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Bamise Wilson Adeosun * and Du Toit Loots

Posted Date: 14 December 2023

doi: 10.20944/preprints202312.1014.v1

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Review

Viral Infections and Medicinal Plants: A Review of Metabolomics Evidence for the Antiviral Properties and Potentials in Plant Sources

Wilson Bamise Adeosun * and Du Toit Loots

Human Metabolomics, North-West University, Private Bag X6001, Box 269, Potchefstroom 2531, South Africa; dutoit.loots@nwu.ac.za

* Correspondence: bmsade@gmail.com

Abstract: Plants have developed unique mechanisms to cope with the harsh environmental conditions to compensate for their lack of mobility. A key part of their coping mechanisms is the synthesis of secondary metabolites. In addition to their role in plants' defense against pathogens, they also possess therapeutic properties against diseases, and their use by humans predates written history. Viruses are a unique class of submicroscopic agents, incapable of independent existence outside a living host. Pathogenic viruses continue to pose a significant threat on global health, leading to unprecedented fatalities on a yearly basis. The use of medicinal plants as a natural source for antiviral agents has been widely reported in literature in the past decades. Metabolomics is a powerful research tool for the identification of plant metabolites with antiviral potentials and can be used to isolate compounds with antiviral activities in plants and study the biosynthetic pathways involved in viral disease progression. This review discusses the use of medicinal plants as antiviral agents, with a special focus on the metabolomics evidence supporting their efficacy. Additionally, suggestions are made for the optimization of various metabolomics methods for characterizing the bioactive compounds in plants and subsequent understanding of the mechanism of their operation.

Keywords: viral infections; antiviral activity; medicinal plants; metabolomics

1. Introduction

The continuous emergence of viral diseases, leading to major global health challenges, warrants an intensified effort from a combined team of researchers and healthcare professionals. Continued/regularly occurring pathogenic viral infections of pandemic proportions, account for millions of deaths annually [1]. Although the development of conventional antiviral drugs has made a significant stride towards curbing this in the last decade, the limitations become increasingly conspicuous due to issues such as drug resistance [2], narrow spectrum of activities [3], costs [4], and adverse side effects [5]. This has led to a resurgence in the exploration of alternative treatment modalities from health stakeholders. Numerous chemical compounds found in natural sources are exclusive to plants, microbes, and marine life [6]. They provide important leads for drug discoveries and can potentially contribute to antiviral treatment/drug development [7–9]. Compounds derived from natural sources against viruses, play a crucial role in drug discovery and the development of new antiviral treatments [7,10]. Medicinal plants has emerged as a promising frontier in the search for innovative antiviral therapies [11].

Throughout history, different cultures have sought healing in the potency of plants for the alleviation of pains, and diseases. Their use in traditional medicine systems globally underscores their potential as a source of valuable antiviral compounds.

Plants respond to biotic and abiotic stress by synthesizing a large array of secondary metabolites with complex chemical combinations [12–14]. Although numerous studies have reported the activities and potentials of plants against viruses [15,16], it is important to validate traditional remedies through clinical trials [17,18].

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The arrival of advanced analytical techniques to modern scientific research presents an opportunity for the exploration of plant-based compounds for their therapeutic effects. Metabolomics has emerged as an indispensable tool for the identification of different classes of antiviral secondary metabolites from plants over the last decade. These include various flavonoids, terpenoids, alkaloids and polyphenols, each of which exhibit various therapeutic effects during different stages of the viral cycle (e.g. viral attachment, entry, viral replication, and release) [19]. These identified antiviral plant metabolites account for about a quarter of all drugs developed and used today [20,21].

The interplay between medicinal plants, viral infections, and metabolomics offers a multifaceted view of the possibilities and potentials inherent in plants towards the development of new antiviral therapeutics. This review highlights the role of metabolomics in the discovery and development of new antiviral bioactive compounds from medicinal plants. It also identifies the obvious gaps in current knowledge and offers comprehensive suggestions to future research directions.

2. Overview of Viral Infections

Viruses have been part of life since time immemorial. They are the smallest known agents of human infections, with a diameter that ranges between 20 - 200 nanometers [22]. Viruses are ubiquitous and can be found in animals, plants, humans, and other living organisms. All viruses are referred to as obligate intracellular pathogens since they cannot complete their life cycle without a living host [23]. Although many of them are benign, non-pathogenic and can even save lives, some however do contribute to a considerable number of infections in humans [24,25]. Viral infections additionally present a significant public health concern. Over the last few decades, there has been an emergence of many new viruses, with a significant number of them having deleterious effect on human health in several ways [26]. Siegel (2017), reported 26 virus families implicated in human diseases with each exhibiting different genomic structure, physiochemical properties, molecular processes, and morphology.

Viral infections are diverse types and include: 1) sexually transmitted infections, including hepatitis B, HIV, herpes simplex virus (HSV) and human papillomavirus (HPV); 2) gastrointestinal infections, which lead to gastroenteritis caused by noroviruses, rotaviruses, adenoviruses and sapoviruses; 3) zoonotic infections, caused by viruses that can be hosted by both animals and humans, e.g. ebola, rabies, and hantaviruses; 4) hepatic infections, which can result in hepatitis, e.g. hepatitis A, B, C, D and E viruses and others which include yellow fever and the Epstein-Barr virus; 5) Respiratory infections such as the common cold (caused by rhinovirus), flu (caused by influenza viruses), COVID-19 (caused by SARS-CoV-2 virus) and the respiratory syncytial virus (RSV) [27–29].

The most common of these viral diseases are those that affect the respiratory system [30]. A collaboration between researchers from several institutions and countries reported that respiratory diseases were the third leading cause of death worldwide between the year 1990-2019, only next to cancer and cardiovascular diseases [31]. The influenza virus, which is the causative agent for the acute respiratory infection-seasonal flu, remains one of the biggest threats to public health according to the World Health Organization (WHO). The organization gave an estimated amount of 290,000 - 650,000 flu related deaths annually [32]. The SARS-CoV-2 has accounted for at least 14.9 million deaths directly or indirectly at the height of COVID-19 pandemic between the years 2020 and 2021 according to WHO [33].

Viral infections are risk factors for other medical conditions also, since they have the potential to weaken the immune system and induce an inflammatory response from the host cell [26,34]. Recent studies confirmed that oncogenic viruses implicated in the development of some cancer, account for about 10% of all global cancer burden [35]and may also be responsible for long-term persistent infections [36]. Viral infections can also result in secondary bacterial infections, a condition in which infected patients are predisposed to health complications from bacterial sources, due to a weakened immune system [37–39]. Cardiovascular diseases have also been linked to viral infections [40]. In 1932, Collins, (1932) reported that the peak period of influenza pandemic in the United States was in direct proportion to an increase in heart diseases. Also, in the wake of Covid-19 pandemic,

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there were many reports of heightened cases of cardiovascular diseases linked to the SARS-CoV-2 virus [42,43]

The unique nature of viruses and their ability to rapidly mutate, leading to an emerging pathogenesis and drug resistance, makes the current therapeutic and prophylactic options available for treating these increasingly smaller (Rouse and Lukacher, 2010; Wong et al., 2017; Moghadas et al., 2008; Strasfeld and Chou, 2010b; Faraz et al., 2022).. Plants have been used for centuries as part of traditional medicine in the treatment of a variety of diseases, including various viral infections. Since the first attempt to screen over 200 plants for anti-influenza activity some 7 decades ago by (Chantrill et al., 1952), many additional studies have shown the vast potential of an enormous array of various medicinal plants across diverse geographical locations, for antiviral activity and the potential for antiviral drug development, and as a standalone or to be used as complementary therapeutic agents to conventional antiviral medicines [47–52].

Metabolomics, which is the study of all metabolites present in a biological system at a given time, has become a valuable tool for the identification and quantification of possible new therapeutic compounds from plants. A combination of techniques including: Nuclear Magnetic Resonance (NMR) and advanced hyphenated mass spectrometry, are now central to metabolomics studies and are routinely applied towards new biomarker identification for the purpose of bettering our understanding of the chemical profiles of plants and their applications to health and disease. The aim of this review is to comprehensively evaluate the available literature on the properties of a diverse range of plant metabolites with antiviral properties, with a specific focus on the evidence from metabolomics studies, and to explore their potential use in the development of novel antiviral therapies.

3. A Brief History of the use of Medicinal Plants Against Viral Infections

Medicinal plant use against a variety of viral infections across various cultures, dates to the dawn of human civilization. Traditional Chinese medicine, Eber papyrus of Ancient Egypt and the Ayurveda of India, are amongst the oldest cultures practicing medicinal plant use with well documented manuscripts available for such [53–55]. Ancient traditional Chinese medicine has a history of about 3000 years or more. Writings based on this practice describing the use of plants for healing purposes are among the oldest medical writings of any culture [56]. Examples of plants used to treat viral infections in ancient China include ephedra (*Ephedra sinica*) for the treatment of common cold [57], *Andrographis paniculata* for treating a cough, cold and influenza [58], *Camellia sinensis* (green tea) with confirmed activities against herpes, hepatitis B and C, and Epstein Barr viruses [59–61]. The Egyptian papyrus contains descriptions of plant and natural product preparations against plethora of diseases, also including various viral infections [62], with one of such plants being garlic (*Allium sativum*) [63], for the treatment of respiratory catarrh, influenza, and recurring colds [64]. Echinacea (*Echinacea purpurea*), also contained in the papyrus, has been reported to have activity against respiratory viral infections [65]. Ayurveda, a natural system of medicine with historical root in India, dating back to the last 3 millennia, describe the plants *Aegle marmelos*, *Ficus religiosa*, and *Azadirachta indica,* amongst others, to have activities against variety of viruses [52,66–68]. European herbal medicine and traditional African Medicine also have long history of incorporating plant use to combat various illnesses, including viral infections. Elderberry (*Sambucus nigra*) for instance has been used in Europe for many years as a remedy for colds and flu [69], while plants like *Sutherlandia frutescens* and *Artemisia afra,* native to Africa, have reported activities against various viral infections [70,71]. The last few decades have seen a resurgence in the use of medicinal plants as an alternative source for the treatment of various viral infections [72]. This is due in part to the rise in the prevalence of viral infections and growing concern about antibiotic resistance [73,74].

4. Mechanism of Actions of Antiviral Secondary Metabolites in Medicinal Plants

Plants' secondary metabolites are organic compounds that are not directly involved in the growth, development, or reproduction of plants. They are produced as a survival strategy for plants against adverse conditions in their surrounding environment, and also to carry out important

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physiological tasks [12]. There are various criteria used in determining the classification of secondary metabolites in plants, and include chemical structure, composition of constituent elements and how soluble they are in water or organic solvents. The most commonly accepted criterion however is their biosynthetic pathway [75]. Based on these pathways, three classes of secondary metabolites have been identified in medicinal plants: 1) alkaloids, 2) terpenoids and 3) phenolic compounds [76]. Each exhibit different phytochemical constituents and pharmacological activities against various viral agents [75,77]. Commonly reported mechanisms of action of plant derived secondary metabolites against viruses include: 1) virus entry attachment [78,79], 2) inhibition of viral replication [80,81], 3) protein synthesis inhibition [82–84], 4) modulation of the host's immune system [85], 5) modulation of cellular signaling pathway [86] and 6) direct virucidal activity [86,87].

4.1. Phenolics

Phenolic compounds are a diverse group of plant derived organic molecules characterized by the possession of at least one phenol group. They are the most widely distributed secondary metabolites in plants [88] and are synthesized as an adaptive response to unfavorable conditions [89]. Phenols are commonly found in all plant organs and are rich constituents of fruits, vegetables, beverages, cereals, and legumes [90].

Some well-known phenolic compounds include flavonoids, tannins, and phenolic acids. The specific mechanism of action of phenols against viruses depends on the type of phenolic compound and the virus been targeted. Phenols exert therapeutic interventions against viruses in a variety of ways, which include the disruption of the viruses' envelopes. The lipid bilayer surrounding virus-encoded membrane-associated proteins, in some viruses responsible for mediating interactions between the virus and host cell, can be inhibited by phenolic compounds. The tannin: epigallocatechin-3-callate, found in green tea [91], has been reported to inhibit the binding of HIV envelope glycoprotein gp120 to the glycoprotein CD4 receptor found on the immune cells surface [92,93]. Phenolic interventions generally disrupt the infectivity of the virus [94,95]. Many phenolic compounds have also been reported to inhibit viral entry into the target host cells [95–98]. These they do by interfering with viral attachment proteins, or the receptors on the host cell's surface [99,100]. An important step in the process of viral infection, is the replication process. Phenols often interfere with the process of viral replication by binding to and subsequently inactivating with various viral proteins or enzymes, and subsequently halt disease progression in the host cells [100–102]. Specific examples of compounds reported to interfere with viral replication includes epigallocatechin-3-gallate (EGCG), a catechin derived from green tea. EGCG has reportedly demonstrated inhibitory potential against M2 protein of influenza A virus. This it does by increasing IFN-λ2 expression in the human lung epithelial BEAS-2B cells, through the p38 mitogen-activated protein kinase signaling pathway [103]. Also, the inhibition of the HIV-1 enzyme reverse transcriptase and cellular DNA and RNA polymerases by four flavonoids namely quercetin, baicalein, myricetin, and quercetagetin were previously reported by ONO et al., (1990). The immunomodulatory effects of some phenolic compounds have also been previously indicated, where they are involved in the stimulation and production of signaling molecules, including cytokines and chemokines [105,106]. A key mechanism of defense against viral infection is programmed cell death [107]. Phenolic compounds can induce apoptotic cell death in host cell, and thereby limit the spread of viral infections [100,108,109]. Figure 1 schematically summarizes the antiretroviral activities of plant derived phenolic compounds effects.

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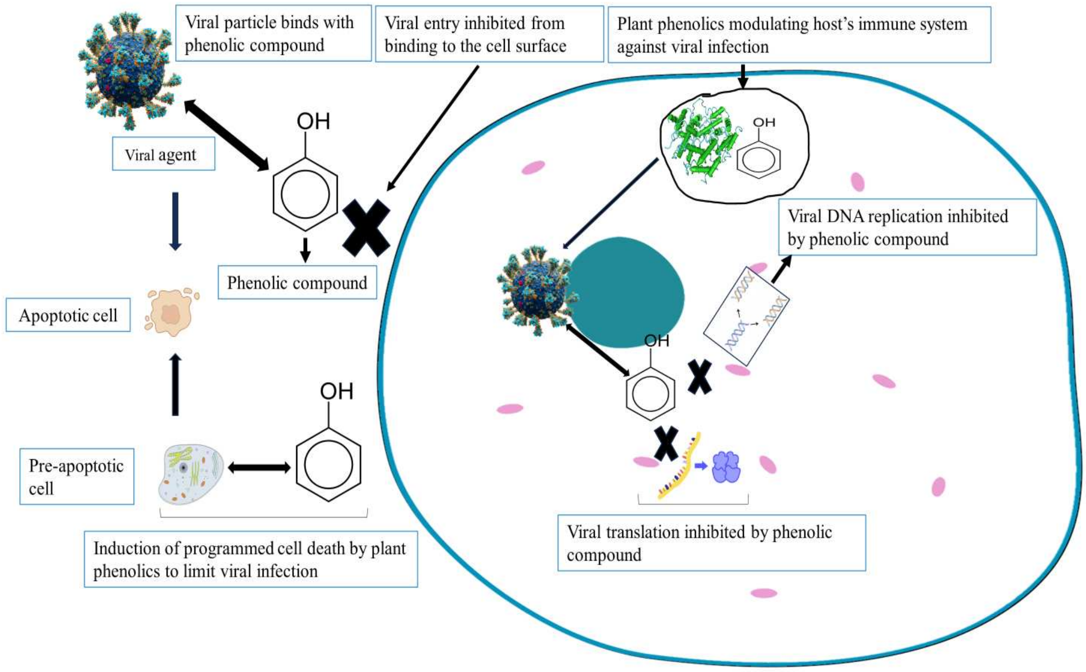

Figure 1. A schematic representation showing the mechanism of actions of the antiviral properties of phenolic compounds**.**

4.2. Alkaloids

Alkaloids, primarily but not exclusively present in plants, are a class of naturally occurring organic compounds containing at least one nitrogen atom. They can be found in many plant structures and have been reported to have pharmacological effects against various microbial diseases and viruses. Alkaloids have in particular been highlighted for their broad-spectrum activities against both DNA and RNA viruses [110,111]. Due to their importance, they have also been identified as the largest class of plants' secondary metabolites investigated to date for such (Abookleesh et al., 2022). The most well-known plant alkaloids found in nature include cocaine, morphine, and quinine.

Alkaloids have been identified as important inhibitors of the flow of genetic information (from the DNA/RNA viral particle to the protein synthesis), necessary to ensure the lifecycle of the virus. The antiviral activities of alkaloids, as proven by experimental evidence, primarily involves inhibition of: 1) DNA and RNA replication, 2) RNA translation, 3) protein synthesis, 4) DNA intercalation, 5) enzymatic activities, 6) the translocation of the ribonucleoprotein complex, 7) DNA synthesis, and 8) protein synthesis. Many studies have reported the use of alkaloids for the treatment and prevention of viral infections [111–113]. Alkaloids can also regulate human immune mechanisms towards viral resistance, by mediating the humoral immune response [114].

Below is a schematic representation of the antiviral activities of alkaloids.

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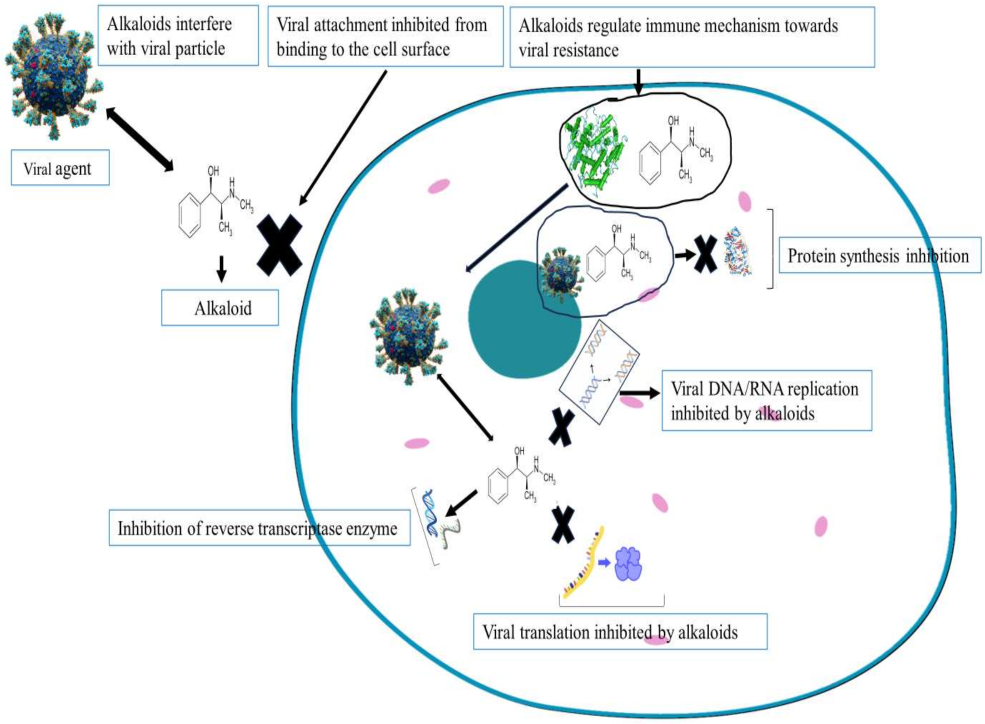

Figure 2. A schematic diagram showing the mechanism of the antiviral activities of alkaloids**.**

4.3. Terpenoids

Terpenoids are a large group of diverse organic products that are ubiquitous in nature. They exist in six categories namely: hemiterpenes, monoterpenes, sesqui-terpenes, diterpenes, sesterpenes, triterpenes, and tetra-terpenoids [115]. As an essential component of all living cells, they are products of both primary and secondary cellular metabolism [116]. Terpenoids are mostly present in the leaves and fruits of higher plants, where they sometimes contribute to their vibrant colors. They are also highly volatile and combustible organic compounds [117]. As aromatic metabolites, they are largely responsible for the flavor and fragrance of plants [118]. Terpenoids are of special interest to medical chemists because of their significant pharmacological activities [119]. Common terpenoids include citral, menthol camphor and salvinorin A.

Various terpenoids have been shown to possess promising antimicrobial and antiviral properties [120]. Those with reported antiviral activities include glycyrrhizin, an important antiviral chemical compound found in the roots of the licorice plant (Glycyrrhiza glabra) [121]. Historical sources from China [122], India [123], and parts of Europe [124] make references to the use of glycyrrhizin in the treatment of viral respiratory tract and liver infection, caused by hepatitis. Fiore et al., (2008), reported the immunomodulatory activities of glycyrrhizin due to induction of interferon gamma, and Richard (2021) described it's anti-inflammatory mechanisms. Glycyrrhizin furthermore inhibits replication of severe acute respiratory syndrome associated with corona virus (SARS-CV) infection, and also prevents the adsorption and penetration of the virus [127]. Isoborneol, a monoterpene present in a variety of different essential oils, totally inhibits the herpes simplex virus (HSV-1) replication, and that at a concentration of only 0.06% [128]. Additionally, β-pinene and limonene monoterpenes present in various essential oils, showed high anti-HSV-1 activity, and function by reducing the viral infectivity by 100%, by directly interfering with free viral particles [129]. Many studies have also indicated that celastrol, a pentacyclic triterpenoid, inhibits the replication of the dengue virus [130], human immunodeficiency virus [131], and hepatitis C virus [132]. Figure 3 shows a schematic summary of the antiviral activities of terpenoids.

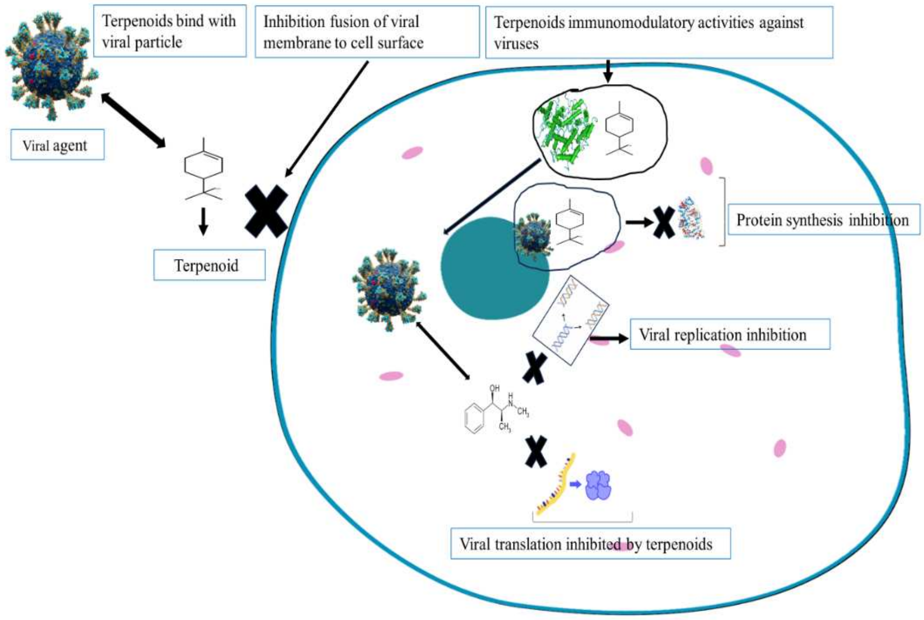

Figure 3. A schematic diagram showing the mechanism of the antiviral activities of terpenoids.

5. Applications of Metabolomics to Plant Antiviral Research

Metabolomics involves the comprehensive study of small molecules known as metabolites in a living system or biological sample. It can give broad insight into both the identity and detailed information of the chemical fingerprints, and the metabolic processes that occur within such a system. Metabolomics is broadly categorized into two types, 1) targeted and 2) untargeted metabolomics. In the targeted approach, the goal is not the identification of all metabolites, but the quantitative measurement of a specific metabolite or metabolites group that have been previously identified and characterized. Untargeted metabolomics however deals with a comprehensive identification and quantification of all detectable metabolites present in a biological sample [133].

Advances in metabolomics techniques now play a significant role in the discovery of antiviral compounds in plants, evident by relevant recent publications. The possibilities for the comprehensive analysis of the complete set of compounds in plants using advanced analytical techniques are endless. Many studies have reported the use of metabolomics towards the targeted screening of plant secondary metabolites [134,135]. The many advantages that metabolomics presents, makes it today an essential and indispensable technique in plant antiviral research.

Arguably the most important application of metabolomics in plant antiviral research is in the identification and characterization of the plant metabolome. Metabolomics, when used for this, can provide a detailed snapshot of a plant's metabolomic profile, with information on both the identification and quantification of the metabolites present within the metabolome. There is an incredible diversity of secondary metabolites that are exhibited by plants, many of which have bioactive compounds [136–138]. The use of metabolomics has additionally assisted in identifying a wide range of metabolites in plants across different geographical locations and seasons, including those with antiviral potential. The specific bioactive compounds responsible for the antiviral activity can then be isolated and further studied for potential therapeutic use.

Metabolomics can also be used for mechanistic or toxicology studies of the isolated plant antiviral compounds in vivo (Halouska et al., 2012; Shahid et al., 2023). Since metabolites are downstream products of cellular metabolism [139], the identification, quantification, and characterization of these compounds in vivo, in the presence of the isolated plant metabolite/drug show the metabolic pathways that are altered in response to plants compound/drug's antiviral activity in the culture or host.

There are many complex metabolic interactions that occur within the plant system. Antiviral compounds can either act alone or in synergy with other compounds to carry out their activities. In studying the synergistic effect of more than one compound on microbes, stronger bioactivities have been reported using metabolomics [141–144]. The metabolomics approach is therefore promising, as a useful strategy for the study of complex interactions between plant metabolites [145,146].

Metabolomics has also been applied to investigating the effect of the different seasons on the chemical profile and biological activities of plants [147,148]. Adeosun et al., (2022b) used metabolomics to study the influence of seasonal change on the anti-HSV1 properties of *Helichrysum aureonitens* and reported a correlation between plants harvested in spring and better antiviral activity. A targeted metabolomics study conducted to determine the effect of seasonal change on the chlorogenic acids content of *H. aureonitens,* further revealed an association between water availability and the production of different isomers of chlorogenic acids [149]. This knowledge is important in determining the optimal season for plant collection, to yield better antiviral activity.

Furthermore, metabolomics can also be used for studying those metabolic pathways involved in plant-pathogen interaction[145,150,151]. These adapted metabolic pathways can also be determined by analyzing those changes in metabolome during a viral infection. This is important in understanding the mechanism by which plants respond to viral infections and can provide insight into the identification of useful metabolites that may be developed as therapeutic candidates towards antiviral intervention. A summary of such studies are given in Table 1 below.

 doi:10.20944/preprints202312.1014.v1

Table 1. Metabolomics Studies on the Antiviral Compounds from Selected Plants.

Plant Species	Metabolomics Technique	Compounds	Targeted virus(es)	Reference
Helichrysum aureonitens	UPLC-qTOF-MS	Chlorogenic acids	Herpes simplex virus	[149]
Euphorbia semiperfoliata	SFC-MS, LC-MS/MS NMR	Diterpene esters	Chikungunya virus, HIV-1	[152]
Phyllanthus brasiliensis	LC-MS/MS	Tuberculatin	Zika virus	[153]
Lampranthus coccineus and Malephora lutea	UPLC-MS	Green synthesized silver nanoparticle	HSV-1, HAV-10 virus, and Coxsackie B4	[154]
Hibiscus sabdariffa	GC-MS	Protocatechuic acid	Human Influenza A Virus	[155]
Elaeodendron croceum, Artemisia afra and *Adansonia* digitata	NMR	13-Hydroxy-9Z,11E-octadecadienoic acid, 13S-Hydroxy-9Z,11E,15Z-octadecatrienoic acid	Rift valley fever virus	[156]
Garcinia cambogia	LC-HRESIMS	Naringin	Covid-19	[157]
Scaevola spinescens	HPLC-MS/MS Q-TOF	Ammarin, nodakenetin	MS2 bacteriophage	[158]
Pinellia ternata	HPLC	Phinellic acid	Nasal influenza	[159]
Ephedra sinica	HPLC-Q-TOF-MS/MS, NMR	4,6-dihydroxyquinoline-2-carboxylic acid, 4-hydroxyquinoline-2-carboxylic acid, and 4-hydroxy-6-methoxyquinoline-2-carboxylic acid	Covid-19	[160]
Rhinacanthus nasutus	NMR, mass spectrometry	Rhinacasutone	Rhinovirus and coxsackievirus	[161]
Bombax ceiba	NMR	Bombasinol A	Hepatitis B	[105]

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Phyllanthus urinaria	NMR, ESI-LCMS	Loliolide	Hepatitis C Virus	[162]
Swietenia macrophylla	NMR LC-MS	3-hydroxy caruilignan C	Hepatitis C Virus	[163]
Tabernaemontana cymosa	NMR, mass spectrometry	Voacangine and lupeol acetate	Dengue virus	[164]

* SFC-MS supercritical fluid chromatography tandem mass spectrometry. * UPLC-qTOF-MS ultra-performance liquid chromatography-quadrupole time-of-flight mass spectroscopy.

6. Steps for the Discovery of Antiviral Compounds in Plant Metabolomics Studies

The discovery of compounds with antiviral activities in plants using metabolomics follows a systematic approach, combining different steps and methodologies. The choice of plant selected for metabolomics studies is often predicated upon prior knowledge of the plant's antiviral properties, either from oral tradition or previous studies. Different plant parts such as stems, roots, leaves, and flowers, are often collected from the wild or form a cultivated environment. Preparation often involves cleaning, drying, and pulverizing/homogenizing the plant materials, followed by extraction of the plant metabolites using various solvents of varying polarities. Phytochemical investigations, typically use a solvent mixture for the extraction of both polar and non-polar compounds, which is typically comprised of a mixture of alcohols (methanol or ethanol) and water, as has reported on previously [165–171]. Extraction may be followed by sample preparation towards NMR, GC-MS, or LC-MS analysis.

Below is a diagram (Figure 4) showing a comprehensive step-by-step procedure from sample collection to clinical trials. In most studies, these steps are never followed completely, with many studies only reporting plant activities without final active compound isolation.

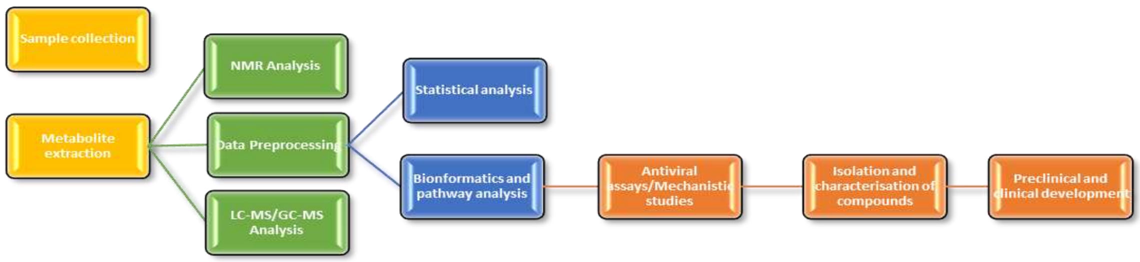

Figure 4. A flow diagram showing the typical steps for the discovery of antiviral compounds in a plant metabolomics study.

7. Future directions for the application of metabolomics towards the development of antiviral therapies from plants sources

In just about 20 years, since the introduction of metabolomics [172], some key advancements and significant progress have been made in the field of medicinal plant natural product research. There still remains immense potential for the full exploration of metabolomics towards medicinal plant

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research, and in the search and development of new therapeutic agents. As Thompson K. D, (2006) noted, although many studies have been conducted on plants to determine their effects on viruses, most studies however do not isolate and identify active compounds responsible for the antiviral potentials of the tested plants. This is further confirmed by the limited number of studies that reached the level of compound identification and isolation in the last couple of years, as listed in Table 1 above. Some studies reported good plant activities against viruses and went as far as isolating compounds, but did not elucidate the compound names [164,174]. This presents difficulty in characterizing the bioactive principles responsible for the biological activity of the plant. Taking advantage of advances in metabolomics techniques to identify, isolate and characterize compounds that have both pharmacological effect and good biological activity, will prove beneficial in the development of antiviral leads as part of an effort towards viral eradication. Furthermore, a detailed search of many scientific databases reveals a lack of information on the biosynthetic pathways responsible for the production of the particular plant bioactive compounds. Future studies should harness metabolomics for elucidating these biosynthetic pathways that are responsible for the formation of identified antiviral metabolites by these plants [175]. This is crucial in optimizing plant cultivation and incorporating genetic engineering strategies for the enhancement of compound synthesis with antiviral bioactivity [172,176].

The emergence of systems biology integrates high throughput data generation and analysis from many platforms to understand complex interactions between different levels of organization in a biological system [177,178]. Omics technology, an indispensable molecular technique in systems biology, incorporates genomics, transcriptomics, proteomics, and metabolomics techniques towards better understanding of biological processes [175,179]. The application of systems biology paradigm in plant studies will provide a more holistic view of the antiviral potentials in medicinal plants.

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