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Recent Advances of Phytochemicals and Their Applications for Antiviral Therapy

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Abstract

Phytochemicals are chemicals produced by plants to serve as a defense against fungal, bacterial, and viral plant diseases. Currently, our world has encountered a plethora of frustrating viral infections. For most people's morbidity and corporality, viral infections are primarily responsible. On the other hand, numerous plants' secondary metabolites such as flavonoids, alkaloids, terpenes, polyphenols and their derivatives have effective potentials to decline the multiplication of different viruses and have the capability to kill them. For instance, flavonoids can be used to treat novel corona virus, influenza A and others; phenols can be used to treat human papilloma virus, herpes and the likes. Understanding these secondary metabolites and their mechanism of actions against viruses is substantially insignificant. Therefore, the current review is ultimately intended to summarize some of the studied bioactive phytochemicals with the practical potential of antiviral activity. The recent articles have been retraced some biologically active materials were critically summarized with their potential efficacy of antiviral activities. Those chemicals are used for the treatment of human diseases. Different studies *in vitro* and *in vivo* assays have depicted effective inhibition against several viral infections. The results from different studies have brought user new hope to overcome the problem of drug resistance and unintentional side effects on patients. Besides, it is understood that the bio functionalization of the active phytochemicals increases the efficiency of the compounds to fight in advance against viral infection. It is also notable that the establishment of new strategies for drug delivery to the target site brings the intended goal. Overall, the present review has summarized that the employment of phytochemicals as antiviral agents is more effective and economically feasible for patients when compared to synthetic chemicals.

Keywords: Antiviral; Antiviral Therapy; Drug delivery; Plant; Phytochemicals

Introduction

Phytochemicals are chemicals produced by plants. Starting earlier, human beings have been contingent on plant sources for their essential needs. The use of modern medicine is anteceded by medicinally active plants. Several biologically active plant products such as alkaloids, flavonoids, polyphenols, tannins, terpenes, and their derivatives are some of the phytochemicals that have been figured out over the line of human evolution. Plants have the capability to synthesize a wide range of compounds. The largest groups of substances that are widely present in the plant kingdom are polyphenolics or flavonoid constituents; and before 2010 GC, more than 8000 different phytochemicals are known [1]. When phytochemicals are used in controlled amounts, it is globally accepted that they are innocuous and display different biological activities. Polyphenols are pertinent for antiviral research due to their wide structural diversity. The ability of phenolic groups such as radical meeting makes them highly interesting to be harnessed as antiviral agents.

The study regarding existing viruses remains a hot research area due to their leading global consequences. To date, several infectious viral diseases have been reported; and novel ones have emerged iteratively. These remain major global causes of morbidity and corporality. Some of the most aggressive viral infections include Ebola, Hepatitis, HIV/AIDS (Acquired Immune Deficiency Syndrome), Herpes, Influenza, Poliomyelitis, SARS-COV (severe acute respiratory syndrome corona virus) and the likes. According to indicated from different studies, these viral infections affect three to five million patients annually [2]. Influenza is at the helm of over three million new cases of severe deaths and 300,000 to 500,000 deaths yearly [3].

Transmission methods such as blood transfusion, organ transplantations, and the use of hypodermic syringes are thoroughly increasing the number of cases diagnosed with viral infections every year. Albeit classic antiviral drugs such as interferon and ribavirin are effective *in vitro* against most viruses, however, they are often ineffective in patients. Nowadays, there is no acquiesced in solution for various viruses; and vaccination is bounded to hepatitis A virus, mumps, and varicella [3].

Besides this, the agents are costly and ineffective due to the resistance capability of viruses and causes side effects. Considering this, naturally based bio products can be an alternative to treating viral disease. Hence, it is required to further search the area of antiviral phytochemicals and highlight system of action to overcome the existing barriers for the agents and successfully reach into their deliberated sites of action.

During recent years, the pandemic of viral diseases has influenced the scholar community to discover less nocuous antiviral plant compounds or phytochemicals instead of utilizing conventional agents such as protease inhibitors, nucleic acid analogs, and other synthetic molecules as antiviral therapeutics. This approved that the development of clinical compounds from Phyto-pharmaceuticals is a tending approach to look for therapeutic molecules with no cytopathic problems. By having knowledge about the molecular mechanisms of viral invasion and multiplication within the host cells, it will be possible to get help in designing effective and inexpensive antiviral drugs and harnessing them to their specific site [4]. Plant phytochemicals such as alkaloids, flavonoids, phenols, tannin, anthocyanin, lignan, terpenoids, and the like are well-known natural products that are utilized as antiviral therapeutics. As the utilization of bioactive compounds against different viral ailments overcome the side effects and drug resistance of conventional antiviral drugs, it is curiously relevant to investigate the molecular mechanism of action of eco-amiable biomaterials against the virus. However, in developing phytochemical based-antivirals, a number of constraints are there that should have to be remediated. Challenges such as the limited understanding of bioavailability and pharmacokinetics, stability and shelf life, the mechanism of action and regulatory system, yield optimization of the targeted bioactive compounds and the likes are the major constraints that are currently faced in developing plant bioactive compound based-antiviral. These constraints can be remediated by figuring out the particular bioactive properties and their active sites against the virus, employing the technological instruments to increase the yields, delineating the potential effects of these natural compounds for consumers to increase the social concerns and perceives and underscoring the detail studies regarding the molecu-

lar actions and pharmacokinetics of those secondary metabolites against the viral infections.

The current review is comprehensively intended to summarize the recent literature on different naturally occurring compounds with antiviral therapeutic ability. Furthermore, the standard models for antiviral activity assays, the mechanism of action and the implication of viral disease prevention will be elucidated briefly.

Literature Review

Plants and Their Antiviral Activity

Herbal medicine is an effective area of research topic to search plant extract and establish curative properties of therapeutic agents. Insignificant amounts of bioactive molecules were explored for their therapeutic uses. However, as it is implicated in different studies, medicinal herbs offer a broad range of therapeutic antiviral chemo types; and this can be manifested through inhibiting viral multiplication by viral adsorption, sticking to cell receptors, preventing viral entry in the host cell, and competing for pathways of actuation of intracellular signals [5]. To get wellness and primary health care throughout the world, people proceed to depend on medicinal plants and their products. This is because herbal medicines have a high capability to cure diseases and their fewer side effects when compared to the conventional synthetic molecules that are harnessed to therapeutic agents.

Currently, the research and development arena keeps customizing mechanisms relying on plant-based products for drug development. Various secondary metabolite compounds are available in plants, including alkaloids, flavonoids, phenols, terpenoids, lignans, tannins, and others, which have a wide range of anti-infection and antioxidant activities. Most viral diseases are treated relying on characteristics they imply after affection. Leading to this, several medicinal phytochemical extracts are under investigation, and some have arrived for clinical attempting. Ti and his collogues conclude that herbal medicines proceed to provide the fundamental raw materials for some of the most crucial anti-viral drugs although there is the proceeded development of new antiviral agents from synthetic sources. The other study also support this idea by elaborating those medicinal plants are at the nucleus of medical sciences and are gradually passing from apothecary vials from the manufactured bags of the trad practicians to the laboratories to make access unlimited new medicines synthesis model [6]. From this implication, it is possible to be said that today's most synthetic chemical drugs will be replaced by herbal medicines in near future.

The reason herbal medicine is selected over synthetic drugs is today's challenge of drug resistance and the side effect of conventional medicine. Most of the widely known drugs approved for antiviral agents derive origin from nucleosides. Those medicines derived from nucleosides are quickly undergoing adaptation conditions with the disease and these consequences to drug resistance. The drug synthesized from a chemical substrate also possesses side effects. Different studies indicated that the chemically synthesized drug have more side effects on the user and is less appropriate than herbal medicines. Because of the beliefs in herbal medicines, populations in developing countries harnessed medicinal plants for primary health care. Hence fore, harnessing herbal medicines for antiviral agents has the potential to relieve the side effects observed due to the usage of chemically synthesized drugs.

Figure 1, Shows the antiviral action of compounds from the plant world

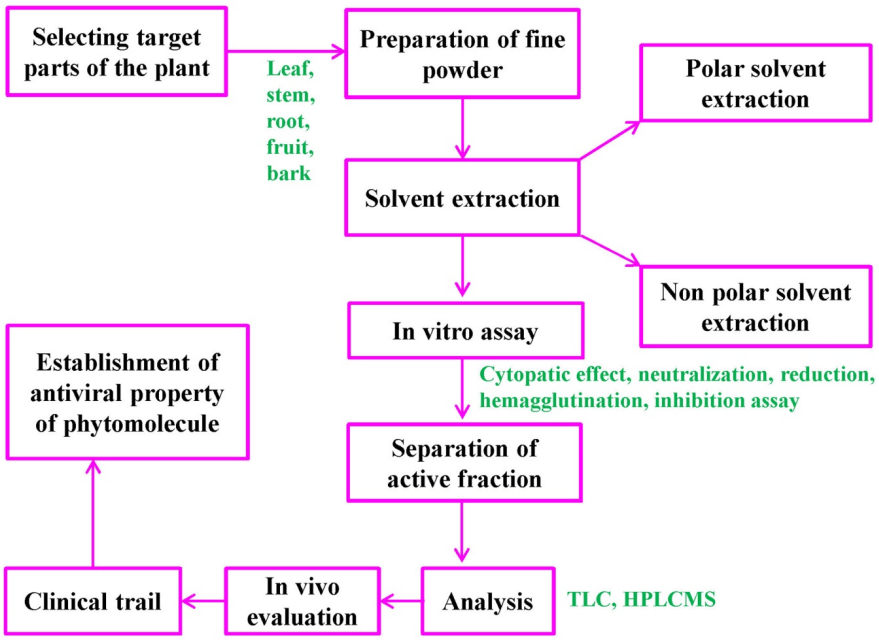

Figure 1: Procedures manipulated with herbal medicines for the establishment of a complement activity for a bioactive agent [7].

Common Models for Antiviral Activity Assay

In vitro and *in vivo* models are an assay employed to evaluate the antiviral activity of natural products such as crude extracts, ingredients, and fractions. Different studies have elaborated that the antiviral models usually employed for these assays are molecular and cellular-level models [7]. Molecular level models are the initial stage in screening a vast number of substances such as extracts for their prevention and action systems on viral enzymes and function proteins. It is an in vitro model assay that can harness different activities such as DNA Polymerase Activity Assay, Reverse Transcriptase Activity Assay, Hemagglutination Inhibition Assay, and others. This provides curious activity information for different strategies including cellular-level models. On the other hand, the cellular level model exploits the capability of viruses to infect and multiplicate cell lines in the cell culture system. The cell culture system is a rapid method to raise viruses at higher Titres to test the anti-viral activity assay of the extracts. After the rapid analysis assay, the extract's potential to be used as an antiviral agent can be evaluated within animal models such as mice, hamsters, ferrets, dogs, monkeys, and others. The authors also elaborated that complementary animal models engender the favored viral infection with clinical symptoms like those observed in humans.

Most known Phytochemicals for Antiviral Activity

Nowadays, the pharmaceutical industries are indulging their focuses towards economically significant ventures of phytochemicals. Components of phytochemicals in this phenomenon are urgently needed to be utilized as alternatives to treat various viral infections including the novel Covid-19.

Flavonoids

Flavonoids are one of the widely studied phytochemicals and can be harnessed for different applications. Different components of flavonoids have been studied for their potential to act as antiviral activities [7-9]. From different studies on this compound, a prominent outcome has been investigated both *in Vitro* and *in Vivo* assay against various viral infections. The compounds can be used as treatment for viral infections such as the novel corona virus (Covid-19), influenza A virus and others. There are different classes of flavonoids and some of them are summarized in Table 1 with their anti-viral actions.

Table 1: Different classes of flavonoids with their potential antiviral activity

Flavonoid class	Target	Mechanism of action	Plant	Ref.
Dichalcone	HSV (1&2)	inhibit RNA replication	*M. leucantha*	[10]
Anthocyanin	Covid-19	inhibits S1 to the Cell's ACE2 receptor	*C. ternatea*	[11]
Flavones	ASFV	inhibit protein synthesis		[12]
Isoflavan	HCV	inhibits viral RNA replication	*G. uralensis*	[7]

Keys: G. Glycyrrhiza uralensis, M. Millettia leucantha, C. Clitoria ternatea

Catechins

Catechin is the other important compounds synthesized in tea plants. Different authors investigated the potential antiviral effects of catechin against mumps viral infection. To investigate the potential efficacy of the compound against the virus, the mumps virus 13V165E2 strain has cultivated within African green monkey kidney Vero cell culture. Eight different catechins namely catechin, epicatechin (EC), Galo catechin (GC), epigallocatechin (EGC), catechin gallate (CG), epicatechin gallate (ECG), Galo catechin gallate (GCG), and epigallocatechin gallate (EGCG) has been evaluated for the inhibitory effects of mumps virus infection in Vero cells. The mumps virus is sensitive to all evaluated catechins except for ECG. The three polyphenols such as epigallocatechin gallate (EGCG), epicatechin gallate (ECG), and gallocatechin-3-gallate (GCG) bind highly with the catalytic residues of Mpro of the virus. These interactions prevent the virus from binding to the hosts' receptor cell and so that reduce the opportunity to be infected by the virus. Hence, the catechin and its precursors are relevant food derived drug candidates to treat the Covid-19 and other viral infections [13].

Apigenin and Baicalin

As elucidated by different scholars, the bioactive molecules, apigenin and baicalin are naturally synthesized phytochemicals obtained from different plants. These molecules can be recruited to treat different viral infections [12]. Rehman and his colleagues explored the potential inhibition effect of apigenin and other bioactive molecules from *Nymphaea alba* extracts [14]. As depicted from the results, apigenin has indicated significant inhibition effects on hepatitis C virus (HCV) using *in vitro* transfection model assay. The inhibition mechanism of the compound is by inactivating the viral gene NS3 which is responsible for viral protease expression.

The research studied by Banerjee and co-investigator explored the effect of baicalin against dengue virus through *in silico* study [15]. The compound prevents the initial stage of viral infection through binding to the viral envelope protein. Besides, baicalin compound extracted from *Radix scutellaria* is a prominent bioactive molecule to prevent influenza virus A infection. As illustrated from *in vivo* experiment, the authors concluded that the baicalin molecule inhibits the Viruses' H1N1 and H3N2 by targeting the miRNA of the virus so that prevent the viral infection.

Phenolic Compounds

As it has been concluded by different scholars, there are different classes of phenolic compounds that can be recruited for different viral infection treatments [2, 7]. The following section depicts the sub classes of phenolic compounds meticulously.

Lignans

Lignans are vastly synthesized by different plants and exist in plant parts such as root, stem, bark, rhizome, leaf, flower, seed, fruit, and others [7]. It is one of the natural bioactive molecules that can be harnessed for the treatment of different viral infec-

tions. As it has been suggested and summarized by Gnabre and his colleagues, this phytochemical can be used for different viral ailments such as human immune deficiency Virus (HIV), human papilloma virus (HPV), herpes simplex and others [16]. Lignans inhibit SP1 gene expression, so that the virus can no longer proceeds multiplication processes and cease to infect the target cells of the host. The recent review done by Cui and coworkers concluded that lignans have been classified in to two main classes based on their chemical similarity i.e., classical lignans and neolignans [17]. Classical lignan, which was extracted from *Larrea tridentata* and *Phyllanthus niruri*, is the major group of lignan which has been deeply explored and belongs to dibenzyl butane subclasses [7]. The authors elaborated that these components of lignan can be recruited against different viral infections such as HSV-1, HSV-2, HIV, HBV and HPV. The compounds prevent infection by avoiding the multiplication of virus within the host's cell.

On the other hand, the second subclasses of the lignan, neolignan have been clearly elucidated [17]. The major class of this phytochemical and its subtypes have been extracted from plants such as *Silybum marianum* and *Peperomia pellucida*. As it has been illustrated by different scholars and researchers, this bioactive molecule and its subtypes can be harnessed as antiviral agents against different viral ailments such as HCV, IAV, HIV, HBV, CHIKV, DENV, Mayaro virus. The main molecular mechanism by which this bioactive compound acts against viral diseases is by inhibiting the multiplication of viral cells within the host cells so that it reduces the infection and even cures the patients.

Tannin

Tannins are classes of phenolic compounds with high molecular weight and possess hydroxyl and carboxyl groups which permit the natural complexes formation [7]. Tannin has been extracted from plants such as *Phyllanthus amarus, Phyllanthus urinaria, Phyllanthus odontadenius, Phyllanthus niruroides, Phyllanthus discoideus,* and *Phyllanthus mullerianus* of leaf, stem and root; however, with different extents [18], *Hamamelis virginiana* of leaf and bark. As it is investigated by different scholars and researchers, the bioactive tannin extracted from different plants can be utilized as antiviral agents against various viral ailments such as IAV, HPV-16, DENV-2, HSP-1 and COVID-19. The molecular mechanism by which tannin acts against those viral infection is through prevent the virus attachments to the host cells, suppressing the replication and multiplication of the virus within the host cells and deactivating the expression of protein and enzyme expression which are so required for viral life proceeding.

Curcumin and Anthraquinone

Curcumin and anthraquinones are the basic classes of phenolic compounds that can be considered as vital for different biological functions. Emodin, which is naturally occurring anthraquinone derivative has been extracted from *Rheum tanguticum* and has been tested against HSV-1 and -2 infection and has investigated its antiviral activity on HSV infection both *in vitro,* in tissue culture cells and *in vivo,* in a mouse model [19]. But it was elucidated from the results that the bioactive compound, emodin can neither prevent nor acts as virucidal against HSV-1 and -2 at pretreatment assay; however, it acts as antiviral activity after the viral infection. The authors also have been demonstrated that the molecules show high potent of inhibition on HSV-1 than HSV-2. The molecular mechanism by which the molecule acts on the virus is by inhibiting the biological function of the virus so that it cannot proceed to infect the host cells.

On the other study, the potential capability of the reported anthraquinone and its derivatives as anti-COVID-19 infections has been investigated by using silico molecular docking tools, namely autodock4 [20]. The authors have elucidated the target binding site of the bioactive molecules against the novel corona virus and these target sites include 3C-like protease, papain like protease and spike protein. Binding to this target site, the compounds inhibit the COVID-19 virus from attaching to the host receptors cells. As it has been predicted from the study, the compounds may be recruited for the treatment of other different viral infections such as adenovirus, CMV, hepatitis B and C virus, herpes, HIV, IAV, influenza, parainfluenza and others depending

on their drug likeness score.

Study regards to the bioactive molecule, curcumin, has investigated myriads application of the compound and its biological functions. As indicated by different reports, the compound can be recruited as antiviral agents for numerical viral infections and could be effective during pretreatments and aftermaths of the viral infections based on the viral phenomenon and behavior [21]. For instance, it can be used to abrogate and prevent viral ailments i.e., HIV, ZIKV, HSV, CHIKV, IAV, DENV, NoV and others. As it has been concluded by these authors, curcumin can prevent and even cure viral diseases by different molecular mechanisms such as inhibition of viral genetic material multiplication, inactivation of gene expression, and as well as attachment to the viral target site. This active biomaterial can be extracted and obtained from different plant types such as *Curcumin longa*.

Alkaloids

Alkaloids are natural phytochemicals that are widely known for their biological activities. The extracts of alkaloid can be obtained from different plant sources such as *Peganum harmala*, *Aconitum carmichaelii, Pancratium trianthum, Annona muricata* and others [22]. This bioactive chemical has been studied widely for its broad spectrum of antiviral activities against different DNA and RNA viruses. The authors concluded that it has shown effective antiviral activities against different viral ailments. As indicated by different studies, this natural compound has shown a significant efficacy to act as antiviral agents against viral ailments such as IAV, HCV, DEV [22].

On the other studies, it has been elucidated that alkaloid and its derivatives such as lycorine extracted from *Lycoris radiate*, Chinese herbal medicine [23], Hom harringtonine extracted from plant species of the *Cephalotaxus* genus, Oxysophoridine extracted from Chinese herbal medicines like *Sophora alopecuroides* and *Siphocampylus verticillatus* [24] can be recruited as anti-SARS-CoV-2. As it has been concluded by the authors, the mechanisms used by some alkaloids derivatives to prevent corona virus replication have not been clarified while lycorine modulates host factors to interfere with viral replication so that it ceases the virus multiplication within host cells. However, the molecular action of those alkaloids' derivatives against the corona virus replication could be by inactivating the viral biosynthesis, blocking the viral gene expression, exerts virucidal activities, suppresses the expression of viral protein, modulates host factors and other mechanisms.

Saponin

Saponins are sugar conjugated natural chemicals with a wide range of biological functions including therapeutic characteristics, antibacterial activity, antiviral activity, and so on. Figueiredo and co-authors have explored saponin from the extracts of root of *Solanum sisymbriifolium* (Solanaceae) plant and seen the inhibition effects of the saponin against DENV. Investigators have used saponin from the ethanol extracts of the plant root and found the high virucidal activity against DENV without a significant cytotoxic effect on the Vero E6 cells. Albeit these authors did not elucidate the molecular action of this chemical against the DENV, it has been illustrated in other studies that the bioactive material can acts inhibitory effects of the cyclic AMP phosphodiesterase [25].

On the other hand, the study manipulated by Lee and co-workers investigated the efficacy of saponin as anti-HCV activity; with 10μg/mL concentration of saponin Huh 7.5 cells infected with HCV (cell culture grown with HCV). The authors have harnessed qPCR, reporter assay, and immunoblot analysis to assure the saponin prohibition effects on HCV replication. According to elucidated on the study, the possible molecular mechanisms by which acts against HCV is through suppressor of cytokine signalling 2(SOCS2) pathways. Saponin leads to overexpress the amount of SOCS2 and this result to supress the HCV replication within the host cells.

Besides, the bioactive chemical, saponin, which has been extracted from *Phaleria macrocarpa* fruit has been assessed to see its capability to act as antiviral agents to treat human herpes virus type-1(HHV-1). Investigators have been utilized the plaque reduction assay to analysis the efficacy of the compound to act as anti-HHV-1 post treatment, pre-treatment, virucidal, attachment and penetration assay. From the study, it has been concluded that the extracts of the saponin from the selected plant disturbs the early steps of the viral life cycle by the attachment and virucidal assays in dose-controlled activity.

Terpenoids

Terpenoids are various classes of naturally available bio compounds with different biological functions. Terpenoid is a derivative of mevalonic acid consists of isoprene unit. These compounds are broadly spread in nature and extracted from different plants and can be recruited as competent antiviral agents. The study held by Gyebi and his co-investigators declared that the plant secondary material, terpenoid, can be harnessed as potential inhibitors of corona virus using *in silico* approaches. The explorers have docked different terpenoid derivatives from the plant's native to Africa to the $3CL^{pro}$ of the novel SARS-COV-2. It has been implied from the ADMET study the drug likeness of the bio compounds and can be utilized as natural competent anti SARS-COV-2 after extended study.

The review summarized by Mishra et al., [26] on the phytochemical and pharmacological properties of *Hyptis suaveolens* has reported that the aqueous alcohol extract of *H. suaveolens* containing pentacyclic triterpenoids and ursolic acid indicates a significant inhibition capability against viral infections such as CHIKV, HIV, SARS-COV-2; and the deepen exploration and analysis enables to establish amiable and cost-effective competent drug against the mutating and resistant RNA viruses to care the plethora of viral pathogens in future. On the other study, it has been predicted from the *in-silico* analysis of docking score and binding energies with predicted pharmacokinetic profiles that the terpenoids phytochemical might possess a capability to act as inhibitors against SARS-COV-2 Mpro. This prediction intrigues to extend the study into *in vitro* and *in vivo* investigation to unravel and verify its inhibitory effects.

Carotenoids

Carotenoids are phytochemical compounds grouped under the class of tetraterpenoids, are derived from polyene chain with tetra carbons that serve as its backbone [7]. From the perspectives of different studies, carotenoids can be classified as xanthophyl, consists of oxygen, e.g., lutein, zeaxanthin and non-oxygenated form of carotenoids, e.g., carotenes [27]. These active biomaterials have been explored; *in vitro*, and the extracted pigment of *Haloarchaea,* prohibited in advance ability to treat HCV and HBV in infected human blood mononuclear cells than currently utilized drugs by suppressing the viral replication through disturbing the normal function of polymerase in the virus [28]. On the other study, it has been reported that classes of carotenoids such as lutein, zeaxanthin, and carotene can also act as antiviral action against HCV and HBV. As it has been illustrated on different study, the carotenoid also indicates significant potential inhibition against the pandemic COVID-19 by targeting the inflammatory storm which is a consequence of the virus infection and could be utilized as a potential drug.

Supported by molecular docking approach, Fatima and co-investigators have reported the *in vitro* antiviral activity of lutein against HCV. This paves a way to demonstrate a promising role of lutein to be act as antiviral drug against HCV. The possible molecular action by which this bioactive can acts on the virus could be deactivating helicase which is curiously important for the HCV replication. On the other hand, crocetin has the capability to treat against different viral infections like DENV by improving the host response to the virus *in vivo* in mice [29] and HPV-16 and HPV-18 via sticking to the viral target site in mucosal epithelial [30]. Thus, the deepen study about these compounds unravel and paves the way for the establishment of the amiable antiviral agents against the virus infection. The overall phytochemical antiviral activity is summarized in Table 2.

Table 2: Some effective phytochemicals, their source, their target viral infection and molecular mechanism of action for the inhibition of viral ailment

Phytochemicals	Source	Target part	Targeted Antiviral	Mechanism of action	Ref.
Tannin	Phyllanthus amarus, Phyllanthus urinaria, Phyllanthus odontadenius, Phyllanthus niruroides, Phyllanthus discoideus, and Phyllanthus mullerianus	leaf, stem and root, bark	IAV, HPV-16, DENV-2, HSP-1 and COVID-19	Block the viral attachment, suppressing the viral replication and multiplication, deactivating the expression of protein and enzyme expression	[31]
Baicalin	Radix scutellaria	Root	DENV, IAV (H1N1 and H3N2)	Target viral miRNA (suppress miR-146a)	[15]
Lignan	Larrea tridentate, Phyllanthus niruri, Silybum marianum, Peperomia pellucida	Leaf, flower, seed, stem, bark	HIV, HPV, HSV type -1 and-2, HBV, CHIKV, DENV, IAV, mayaro virus	Inhibit the viral multiplication	[7]
Anthraquinone	Rheum tanguticum	Root	HSV-1 and -2, COVID-19, adenovirus, CMV, HCV, HBV, HSV, HIV, IAV,	inhibiting the biological function of the virus	[19]
Alkaloids	Peganum harmala, Aconitum carmichaelii, Pancratium trianthum, Annona muricata, Siphocampylus verticillatus,	Seed, leaf, bulbs, root	IAV, HCV, DEV, COVID-19	inactivating the viral biosynthesis, blocking the viral gene expression, exerts virucidal activities, suppresses the expression of viral protein, modulates host factors	[22]
Saponin	Solanum sisymbriifolium, Phaleria macrocarpa	Root, fruit	DENV, HCV, HHV-1,	Inhibit the cyclic AMP phosphodiesterase, prohibit viral replication, block viral attachement	[25]
Terpenoids	Hyptis suaveolens	Leaf	CHIKV, HIV, SARS-COV-2,		[32]
Carotenoids	Haloarchaea		HCV,HBV, COVID-19, DENV, HPV-16 and -18	suppressing the viral replication, targeting the inflammatory storm, improving the host response, sticking to the viral target site	[28]

Drug Delivery Strategies of Phytochemicals

A plethora of challenges are there in developing the phytochemical based antiviral. These include the bioavailability and pharmacokinetics challenges, the understanding gap on bioactive mechanism of actions, scale up constraints and so on. To overcome these constraints, it is the way to develop the target bioactive drug delivery for patients and increase their solubility on the site. As phytochemicals represent the basis for naturally amiable and alternative pharmacotherapy combat several viral ailments, it is curiously significant to envisage potential delivery of applications of these bioactive chemicals. Adapting pharmaceu-

tical nanotechnology into the fields of natural medicines has ushered in a new hope for the delivery of poorly soluble phytochemicals and plant extracts and enables to improve pharmacokinetics and clinical outcomes. Currently the iteratively used strategies for this purpose includes phytosomes, nanoparticles, transferosomes, hydrogels, microspheres, micelles, nanosuspensions, solid dispersions, ethosomes, self-micro emulsifying drug delivery system (SMEDDS), and self-nano emulsifying drug delivery system (SNEDDS) . The exploration has aimed to improve the solubility and oral bioavailability of myricetin (Myr). After evaluation of the four Myr-SNEDDS prepared, the authors have suggested that the SNEDDS formulations indicated swift release profile when compared to free drugs. Using nanoprecipitation approach, investigators have enhanced the dissolution rate and oral bioavailability of *Terminalia arjuna* bark extract by using polysorbate-80 as a stabilizer. Delivery strategies for some antiviral phytochemicals have been summarized below in the **T**able 3.

Table 3: Summary of applied delivery strategies recruited for some anti-viral phytochemicals \

Phytochemicals	Virus	Study type	Types of cell oranimal model	Delivery mechanism	Ref.
Alkaloids	IAV, HCV, DEV, COVID-19	*In vitro*	human embryonic kidney cells	Phytosome, hydrogel, Nano emulsion, SNEDDS, SMEDDS	[22]
Catechin	Mumps virus infection	*In vitro*	Vero cells	Hydrogel, phytosome, nanoparticle, Nano emulsion, Nano-encapsulation, encapsulation	[33]
Baicalin	DENV, IAV (H1N1 and H3N2)	*In vivo*	mice	Phytosome, liposome, Nano emulsion, SMEDDS, SNEDDS	[34]

Drug delivery strategy of phytochemicals is significantly required for the bioavailability and solubility of the molecules to enable it to act at the target sites. The following **Figure 2** depicts different strategies that are applicable for the delivery mechanism.

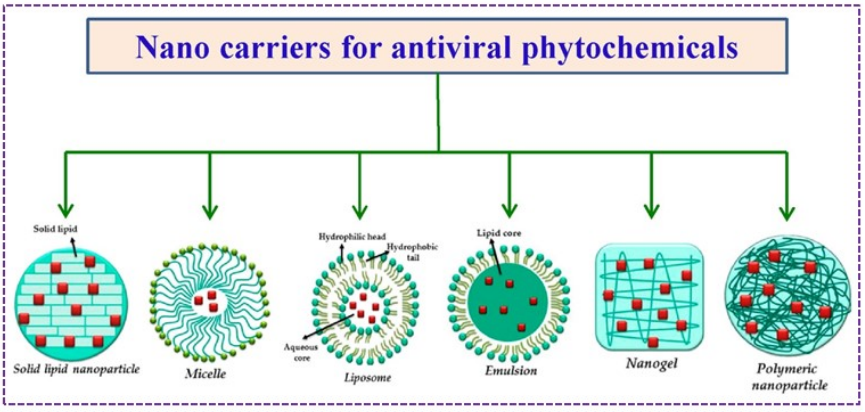

Figure 2: Some applied Nano-carriers for plant active and extracts to increase their efficacy against viral infection: Taken from Singh et al., [35].

Summary

The potential efficacies of phytochemicals are varying *in vitro* and *in vivo* against different viral ailments. Most known phytochemicals that are effective in anti-viral activity include alkaloids, phenols, flavonoids, curcumins, tannins, anthraquinones, carotenoids, terpenoids, catechins, lignans, apigenin, and saponins. Each chemicals has their own properties and target viral

treatment. Most widely known viral treated by phytochemicals are HCV, Covid-19, mumps viral infection, HSV, HPV, IAV, CHIKV, DENV, ZIKV, HIV, NoV, F-MuLV. These biomaterials can be recruited as alternative antivirals to conventional antiviral drugs. Due to the drug resistance and unintended side effects of chemically synthesized antiviral medicines and vaccines, it is curiously essential to explore the solution from natural sources which are cost-effective and amiable for patients. Various viral infections HIV, HSV, and HCV do not have a complete vaccine yet. The researchers came up with phytochemicals as a remedy and harnessed those phytochemicals from different plants against virus disease in vitro and in vivo assay. This has brought a new usher to fight the devastating viral ailments including the pandemic novel COVID-19.

However, a comprehensive study regarding phytochemicals as antiviral activity is strongly required to unravel the molecular mechanism of action of the bioactive on the virus, establish economical drug delivery strategies to the intended site, and the modification and bio functionalization of the materials to enable it to act more effectively against the virus infection.

In a nutshell, the review concluded that phytochemicals are biologically active chemicals with multifarious functions and potential efficacy to inhibit a plethora of viral infections; and should have to compensate for the utilization of chemically synthesized antiviral drugs which have unintentional side effects on the patients. In averting the adapted landscape of antiviral therapies, the exploration of secondary metabolites as sources of antiviral agents does have prominent roles. Therefore, it is a positive alternative to harness the efficacious secondary metabolites as antiviral agents to overcome the side effects that can be caused by conventional antiviral drugs.

Ethical Approval and Consent to Participate

Not applicable

Consent for Publication

All authors have given approval for the final revision of the manuscript

Author Contributions

Digafe Alemu: Conceptualization, Supervision, editing, manuscript preparation and; **Belete Ketema:** reviewing and writing; **Ajoy Kanti Mondal:** design, reviewing, supervising and validating the manuscript. Finally all authors have read and agreed to publish of the manuscript

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Data Availability

The data used to support the findings of this study are included within the article

Conflicts of Interest

The authors declare no competing financial interest

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