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Mini Review

Plant Extracts as Antiviral Agents

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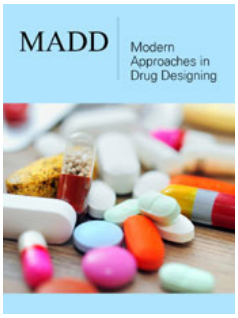

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Abstract

With the advent of COVID-19, an infectious disease, caused by severe acute respiratory syndrome corona virus 2 (SARS-COV-2), which has claimed the death of thousands around the globe, there is an urgent intense need to screen plant extracts, in addition to the search for synthetic medicines and a vaccine to neutralize the coronavirus. Whilst the use of plant extracts for antimicrobial, antidiabetic and other assays have reached their zenith, research in the use of plant extracts as antiviral agents lacks comparison. Such research would also come in close scrutiny in the future, considering that the virus can mutate and lead to antiviral strains. Thus, research in this area, should seek the approval of health organisations, locally and international and may become increasing difficult to pursue, considering the emergence of COVID-19 disease. Viruses can mutate in the presence of chemicals and other mutating agents to produce Novel viral strains, with devastating effect on the human race. Viruses detrimental to the human race, can emerge from any countries. Once approval is sought, for antiviral research, herbal antiviral medicinal research should intensified. Guyana diverse flora offers a promising source for natural antiviral agents and needs continual screening in this direction. However, it would need approval from world health organisations for antiviral testing.

Keywords: COVID-19; SARS-COV-2; Antiviral; Antimicrobial; Viruses; Mutate

Introduction

Viruses are obligate intracellular parasites. They contain little more than bundles of gene strands of either RNA or DNA, and are surrounded by a lipid containing envelope, that is derived from the host cell membrane [1]. A complete virus particle, also known as a virion, consists of nucleic acids, surrounded by a protective coat of protein, the capsid. These are formed from proteinaceous capsomeres. The capsid is made from proteins, under the genetic instructions of the viral genome. Its shape serves as a basis for morphological distinction. In general, there are four (4) main morphological virus types: helical, icosahedral, prolate and envelope [2-5]. Viruses utilize the synthetic environment of the host cell, to propagate new viruses or replicate. This is unlike bacterial cells, which are free living entities, outside of the host. There seems to be a current dispute whether viruses are living or non-living outside of the host. Amongst the viruses that induce diseases are herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV), hepatitis C virus (HCV), hepatitis B virus (HBV), influenza human immunodeficiency virus (HIV), respiratory syncytial virus (RSV) and recently, SARS-COV-2. Viruses induce a wide range of diseases. These include Lassa fever, Ebola fever, AIDS, papillomavirus (HPV), infectious mononucleosis, mumps, measles and rubella, shingles, viral gastroenteritis (stomach flu), viral hepatitis, viral meningitis, viral pneumonia, common cold. These diseases appear to have no cure or vaccine to date [6,7].

Viruses have been successful as invasion hosts due to four attributes. These include genetic variation, variety in means of transmission, efficient replication within host cells and the ability to persist in the host1. In addition, viruses can mutate to a more resistant strain. The presence of mutating agents such as certain chemicals can cause this mutation. Each strain of virus has its own unique configuration of surface molecules [1]. The surface molecules work

like lock and keys, enabling viruses to enter into hosts by precisely fitting the molecules on their surface to those on the membranes of target cells. In addition, viruses can change their conformation, as a result of mutation, making it difficult for a particular drug, which may show initial antiviral activity to become non-functional later. This makes it difficult to eradicate viruses. Hence, combination cocktail drug treatment has been used recently and has shown to be successful against viruses.

However, to date, there are few drugs or vaccine developed to eradicate viruses. To eradicate viruses, one has to know the life cycle of the virus, especially the critical steps. Viral replication involves several steps. Antiviral agents, both synthetic and of plant extracts origin can target any of these steps. Antiviral agents are expected to work via the inhibition of viral DNA or RNA synthesis or an inhibition of the activity of viral replication in the host environment or viral genome synthesis. Antiviral agents can get incorporated into viral DNA and causes DNA chain termination. Antiviral agents can be synthetic drugs, vaccines and plant extracts. Antiviral drugs can exert their actions at several stages of viral replication, including adsorption and penetration, nucleic acid synthesis, late protein synthesis, processing and in the final stages of viral packaging and virion release. Amongst the synthetic antiviral drugs currently in use are: Famciclovir, Penciclovir, Docosanol, Trifluride, Ganciclovir, Valganciclovir, Foscarnet, Cidofovir, Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir disoproxil fumarate, Zidovudine, Delavirdine, Efavirenz, Etravirine, Nevirapine, Rilpivirine, Atazavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir, Enfuvirtide, Maraviroc etc. These synthetic antiviral agents, which when administered can in addition to suppress the proliferation of the virus can cause irreversible side effects [7]. Thus, there is a need to use alternative or complementary medicines such as plant extracts.

Plant extracts, in their crude state or via the isolation and purification of natural products have been used as antimicrobial [8-22], antidiabetic [23-31], anticancer agents [32-44]. Isolated natural products from plants have provided the platform for the design and synthesis of drugs in the Pharmaceutical industry. Over 50% of modern drugs are derived from natural products or derivatized natural products. There is also an increase use of plant extracts as medicinal therapeutics. However, truly lacking in ant virology studies is the use of plant extracts as antiviral agents. Research in this direction has been progressing *in vivo* and *in vitro* and needs to be intensified, in comparison to antimicrobial studies or other bioassays. The same plant extracts can have different antiviral activity against RNA and DNA viruses. However, such research needs to be fast tract, considering the emergence of new viral strains such as which has been the cause of Covid-19 [45]. A wide range of natural products such as flavonoids, terpenoids, lignans, sulphides, polyphenolics, coumarins, saponins, furyl compounds, alkaloids, polyenes, thiophenes, proteins and peptides have been identified as possible antiviral agents [46-50]. In addition, selected essential oils of culinary herbs, spices and herbal teas have been shown to exhibit a significant level of antiviral activities [51,52]. Due to the high prevalence of viral infections, having no specific treatment and the constant appearance of resistant viral strains, the development of novel antiviral agents is essential. Figure 1 and Figure 2 show a list of natural products with promising antiviral activities and which should form the platform for other synthetic drugs mimicry.

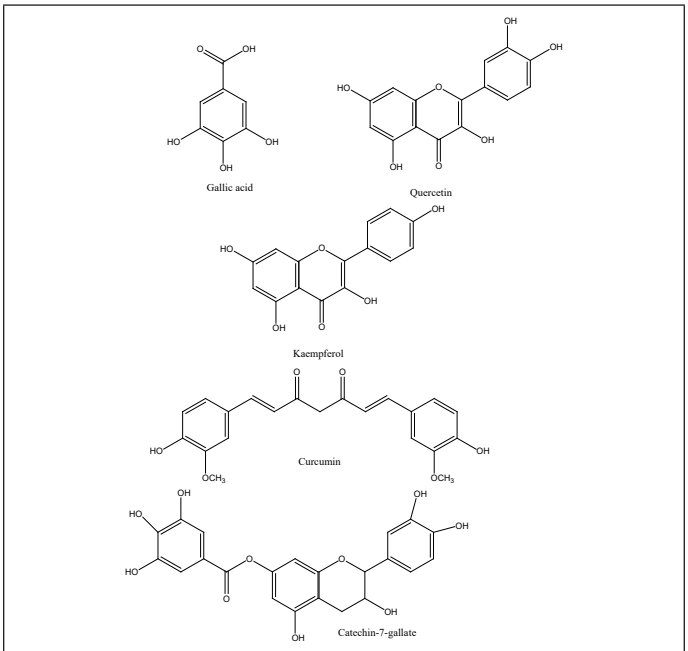

Figure 1: Some natural products with promising antiviral activities.

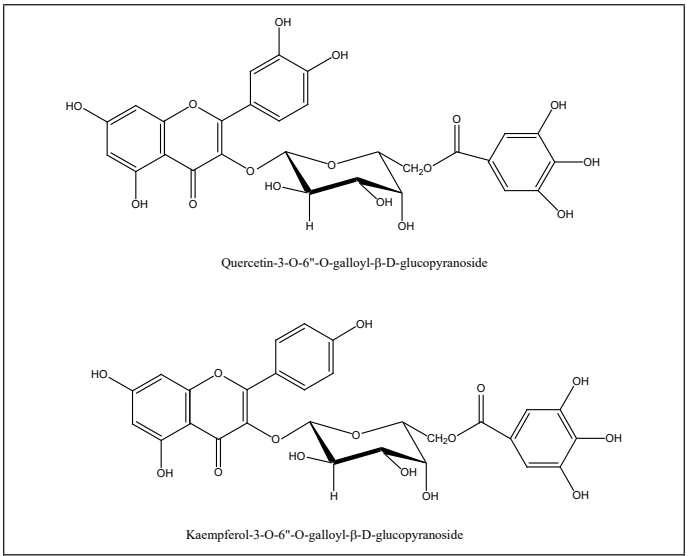

Figure 2: Some natural products with promising antiviral activities.

There are reports of plant extracts being used as anti-viral agents. Several can be cited [53-58]. A study was carried out to investigate the antiviral screening activities of twenty seven (27) medicinal plant extracts, belonging to twenty six (26) different plant

species from Nigerian ethnobotany, against echovirus 7, 13 and 19 serotypes (E7, E13 and E19, respectively [53]. Echoviruses infect millions of people globally and there is no specific drug treatment or vaccine available for its management currently. It was found that the crude extract of *Macaranga barteri* leaves had the highest cytotoxicity effect, followed by *Crinum jagus* and *Terminalia ivorensis*. Ten out of the twenty-seven crude plant extracts tested were active on E7 and E19, inhibiting the cytopathic effect of the virus in tissue culture. None of the extracts inhibited the cytopathic effect caused by E13 serotype. The methanol extract of *M. barteri* leaves had the highest antiviral activity on both E7 and E9, followed by the Ageratum conyzoides extract and *Mondia whitei* extract. Amongst the fractions of *M. barteri*, the DCM fraction was most the active and selective on E7.

The evaluation of the *in vitro* anti-herpetic activity of twenty-five (25) Egyptian plants extracts against Herpes Simplex Virus type 1 was investigated on Vero cell lines by cell viability. Only two plants extracts; namely *Euphorbia coopire* (Euphorbiaceae) and *Morus alba* (Moraceae) showed potent anti-herpetic activity and six other extracts showed moderate inhibition. In contrast, a bioassay monitored phytochemical exploration of these two plants led to the isolation of pure flavonoid compounds. The antiviral activity of the isolated compounds was also examined. Seven pure compounds namely; 7-galloyl catechin, gallic acid, kaempferol 3-O-β-(6″-O-galloyl)-glucopyranoside, quercetin 3-O-β-(6″-O-galloyl)-glucopyranoside, curcumin, quercetin and kaempferol exhibited significant inhibition [54].

Ninety aqueous and hydroaloholic extracts from thirty-six (36) native plants of Chile and introduced plant species were screened for antiviral activity on herpes (HSV-1 and HSV-2) and HIV viruses. Furthermore, the samples were assayed for antimicrobial effect on pathogenic bacteria and a yeast. Plants were selected according to their indication of use for treating symptomatology of possible viral aetiology in Chilean folk medicine. The hydroaloholic extracts of *Cassia stipulacea* and *Escallonia illintia* exhibited detectable antiviral effects towards HSV-1 with IC_{50} values of 80 and 40μg crude extract/mL, respectively. Samples belonging to *Aristotelia chilensis* (IC_{50} of 40μg/mL), Drymis winteri (IC_{50} values of 35 and 80μg/mL), Elytropus chilensis and Luma apiculata, with an IC50 value of 100μg/mL showed activity against HSV-2. None of the extracts showed activity against HIV at extract concentrations which were nontoxic for cells [56].

The organic and aqueous extract from *Baccharis gaudichaudiana*, *B. spicata*, *Bidens subalternans*, *Pluchea sagitallis*, *Tagetes miauta* and *Tessaria absinthiodes* were investigated for their antiviral activity against bovine viral diarrhea virus, herpes simplex virus type 1 (HSV-1), poliovirus type 2 (PV-2) and vesticular stomatitis. There was also a characterization of the antiviral activity of the organic and aqueous extract of *B. gaudichaudiana*. The bio-assay guided fractionation of the former led to the isolation of an active compound, apigenin: 5, 7-dihydroxy-2-(4-hydroxylphenyl)-4H –chromen-4-one [57] Figure 3.

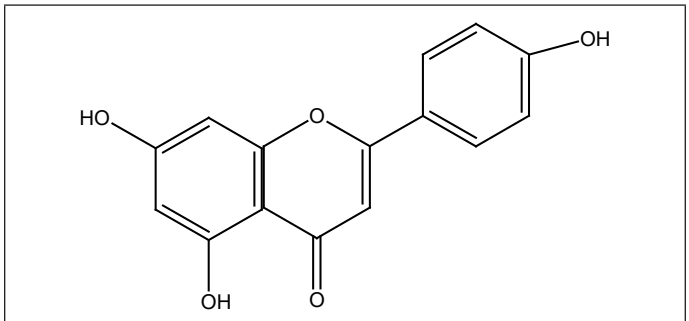

Figure 3: Apigenin: 5, 7-dihydroxy-2-(4-hydroxylphenyl)-4H –chromen-4-one, $C_{15}H_{10}O_5$.

Selective antival activity was seen by the liquid root extract of *Eleutherococcus senticosus*. The root extract exhibited antiviral activity against the human rotavirus (HRV), RSV and influenza A virus. In constrast, the DNA viruses, adenovirus and HSV type 1 virus (HSV-1) were not inhibited by the extract. Thus, the antiviral activity of *Eleutherococcus senticosus* is viral dependent [58]. Table 1 gives a list of plant extracts tested positive for their antiviral activity. Also, their isolates.

Table 1: A list of plant extracts tested positive for their antiviral activity. Also, their isolates.

Plant Source	Class of Natural Products	Mechanism of Action
Rutaceae, *Camptotheca acuminate*, *Atropa belladona*, *Swainsona canescens*	Alkaloids constituents: carbolines, furanoquinolines, camptothecin, atropine, caffeine, indolizidines, vinblastine	Inhibit the synthesis of DNA and other polynucleotides and virions proteins.
Ricinus communis, *Abrus precatorious*, *Adenia digitata*	Dimeric cyctotoxins	Interaction with ribosome function in the infected cell and inhibit viral proteins synthesis
Rutaceae and *Umbelliferae (Apiaceae)*	Furocoumarins and Furanochromones	DNA and RNA genomes
Canavalia ensiformis, *lens culinaris*, *Phaseolus vulgaris*, *Triticum vulgaris*	Lectins	Viral membranes interactions
Amanoa aff. Oblongifolia, *Juniperus communis*, *Justicia procumbens*, *Podophyllum peltatum*	Lignans: Podophyllotoxin and related lignans	Blocks viral replication
Kadsura matsudai	Dibenzocyclooctadiene lignans such as schizarin B and taiwanschirin D Rhinacanthin E and rhinacanthin F	Blocks influenza virus type A replication

Aloe barbadensis, *Aster scaber*, *Cassia angustifolia*, *Dianella longifolia*, *Euodia roxburghiana*, *Geum japonicum*, *Hamamelis virginiana* etc.	Lignans: Miscellaneous phenolic compounds: anthraquinone, chrysophanic acid, caffic acid, eugenlin, hypericin, tannins (condensed)	Inhibition of viral RNA and DNA replication.
Asteraceae, *Apiaceae, Campanulaceae Panax ginseng*, *Chrysanthemum sibiricum*	Polyacetylenes (polylines)	Membrane interaction. Phototoxic activity
Achyrocline flaccida, *Bostrychia montagnei*, *Cedrela tubiflora*, *Prunella vulgaris*, *Sclerotium glucanicum*, *Stevia rebaudiana*, *Rhizophora mucronata*	Polysaccharides	Blocks viral binding
Ricinus communis, *Abrus precatorius*, *Adenia digitata*	Dimeric cytotoxins	Interaction with ribosome function in the infected cell.
Aspilia, *Chenactis douglasii*, *Dyssodia anthemidifolia*, *Eclipta alba*, *Eriophyllum lanatum*	Polysaccharides	Blocks virus binding

Conclusion

There is indeed an urgent continuing need to screen plant extracts for their antiviral activity in light of COVID-19. Also, the isolation and structural elucidation of the antiviral isolates which can form the platform for the synthesis of novel antiviral drugs. Plants antiviral activity may overlap with its antimicrobial, antidiabetic, anticancer activity, etc. The same class of natural products may have versatile medicinal roles. Current, synthetic antiviral drugs can be modified synthetically to study their antiviral structure activity relationship. Since viruses mutate, it seems as though combination cocktail drug treatment and the use of combined plant extracts may be the way forward for antiviral treatments. Antiviral research in any country will need approval from WHO in the future, as any virus in any country can mutate to a resistant strain, that could affect the entire world.

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