

Iraqi Medicinal Plants with Antiviral Effect- A Review

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Abstract: Several phytochemicals exhibited high level of antiviral activity[1-5]. Medicinal plant possessed antiviral activity via many mechanisms included inhibition of viral replication, inhibition of the assembly of intracellular infectious virus particles, inhibition of viral infectivity, inhibition of RNA polymerase, DNA polymerase, viral neuraminidase, protease, reverse transcriptase and viral protein expression and many other mechanisms[6-12]. The current review discuss the medicinal plants with antiviral activity with their mechanisms of action.

Keywords: Medicinal plant, pharmacology, antiviral

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I. INTRODUCTION

Human viral infections are significant health problem worldwide. Natural compounds are an important source for the discovery and the development of novel antiviral drugs because of their availability and expected low side effects. Several phytochemicals exhibited high level of antiviral activity[1-5]. Medicinal plant possessed antiviral activity via many mechanisms included inhibition of viral replication, inhibition of the assembly of intracellular infectious virus particles, inhibition of viral infectivity, inhibition of RNA polymerase, DNA polymerase, viral neuraminidase, protease, reverse transcriptase and viral protein expression and many other mechanisms[6-12]. The current review was designed to highlight the medicinal plants with antiviral activity with their mechanisms of action.

II. MEDICINAL PLANTS WITH ANTIVIRAL EFFECTS

Adiantum capillus-veneris

Ethanol extract from the rhizome of *Adiantum capillus-veneris* exerted *in vitro* antiviral activity against vesicular stomatitis virus [13-14].

Agrimonia eupatoria

Ethanol extract of *Agrimonia eupatoria* was reported to be active against Columbia SK virus [15-16]. The inhibitory activity of an aqueous extract of the aerial parts (stems and leaves) of *Agrimonia eupatoria* against HBsAg release against hepatitis B virus (HBV) was investigated. The extract prepared at 60 degrees C was found to have the greatest effect. The inhibitory activity of *Agrimonia eupatoria* extracts on HBsAg secretion varied over the growing season and was the highest at mid-July. This inhibitory activity suggest that *Agrimonia eupatoria* contain potential antiviral activity against HBV [17-18].

Ailanthus altissima

Three neolignan glycosides extracted from the ethanolic extract of the root bark of *Ailanthus altissima* (7,9,9'-trihydroxy-3,3',5'-trimethoxy-8-O-4'-neolignan-4-O-β-D-glucopyranoside, sonchifolignan B and citrusin B) exhibited moderate *in vitro* inhibitory effect on tobacco mosaic virus replication with IC₅₀ values 0.30, 0.35 and 0.26 mmol/l, respectively [19]. When the ethanol extract of *Ailanthus altissima* was partitioned with systemic solvent and isolated on silica gel column chromatography in a bioassay-guided fractionation, two active fractions(Fr3 and Fr6) were obtained from chloroform fraction of ethanolic extract. Fr3 and Fr6 were further chromatographed on a silica gel column, eluted with CHCl₃ /MeOH solvent system to isolate four active constituents(C1-C4). The bioassay showed that antiviral effect of these constituents was not as strong as that of the ethanol extract, and the inhibition of them on systemic infection by tobacco mosaic virus was low [20]. The methanolic stem bark extract of *Ailanthus altissima* showed potent anti-HIV activity (74.9 ± 4.4%) at a concentration of 100 microg/ml (applied to a syncytia formation inhibition assay, which is based on the interaction between the HIV-1 envelope glycoprotein gp120/41 and the cellular membrane protein CD4 of T lymphocytes) [21]. Ailantanol E, ailantanol F, and ailantanol G, and related compounds isolated from *Ailanthus altissima* grown in Taiwan, were evaluated for its antitumor promoting effects against Epstein-Barr virus early

antigen activation introduced by 12-O-tetradecanoylphorbol-13-acetate in Raji cells. Quassinoids were found to show potent activity [22]. The anti-viral activity of *A. altissima* crude extract was investigated against Rice stripe virus (RSV) in rice suspension cells, determined by inhibiting RSV crude protein transcript and expression using real-time reverse transcription polymerase chain reaction and Western blotting. The *A. altissima* crude extract showed a strong inhibitory activity against RSV at a medium effective concentration of 0.55 µg/ml. No significant cytotoxicity in rice suspension cells was shown. *A. altissima* crude extract would likely be a valuable antiviral agent for control of RSV [23-24].

Allium sativum

The antiviral activity of hydro-distilled essential oils of *Allium sativum* (bulbs) against (HSV1) was tested by using cytopathicity (CPE) assay. African green monkey kidney (Vero) cell line (virus infected cells) was incubated with different levels of essential oils. The antiviral activities were increased with increasing essential oils concentrations. The additions of 200, 500 and 1000 µg/ml of garlic essential oils increased antiviral activity percentages to 37.66, 72.94 and 93.81%, respectively [25]. Nagai reported that garlic extract has preventive effect against infection with influenza virus [26]. Garlic extracts have been shown to have *in vitro* and *in vivo* antiviral activity against the human cytomegalovirus, influenza B, herpes simplex virus type 1, herpes simplex virus type 2, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2. Ajoene was found to block the integrin-dependent processes in a human immunodeficiency virus-infected cell system [27-29]. The antiviral effect of diallyl thiosulfinate (allicin), allyl methyl thiosulfinate, methyl allyl thiosulfinate, ajoene, alliin, deoxyalliin, diallyl disulfide, and diallyl trisulfide was determined against selected viruses including, herpes simplex virus type 1, herpes simplex virus type 2, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2. The order for virucidal activity generally was: ajoene > allicin > allyl methyl thiosulfinate > methyl allyl thiosulfinate. Ajoene was found in oil-macerates of garlic but not in fresh garlic extracts. No activity was found for the garlic polar fraction, alliin, deoxyalliin, diallyl disulfide, or diallyl trisulfide. Fresh garlic extract, in which thiosulfates appeared to be the active components, was virucidal to each virus tested. The predominant thiosulfate in fresh garlic extract was allicin. Lack of reduction in yields of infectious virus indicated undetectable levels of intracellular antiviral activity for either allicin or fresh garlic extract [30]. The *in vitro* anti-viral activity of garlic extract (GE) on human cytomegalovirus (HCMV) was evaluated by tissue culture, plaque reduction and early antigen assay. A dose dependent inhibitory effect of GE was evident when GE was applied simultaneously with HCMV. But the effect was stronger when the monolayers were pretreated with GE. In addition, the anti-viral effect of GE persisted long in infected cells after its being removed from the culture medium. The strongest anti-viral effect of GE was demonstrated when it was applied continuously [31]. *Allium sativum* extraction has been reported having anti-HCMV efficacy by a mechanism associated with suppression of ie gene transcription. The effect of allitridin (diallyl trisulfide, a compound from *A. sativum* extraction) on the replication of HCMV and the expression of viral immediate-early genes was investigated. In HCMV plaque-reduction assay, allitridin appeared a dose-dependent inhibitory ability with EC₅₀ value of 4.2 microg/ml. Time-of-addition and time-of-removal studies showed that allitridin inhibited HCMV replication in earlier period of viral cycle before viral DNA synthesis. Both immediate early gene (ie1) transcription and IEA (IE(1)72 and IE(2)86) expression was suppressed by allitridin. In addition, allitridin appeared stronger inhibition on IE (2)86 than on IE (1)72. Decrease of viral DNA load in infected cells was also detected under allitridin treatment, probably due to an indirect consequence of the reduction in ie gene transcription [32]. Allitridin ((diallyl trisulfide, a compound from *A. sativum* extraction) can inhibit HCMV, IEA expression *in vitro* remarkably which is probably one of the major mechanisms of Allitridin anti-HCMV activity because IEAs are the very important regulatory factors for the expression of all HCMV genes. The cytotoxicity of Allitridin was evaluated through MTT colorimetry and cell morphology. HCMV IEA levels were quantitatively detected by Flow Cytometry. Allitridin was given before (pretreated for 24 h), during, or after viral inoculation in which serial doses (maximum tolerant concentration, MTC for human embryo lung cells, HEL) of Allitridin was used to treat HCMV infected HLE cells for different durations (24, 48, 72, 96 h) after viral infection. The MTC of Allitridin was 9.60 mg x L⁻¹. Allitridin remarkably inhibited the expression of HCMV IEA *in vitro*. Within MTC, the inhibitory rate had a significant correlation with its dosage (r = 0.96). At the time of IEA highest expression (72 h after infection), inhibitory effect was the greatest (inhibitory rate: 89.3%). With pretreatment of Allitridin, the inhibitory rate was 28.6%. When Allitridin was used together with HCMV inoculation, IEA inhibitory rate was only 10.3% [33]. Garlic inhibited CBV3 and ECHO11 at the concentration ranged from 2.5 micrograms/ml to 7.5 micrograms/ml and 5 micrograms/ml was the most effective [34-35].

Ammi majus

Ammi majus coumarins were evaluated for antiviral effects against two mammalian viruses, HSV-1 and VSV. The antiviral activity was determined by means of the end titration technique that depends on the ability of plant extract dilutions to inhibit the produced cytopathogenic effect. *Ammi majus* coumarins exerted antiviral activity against vesicular stomatitis virus (VSV) in a concentration- dependent manner at complete non-toxic concentration range 10-100 µg/ml. *Ammi majus* coumarins found to have no reliable antiviral activity against herpes simplex virus (HSV) [36]. A dose of 400 mg/kg body weight of a hot aqueous extract and 15.0 mg/kg bw of petroleum ether extract of the *Ammi majus* fruits daily for six days reduced the *Schistosoma mansoni* worm burden in mice by 49.3–72.3% [37-38].

Anchusa italica

The antiinfluenza virus activity of aqueous and alcoholic extract of *Anchusa italica* plant (2.5-80 µg/ml) was investigated on the viral infected Madin-Darby -Canine Kidney cell monolayer. *Anchusa italica* extracts possessed higher antiviral properties when used one hour before infection compared to their usage after infection. However, the antiviral effect of alcoholic extract was more pronounced than that of the aqueous preparation. The antiviral activity of *Anchusa italica* was likely due to interference with viral replication and transcription, accordingly *Anchusa italica* can be used such as amantadin for the treatment of influenza [39-40].

Aristolochia maurorum

Antiviral properties of the plant extracts were determined by cytopathic effect inhibition assay and plaque reduction assay. *Aristolochia maurorum* extracts exhibited significant antiviral activity against HSV-1 and adenovirus type 5 at a concentration non toxic to the cell lines used. The extracts of *Aristolochia maurorum* showed great anti viral activity against HSV-1 and partial activity against adenovirus at higher concentrations [41].

Asclepias curassavica

The ethanolic extract (80%) of freeze dried entire plant showed no antiviral activity against Adenovirus, Coxsackie b2, Herpes type-1, Measles, Poliovirus-1 and Semliki forest virus by cell cultured method [42-43].

Astragalus hamosus

In the evaluation of the anti-viral effect of emodin plus astragalus polysaccharide (APS) in hepatitis B virus (HBV) transgenic mice, emodin and astragalus had a weak but persistent inhibitory effect on HBV replication in mice which may function as a supplementary modality in the treatment of hepatitis B infection. After 21 day of treatment with physiological saline containing (emodin and astragalus, 57.59 and 287.95 mg/kg per day, respectively), HBV-DNA levels was significantly declined when compared with normal control group. A reduction in the contents of HBsAg, HBeAg and HBcAg in the mice was observed when compared with normal control group [44-45].

Betula alba

Betulinic acid showed an inhibitory activity against HIV-1 replication with an EC₅₀ value of 1.4 µM and inhibited uninfected H9 cell growth with an IC₅₀ value of 13 µM. Betulinic acid inhibited HIV-1NL4-3 and HIV-1JRCSF with IC₅₀ values of 0.04 and 0.002 µg/ml, respectively [46]. It also showed anti-HIV-1 activity by syncytium and RT assays with IC₅₀ value of 9.8 µg/ml and 10.8 µg/ml respectively [47]. Three triterpenoids derived from the bark of *Betula alba*, betulin, betulinic acid and oleanolic acid, have been evaluated for antiviral activity against vesicular stomatitis virus (VSV) and encephalomyocarditis virus (EMCV). The virucidal activity of all the compounds was poor (concentrations of triterpenoids effective in inactivation of 50% of viral particles above 26mg/ml but all the three examined triterpenoids inhibited replication of both viruses with EC₅₀ values below 1.3 mg /ml and therapeutic index (TI) higher than 18 [48]. Sixty two patients with positive Human Papilloma Virus (HPV) -test were treated with topical products, vaginal ovules, containing betulinic acid and betulin. After six months, the percentage of negative HPV-test was 93% in the treated group [49]. The hepatoprotective effect of birch bark extract (BBE) in patients with chronic hepatitis C (CHC) was studied. Forty-two patients with serologically confirmed chronic hepatitis C were treated for 12 weeks with 160 mg standardized BBE per day. The primary outcome parameter measured was the rate of alanine aminotransferase (ALT) normalization after 12 weeks. Secondary parameters included the course of ALT, aspartate aminotransferase (AST) levels, quantitative HCV RNA levels, subjective symptoms associated with CHC (fatigue, abdominal discomfort, depression, and dyspepsia), safety and compliance. The qualitative-quantitative analysis of BBE was made using high performance liquid chromatography to confirm the presence of 75% betulin and 3.5% betulinic acid. Significant differences in the mean ALT and HCV RNA levels were observed after 12 weeks of treatment. The level of ALT was decreased in 54.0% and normalized (p=0.046). HCV RNA

was reduced in 43.2% ($p=0.016$). After 12 weeks of treatment, reports of fatigue and abdominal discomfort were reduced by 6-fold ($p=0.028$) and 3-fold ($p=0.05$), respectively. Dyspepsia was no longer reported ($p=0.042$) and the effect was significantly different from baseline [50]. Synthetic betulinic derivatives showed anti-HIV activity and an inhibition of Semliki Forest virus (SFV) replication [51-54].

Caesalpinia crista

The ethanolic extract of the root and stem exhibited activity against the vaccinia virus. The antiviral activity of *Caesalpinia crista* was investigated against paramyxovirus and orthomyxovirus isolates. Aqueous, ethanol and methanolic extracts of *Caesalpinia crista* showed complete inhibition of paramyxovirus and highly significant inhibitory activity of orthomyxovirus [55-56].

Calendula officinalis

Extracts of dried flowers from *Calendula officinalis* were examined for their ability to inhibit the human immunodeficiency virus type 1 (HIV-1) replication. Both organic and aqueous extracts were relatively nontoxic to human lymphocytic Molt-4 cells, but only the organic one exhibited potent anti-HIV activity in an *in vitro* MTT/ tetrazolium-based assay. In addition, in the presence of the organic extract (500 micrograms/ ml), the uninfected Molt-4 cells were completely protected for up to 24 h from fusion and subsequent death, caused by co-cultivation with persistently infected U-937/HIV-1 cells. It was also found that the organic extract from *Calendula officinalis* flowers caused a significant dose- and time-dependent reduction of HIV-1 reverse transcription (RT) activity. An 85% RT inhibition was achieved after a 30 min treatment of partially purified enzyme in a cell-free system [57]. A chloroform extract also inhibited HIV-1 reverse transcriptase activity in a dose-dependent manner (ED_{50} : 51.0 mg/ml). A 5% hot aqueous extract of the flowers (2 ml) inhibited the replication of encephalitis virus after intraperitoneal administration to mice [58]. A tincture of the flowers suppressed the replication of herpes simplex, influenza A2 and influenza APR-8 viruses *in vitro* [59-60].

Canna indica

A novel 10 kDa protein with anti-HIV-1 reverse transcriptase (RT) inhibitory activity was isolated from leaves of *Canna indica* L [61-62].

Capparis spinosa

In studying the antiviral and immunomodulatory properties of a methanolic extract of *C. spinosa* buds (CAP), it was found that CAP treatment interferes with HSV-2 replication in human peripheral blood mononuclear cells (PBMCs), inhibiting the extracellular virus release up-regulating their production of IL-12, IFN- α and TNF- α . Accordingly, CAP contribute in improving immune surveillance of PBMCs toward virus infection by up-regulating expression of peculiar pro-inflammatory cytokines, the authors postulated that it can be successfully employed for treatment of HSV-2 infections in immune-compromised hosts [63-64].

Carthamus tinctorius

The antiviral activity of *Carthamus tinctorius* L. (CT) was examined against gamma herpes virus infection. The results showed that treatment with CT extracts disrupted KSHV latency in the viral-infected host cells. n-Hexane and ethanol fractions of CT extracts critically affected at least two stages of the KSHV life-cycle by abnormally inducing KSHV lytic reactivation and by severely preventing KSHV virion release from the viral host cells. In addition to the effects on KSHV itself, CT extract treatments induced cellular modifications by dysregulating cell-cycle and producing strong cytotoxicity[65]. A hot aqueous extract of the flowers inhibited replication of poliomyelitis virus type 1 *in vitro* [66-67].

Celosia cristata

Preinoculation treatment with *Celosia cristata* leaf extract prevented lesion production by sunnhemp rosette virus, tobacco mosaic virus and potato virus X in several local lesion hosts. The extract inhibited lesion formation only in treated areas, and did not act on the virus directly, but only *via* the host. The persistence of inhibitory activity in test hosts for up to 6 days indicates that the site of virus attachment is blocked semipermanently [68]. Two N-terminally blocked antiviral glycoproteins, CCP-25 and CCP-27 were purified from the leaves of *Celosia cristata*[69].

Study the anti-BVDV toxicity on EBTr cells, anti-BVDV protection in EBTr cells and anti-HBV effect in Hep G2, showed that the plant had no anti-BVDV toxicity on EBTr cells, anti-BVDV protection in EBTr cells, but it had anti-HBV effect in Hep G2 in high concentration [70-71].

Ceratopteris thalictroides

CVN (cyanovirin-N) isolated *Ceratopteris thalictroides* is an anti-HIV protein. CVN can resist detergents, denaturants organic solvents and multiple freeze-thaw cycles. Even boiling at 100 °C cannot damage its anti-HIV activity. CVN successfully blocks the virus-cell fusion process mediated by HIV envelope glycoprotein. *In vitro* studies show that CVN inhibits HIV envelope-mediated cell fusion at nanomolar concentrations by interfering with the interaction between gp120 and cellular receptor CD4. CVN possessed high activity against HIV in various target cells, including HIV-1 laboratory strains, RF, IIIB, MN, G910-6, A17, 214, SK1 and 205, G1, and HIV-1 primary isolates WEJQ, VIHU, BAKI, WOME, 89.6, Ba-L, Ada-M and SLKA. In addition, CVN has other antiviral activity, such as Ebola and the influenza virus [72-73].

Chenopodium album

Two proteins, CAP-I and CAP-II purified from the leaves of *Chenopodium album* induced systemic resistance against tobacco mosaic virus (TMV) and sunnhemp rosette virus (SRV) in both hypersensitive as well as systemic hosts. Both CAP-I and CAP-II caused *in vitro* degradation of TMV RNA. It is suggested that the CAP-I and -II are multi-functional and may be acting at multiple levels to ensure maximum possible inhibition of viral infection [74-75].

Chrysanthemum cinerariaefolium

Pyrethrins, complex esters extracted from *Chrysanthemum cinerariaefolium*, exhibited only minimal *in vitro* activity against herpes simplex virus (HSV). However, in employing a guinea pig model of HSV genital infection, no *in vivo* activity was recorded [76].

Cicer arietinum

The antiviral activities of the extracts from the seed, fruit skin and aerial parts of ten varieties of *Cicer arietinum* (Chickpea) were evaluated against Herpes *simplex* type 1 (*HSV-1*) and *Parainfluenza-3* (*PI-3*) viruses. Madin-Darby Bovine Kidney and Vero cell lines were employed for antiviral assessment of the *Cicer arietinum* L. extracts, in which acyclovir for *HSV-1* and oseltamivir for *PI-3* were tested as reference drugs. *Cicer arietinum* seed extracts (Aydin 92 variety) possesses significant antiviral activity against both DNA (max to min CPE inhibitory conc: 32-4 µg/ ml) and RNA (max to min CPE inhibitory conc: 32-16 µg/ ml) viruses compared to the fruit skin and aerial part extracts as well as the controls. Besides, the extracts of fruit skin (Menemen 92 variety) and aerial parts (Aydin 92 variety) showed remarkable activity against DNA viruses at 32 - 1 µg/ ml concentration [77-78].

Cichorium intybus

The antiviral activity of protein extracts from transgenic plants of *Cichorium intybus* was investigated against vesicular stomatitis virus. It was shown that the extracts from the hairy roots of chicory possess antiviral activity [79-80].

Citrus species

Citrus aurantifolia juice destroyed human immunodeficiency virus (HIV). Ten percent of *Citrus aurantifolia* juice produced a 1000-fold reduction in HIV activity in a laboratory sample [81].

To evaluate the effect of extracts of peels of *Citrus sinensis* (Cs) on the replication of coronavirus (CoV) and on the expression of TRP genes during coronavirus infection, HeLa-CEACAM1a (HeLa-epithelial carcinoembryonic antigen-related cell adhesion molecule 1a) cells were inoculated with MHV-A59 (mouse hepatitis virus-A59) at moi of 30. 1/50 dilution of the extracts was found to be the safe active dose. ELISA kits were used to detect the human IL-8 levels. Total RNA was isolated from the infected cells and cDNA was synthesized. Fluidigm Dynamic Array nanofluidic chip 96.96 was used to analyze the mRNA expression of 21 TRP genes and two control genes. Data was analyzed using the BioMark digital array software. Determinations of relative gene expression values were carried out by using the $2^{-\Delta\Delta Ct}$ method (normalized threshold cycle (Ct) value of sample minus normalized Ct value of control). TCID₅₀/ml (tissue culture infectious dose that will produce cytopathic effect in 50% of the inoculated tissue culture cells) was found for treatments to determine the viral loads. TRPA1, TRPC4, TRPM6, TRPM7, TRPM8 and TRPV4 were the genes which expression levels changed significantly after Cs extract treatments. The virus load decreased when Cs extracts was added to the CoV infected cells. Extract treatment had an effect on IL-8 secretion, TRP gene expression and virus load after CoV infection [82-83].

Clerodendrum inerme

Clerodendrum inerme showed antiviral activity against Hepatitis B virus with ED₅₀ value of 16 mg/ml [84-85].

Cordia myxa

Extracts of *Cordia myxa* were tested for their anti-HIV-1 activity using the syncytia formation assay. All the extracts showed a weak anti-HIV-1 activity [86-87].

Cuminum cyminum

The essential oils of *Cuminum cyminum* showed antiviral activities against herpes simplex virus 1 (HSV-1) using cytopathicity (CPE) assay. At concentration of 1000 μg the antiviral activity reached 91.60 ± 1.93 [88-89].

Cupressus sempervirens

Ethanol extracts of *Cupressus sempervirens*, *C. sempervirens* var. *horizontalis* and *Cupressus sempervirens* var. *cereiformis* were used to test their influence on herpes viruses (HSV-1). HeLa cells monolayers were infected with herpes viruses (HSV-1). Antiviral activity of the plant extracts assessed using Hematoxylin & Eosin method and observed under a light microscope. All tests were compared with a positive control, acyclovir. Results showed that all three plants have antiviral activity against HSV-1 virus. The most active extract was the extract obtained from *C. sempervirens*. Among the different parts tested, the fruit's extract possessed the strongest anti- HSV activity [90].

A proanthocyanidin polymer fraction (MW 1500–2000 daltons) isolated from *Cupressus sempervirens* L. exhibited true antiviral activity *in vitro* against two retroviruses, HIV and HTLV III B. No toxicity was observed at concentrations of 50 $\mu\text{g}/\text{ml}$ which exceeded the IC_{50} values (1.5 to 15 $\mu\text{g}/\text{ml}$ for HIV and 5 to 25 $\mu\text{g}/\text{ml}$ for HTLV) [91-92].

Cydonia oblonga

Anti-influenza viral activities of quince fruits phenolic extract was studied. Quince phenolics showed anti-influenza viral activity on the hemagglutination inhibition test [93-94].

Cynodon dactylon

Antiviral activity of a large scale produced plant extract of *Cynodon dactylon* on white spot syndrome virus (WSSV) was studied in black tiger shrimp *Penaeus monodon* by an *in vivo* testing. The plant extract of *Cynodon dactylon* was incorporated with artificial pellet feed at a concentration of 1% or 2%. *Cynodon dactylon* was highly effective in preventing WSSV infection with no mortality [95].

The *in vitro* virustatic and virucidal tests of the crude extract of *Cynodon dactylon* against infection with porcine reproductive and respiratory syndrome virus (PRRSV), were studied. Crude extract of *Cynodon dactylon* was prepared for cytotoxicity on tissue-culture cells that were used to measure virustatic and virucidal activities against PRRSV. Crude extract of *Cynodon dactylon* at 0.78 mg/ml showed no cytotoxicity on the cell line, and at that concentration significantly inhibited replication of PRRSV as early as 24 hours post infection. *Cynodon dactylon* also inactivated PRRSV as determined by immunoperoxidase monolayer assay (IPMA) compared to the control experiments [96].

The luteolin and apigenin rich fraction was obtained from the ethanolic extract of *Cynodon dactylon*, and it was evaluated for cytotoxicity and anti-Chikungunya potential using Vero cells. The fraction exhibited potent viral inhibitory activity (about 98%) at the concentration of 50 $\mu\text{g}/\text{ml}$ as observed by reduction in cytopathic effect, and the cytotoxic concentration of the fraction was found to be 250 $\mu\text{g}/\text{ml}$. RT-PCR analyses indicated that the reduction in viral mRNA synthesis in fraction treated infected cells was much higher than that of viral infected control cells [97-98].

Cyperus rotundus

Cyperus rotundus exerted virucidal effect against HSV [99]. Anti-HBV active constituents was isolated from the rhizomes of *Cyperus rotundus*. Five new patchoulane-type sesquiterpenoids, namely cyperene-3, 8-dione, 14-hydroxy cyperotundone, 14-acetoxy cyperotundone, 3 β -hydroxycyperenoic acid and sugetriol-3, 9-diacetate, along with 32 known sesquiterpenoids were isolated from the active fractions of *Cyperus rotundus*. Nine eudesmane-type sesquiterpenoids significantly inhibited the HBV DNA replication with IC_{50} values of 42.7 ± 5.9 , 22.5 ± 1.9 , 13.2 ± 1.2 , 10.1 ± 0.7 , 14.1 ± 1.1 , 15.3 ± 2.7 , 13.8 ± 0.9 , 19.7 ± 2.1 and 11.9 ± 0.6 μM , of which, 4 compounds possessed high SI values of 250.4, 125.5, >259.6 and 127.5. Two patchoulane-type sesquiterpenoids effectively suppressed the secretion of HBsAg in a dose-dependent manner with IC_{50} values of 46.6 ± 14.3 (SI=31.0) and 77.2 ± 13.0 (SI=1.7) μM . Other 6 compounds possessed moderate activities against HBsAg secretion with IC_{50} values of 162.5 ± 18.9 (SI=13.3), 399.2 ± 90.0 (SI=10.6), 274.7 ± 70.8 (SI=5.2), 313.9 ± 87.5 (SI=7.2), 334.0 ± 70.4 (SI=9.9) and 285.3 ± 20.9 (SI=15.5) μM [100-101].

Dactyloctenium aegyptium

The antiviral activity against HSV-2, HSV-1 and HAV-10 of *Dactyloctenium aegyptium* aerial parts extracts was investigated using cytopathic effect inhibition assay. The ethyl acetate showed weak antiviral activity, *n*-butanol extracts of *Dactyloctenium aegyptium* showed moderate antiviral effects against HAV-10 and HSV-1. The *n*-hexane extract showed strong antiviral activity against all viruses tested [102-103].

Datura metel

The antiviral activity of atropine was evaluated by plaque reduction test against *Herpes Simplex* virus, *Influenza* virus, *New Castle Disease* virus, *Sindbis*, *Vaccinia*, *Adenovirus* and *Japanese encephalitis* virus. Viruses were cultivated on primary chick embryo (CE), HeLa S3, primary monkey kidney cells (MK). Atropine inhibited only the growth of enveloped viruses independent of the nucleic acid content of the virus. It also blocked the glycosylation of viral proteins of *Herpes* virus and hence the production of new virions. Virions formed in the presence of atropine were non infectious [104-106].

Dianthus caryophyllus

Crude extract of *Dianthus caryophyllus* was tested for their antiviral activity against herpes simplex virus-1 (HSV-1) and hepatitis A virus-27 (HAV-27). Non-toxic concentration (20 µg/ml) of *Dianthus caryophyllus* seed extract to both Vero and HepG2 cells showed potent antiviral activity against HSV-1 and HAV-27 using plaque infectivity count assay. No effect was detected for the extract on adsorption or on the stages of virus replication. A comparison has been done between the antiviral activity of two therapeutic drugs (acyclovir and amantadine used as controls for HSV-1 and HAV-MBB, respectively) and the tested seed extract. The results revealed that the seed extract was more efficient in its inhibitory activity than synthetic chemical drugs against the same viruses [107-108].

Dodonaea viscosa

The *in vitro* antiviral activity of different extracts from *Dodonaea viscosa* leaves was studied against coxsackievirus B3 (CVB3) and rotavirus SA-11 (RV SA-11) infections. *Dodonaea viscosa* exhibited therapeutic index (TI) ranging from 0.3 to 25 with reduction in virus titer ranging from 0.25 to 5 log₁₀ TCID₅₀/0.1 ml for CVB3, whereas TI ranging from 0.4 to 29.2 with reduction in virus titre ranging from 0.25 to 5.25 log₁₀ TCID₅₀ for RV SA-11. Crude extract provided the potent inhibition of CVB3 and RV SA-11, replication by binding to a viral capsid of CVB3 and viral receptor of RV SA-11 preventing viruses entry into host cells for both viruses [109].

Petroleum ether, chloroform and methanol 80% extracts of *Dodonaea viscosa* aerial parts were tested for their anti-HIV-1 activity using the syncytia formation assay. Petroleum ether extract of *Dodonaea viscosa* was the most active as an anti-HIV-1 agent while other extracts were less effective. The authors concluded that the antiviral effects could be attributed to β -sitosterol and stigmasterol identified in the petroleum ether extract of *Dodonaea viscosa* [110-111].

***Dolichos lablab* (Syn: *Lablab purpureus*)**

Dolichin, was also capable of inhibiting human immunodeficiency virus (HIV) reverse transcriptase and alpha- and beta-glucosidases which were glycohydrolases implicated in HIV infection. It had very low ribonuclease and cell-free translation-inhibitory activities [112-113].

Equisetum arvense

The water extract of aerial parts of *Equisetum arvense* possesses inhibitory effect on HIV-1 induced cytopathy [114-115].

Erigeron canadensis

The methanol extract of aerial parts of *Erigeron canadensis* was extracted with four organic solvents (petroleum ether, chloroform, ethyl acetate and butanol) and investigated for antiviral activity against human cytomegalovirus (HCMV) AD-169 and Cox-B3 viruses by modified shell-vial assay. The results showed that chloroform, ethyl acetate, butanol and methanol extracts possessed antiviral activity, however, butanol extract antiviral activity was 95.75 and 90.10 % for 200 and 100 µg/ml of the extract respectively and methanol extract antiviral activity was 100 and 99.10% for 200 and 100 µg/ml of the extract respectively [116-117].

Erodium cicutarium

Extracts from *Erodium cicutarium* were tested for antiviral and interferon inducing properties. Both water extract and methanol extract as well as its fractions exerted antiviral effect in relation to myxoviruses,

herpes virus type 1, vesicular stomatitis and vaccinia virus. None of these extracts did induce interferon in a suspension of human leukocytes [118-120].

***Eucalyptus* species**

The antiviral effect of the leaf essential oil of *Eucalyptus camaldulensis* was studied against many viruses. Rotavirus Wa strain, Coxsackievirus B4, and herpes virus type 1 were affected by essential oil with percentage of reduction 50%, 53.3%, and 90% respectively, but no effect was found against adenovirus type 7 [121-122].

The methanolic extracts of *Eucalyptus camaldulensis* was tested against human enteroviruses: Poliovirus type I, Coxsackievirus B and Echovirus 6. The virucidal tests showed that the crude extracts were active against the tested viruses. Poliovirus type 1, coxsackievirus B and echovirus 6 giving a neutralization index of one log and above [123].

Euphorbia hirta

The antiretroviral activities of extracts of *Euphorbia hirta* were investigated *in vitro* on the MT4 human T lymphocyte cell line. The cytotoxicities of the extracts were tested by MTT cell proliferation assay, and then the direct effects of the aqueous extract on HIV-1, HIV-2 and SIV(mac251) reverse transcriptase activity were also determined. A dose-dependent inhibition of reverse transcriptase activity was observed for all three viruses. The 50% methanolic extract was found to exert a higher antiretroviral effect than that of the aqueous extract. The 50% methanolic extract was subjected to liquid-liquid partition with dichloromethane, ethyl acetate and water. Only the remaining aqueous phase exhibited significant antiviral activity and after removal of the tannins from the aqueous extract, the viral replication inhibitory effect was markedly decreased, therefore the authors concluded that tannins were most probably responsible for the high antiretroviral activity [124-125].

Ficus religiosa

The antiviral activity of *Ficus religiosa* was investigated against RSV and HRV *in vitro* by plaque reduction and virus yield assays, and the major mechanism of action was investigated by virus inactivation and time- of- addition assays. *Ficus religiosa* methanol bark extract was most active against HRV with an EC₅₀ of 5.52 µg/ml. This extract inhibited late steps of replicative cycle. Water bark extract was the most active against RSV with an EC₅₀ between 2.23 and 4.37 µg/ml. Partial virus inactivation and interference with virus attachment were both found to contribute to the anti-RSV activity. Replication of both viruses was inhibited in viral yield reduction assays [126-127].

Fraxinus ornus

Esculetin (6,7-dihydroxycoumarin) isolated from dried stem bark from mature trees of *Fraxinus ornus*, and its diacetate exhibited a marked inhibitory effect on Newcastle disease virus replication in cell cultures at concentrations of 36 µM and 62 µM, respectively [128-129].

Glycyrrhiza glabra

Glycyrrhiza glabra extracts and glycyrrhizic acid inhibited the replication of several viruses included Epstein-Barr virus, Herpes simplex virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Human cytomegalovirus, Human immunodeficiency virus, Influenza virus, SARS coronavirus and Varicella zoster virus [130-141].

Two coumarins of *G. glabra*, glycocoumarin and licopyranocoumarin, inhibited giant cell formation in HIV-infected cell cultures without any cytotoxicity. licochalcone A also had anti-HIV activity [142-143].

Glycyrrhizin was investigated as a therapy of human immuno-deficiency virus (HIV) in 42 hemophilia patients with HIV-1 infection. Patients showed improvement in their clinical symptoms (oral candidiasis, lymph node swelling and rash), immunological functions and liver functions [144].

Many studies have demonstrated that glycyrrhizin was responsible for the antiviral activity of licorice. The possible antiviral mechanisms of this compounds were (HCV): affected release step while infectious HCV particles are infecting cells. Inhibited HCV full length viral particles and HCV core gene expression; (HSV): reduced adhesion force and stress between CCEC and PMN, (CVB3): blocked the degradation of nuclear factor κB inhibitor IκB; (DHV): activated T lymphocyte proliferation; (H5N1): weakened H5N1-induced production of CXCL10, IL-6 and CCL5, and suppressed H5N1-induced apoptosis, (Influenza virus): reduced HMGB 1 binding to DNA, and inhibited influenza virus polymerase activity, (CVA16 EV71): inactivated CVA16 directly, while the effect of anti-EV71 was associated with an events during the virus cell entry, (HSV1): established a resistance state to HSV1 replication and (Rotavirus): reduced the levels of viral proteins VP2, VP6 and NSP2 at a step or steps subsequent to virus entry [145-146].

***Gossypium* species**

Gossypol has been reported to possess antiviral properties against enveloped viruses, including HIV-1, HSV-2, influenza, and parainfluenza [147-151].

Incubation of HTLV-III B strain of human immunodeficiency virus with gossypol in a cell-free, showed that gossypol prevented recovery of viable viruses when subsequently incubated with H9-T cells [147].

Racemic mixture and both enantiomers of gossypol inhibit the replication of human immunodeficiency virus-type 1 (HIV-1). Variety analogs of gossypol showed more activity against immunodeficiency virus-type 1 (HIV-1) [152].

The antiviral effect of water extracts of *G. hirsutum* leaves was investigated for their inhibitory activities on the yellow fever virus in the tissue cell culture using Vero cells. The extracts showed antiviral activities against yellow fever virus. *G. hirsutum* inhibited yellow fever viruses at MICs of 0.079mg/ml [153-154].

Hedera helix

The potential antiviral properties was evaluated against influenza A/PR/8 (PR8) virus in a mouse model with suboptimal oseltamivir that mimics a poor clinical response to antiviral drug treatment. Suboptimal oseltamivir resulted in insufficient protection against PR8 infection. Oral administration of ivy extract with suboptimal oseltamivir increased the antiviral activity of oseltamivir. Ivy extract and its compounds, particularly hederasaponin F, significantly reduced the cytopathic effect in PR8-infected A549 cells in the presence of oseltamivir. Compared with oseltamivir treatment alone, coadministration of the fraction of ivy extract that contained the highest proportion of hederasaponin F with oseltamivir decreased pulmonary inflammation in PR8-infected mice. Inflammatory cytokines and chemokines, including tumor necrosis factor-alpha and chemokine (C-C motif) ligand 2, were reduced by treatment with oseltamivir and the fraction of ivy extract. Analysis of inflammatory cell infiltration in the bronchial alveolar of PR8-infected mice revealed that CD11b+Ly6G+ and CD11b+Ly6Cint cells were recruited after virus infection; coadministration of the ivy extract fraction with oseltamivir reduced infiltration of these inflammatory cells [154].

The antiviral activity of hederasaponin B from *Hedera helix* against EV71 subgenotypes C3 and C4a was evaluated in vero cells. The results demonstrated that hederasaponin B and 30% ethanol extract of *Hedera helix* containing hederasaponin B showed significant antiviral activity against EV71 subgenotypes C3 and C4a by reducing the formation of a visible CPE. Hederasaponin B also inhibited the viral VP2 protein expression, suggesting the inhibition of viral capsid protein synthesis [155-156].

Hibiscus sabdariffa

The antiviral effects of aqueous extracts of *H. sabdariffa* (HE) was studied against human norovirus surrogates (feline calicivirus (FCV-F9) and murine norovirus (MNV-1)) and hepatitis A virus (HAV) at 37 °C over 24 h. FCV-F9 titers were reduced to undetectable levels after 15 min with both 40 and 100 mg/ml HE. MNV-1 was reduced by 1.77 ± 0.10 and 1.88 ± 0.12 log PFU/ml after 6 h with 40 and 100 mg/ml HE, respectively, and to undetectable levels after 24 h by both concentrations. HAV was reduced to undetectable levels by both HE concentrations after 24 h [157].

The aqueous extract of *Hibiscus sabdariffa* (AEHS) and its bioactive constituent protocatechuic acid (PCA), were evaluated in vitro for their antiviral activity against HSV-2 clinical isolates and anti-enzymatic activity against urease. PCA showed potent anti-HSV-2 activity compared with that of acyclovir, with EC₅₀ values of 0.92 and 1.43 µg/ml, respectively, and selectivity indices > 217 and > 140, respectively. AEHS exerted anti-urease activity, with an IC₅₀ value of 82.4 µg/ml [158].

The antiviral effects of aqueous *H. sabdariffa* extracts was evaluated against Aichi virus (AiV) (a foodborne pathogen that causes gastroenteritis). AiV did not show any significant reduction with 1:1 (100 mg/ml) or 1:5 (40 mg/ml) diluted aqueous hibiscus extracts after 0.5, 1, or 2 h at 37 °C. However, AiV titers were reduced to non-detectable levels after 24 h with all the three tested concentrations. AiV was reduced by 0.5 and 0.9 log PFU/ml with undiluted extracts (200 mg/ml) after 2 and 6 h, respectively [159].

The leaves extracts of *Hibiscus sabdariffa* (red and green leaved) were studied for antiviral activities against Measles Virus (MV) as well as the effects of the extracts on Hep-2 cells. Ethanol extract of the leaves showed no toxicity to the Hep-2 cells at all concentrations used (5, 10 and 15 mg/ml). The pre-inoculative treatment of Hep-2 cells with plant extracts showed that *H. sabdariffa* had antiviral activities only at 10 and 15 mg/ml on MV. The post-inoculative treatment of Hep-2 cells with plant extracts showed that at 5, 10 and 15 mg/ml concentrations, *H. sabdariffa* had antiviral activities on MV [160-161].

Hypericum triquetrifolium

The essential oils of *Hypericum triquetrifolium* did not show antiviral activity against coxsackievirus B3 [162-163].

Jasminum officinale

The antiviral effect of oleuropein derived from the flowers of *Jasminum officinale* was studied on hepatitis B virus (HBV) replication in HepG2 2.2.15 cell line *in vitro* and duck hepatitis B virus (DHBV) replication in ducklings *in vivo*. Oleuropein blocked effectively HBsAg secretion in HepG2 2.2.15 cells in a dose-dependent manner ($IC_{50} = 23.2$ microg/ml). Oleuropein (80 mg/kg, intraperitoneally, twice daily) also reduced viremia in DHBV-infected ducks[164].

The effect of 8-*epi*-kingiside (8-Epik) derived from the buds of *Jasminum officinale* var. *grandiflorum* (JOG) was evaluated on hepatitis B virus (HBV) replication in HepG2 2.2.15 cell line *in vitro* and duck hepatitis B virus (DHBV) replication in ducklings *in vivo*. 8-Epik effectively blocked HBsAg secretion in HepG2 2.2.15 cells in a dose-dependent manner ($IC_{50} = 19.4 \pm 1.04$ µg/mL). 8-Epik (40 or 80 mg/kg, ip, twice daily) also reduced viremia in DHBV-infected ducks[165-166].

Jasminum sambac

Anti-herpes simplex viruses (HSV-1 and HSV-2) and antiadenoviruses (ADV-3, ADV-8 and ADV-11) activities of hot water extract of *Jasminum sambac* flowers was evaluated using XTT-based colorimetric assay. The results revealed that hot water extracts exhibited anti-HSV and anti-ADV activities[167-168].

Juglans regia

95% ethanol and ethyl acetate leaves extract of *J. regia*, inhibited tobacco mosaic virus, while, the methanol extract inhibited *Sindbis* virus at a concentration of 1.5 µg/ml[169-171].

Juncus maritimus

The extract of *J. maritimus* rhizomes possessed high activity against hepatitis C virus (relative infection < 10% at 50 µg/ml). Bioactivity-directed fractionation of the *J. maritimus* rhizomes extract showed that the methylene chloride partition was most likely responsible for antiviral activities. The two major compounds of the methylene chloride partition were identified as phenanthrene derivatives[172].

Lagerstroemia speciosa

The anti-human rhinovirus activity of orobol 7-O-d-glucoside isolated from *Lagerstroemia speciosa* was evaluated in Hela cells by using a cytopathic effect reduction method. Orobol 7-O-d-glucoside showed a broad-spectrum anti-human rhinovirus activity with IC_{50} ranging from 0.58 to 8.80 microg/ml. The CC_{50} of orobol 7-O-d-glucoside was more than 100 microg/ml[173].

The antiviral activity of quercetin 7-glucoside isolated from *Lagerstroemia speciosa* was investigated against human rhinovirus 2 (HRV2) using a cytopathic effect reduction method. Quercetin 7-glucoside showed strong anti-HRV2 activity by reducing the formation of cytopathic effect. Quercetin 7-glucoside also inhibited virus replication in the initial stage of virus infection by indirect interaction with virus particles[174].

Aqueous and 50 per cent ethanolic extracts of the leaves and stems of *Lagerstroemia speciosa* were evaluated for anti-HIV activity using *in vitro* reporter gene based assays. All the extracts showed a dose dependent inhibition of HIV-1-infection in TZM-bl and CEM-GFP cell lines, with $IC_{50} = 1$ to 25 µg/ml[175].

The antiviral activities and possible mode of action of the tannin ellagic acid from the leaves of *Lagerstroemia speciosa* toward HRV-2, -3, and -4 were studied. As judged by 50% inhibitory concentration values, natural ellagic acid was 1.8, 2.3, and 2.2 times more toxic toward HRV-2 (38 µg/ml), HRV-3 (31 µg/ml), and HRV-4 (29 µg/ml) than ribavirin, respectively. The inhibition rate of preincubation with 50 µg/ml ellagic acid was 17%, whereas continuous presence of ellagic acid during infection led to a significant increase in the inhibition (70%). Treatment with 50 µg/ml ellagic acid considerably suppressed HRV-4 infection only when added just after the virus inoculation (0 h) (87% inhibition), but not before -1 h or after 1 h or later (<20% inhibition)[176].

Lallemantia royleana

The essential oils from *Lallemantia royleana* were screened for their inhibitory effect against herpes simplex virus type 1 (HSV-1) *in vitro* on Vero cell line CCL-81-ATCC using a plaque reduction assay. Results showed that the inhibitory concentration (IC_{50}) was determined at 0.011% for *L. royleana* oil with a high selectivity index (6.45)[177].

Lithospermum officinale

Shikonin possessed antiviral activity against HIV type 1, Adv3 and HCV[178-181].

Luffa cylindrica

Antiviral effects of extract of *Luffa cylindrica* vine against Japanese B encephalitis virus were reported. A significant prophylactic effect of the extract was proved when the extract was given to mice prior to sc, infection with Japanese B encephalitis virus and a partial protection was observed when administered 3.5 h post infection. The results showed that the extract didn't possess direct inactivating activity and, it showed no toxic effect both on tissue culture cells and in animals when given in considerably large doses[182-183].

Lycium barbarum

The effects of four sulfated *Lycium barbarum* polysaccharides (sLBPSs) on cellular infectivity of Newcastle disease virus were assayed by MTT method taking the non-modified LBPS as control. The results showed that sulfated *Lycium barbarum* polysaccharides significantly inhibit the infectivity of Newcastle disease virus to embryo fibroblast[184].

The antiviral activity of methanol extract of *Berberis lycium* was investigated against hepatitis C virus (HCV) infected HepG2 cells. HepG2 cells were seeded with HCV positive and negative serum and nontoxic doses of plant extract for 24 and 48 h. RNA was extracted and viral load was determined using Real-time PCR. *B. lycium*, showed mild toxicity at 40 µg/ml and were extremely toxic at 60 µg/ml. Real-time PCR quantitation result revealed that after 24 h treatments showed *B. lycium* extract had low (35%) antiviral effects. The 48 h treatments showed an increase antiviral activity[185].

Mangifera indica

The antiviral activity of *Mangifera indica* aqueous leaves extracts was studied against Newcastle disease virus (NDV) and IBD (*Birna viridae*). The aqueous leaves extracts at concentration of 0.5- 30 mg/ml; 50 µl showed significant antiviral activity against peripheral blood mononuclear cells at higher doses with respect to decline in proliferation assay, TNF α production and CD14 monocyte surface marker as compared to control[186].

The antiviral effect of mangiferin, extracted from the leaves of mango (*Mangifera indica*) was tested against herpes simplex virus type 2 (HSV-2) in vitro. The EC₅₀ of mangiferin against HSV-2 plaque formation in HeLa cells was 111.7 micrograms.ml⁻¹, and the concentrations of 33 and 80 micrograms.ml⁻¹ reduced the virus replicative yields by 90% (EC₉₀) and 99% (EC₉₉), respectively. The therapeutic index (IC₅₀/EC₅₀) was 8.1[187].

Four methods were used to evaluate the antiviral effect of mangiferin and isomangiferin against type I herpes simplex virus (HSV-I) (in vitro direct action, simultaneous addition of drug-virus-inoculum to cell bottle, virus inoculation preceding drug addition, and drug addition followed by virus inoculation). It was found that isomangiferin somewhat exceeded such control drugs as acyclovir, idoxuridine, and cyclocytidine, and that mangiferin was lower than isomangiferin. The average plaque reduction rates of mangiferin and isomangiferin were 56.8% and 69.5% respectively. The antiviral effect of mangiferin and isomangiferin was due to their capability of inhibiting virus replication within cells[188].

III. CONCLUSION

Many traditional medicinal plants have been reported to have strong antiviral activity and some of them have already been used to treat animals and people who suffer from viral infection. Analysis of the active ingredients revealed many useful antiviral compounds. The current review was designed to highlight the medicinal plants possessed antiviral effect and their mechanisms of action.

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