

REVIEW ARTICLE

Important Jamaican Medicinal Plants with special reference to their antiviral activity.

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Abstract: Plants have had historical significance in medicine since the beginning of civilization. The oldest medical pharmacopeias of the African, Arabian, and Asian countries solely utilize plants and herbs to treat pain, oral diseases, skin diseases, microbial infections, multiple types of cancers, reproductive disorders among a myriad of other ailments. The World Health Organization (WHO) estimates that over 65% of the world population solely utilize botanical preparations as medicine. Due to the abundance of plants, plant-derived medicines are more readily accessible, affordable, convenient, and have safer side-effect profiles than synthetic drugs. Plant-based decoctions have been a significant part of Jamaican traditional folklore medicine. Jamaica is of particular interest because it has approximately 52% of the established medicinal plants that exist on earth. This makes the island particularly welcoming for rigorous scientific research on the medicinal value of plants and the development of phytomedicine thereof. Viral infections like human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2), *hepatitis virus B* and *C*, *influenza A* virus, the *severe acute respiratory syndrome coronavirus 2* (SARS CoV-2) have significant global burden. This is a review of some important Jamaican medicinal plants, with particular reference to their antiviral activity.

Keywords: phytomedicine; viral infections; antivirals; phytoantiviral

1. Introduction

Viral infections like the human immunodeficiency viruses types 1 and 2 (HIV-1 and HIV-2), herpes simplex virus (HSV), respiratory viruses like; rotaviruses, respiratory syncytial viruses (RSV), influenza A virus, the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) that causes the human coronavirus (COVID19), tuberculosis, and hepatitis B and C viruses, malaria,

yellow fever virus (YFV), human papilloma virus (HPV), dengue-virus type 2 (DENV-2) and coxsackie virus all have significant global burden. In modern Western medicine, natural preventative and therapeutic alternatives are increasingly gaining attention because they have fewer and less adverse side-effects, are safer, and have potentially greater therapeutic efficacy than synthetic drugs. These make natural alternatives more desirable as novel drug therapies. Interest in phytoantivirals has also been renewed because of the increasing global burden of viral infections, particularly those that are newly emerging, and increasing antiviral resistance among viral strains against conventional synthetic antiviral drugs like Acyclovir and Ganciclovir.

In many parts of the world, particularly in rural, developing countries, herbalism is the only form of traditional medicine. In 2011, the WHO estimated that between 65 and 80% of the world population use botanical preparations as medicine [1]. Thousands of years of anecdotal evidence support the medicinal claims of these plants, but for the vast majority, rigorous scientific monitoring and research are required to study the mechanisms of action of the bioactive compounds, and their safety and efficacy [2]. It is estimated that some 25% of medicines on the global market are synthesized from natural products [3]. Plants from which popularly used drugs worldwide have been derived include; *Ephedra sinica* used to make methamphetamine and pseudoephedrine, Willow bark to make Aspirin, *Penicillium chrysogenum* to make Penicillin, *Papaver somniferum* (opium poppy) to make morphine, codeine and heroin, *Taxus brevifolia* to make taxol, and *Vinca rosea* to make vincristine. The WHO has also estimated that the value of the global market for plant-derived products is around 83 billion [1].

Through ethnobotanical screening, thousands of plants and their biologically active ingredients have been identified. Of the estimated 300,000 plant species that exist worldwide, only around 15% have been evaluated for their pharmacological activity [4]. It is estimated that two-thirds of the world's plant species have medicinal value [5]. These medicinal plants produce primary and secondary metabolites, that, in addition to providing health benefits to humans, may have original intended use in the plant as biological defenses against herbivores. The plant kingdom (including microbes, lichens, algae, and higher plants) produce an estimate 600,000 to 700,000 phytochemicals, with at least 150,000 to 200,000 being bioactive compounds [9].

Some active compounds in these plants responsible for the therapeutic effects of phytoantivirals include alkaloids, anthraquinones, coumarins, polyphenols (flavonoids, tannins and rosmarinic acid), phenolic acids, lignans, naphthoquinones, peptides, alkaloids, nitrogenated compounds, polysaccharides and terpenes. Lipophilic terpenoids (essential oils) disrupts the virus envelope's lipid double layer and may even cause it to lyse [10]. Polyphenols (e.g. flavonoids) and phenolic acids may prevent the virus from docking to the host cell [10]. Phytochemicals like alkaloids (e.g. quinoline), furanocoumarins, aristolochic acid, macrozamin and cyasin can attack and mutilate nucleic acids (DNA and RNA) either by alkylating the DNA molecule or intercalating within the DNA molecule [10]. Other active ingredients that have been used in ancient/traditional medicine include extracts of strychnine, quinine, and morphine (European medicine), camptothecin and taxol (Chinese medicine), and Vinca alkaloids vincristine and vinblastine extracts from the Madagascar periwinkle (*Catharanthus roseus*) [11]. Other important biological actives that have been discovered from plants include resveratrol and curcumin.

Despite the increasing clinical research on phytoantivirals, there is need for more rigorous screening of more plants to identify new phytochemicals. Further research is required to determine the efficacy, dosage standards, optimum extraction methods/solvents, cytotoxicity/hepatotoxicity, pharmacokinetics, molecular mechanisms of action, phytoantiviral screening methods, and drug interactions for many phytoantivirals.

Modern research around the world needs to now focus on the pharmacological activities of the constituent compounds of these plants and mapping their genomes and transcriptomes to produce target drugs. These compounds include alkaloids, anthraquinones, coumarins, polyphenols (flavonoids, tannins and rosmarinic acid), phenolic acids, lignans, naphthoquinones, peptides, polysaccharides and terpenes. The Medicinal Plant Transcriptomics Database is a publicly-available, comprehensive genomic and transcriptomic medicinal plant database. Using sequencing technology and synthetic biology, this genomic and transcriptomic mapping database will allow for the development of synthetic drugs that will be able to target a certain molecular pathway in a given disease process. The Herbal Medicine Omics Database (HMOD) also provides transcriptomic and genomic profile databases for medicinal plants.

A 2017 book titled *State of the World's Plants* by B. Allkin (edited by KJ Willis) reports that at least 28,187 plants are known to have medicinal use. The scientific names of these medicinal plants were recorded by Kew's Medicinal Plant Names Services (MPNS) who determined that of the 20 largest plant families, most medicinal plants in used worldwide are only distributed across the top 12 families. The top seven plant families are Fabaceae, Lamiaceae, Euphorbiaceae, Apocynaceae, Apiaceae, and Ranunculaceae [12].

The purpose of this article is to review the state -of-the-art developments in phytomedicines in Jamaica, with particular focus on antivirals. This should provide a valuable reference for further studies on development and clinical translation of these phytomedicines.

2. Jamaican plants with medicinal potential

Medicinally, there is increasing focus on Jamaica because of the wide biodiversity of strains. Plant-based decoctions have been a significant part of Jamaican traditional folklore medicine primarily to treat the common cold, flu, headache, nausea, pain reproductive system disorders and digestive issues, among some of the aforementioned diseases that are of significant global burden. Popular medicinal plants used in traditional Jamaican folk medicine include *Momordica charantia* L. (Cerasee), *Aloe barbadensis miller* (Aloe Vera), *Cannabis sativa* (Ganja), *Cola acuminata* (Bissy), *Morinda citrifolia* (Noni), *Pothomorphe umbellad* (Cowfoot Leaf), *Cinnamomum tamala* (Bay leaf), *Zingiber Officinale* (Ginger), *Bryophyllum pinnatum* (Leaf-of-life), *Moringa oleifera* (Moringa), *Panax ginseng* (Ginseng), *Mikania micrantha* (Quako), *Marrubium Vulgare* (White horehound/"Mint"), *Andrographis paniculate* (Rice bitters), *Curcuma Longa* (turmeric), *Petiveria alliacea* (Guinea hen weed), *Camellia Sinensis* ("Tee tree"), *Alysicarpus vagilinas* (Medina) and *Allium Sativum* (Garlic). Jamaicans have used a combination of these plants for detoxing and to treat a wide range of health conditions including, but not limited to; headache/migraine, sinusitis, asthma, diarrhea, constipation, nausea, pain, inflammation, cancer, diabetes, reproductive disorders, period cramps, common cold, flu, arthritis, skin disorders, prostate disorders, nerve disorders, mood disorders, vomiting, food poisoning, and hypertension [12].

Popular in the Jamaican ethnomedical heritage is what is known as a “root tonic” or “strong back”. This drink is a decoction of plants including, but not limited to *Smilax balbisiiana* (“chainy root”), *Smilax ornata* (sarsaparilla), *Zingiber officinale* (“ginger”), *Alysicarpus vaginalis* (“medina”), *Morinda royoc* (“redgal”), *Desmodium incanum* (“tick clover”), *Cuphea parsonsia* (commonly referred to as “strong back leaf”), *Trophis racemosa* (“ramoon”), and *Iresine diffusa* (“nerve west”) [14]. This decoction is commonly used by males to treat impotence, and increase stamina. However, many of these constituents like *Zingiber officinale*, *Cuphea parsonsia*, *Smilax ornate*, and *Alysicarpus vaginalis* have noted anti-viral activity.

A 2011 ethnomedicinal survey by Picking and colleagues investigated popular medicinal plants in Jamaica and confirmed the significance of plants and herbs in primary health care in Jamaica [13]. This survey followed the TRAMIL network ethnomedicine methodology. The TRAMIL network is a Caribbean-based network of collaborators conducting scientific evaluations of medicinal plants in the region. The questionnaire was administered to 407 randomly selected adults, from randomly selected geographical clusters across Jamaica. The survey revealed that respondents used 116 medicinal plants for various ailments. Of these, 94% (107 plants) were distributed across fifty-one plant families. The top 5 families with the most frequent plant families identified were Fabaceae, Lamiaceae, Asteraceae, Malvaceae, and Piperacerae [13]. Common plants of the Fabaceae family include Legumes, Maranga, Strong Back, Dandelion and Medina. Common herbs of the Lamiaceae family include Basil, Sage, Rosemary, Oregano, Thyme, Mentha and Lavender. The Lamiaceae family is commonly known as the Mint family. Some plants of the Asteraceae family include of Marogold, Spanish Needle, Quaco Bush. Common plants of the Malvaceae family include Bissy, Sorrel, and Hibiscus.

Of the 107 plants identified by survey respondents, 8 are endemic to Jamaica. These are *Piper amalago* (Pepper elder), *Rhytidophyllum tomentosum* (“Search-mi-heart”), *Bidens reptans* (“McKatty Weed”/“Marigold”), *Peperomia amplexicaulis* (“Jackie’s saddle”), *Oryctanthus occidentalis* (“Godbush”), *Pilea microphylla* (“Baby puzzle”), *Smilax balbisiiana* (“Chany Root”), and *Boehmeria jamaicensis* (“Doctor Johnson”). Of these, *Piper amalago* has the most notable medicinal use [13].

The common cold, which may be caused by different viruses, was among the most prevalent health issues in Jamaica. Leaf of Life (*Bryophyllum pinnatum*) and Jack-in-the bush (*Eupatorium odoratum* L.) with equal or greater than 20% frequency of use for these viral infections in Jamaica [13].

A 2006 study by Mitchell and Ahmad investigated and summarized all the medicinal plant research carried out on Jamaican medicinal plants between 1948 and 2001 at the Faculty of Pure and Applied Science, University of the West Indies (UWI), Mona, Jamaica [15]. Mitchell and Ahmad report that Jamaica has at least 334 medicinal plant species. However, only 193 were tested for their bioactivity—80 plants of which were reported to have reasonable bioactivity. Natural products were also identified from 44 of these plants. Of the plants tested at UWI, only 31 were endemic to Jamaica. Some 23% percent of these 31 plants were tested and found to be bioactive [15].

3. Jamaican plants with major antiviral activity.

Of the many plants which have important antiviral activity, those used most frequently in Jamaica for the common cold and influenza viruses are: Cerassee (*Momordic charactia*), and

Fevergrass (*Cymbopogon citratus*), Tamarind leaves (*Tamarindus indica*, Thyme (*Thymus vulgaris*), Sarsaparilla (dried root) (*Smilax ornata*), Soursop leaf (*Annona muricata*), Pimento Leaf (*Pimenta dioica*), Garlic (*Allium sativum*), Leaf of Life, Search-mi-heart (*Rhytidophyllum tomentosum*), Mint (*Mentha piperita*), Cinnamon (*Cinnamomum verum*), Pimento leaf (*Pimenta dioica*), Oregano (*Oregano vulgare*), Papaya leaf (*Carica papaya*), and Medina (*Alysicarpus vaginalis*). Some Jamaican plants reported to have antiviral activity are shown in Figure 1 and are discussed below.



Ball Moss/\"/>

Anti-viral activity against *HIV*.



Aloe Vera/\"/>

Anti-viral activity against *herpes simplex virus* types 1 and 2 (HSV-1 and 2), *varicella-zoster virus* (VZV), *pseudorabies virus*, common cold (multiple etiological agents), *cytomegalovirus* (CMV) and the human *Influenza viruses*.



Ganja
(*Cannabis Sativa*)

Anti-viral activity against *HIV/AIDS* wasting syndrome, *Hepatitis viruses*, *human coronavirus*, common cold.



Guinea Hen Weed
(*Petiveria alliacea*)

Anti-viral activity against *HIV*, common cold, *Human Influenza viruses*, *Hepatitis C*.



Ginger
(*Zingiber officinale*)

Anti-viral activity against the common cold, *Human Influenza viruses*, *Respiratory syncytial virus*.



Turmeric
(*Curcuma longa*)

Anti-viral activity against *Hepatitis C*, *Epstein-Barr Virus* (EBV), *HIV-1*, *Human Influenza viruses*, *parainfluenza viruses*



Moringa
(*Moringa oleifera*)

Anti-viral activity against *Infectious Bursal Disease Virus*, *Human Influenza viruses*, *HSV-1 and 2*, *HIV/AIDS*, *Epstein-Barr Virus* (EBV), *Hepatitis B Virus*,



Lignum Vitae
(*Guaiacum officinale*)

Anti-viral activity against *HIV*. Also used to treat reproductive disorders in the Caribbean.

1, 2 and 3, adenovirus and respiratory syncytial virus, H1N1, H6N6.

Foot and Mouth Disease Virus in animals, and Newcastle Disease Virus in birds.



Garlic

(*Allium sativum*)

Anti-viral activity against *Human Influenza viruses*, *Parainfluenza virus type 3*, *vaccinia virus*, *HSV 1*, *HSV 2*, *human rhinovirus type 2*, *vesicular stomatitis virus*.



Sorrell

(*Hibiscus sabdariffa* L.)

Anti-viral activity against *Human Influenza viruses*, *HSV-2 virus*,

Figure 1. Jamaican plants reported to have antiviral activity.

3.1 *Ball Moss*/"Old Man's Beard" (*Tillandsia recurvata*)

The *Tillandsia* L. genus is made up of approximately 650 species and belongs to the Bromeliaceae family endemic to North and South America and the Caribbean. Pineapples, although of a different genus (*Ananas*), are also of the Bromeliaceae family. These species differ in growth habit, trichome distribution, type of fruit, seed, leaflet, photosynthesis, type of pollinator, and its epiphytes [16]. *Tillandsia recurvata* (Ball Moss) has been used in traditional medicine to treat kidney inflammation (Bolivia), rheumatism, ulcers and hemorrhoids (Brazil), menstrual disorders (Mexico), eye infection (Uruguay), and Leucorrhea (USA). Most species of the *Tillandsia* L. genus are epiphytes on trees, inert substrates, rocky slopes, phone wires, electricity lines, or may survive independently in soil. It should be noted that *T. usneoides* ("Spanish Moss") and *T. recurvata* ("Ball Moss") are not mosses but, instead, angiosperms – produces flowers. The primary compounds in *Tillandsia* genus are triterpenoids and sterols (51%), flavonoids (45%) and cinnamic acid (4%). Lowe and colleagues discovered Dicinnamoyl-Glycerol Esters in the Ball moss plant, with both anti-Cancer and anti-HIV properties (US patent #US8907117B2) [17]. These anticancer and anti-viral properties may also be due to the naturally occurring cycloartanes found in the ball moss plant – cycloartane-3,24,25-diol and

cycloartane-3,24,25-triol [18]. A 2020 study by Gao and colleagues also confirmed anti-HIV properties of tillandsia [19].

3.2 *Aloe Vera (Aloe barbadensis miller)*

The antiviral activity of *Aloe barbadensis miller* may be due to a number of phytochemicals including vitamins, minerals anthraquinones like (emodin, chrysophanic acid and hypericin), polyphenols (e.g. flavonoids), polysaccharides, phenolic acids and sterols [20]. A 2018 study by Gansukh and colleagues investigated the anti-influenza activity of flavonoids and phenolics found in Aloe vera [21]. A 5-minute ultrasonic water extraction of Aloe emodin, an anthraquinone prepared from aloin from the *Aloe barbadensis miller* plant, showed anti-influenza activity with zero cytotoxicity [21]. Aloe emodin was also able to inactivate herpes simplex virus types 1 and 2, varicella-zoster virus, pseudorabies virus, and the influenza virus, by partial destruction of the virus' envelope [22]. Lectins, extracted from the gel portion of the leaves of *Aloe barbadensis miller* also showed antiviral activity against the human cytomegalovirus (CMV) in cell culture [23].

Aloe vera's anti-HSV-1 activity was also assessed and confirmed in a 2016 study by Rezazadeh and colleagues [24]. A preparation of aloe vera gel showed significant (0.2-5%) inhibition of herpes simplex virus-1 cells isolated from the lip lesions of a patient and grown cell culture (Vero cells) [24]. Aloe vera was also shown to inhibit HSV-2 attachment and post-attachment processes, and entry into Vero cells [25].

3.3 *Ganja (Cannabis sativa)*

It is estimated that the Cannabis plant (*Cannabis sativa* L.) produces around 545 [26]. chemical compounds belonging to biogenetic classes [27]. Of these compounds, the two most prominent and most studied are the secondary metabolites (phytocannabinoids)— Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) and Cannabidiol (CBD), both of which have a wide therapeutic window against many ailments. In addition to these secondary metabolites, the Cannabis plant produces hundreds of non-cannabinoids secondary metabolites, also with a wide range of therapeutic applicability against many ailments. These include terpenoids, flavonoids, stilbenes, lignans, and alkaloids. Some of these phytochemicals have antiviral activity. Resveratrol (3,4',5-trihydroxy-*trans*-stilbene), a common stilbenoid found in Cannabis, cranberries, grapes and other plant species has antiviral activity [28]. The following terpenes also have antiviral activity— Limonene [29] and Ocimene [30]. A 2020 study by Ngwa and colleagues reported that a small antiviral flavonoid molecule Caflanone has selective activity against the human coronavirus hCov-OC43 (Covid-19) [31].

Cannabidiol (CBD) is one of 100 pharmacologically active terpenophenic/lipophilic compounds called Cannabinoids—found in the Cannabis sativa plant. CBD It is the major non-psychoactive/non-intoxicating component of the cannabis plant. This simply means that it doesn't get you "high". CBD still, however, retains its therapeutic properties and benefits.

CBD can be used to regulate the immune system's response to viruses (and other invading pathogens). The Immune systems uses oxidative stress (via reactive oxygen species) to

combat invading pathogens. During many disease processes, the cells of the body accumulate high levels of reactive oxygen species (R.O.S.). This may be due to reasons including, but not limited to; increased metabolic activity, increase oxidase activity, and/or increased mitochondrial activity. In excess, oxidative stress can cause tissue and organ damage. Numerous studies show CBD's potential as an anti-oxidant. CBD inhibits neurotoxicity and oxidative stress by reducing inflammation, production of reactive oxygen species and other oxidative stress parameters [32] associated with infections by pathogens. A proposed mechanism of action of CBD is the induction of ROS production. When oxygen is metabolized in the body, ROS is produced. In moderation, ROS is involved in homeostasis and signaling and are associated with the maintenance of healthy cells [32]. Antioxidants like CBD mitigate excessively produced reactive oxygen species within the cells, and in doing so, reduce the oxidative stress in cells [5]. Antioxidants may therefore have therapeutic applicability against many human diseases including but not limited to viral infections, but also cancer cardiovascular diseases and inflammatory diseases [5].

3.3.1 *Cannabidiol (CBD) and HIV/AIDS*

CBD is used to alleviate the wasting syndrome associated with HIV and AIDS [33]. It is used as an antiemetic and orexigenic agent (appetite stimulant), and may generally just improve the overall quality of life of an HIV/AIDS patient. Anecdotal evidence suggests that CBD in HIV/AIDS patients may improve appetite, reduce nausea and vomiting, increase caloric intake, promote weight gain, improve memory and dexterity, improve mood, and mitigate the negative side effects of current anti-retroviral therapeutic agents [33]. In terms of disease progression (morbidity) and delaying the likelihood death from HIV/AIDS, current studies show that CBD is not effective [33].

3.3.2 *Cannabidiol (CBD) and Hepatitis viruses*

Liver disease in general, is a major global health burden. Viral hepatitis is a disease of the Liver characterized by liver inflammation and damage as a result of viral infection. Viral hepatitis is commonly caused by one of five hepatotropic viruses (hepatitis A, B, C, D and E), but may be caused by other viruses like the Herpes simplex virus (HSV) Yellow fever virus (YFV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Hep A, Hep B, and Hep C are the most common causes of viral hepatitis. Hep A and Hep E are spread by the fecal-oral route, that is, contamination via contaminated food or water. Hep B, Hep C and Hep D are spread through blood-transfusion. There's evidence that these may also be spread sexually.

Hepatitis may also be caused by other types of micro-organisms including bacteria, fungi and even parasites, non-infectious agents like drugs and alcohol, and other metabolic and autoimmune diseases [34]. Hepatitis infections may either be acute (short-term), where the body will be able to resolve the infection or chronic (long-term), where the body is unable to resolve the infection, resulting in liver failure, liver cirrhosis and liver cancer.

In a 2017 *in vitro* study by Lowe and colleagues explored the bioactivity of CBD against Hepatitis B and C viruses [35]. The anti-hepatitis B assay was carried out using HepG2 2.2.15 cells that produce high levels of the HBV wild-type ayw1 strain. The anti-hepatitis C assay utilized Huh7.5 cells mixed with cell-culture derived HVC. In both assays, cells were plated in a 96-well microtiter plate. A single concentration of 10 μ M of these test compound (CBD) was

then added to both microtiter well plates, incubated, and an analysis of antiviral activity was determined by calculated the percent inhibition of viral replication. CBD was shown to have inhibitory effects against Viral Hepatitis C (HCV) but not Viral Hepatitis B (HBV). In a dose-response assay, at a single concentration of 10 μ m, CBD was able to dose-dependently inhibit HCV replication by 86.4% [35]. CBD also seems to have therapeutic efficacy against Autoimmune/Non-viral hepatitis [35]. CBD shows *in vivo* activity through its interaction with the CB2 receptor. This interaction inhibits the pathogenesis of autoimmune hepatitis by inducing the apoptosis of thymocytes and splenocytes. This in turn, inhibits T-cells and macrophages attacking the liver thereby inhibiting the release of pro-inflammatory cytokines [35].

Myeloid-derived suppressor cells (MDSCs) are responsible for regulating the immune system by suppressing T-cell function and inhibiting liver inflammation. Through interaction TRPV1 receptor, CBD is shown to activate MDSCs, thereby inhibiting inflammation and hepatitis in a murine model [36]. In a concanavalin A model of acute hepatitis in mice, Hegde and colleagues report that CBD was able to reduce ConA-induced inflammation by inhibited the production and release of various pro-inflammatory cytokines, and protect the mice from acute liver injury [36].

3.3.3 *Caflanone (a non-cannabinoid secondary metabolite found in Cannabis sativa)*

Caflanone is a small phytoantiviral flavonoid molecule with selective activity against the human coronavirus hCov-OC43 (Covid-19) belonging to clade b of the genus Betacoronavirus same as SARS-COV-2 [34]. In preclinical studies, Caflanone inhibited the hCov-OC43 human Coronavirus with an EC50 of 0.42 μ M [31]. In Silico studies show that the Caflanone molecule carries out its prophylactic mechanism of action by inhibiting the Angiotensin-converting enzyme 2 (ACE2) receptor found in the lung and respiratory tract, used by the virus to cause an infection [31]. Caflanone was also shown to have strong binding affinity to two of the proteases (PLpro & 3CLpro) are vital to the replication of SARS-COV-2 in humans, which would inhibit viral entry to and/or replication within human cell [31].

The following phytoantivirals were investigated and compared to Chloroquine (CLQ), a potential COVID-19 prophylactic and therapeutic agent currently in clinical trials. The docking/binding studies results below show that the phytoantiviral Flavonoids (Hesperetin, Myricetin, Linebacker, and Caflanone) could bind equally or more effectively than CLQ [31]. (Figure 2)

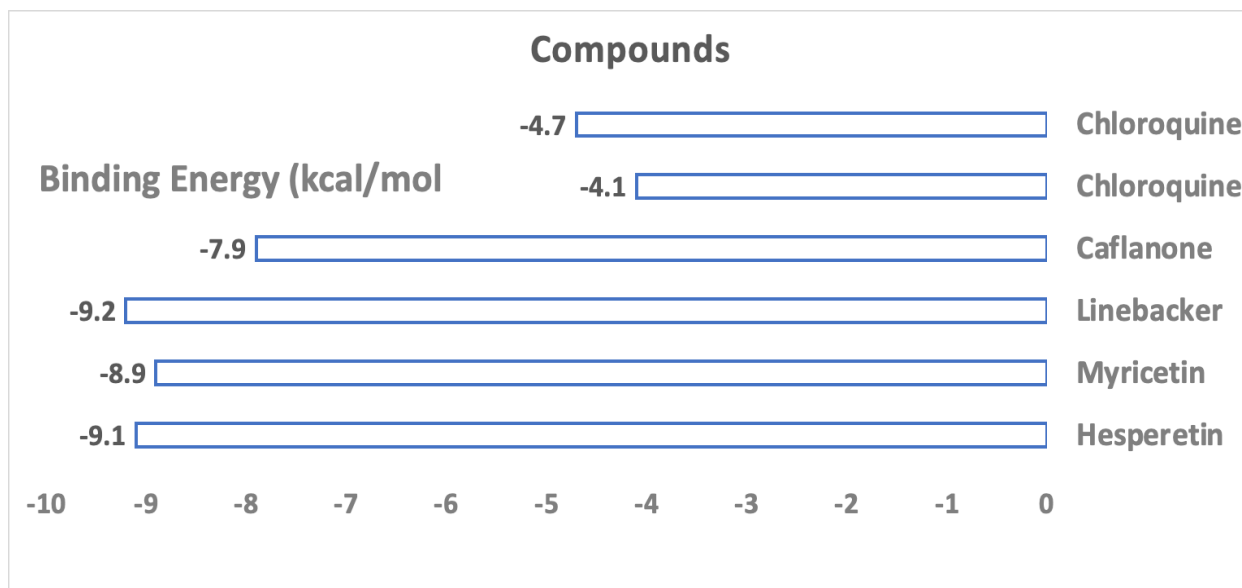


Figure 2: Chart showing docking study results for flavonoid molecules from plants that can bind very effectively to the ACE2 receptor used by SARS-CoV-2 virus to infect cells. Results are shown in comparison to chloroquine which has two possible binding energies (adapted from [31])

3.3.4 Terpenoids as antiviral agents.

The Medical Cannabis Network of Israel also reports that a current study is being undertaken by researchers at the Israel Institute of Technology investigating the therapeutic efficacy of a cannabis terpene inhalant formulation in suppressing the immune system response against COVID-19 [37]. A molecular docking analysis also reported the antiviral activity of Ginkgolide A, a terpenoid produced by the *Ginkgo biloba* tree, against COVID-19 [38].

3.4 Guinea Hen Weed (*Petiveria alliacea*)

P. Alliaceae is a herbaceous shrub belonging to *Petiveriaceae*, the pigeonberry family. It is native to tropical regions like Africa, India, the Caribbean, tropical areas of North and Central America. *P. Alliaceae* produces a number of bioactive compounds including polyphenols, alkaloids, tannins, coumarins, steroids, essential oils, dibenzyl trisulphide, and flavonoids [39]. These phytochemicals are responsible for Guinea hen weed's wide therapeutic window as an anxiolytic, anticonvulsant, antinociceptive, neuroprotector, cognitive enhancer, and antidepressant [39].

Dibenzyl trisulphide/DTS ($C_{14}H_{14}S_3$) in the Guinea Hen Weed is responsible for its anti-cancer, anti-HIV, and anti-hepatitis C properties [40, 41]. The anti-cancer and anti-viral properties of this compound may be due to its interaction with the mitogen activated protein, extracellular-regulated kinases 1 and 2 (MAP Kinases Erk 1/Erk2) pathway [41]. The mechanism by which DTS inhibits HIV-1 activity is by inhibition of the reverse transcriptase (RT) activity of the HIV-1 virus [40]. Anecdotal evidence also suggest that Guinea Hen Weed may also be used to combat the influenza viruses.

3.5 Ginger (*Zingiber officinale*)

Ginger is frequently used in Jamaica as an antiemetic and antinauseant. In addition to being an antioxidant, antimicrobial, anti-inflammatory, and anticoagulant [42], fresh ginger, as opposed to dried, has also been reported to be antiviral, inhibiting human respiratory syncytial virus-induced plaques in vitro [42]. The cells evaluated were of the human upper (HEp-2) and low (A549) respiratory tract cell lines. The bioactive compounds in ginger that are responsible for the wide therapeutic window of ginger include ketones, phenolic compounds, terpenoids (monoterpenoids and sesquiterpenoids), esters, aldehydes, and alcohols [43].

3.6 Turmeric (*Curcuma Longa L.*)

Turmeric (*Curcuma longa L.*) is the belowground portion (rhizome) of the ginger plant, of the family Zingiberaceae. Turmeric is a widely used spice, food preservative, food coloring and dye but has also been employed for its medicinal value [44]. It has a wide therapeutic window as an antiviral, aseptic, antibacterial, antifungal, anticancer, anti-phlegmatic antiprotozoal, antioxidant, anti-inflammatory, antifibrotic, antifertility, antiulcer, antivenom, anticarcinogenic and anticoagulant [44]. In traditional Eastern medicine it is used to treat respiratory ailments, eating disorders, digestive disorders, hepatic disorders and biliary disorders [44].

The primary phenolic compounds (curcuminoids) produced by turmeric are curcumin (diferuloylmethane), demethoxycurcumin and bisdemethoxycurcumin [44]. Other bioactive compounds produced include *sodium curcuminat*e, essential oils (e.g. turmerone, zingiberene and sesquiterpenes), monoterpenoids, and sesquiterpenoids. In addition to being an antiviral, curcumin is anti-inflammatory, anti-tumorigenic and anti-oxidant [45]. It is also responsible for the orange-yellow colour of Turmeric. An *in vitro* study reported the antiviral activity of curcumin against three major molecular pathways responsible for Epstein-Barr virus reactivation, and was shown to inhibit the transcription of BamH fragment Z left frame 1 (BZLF1) gene [46]. The anti-HIV-1 activity of curcumin was also assessed and confirmed via inhibition of the HIV-1 integrase [47]. Turmeric was also shown to display slight anti-viral activity against respiratory viruses. A 2007 study by Huang and colleagues demonstrated activity against the influenza viruses, parainfluenza viruses 1, 2 and 3, adenovirus, and respiratory syncytial virus [48]. Curcumin was also reported to inhibit H1N1, H6N6, herpes virus, coxsackievirus B3 (CVB3), human T-cell leukemia virus type 1, hepatitis C virus, high risk human papillomaviruses 16 and 18 (HPV-16 and HPV-18) [49].

3.7 Moringa (*Moringa oleifera*)

Moringa (*Moringa oleifera*) is popular tree native to India where it is widely eaten as a vegetable and utilized in traditional medicine. It is also used in the Western hemisphere for the same purposes. Moringa has a wide window of benefits, due primarily to bioactive compounds like phenolic compounds, saponins, tannins, amino acids, proteins, phytates, tocopherols (γ and α), carbohydrates, unsaturated fatty acids, oils, antioxidant compounds, and glucosinolates [50]. Other bioactive compounds include vitamins A, B1, B2, B3, B7, C, D, E, K, calcium, potassium, iron, magnesium, phosphorus and zinc [51]. The pharmacological compounds found in the moringa plant have medicinal properties including antimicrobial activity against viruses, bacterial, fungi and parasites. It is also generally known to boost the immune system.

Leaf extracts from *Moringa oleifera* showed anti-herpetic activity and were reported to successfully inhibit the growth of HSV-1 and 2 in Vero cells by 43.2 and 21.4%, respectively [52]. Ethanol leaf extracts of *Moringa oleifera* were also reported to have anti-influenza activity *in vitro* [53]. A 1998 study by Murakami and colleagues reported that Niaziminin, a thiocarbamate, and 4-[(4'-O-acetyl-alpha-L-rhamnosyloxy)benzyl] isothyanate (ITC) and allyl- and benzyl-ITC (two isothyanate-related compounds), were all able to inhibit Epstein-Barr virus (EBV) *in vitro* [54]. In another *in vitro* study, the effects of an aqueous extract of *M. oleifera* (leaves) were able to decrease the expression of hepatitis B virus genotypes C and H in Huh7 cells [55].

3.8 Lignum vitae (*Guaiacum officinale*)

The *Lignum vitae* (which translates to “wood of life”) is native to the Caribbean and South America. The wood has many industrial purposes, for example to make furniture. The flower is the national flower of Jamaica. In tradition Caribbean medicine, it is used as a stimulant, antiseptic, and to treat syphilis [56]. In Trinidad and Tobago, it is used to control fertility [56]. A 2014 study by Lowe and colleagues screened and investigated the anti-HIV properties of leaf, seed and twig extracts of the lignum vitae plant biomass against HIV-1 (strain HIV-1 BaL) infected peripheral blood mononuclear cells (PBMCs) [57]. The bioactivity is due to disaccharide arabinogalactan, a phenolic extract [57]. The main pharmacological compounds in this plant are Saponins. All the types of extracts/compounds tested inhibited HIV-1 replication in the infected PBM cells.

3.9 Garlic (*Allium sativum*)

Garlic (*Allium sativum*) is a member of the onion genus, *Allium*. It is another spice that is traditionally used in fundamental dishes around the world, but has also been used in traditional medicine for thousands of years. It has a wide therapeutic window as an antiviral, antioxidant antibacterial against both Gram-negative and Gram-positive bacteria, antifungal against *Candida albicans*, and antiprotozoal against *Giardia lamblia* and *Entamoeba histolytica* [58]. Anecdotal and scientific data also confirm Garlic’s therapeutic efficacy against diabetes, cancer, free-radical damage, atherosclerosis, heavy metal intoxication and hyperlipidemia. Garlic produces many bioactive compounds including flavonoids, enzymes, fructo-oligosaccharides, Maillard reaction products, and organosulphur compounds like S-allylcysteine, diallyl polysulfides, alliin, vinylidithins, allicin (diallyl thio-sulfinate), allyl methyl thiosulfinate, and ajoene [59]. These are responsible for garlic’s wide therapeutic window. These compounds are released and may be extracted from the cells of fresh, crushed garlic bulbs, and are responsible for the characteristic garlic smell. This is why it is usually eaten raw. Allicin is the main bioactive compound found in Garlic [58]. The bioactivity of Allicin and other organosulphur compounds may be attributed to their chemical interaction with thiol groups of other molecules [60].

A 2009 study by Mehrbod and colleagues reported Garlic’s anti-viral activity against the Influenza virus *in vitro* [60], further confirming the anecdotal evidence for its frequency of use in Jamaica against the flu and to “boost the immune system”. Garlic is frequently used in Jamaica to treat the common cold, too. A 2001 study by Josling evaluated an allicin-containing supplement against the common cold and confirmed this bioactivity [61]. In another study, an aged garlic extract supplement was reported to boost the immune system by inducing NK cell

function and proliferation of $\gamma\delta$ -T cells [62]. *In vitro* studies of Garlic extracts were also shown to produce anti-Influenza B and anti-herpetic activity (anti-HSV-1)[63]. This bioactivity was dose-dependent. Further studies are required to assess the antiviral activity of Garlic in human and animals. Garlic is also reported to be good for the cardiovascular system, having the ability to lower systolic blood pressure and ultimately treat uncontrolled hypertension [64]. A 2013 study by Ashraf and colleagues also confirm garlic's dose dependent and duration dependent ability to significantly lower both systolic blood pressure and diastolic blood pressure [65]. Garlic is further reported to be good for lowering cholesterol and thus may be used to treat hypercholesterolemia (a form of hyperlipidemia) [66].

3.10 Sorrel (*Hibiscus sabdariffa* L.)

In Jamaica the fresh calyx of the flower of Sorrel is commonly made into a drink and eaten in salads. However, it possesses significant medicinal value and may have applicability as a diuretic, sedative, emollient, demulcent antiscorbutic, analgesic, purgative, antipyretic, cholagogue, antiseptic, anti-tumorigenic, anti-cancer, aphrodisiac, and may be used to treat dyspepsia, disorders of the heart, hypertension, biliary disorders and abscesses [67]. Sorrel is also known antimicrobial, antioxidant, and anti-inflammatory. The antiviral activity of Sorrel was also assessed and shown to inhibit HSV-2 *in vitro* with safe cytotoxicity [68]. Sorrel was also reported to have anti-human *Influenza A* virus activity in vitro [69]. This bioactivity attributed to Sorrel may be attributed to a number of secondary metabolites including saponins, flavonoids, organic acids like protocatechuic acid, anthocyanins, glycosides, and alkaloids phenolic compounds [67].

4. Other Jamaican medicinal plants.

Other prevalent medicinal plants used in Jamaica are *Annona muricata* L. (soursop), *Solanum torvum* Sw. (Susumber), *Gliricidia sepium* Kunth (Maranga), *Morina citrifolia* L., (Noni), *Picrasma excelsa* (Sw.) Planch. (Bitterwook), *Cassia occidentalis* L. (Dandelion), *Mikania micrantha* Kunth (Quaco Bush), *Cola acuminata* (Bissy), Eucalyptus leaf/oil (*Eucalyptus radiata*), *Ricinus communis* L. (Castor Oil), Gum arabica (*Acacia nilotica*), Wormwood (*Artemisia absinthium*), Blackberries (*Rubus racemosus*) and raspberries (*Rubus rosifolius*), and *Hymenaea courbaril* ("Stinking toe").

5. Economic Analysis of Phytomedicines related to anti-viral drugs

According to a report titled "*Anti-Viral Drug Therapy Global Market Report 2020-30: COVID-19 Implications and Growth*" by Research and Markets, the global anti-viral drug therapy market is expected to grow from \$52.2 billion in 2019 to about \$59.9 billion in 2020 [70]. This is primarily due to the increase in demand for antiviral drugs for the treatment of COVID-19. The market is expected to stabilize and reach \$62.6 billion at a CAGR of 4.6% through 2023 [70]. According to a report titled "*Global Herbal Medicine Market Research Report - Forecast To 2023*" by Market Research Future, the Herbal Medicine Market is expected to reach \$ 111 billion by the end of 2023 [71]. The global herbal medicine market is projected to grow at a Compound Annual Growth Rate (CAGR) of ~ 7.2 % from 2017 to 2023 [71]. Jamaica's medicinal

cannabis market value is estimated to be around USD \$300-\$400 million. In consideration of the wide biodiversity of other Jamaican medicinal plants, this value could increase three-fold.

6. Conclusions and Future prospects

As estimated by the World Health Organization (WHO), over 65% of the world population utilize botanical preparations as medicine [1]. Natural alternatives are increasingly gaining attention because they have fewer and less adverse side-effects than synthetic drugs. This makes natural alternatives more desirable as novel drug therapies. Thousands of plant species still remain to be screened for their bioactivity. Only approximately 15% of some 250,000 species of higher plants have been studied for their pharmaceutical potential [4]. Only 5% of these plants had one or more biological activity [72]. This means that there is an enormous, untapped potential for the development of a myriad of plant-based therapeutics and pharmaceutical-grade proteins like vaccines, hormones, antibodies and cytokines [73].

Some 52% of the established medicinal plants that exist on earth grow in Jamaica. This makes the island particularly welcoming for rigorous scientific research on the medicinal value of plants and the development of phytomedicine thereof. This could have great economic and medicinal implications, not only for Jamaica, but for the region. Modern research around the world should now focus on the pharmacological activities of the phytochemicals and mapping their genomes and transcriptomes to produce target drugs. There is a need for more systematic botanical, physicochemical and chemical analyses of thousands of potential medicinal plants. Further research is required to determine the efficacy, dosage standards, optimum extraction methods/solvents, cytotoxicity/hepatotoxicity, pharmacokinetics, molecular mechanisms of action, phytoantiviral screening methods, and drug interactions for many phytoantivirals.

Creating and using universal sets of primers, databases and standards to catalogue species by research groups all around the world, would increase the level of reliability and the number of species available for study (which has reached the greatest level ever achieved by the scientific community) while also making it possible to identify an ever-growing number of species [74]. Also, a greater awareness of efficacies, toxicities and drug to drug interactions of traditional herbal medicines is required. Most importantly, before these plant-based drugs can be incorporated into conventional medicine, more randomized, double-blind, placebo-controlled clinical trials are needed on a larger scale. Data generated from such experiments should also be logged in a universal, open-access database. Countries dependent on traditional, synthetic medicine, need to re-shift focus to programs aimed at systematically studying the bioactive compounds from plants, and synthesizing new drugs from said compounds.

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