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An Appraisal on Antiviral Potential of Medicinal Plants

[1]Ashwini Dokhale, [2]Akanksha Shinde, [3]Shraddha Shelke, [4]Sonali Pawar, [5]Abhijit Shinde,

[1]Asst. Professor, [2]UG Student, [3]UG Student, [4]UG Student, [5]UG Student,
[1]Department of Pharmaceutics,
MGV Pharmacy College, Panchavati Nashik, Maharashtra, India

Abstract: Herbal plants are broadly utilized in infectious and non-infectious illnesses since prehistoric times. In the present time, generally utilized medications likewise contain extracts separated from natural plants. A few natural plants offer a source for drug exploration where humankind is confronted by recently arising infectious illnesses. Viral diseases especially connected with SARS-Covid 19 have challenged humanity's endurance. Certain collections of herbal plants have demonstrated a guarantee to treat viral diseases by having antiviral potential. There are a few drawbacks concerning the utilization of synthetic medications like having after-effects that happen now and again, significant expense, low accessibility. Because of these restrictions, there is an expanding pattern in the field of research and drug discovery to discover natural options because of their wide accessibility and ease. The pharmaceutical industry is dynamically focusing on phytochemical extricates, herbal plants, and fragrant herbs with the point of distinguishing lead compounds, focusing primarily on alternative antiviral medications, in particular for SARS-Covid 19. The discovery and improvement of safe, effective, and economical antiviral moiety are among the top general urgencies of medication research. This review elaborates the likely antiviral properties of some herbal plants which can be utilized against viral infections.

Keywords: Antiviral, Zingiber officinale, Curcuma longa, Azadirachta indica, Panax ginseng, Glycyrrhiza glabra, Andrographis paniculata, Artemisia annua

INTRODUCTION

Viral infections overall remain the reason for morbidity and mortality. Among the most forceful viral diseases are Ebola, AIDS (acquired immunodeficiency syndrome), flu, and SARS (severe acute respiratory syndrome). For instance, influenza is the reason for over three million new cases of severe disease, and about 500,000 deaths yearly [1, 2]. Alarmingly, the quantity of patients determined to have viral diseases is expanding each year with more blood transfusions, organ transplantations, and the utilization of hypodermic needles.[2] The World Health Organization has called recognition to conventional medication is a significant commitment to its wellbeing objectives. Viral infections, including arising and chronic infections, are an expanding overall health concern. Because of the worldwide illness trouble brought about by viral contaminations, there is an earnest requirement for novel and more successful antiviral medications.

Nowadays viral infections are becoming a great danger to humans and often cause death. Before, lethal infections caused pandemics on the planet. Viruses have metabolic properties due to that they are difficult to control and until now there are relatively few drugs for the treatment of viral diseases. The main problem accrued in treating viruses is their rapid adaptation and drug resistance developed by them. [3] Because of that, naturally based pharmacotherapy might be a better option for treating viral infections. Along these lines, it is very important to additionally lookout for sources of antiviral phytochemicals, featuring drug-delivering applications in defeating the different biological barriers existing for antiviral specialists to effectively reach their intended site(s) of activity. The current review centers around the antiviral properties of herb extracts and bioactive constituent isolate from therapeutic plants, and the efforts to get their effective delivery.

The use of herbs and extracts from herbs as an antiviral agents began following World War II in Europe, and the research was later developed worldwide. [4]Although vaccines have been very successful in controlling many viral diseases, some diseases are possible to be controlled only by antiviral chemotherapy. The concept of antiviral drugs has only been accepted slowly, partly because of the toxicity of many of the earlier antiviral agents. In contrast to the development of antibiotics, attempts to develop antiviral drugs have indeed met a variety of problems. Viruses are only dependent on cellular metabolic processes, have only scanty intrinsic enzyme systems and building blocks that can be specific targets for a drug to act. [5]

Many viral infectious diseases yet cause deaths. Even though antiviral chemotherapy exhibits magnificent progression, antiviral agents are yet needed. Drug resistance accrued in treatment raise the difficulty for effective therapy. [6] This review article emphasizes some herbal medicinal plants having antiviral potential.

2. Literature Review

2.1 Overview of Viruses

Viruses are obligate intracellular spongers a having DNA or RNA and protein envelope called a capsid. Viruses don't possess their metabolism and they cannot replicate by own or carry out biosynthesis. They utilize and control the host cell. They can be transmitted by droplet infection, exchange of fluids of the body, person-to-person contact, and blood-sucking insects. [7]

For the ages, viruses were defined by their virions, the viral particles produced during infection, yet there is confusion. As a result of this misperception, viruses have been defined as simple structures and absence of metabolic activity. Being that several virions could crystallize, viruses could be regarded as molecular structures. [8]

2.2 Modes of entry

Viruses that are enveloped and non-enveloped have similar main steps and ways of virus entry —

1. It starts with attachment to the surface of cell receptors and terminates with the entry of the viral genome to the cytoplasm of the cell.
2. Next to the binding to cell receptors (carbohydrates, lipids, or proteins)-

There are two modes of entry-

1. Endocytic – transport via Claritin and non-Claritin coated vesicles, caveolae, micropinocytosis
Some exceptions are there that those viruses use internalization by endocytosis (Simirin Virus 40)
2. Non-endocytic routes- By surpassing the membrane of plasma at neutral pH. Some viruses that use the non-endocytic route could also enter by endocytic route into cells e.g. HIV

Membrane fusion — It is the basic process required for pinocytosis, vesicular trafficking as well as phagocytosis— It is the chief approach of entry for viruses that are enveloped that uses non-endocytic as well as endocytic routes. This procedure is controlled and directed by proteins on membranes. When the membranes are near to each other.

Entry into cells by non-enveloped and enveloped viruses includes changes in the conformation of the viral entry proteins or receptors of the host, which could be induced when endosomal pH is low. This could be done by penetration for non-enveloped viruses or by fusion for viruses that are enveloped. After entering into the cell of the host they get transported into the cytoplasm as complexes of nucleoprotein.

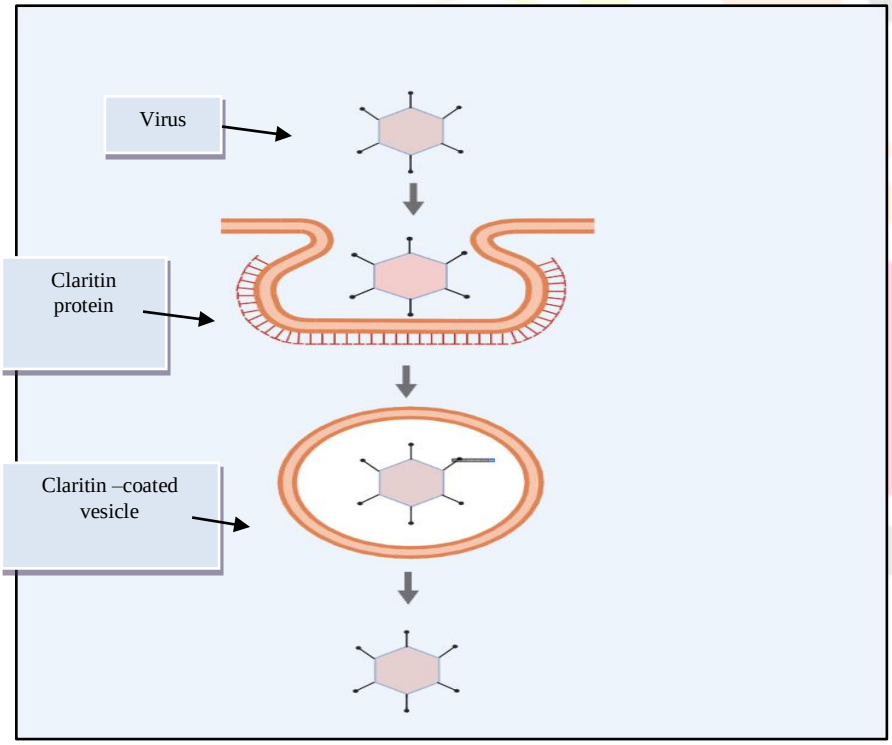

Figure 1: Endocytic Route

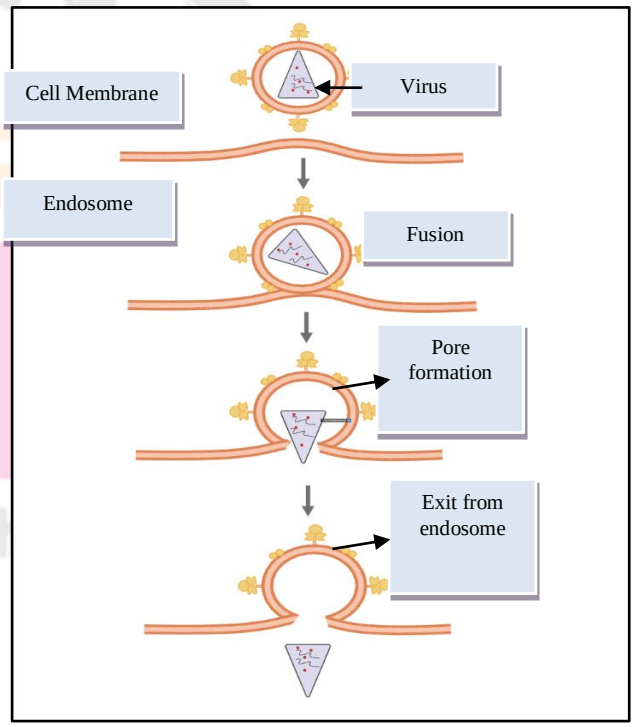

Figure 2: Non Endocytic Route

2.3 Mechanisms of action of some antiviral drugs

Prevention of virus entry into the cell, avoiding its adsorption, e.g. by specific ligands or antibodies.
Inhibition of virus uncoating following endocytosis by Capsid (protein shell of a virus) stabilizing agents as well as blockade ion channels of endosomes.
Suppression of DNA or RNA by inhibiting DNA- or RNA-polymerases by endonucleases. [9]

Table 1: Partial list of medicinal plants with viruses they inhibit

Plant	Part	Type of extract	Viruses inhibited	Mechanism of action	Ref
Zingiber officinale	Fresh rhizomes	Hot water extract	HRSV	Inhibition of viral attachment, internalization, as well as possibly stimulating IFN-b secretion.	[11]
	Dried rhizomes	Aqueous extract	Chikungunya virus	[6]-gingerol could inhibit CHIKV infection by suppressing viral replication.	[13]
Curcuma longa	Rhizomes	Alcoholic extract	Dengue virus	Curcumin (weak inhibitor of viral protease) inhibiting DENV infectivity in plaque assays that the cellular pathway essential for replication of viruses or assembly is targeted by these compounds	[15]
	Rhizomes	Aqueous extract	Hepatitis B virus	Curcuma longa extract represses the replication of HBV by enhancement of the level of p53 protein	[16]
	Rhizomes	Hydro alcoholic Extract	HSV 1 virus	Inhibiting the formation of viral plaque.	[17]
Azadirachta indica	Leaves	Aqueous extract	Poliovirus	Effective to inhibit PV-1 replication, as well as the sulfation, improved these activities.	[19]
	Leaves	Aqueous extract	Dengue virus type-2	-	[20]
Panax ginseng	Roots	Aqueous extract	RSV	Improves the survival of human lung epithelial cells against RSV infection and inhibits replication of RSV. Inhibition of attachment of virus, membrane penetration, as well as replication.	[21]
Glycyrrhiza glabra	Root	Aqueous Extract	Herpes Simplex Virus 1	HSV attachment inhibition through direct contact between the virus and the extract.	[23]
	Root	-	Hepatitis C	Glycyrrhizin inhibits HCV 3a core gene expression both at mRNA and protein levels	[24]
	Root	Ethanol extract	Influenza	Improvement in survival time of animals after infection; an increase of IFN-γ production Inhibition of virus growth; inhibition of inflammatorycytokines Improvement in survival time of animals after infection; an increase of IFN-γ production Inhibition of virus growth; inhibition of inflammatorycytokines Improvement in survival time of animals after infection; increase of IFN-γproduction Inhibition of virus growth; inhibition of inflammatorycytokines Improvement of survival time of animals after infection; increase in IFN-γ production Inhibition of growth of viruses; inhibition of inflammatory cytokines	[25],[26]

	Roots	Glycyrrhizin glycyrrhizic acid derivatives Glycyrrhizin glycyrrhizic acid derivatives -	SARS -related coronavirus	Glycyrrhizin, glycyrrhizic acid derivatives inhibit replication of viruses; induction of cellular NO-synthase	[27]
Andrographis paniculata	Leaves	Ethanol extract	SRV virus	Andrographolide could inhibit the production of viral particles.	[28]
	Leaves	Ethanol extract	HSV-1	Andrographolide, neoandrographolide, and 14-deoxy-11,12-didehydroandrographolide, ent-labdane diterpenes isolated from Andrographis paniculata showed virucidal activity against HSV-1	[29]
Artemisia annua	Whole plant	Hexane-ethyl acetate extract	-	Reduction in lesion size, the diameter of the lesion. This report shows sterols present in A. annua plant had shown virus inhibitory activity.	[32]

2.4 Antiviral medicinal plants

2.4.1 Zingiber officinale

Zingiber officinale is a likely used spice in the world, and it is used as a folk medicine in China and Japan for treating disorders related to the gastrointestinal tract, vomiting, diarrhea, nausea as well as in cough. Chemical constituents IN *Zingiber officinale* are diarylheptanoids, volatile oil as well as gingerol-related compounds, ketones (phenolic).Extracts of ginger have shogaols, gingerols gingerdiols, zingiberene, beta-bisabole. The gingerols and phenolic compounds which are present in the root of ginger which is having about 1 to 3 % gingerol [10]

Fresh rhizomes of *Zingiber officinale* possess antiviral activity against Human Respiratory Syncytial Virus by reducing plaque formation in mucosal cells of the respiratory tract. An excessive amount of *Z. officinale* could trigger mucosal cells to produce IFN-β that could prevent infections caused by the virus by decreasing the attachment of viruses and their internalization. [11] This effect could help manage the common cold as well as fever linked with that mucosal secretions and treating cough and conditions related to asthma

The active ingredient present in *zingiber officinale* that is allicin has ant influenza cytokines. So, *Zingiber officinale* can be used as an antiviral agent against influenza A (H1N1). [12]

The aqueous extract of this plant exhibits activity against chikungunya. A huge number of components may include in counteracting the virus. Extracts from the plants are relatively conventional, efficient, cost-effective, and also friendly to the environment in contrast to drugs that are chemically synthesized. Plants having significant medicinal effects could be a better option to develop a broad span of antiviral agents which will be an alternative treatment for viral infections. *Zingiber officinale* is having therapeutic activity and also counteracts drug resistance in an antivirals against the chikungunya virus. It is recommended that before the use of aqueous extract of the plants as therapeutic agents antiviral therapy, toxicity, or side-effects related with that and mechanism of action should be properly studied. [13]

2.4.2 Curcuma longa

Rhizomes of *Curcuma longa* utilized as an antimicrobial agent for ages. Some experiments outlined the antimicrobial effect for curcumin which includes its antifungal, antibacterial, antiviral as well as antimalarial effects. Curcumin possesses prolong antimicrobial effects as well as safety at 12g/day which was examined by clinical trials, hence it has been used as a sample to construct newly adapted and enhanced antimicrobial effects through synthesizing several derivatives associated with *Curcuma longa*. *Curcuma longa* L. and its polyphenolic derivatives, curcumin had been exposed to various investigations related to antimicrobial effect because it is having to prolong traditional utilization and fewer side effects. [14]

Balasubramanian et.al [15] recognize that curcumin could inhibit DENV2 NS2B/NS3 protease in high-throughput, 4 analogs of curcumin were synthesized by them and examined their in – vitro protease effect and also studied hampering of replication using cell-based assays. The conclusions obtained indicate that curcumin causes weak inhibition of viral protease.

Nevertheless, the analogs disclosed more efficient inhibition of DENV infection in plaque assays advises that for viral replication cellular pathways are essential or these compounds target assembly. Furthermore, studies have shown in DENV-2 infected cells inhibition of genes involved in lipid biosynthesis and inhibition of actin polymerization was taken place by curcuminoids, which could be regarded as their mode of action in DENV infection. [15]

Curcuma longa Linn could be used in the treatment associated with several liver diseases which are caused by infection of hepatitis

B virus. Curcuma longa extract possesses an antiviral effect against the HBV virus in that it reduces the transcription procedure of the HBx gene and it doesn't show cytotoxicity to liver cells. Curcuma longa extract effectively increased the accumulation of cellular p53 protein by p53 transcriptional activation as well as inhibits degradation of p53. This result shows that the antiviral activity of Curcuma longa extract against HBV virus and it is due to the inhibition of gene expression. Therefore, Curcuma longa extract could be used as effective herbal medicine for viral infection. [16]

Hydro-alcoholic extract of Curcuma longa had an antiviral effect on the HSV-1 virus, so this extract could be used in the management of HSV-1 viral infection. [17]

Curcumin isolated from Curcuma longa could be used to reduce influenza A virus replication it was proved that curcumin possesses promising ant influenza activity and safety profile. [18]

2.4.3 Azadirachta indica

For over two thousand years *Azadirachta indica* A. Juss, also recognized as neem and is broadly used in the Ayurvedic system of medicine by the Population of India. It's been used for centuries to treat a variety of diseases. Organic products and their variants are a great place to look for new antiviral medications.

The conventional usefulness of neem leaves as antiviral is identified for treating animals infected with bovine and avian poxviruses by spreading a paste of neem leaves specifically to the infected skin. It was found that methanolic extracts of neem leaves prevented the development of plaques in many coxsackievirus B serogroups. Neem oil has been shown to inhibit poliovirus transcription and neem's aqueous leaf extract inhibited dengue virus type. Neem tree aqueous extract has a strong anti-HSV-1 ability in addition to inhibiting virion glycoprotein-mediated cell-cell fusion and the development of polykaryocytes in cell culture. It was discovered that polysaccharides extracted from neem leaves extract had a strong antiviral activity towards BoHV-1 replication in HEp-2 cells. The antiviral activity of polysaccharides obtained from *Azadirachta indica* plants and their chemically sulfated extracts was determined to be successful in inhibiting PV-1 replication, with the sulfation improving these activities. While we believe that these compounds' antiviral activity occurs during the initial stages of viral replication, like adsorption and/or penetration, virucidal activity and viral protein synthesis inhibition cannot be excluded out. To summarise, these polysaccharides can function as natural antivirals, and more research in clinical testing should be supported. [19]

Neem is having hypoglycaemic, antipyretic, and anti-inflammatory as well as having anticancer and antimicrobial properties. Various segments of neem trees are being studied for their therapeutic and insecticidal activities. Neem leaves have long be present to treat a variety of bacterial and fungal infections. However, only a few viruses have remained experimented with for antiviral properties: HIV, chickenpox, measles, and HSV. Several studies have also shown that aqueous extract (aq. ext.) of neem leaves (NL) has potent antiviral activity against Fowlpox, Smallpox, HSV, and Polio, as measured by virus suppression assays. Although the Vaccinia viruses, Measles, and Chikungunya were substantially blocked, other viruses, like HSV-1, Dengue virus type-2, Parainfluenza, Mumps, West Nile, and Japanese Encephalitis, showed no such behavior. Polio viruses as well as HIV viruses and have been confirmed to be suppressed by an aqueous extract of Neem and a portion of neem oil (NIM-76). An initial effort to identify the inhibitory ability of NL aq. extract against Dengue virus type-2 revealed no resistance. [20]

2.4.4 Panax ginseng

Panax ginseng is a quite known herbal remedy that has been used for thousands of years to treat a variety of ailments. Ginseng seems to modulate the host immune system and enhance the outcomes of inflammatory human diseases. Ginseng along with its components like ginsenoside protopanaxatriol has also been shown to protect endothelial cells by scavenging hydroxyl radicals and by modulation of angiogenesis of endothelial cells.

Respiratory Syncytial Virus is the main reason for severe infections related to the respiratory tract in children along with in the elderly and individuals having weak immunity. Panax ginseng has been recognized to have several immuno-modulatory effects. In an experimental study, scientists examined whether Panax Korean red ginseng extract has in vitro and in vivo antiviral activity on respiratory syncytial virus infection, ginseng enhances the longevity of epithelial cells of lungs against respiratory syncytial virus infection and inhibited replication of the respiratory syncytial virus. Supplementary treatment with ginseng inhibits the RSV-induced inflammatory cytokine genes expression and the formation of reactive oxygen species in epithelial cell cultures.

Even though ginseng itself has direct antiviral activity by hindering viral attachment, penetration to the membrane, and its replication. [21]

2.4.5 Glycyrrhiza glabra

This herb is found in Asia and subtropical regions. Its common name is licorice, and it is having a sweet taste. Licorice word is derived from Greek word which means sweet roots. Licorice is commonly used medicinal herbs all over the world. Most of the traditional formulas include licorice because it is having medicinal significance. Glycyrrhiza glabra is mostly used in dry cough formulation. The use of the *Glycyrrhiza glabra* plant can be tracked down to ancient Egyptian, Chinese as well as Indian cultures. The major chemical constituents found *in Glycyrrhiza glabra* roots are triterpene saponins. Glycyrrhizin is main constituents found in Liquorice having concentrations of about 1% and 9% depends on the procedure for the extraction and geographical location of the plant. [22]

Licorice root extracts have antiviral activity against the HSV-1 virus. There are a number of mechanisms involved for antiviral activity against HSV-1 which include the inactivation of viruses, Glycyrrhiza glabra extract possesses an antiadhesive property that could hamper the adhesion of the virus to the host cell. Polysaccharides isolated from *Glycyrrhiza glabra* root have potent anti-adherent properties which could inhibit the adhesion of Helicobactor payroll to gastric mucosa of humans. It was also suggested that glycyrrhizin and glycyrrhizic acid are responsible for inhibiting the growth of HSV, in addition to that it was also advised that suppression of HSV-1 replication is due to interruption of late stages gene expression. Several studies indicated that the roots of *Glycyrrhiza glabra* and its component permanently inhibit the HSV virus, glycyrrhizic acid present in licorice roots could inactivate HSV particles. [23] *Glycyrrhiza glabra* could inhibit the Hepatitis C virus [24]

Compounds derived from Glycyrrhiza glabra like glycyrrhizin reduced damage to hepatic cells in hepatitis B and C. Some in-vitro studies reported that licorice extract has an antiviral effect against SARS-related coronavirus, HSV, HIV-1 virus, Vaccinia virus. [25]

Glycyrrhizin possess antiviral activity against the influenza virus [26]

The spread of SARS leads to the investigation of antiviral agents for the treatment of disease. One study indicated that glycyrrhizin could hinder replication of SARS so further study is needed to assess its efficacy related to SARS. [27]

2.4.6 Andrographis paniculata

Andrographis paniculata is commonly regarded as the most bitter herb. In India, Thailand, Malaysia, China this medicinal plant is broadly utilized for the treatment of upper respiratory tract infections as well as a sore throat. Andrographolides are one of the main constituents of *Andrographis paniculata* having anti-cancer, anti-inflammatory, antibacterial, antitumor, antiviral, antidiabetic activities. Methanolic, chloroform, as well as hexane extracts of *Andrographis paniculata*, were reported to hinder fungal and bacterial pathogens. Aqueous extract of *Andrographis paniculata* have antiviral activity against HIV neoandrographolide, andrographolide exhibited viricidal activity against herpes simplex virus 1 (HSV-1). The ethanol extract of *Andrographis paniculata*, as well as andrographolides, could suppress the expression of the Epstein-Barr virus.[28] Data obtained from experimental studies show that isolates of plant i.e., neoandrographolide, a glucoside have the highest rates of anti-herpes activity which confirms an antiviral potential of the plant. [29]

2.4.7 Artemisia annua

Artemisia annua L has been used for various diseases since the ancient era. Artemisinin isolated from Artemisia annua possesses excellent activity against malaria, with this discovery related to antimalarial effect it has been disclosed that Artemisia annua have activity against some parasites, fungi, viruses including Hepatitis A virus, HSV 1 virus, HIV. Artemisia annua extract exhibits antiviral activity inhibiting viral attachment to cells of the host. The methanolic extract has antiviral activity against HSV-1 while aqueous extract shows antiviral activity against HSV-2. Mechanism of action for the anti-viral effect of A. annua was yet unclear and further investigation is needed.

Artemisinin from *Artemisia annua* is the most promising compound investigated for the last two decades. The medicinal value of this compound is not limited only up to malaria but also cancer cells and various viral diseases. Due to the multifunctional nature of artemisinin, its awareness is increasing. [30]According to a recent study, there is a possibility that Artemisia annua could be uses to combat the current challenge of COVID -19 [31]

Low molecular weight sterols are present in Artemisia annua isolated and recognized as stigmasterol and sitosterol, it was found that these sterols affect the host than viruses, according to the study it was found that size and number of lesions are reduced. This was the first report related to sterols present in Artemisia annua.[32]

3. Future prospective

Countries having an abundance of medicinal plants should arrange investigation studies for identification of active constituents from them and their potential to exhibit antiviral activity. Isolation of active compounds is the major hurdle in the screening of their potential against viruses. To study antiviral effects there is a risk of infection to avoid that vector-based studies should be incorporated. Studies regarding safety and efficacy associate with the usage of medicinal plant extracts as well as plant actives should have a more promising nature for that clinical trials should be performed. As there are lesser harmful effects associated with traditional medicine than that of chemically derived treatments, the use of traditional plants along with allopathic medicine will give a more promising nature to combat viruses.

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