glycans maturation. In 1999, the castanospermine existing naturally as saccharide was identified in LCMS analysis of the same plant's crude extract. Castanospermine and its derivative celgosivirare are currently used for the treatment of Hepatitis C virus, HIV-1, and dengue virus (Michael, 2016).

Studies prove that Castonospermine has potential in inhibiting dengue virus, a mosquito-borne disease. In vitro studies have shown that Castonospermine could block the secretion and infection in four serotypes of the dengue virus in baby hamster kidney-21 cells. Around 90% of the mice injected with the castanospermine survived the virus after treatment with a daily dose of 50mg/kg as higher doses cause gastrointestinal toxicity. Diseases like yellow fever and Nile Flavivirus have shown fewer effective results to the castanospermine. A pharmacokinetic analysis verified that celgosivir converted relatively quickly into castanospermine in vivo. Clinical trials were run based on the anti-viral activity of hepatitis C virus (HCV), and investigations had shown that castanospermine could interrupt the growth of infectious bovine viral diarrhoea virus (BVDV), an animal model for HCV, in a dose-dependent manner. Celgosivir was later determined to be almost with the same intensity but far more capable of inhibiting BVDV than the parent alkaloid. In contrast, dual combinations of either the alkaloid or its ester with interferon-a or ribavirin anti-HCV drugs may improve their anti-viral efficacy. The triple combination of celgosivir with pegylated interferon alpha-2-band ribavirin in hepatitis C patients which failed to react to the interferon and ribavirin alone produced positive reductions at after 12 weeks of treatment in average serum HCV RNA levels, thus creating a phase II confirmation on this approach of study (Durantel, 2000).

Goud *et al.* (2003) isolated two bisquinolizidine alkaloids and petrosins from Indian marine sponge *Petrosia similes* which inhibits the reverse transcriptase of HIV-1 replication. Molecular docking studies of Indolinepyrrolidine, indonylpiperazine and indole and indonylindolinone derivatives showed potent inhibition of the RNA dependent DNA polymerase reverse transcription function of HIV at the micromolar range.

Phenanthroindolizidine alkaloids

Phenanthroindolizidine alkaloids and its derivatives act as antagonists for coronavirus transmissible gastroenteritis virus (TGEV), SARS corona infection, asthma, anaphylaxis, and other inflammatory-related problems. Tylophorine, tylocrebrine and tylophorinine are phenanthroindolizidine alkaloids mostly present in the species of *Cynanchum, Tylophora, pergularia* and *Asclepiadaceae*. Traditional Indian medical system used six leaves of *Tylophora indica* per day to cure dermatitis and bronchial asthma. Tylophora plants and derived alkaloids are potent inhibitors for viral infection with EC_{50}=340nM. Wang *et al.* (2010) demonstrated anti-viral activities of the synthetic derivatives, racemic tylophorine, autofine, deoxythylophorinine and S+ / R- pure tylophorine alkaloids against plant tobacco mosaic virus at 100μg/ml.

Benzyl isoquinoline alkaloids

Actinophnine isolated from *Actinodaphne hookeri* has an effect of herpes simplex virus. Biopterin separated from *Crithida fasciculate* has significant inhibitory activity. Buchapine from *Etodiarox burghiana* showed anti-viral activity of HIV-1 reverse transcriptase. Camptothecin and its isomer 10-methoxy camptothecin isolated from *Ophior rhizamungos* leaves were active against the herpes virus, and the methoxy analogue is eight times more productive than camptothecin. Canavanin from *Carnava liaensiformis* L belonging to Leguminosae

family is found to inhibit semliki forest virus and influenza virus. Caffeine, obtained from *Theobroma cacao* L (Sterculiaceae) and Coffea sp. (Rubiaceae) were found to suppress the growth of poliovirus, herpes, influenza, vaccinia, echonovoruscoxsackie virus. Carnitine isolated from bulbs of *Zephyranthe scarinata* (Amaryllidaceae) has anti-viral activity. Columbamine, palmatine and berberine, are also considered to be potent against HIV. Chelidonine *Chelidonium majus* L. belonging to Papaveraceae has a significant response on influenza virus and herpes virus. The 5-hydorxynoracronycine, 11-hydroxynoracronycine acridone alkaloids and acrimarine derived from *Citrus alata* (Tanaka) plants were effective against the Epsteine Barr virus (Tabarrini *et al.*, 2006).

Pyrrolizidine alkaloids

Pyrrolizidine alkaloids are mostly present in plants including Leguminosae, Concvolvulaceae, Boraginaceae, Compositae, Poaceae and Orchidaceae. This alkaloid contains five-membered aza rings derived from lysine and ornithine. Hydromethanolic extract of propolis (plant exudates) of *Scaptotrigona postica* has an anti-viral activity by reduction of 98 per cent of herpes simplex virus replication. It interferes with virion envelope protein formation in the vera cells. Hydromethanolic extract has the primary compounds of pyrrolizidine alkaloids such as 7-(3-methoxy-2-methylbutyryl)-9-echimidinylretronecine and vicenin2 flavones. The family of lamellarin α20-sulfate is a group of coumarin nucleus containing DOPA-(2-amino, 3-(3',4'-dihydroxypheyl) propionic acid)-derived from pyrrole alkaloid which exhibits the inhibition of integrase protein in viral replicated cells. Australine (3-hydroxymethyl)-1,2,7-trihydroxy pyrrolizidine) isolated from *Castanospermum australe*, inhibits the alpha-glucosidase enzyme competitively on the process of glycoprotein synthesis. Heliotrine and 7-angeloyl heliotrine were major pyrrolizidine alkaloids isolated from *Heliotropicum subulatum*, and these reduce the activity of coxsackie, poliomyelitis, vesicular stomatitis, and measles in the IC_{50} range 100 -500 μg/ml (Singh *et al.*, 2002).

CONCLUSION

This review seeks to present essential insights into the development of anti-viral drugs with novel alkaloids, commercialised and experimental alkaloids. In the past four decades, researches have been summarising sources and biological activities of reported alkaloids. Since the 1990s substantial research has been dedicated to anti-viral drug development. A variety of natural, semi-synthetic, their analogues and synthetic alkaloids have been identified as potential anti-viral agents that are active to encounter a wide range of respiratory viruses. Alkaloids possess anti-viral activities at various stages of replication of the virus, such as the inhibition of production of envelope proteins but the steps they inhibit in the viral replication cycle are not clear. But there are certain alkaloids which inhibit certain enzymes such as reverse transcriptase, which is required for the viral replication and translation. Numerous groups of derelict alkaloids could be further enriched by their effectiveness, target selectively or attaining optimum drug response and exposure properties. Because of all these impressive outcomes and the potential candidates with anti-viral activity, alkaloids can be used further in the clinic. Besides, this report will undoubtedly serve us with a contemporary frontier of anti-viral drug research as well as provides a profound description of the importance of such agents are in infections and how potent these natural therapeutic agents.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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