



E-ISSN: 2278-4136

P-ISSN: 2349-8234

[www.phytojournal.com](http://www.phytojournal.com)

JPP 2021; 10(6): 372-378

Received: 22-09-2021

Accepted: 24-10-2021

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## Medicinal herbs and its bioactive ingredients: The alternative green resources against viruses

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DOI: <https://doi.org/10.22271/phyto.2021.v10.i6e.14314>

**Abstract**

In nature, there are plenty of medicinal herbs and plants which contain active compounds decisive for their diverse prophylactic/ therapeutic behaviour against many human diseases. A thorough analysis of these phyto-compounds for antimicrobial activities has considered greater importance in the context of recent days. There is an urgent need for alternative medicine to control the current pandemic of SARS-CoV-2 and its different variants, including delta strain and Omicron. Extensive research has revealed that identification and establishment of anti-viral activities of various prospective medicinal plants were limited due to: (a) infectious nature of viruses (b) absence of uncoupling techniques for the invention of anti-viral components from plants. With time progression of vector-based attempts, during which non-infectious molecular replica of an epidemic might be utilised for beneficial screening purposes alongside the development of separation techniques, offers the prospect for medicinal plants usage in current drug for the betterment of the society generally. The anti-viral mechanism of those agents could also be elucidated based on their scavenging abilities, inhibiting viral DNA replication, antioxidant activities, RNA synthesis, inhibition of the viral invasion, or inhibiting the viral propagation. A sizable amount of testing substances like phytochemicals and their synthetic residues are identified by consolidating *in vitro* and *in vivo* studies in various biological assays. In this review, comprehensive information on the recent advancement of plant-derived divergent phytochemicals as a probable non-conventional anti-viral substitute has been well explained.

**Keywords:** medicinal plants, synthetic drugs, antiviral, novel coronavirus, cytotoxicity, screening methods for new drugs

**Introduction**

Viruses are intracellular obligate parasites, constitute a small cluster of RNA or DNA gene strands, and should be enclosed by a lipid-containing bilayer envelope. Viruses are complex in nature. It uses the host cell environment to strengthen its effects on the physical body, whereas bacterial cells are lifestyle organisms. Numerous invasive strategies are utilised, and every strain of the virus has its own exclusive configuration of surface molecules<sup>[1]</sup>. These surface molecules work like keys and locks, allowing viruses to enter into hosts by the definite fitting of the surface molecules to those on the membranes of target cells. Four general characteristics: efficient multiplication within host cells, genetic variation, variety in transmission, and therefore the capability to persevere within the host cell results in the success of viruses in progression<sup>[2]</sup>. Many viruses encode proteins that enhance virulence by modulating host immune responses. For example, influenza A NS1 protein interferes with activation of cellular innate immune responses to viral infection,<sup>[3]</sup> and thereafter the translation products of the adenovirus E3 transcriptional unit, which serve to prevent cytotoxic T-cell recognition of virally infected cells and block immunologically activated signalling pathways that lead to infected-cell death<sup>[4, 5]</sup>. These proteins are dispensable for viral replication in cultured cells in many cases. In this way, immunomodulatory viral virulence determinants resemble classic bacterial virulence factors such as various secreted toxins.

Medicinal plants have played a significant role since the emergence of human civilisation on earth. Most of those plants were used to treat contagious virus infections in the past. However, the Boots pharmaceutical company (Nottingham, England) was the primary organisation to acknowledge their interest in developing anti-viral and screen 288 plants for anti-influenza activity<sup>[6]</sup>. Secondary metabolites from plant extracts have inhibitory effects on various virus types found in later studies. Viruses that showed potent inhibition against plant extracts are-Human Immunodeficiency Virus type1<sup>[7]</sup>, Herpes Simplex Virus type2, poxvirus and Severe acute respiratory syndrome (SARS) virus stomatitis virus, Ebola<sup>[8]</sup>.

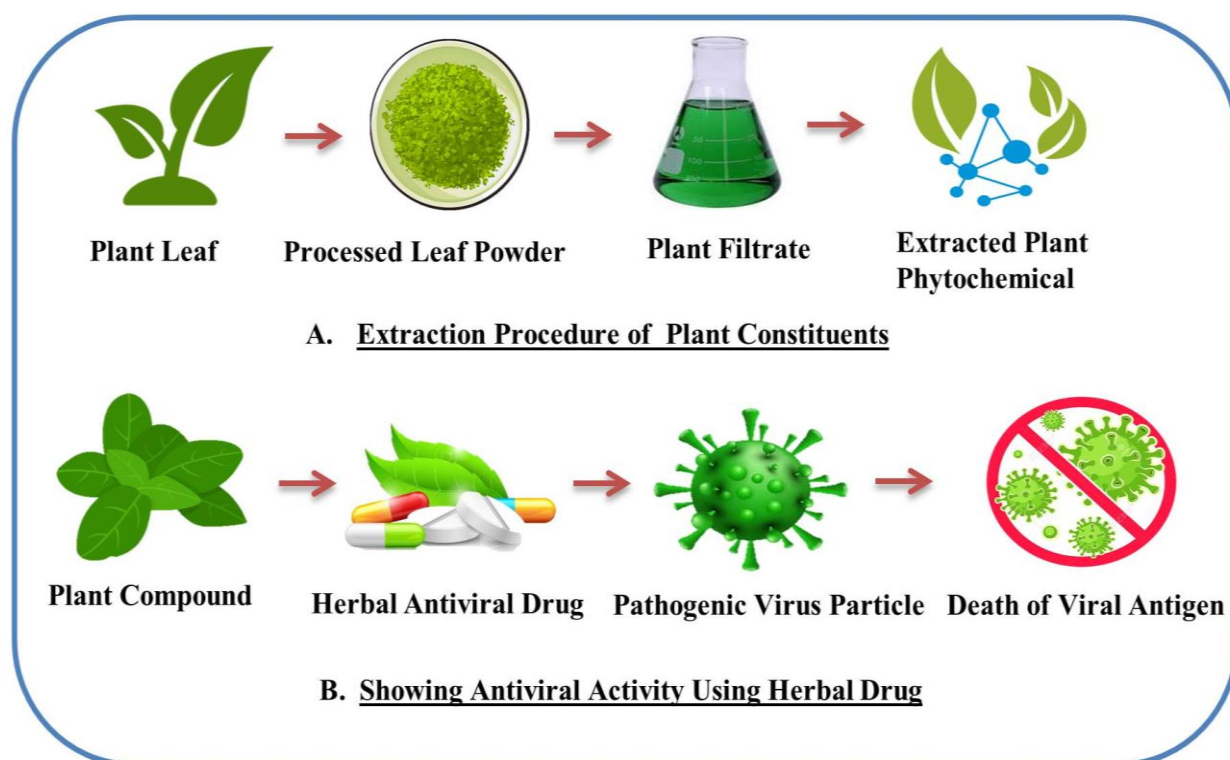
Nevertheless, morbidity and mortality remain the leading worldwide explanation for viral infections. It's been confirmed that influenza is liable for over 3 million new cases of severe diseases and between 300,000–500,000 deaths per annum.

There are several viruses whose effective remedies are yet to be discovered, and vaccination is constrained to hepatitis A virus, mumps and Varicella [9]. Additionally, these remedial agents are expensive and ineffective to viral resistance, which results in side effects. Therefore, we feel that reviewing the consequences of phytochemical drugs on viral infections is helpful. India has a rich cultural heritage, constituting of two sorts of medications: Ayurvedic and Unani Systems [10]. In Ayurveda, numerous plants contain various chemical compounds that can function as a source of varied therapeutics agents to recover disorders correlated with public health [11]. Ethnopharmacological awareness of traditional herbal medicine practice is a crucial origin of data. It has shown to be very efficient in recognising bioactive compounds, even in comparison to the high-quality volume random screening procedures [12]. Although the sector of Ayurveda has vast opportunities in current medical sciences and holds commitments for the longer term, it also has its

limitations since most of the herbal medicines will ultimately depend upon the supply of plants components which directly or indirectly will depend upon several factors like growth cycle of the precise plant, its local availability and also the government restrictions. Homeopathy treatment for viral infections is steadily gaining popularity as a natural way to deal with viral infections. These medicines help reduce the frequency and intensity of acute symptoms like weakness, fever, body pain, etc. These help with quick recovery.

In some cases, they reduce the chances of further complications. Homeopathy treatment for viral infections treats the symptoms not by suppressing them but by strengthening the immune system. It activates the body's natural restorative properties by producing symptoms similar to the ones experienced by the patients. This method helps settle underlying internal disturbances in the body. Homeopathy treatment for viral infections also minimises the weakness and fatigue commonly encountered due to the illness [13].

The review focuses on the anti-viral action of herb extracts and bioactive components identified from medicinal plants. Therefore the efforts to acquire their efficient delivery is represented in figure 1.



**Fig 1:** A. Extraction procedure of plant constituents & B. Showing anti-viral activity using herbal drugs

### Synthetic Drugs and Their Objectives

Numerous viral infections are still an excellent threat to humanity and sometimes fatal. Harmful viruses result in pandemics across the planet. Nowadays, the danger of spreading viruses among continents and countries is even more prominent. Being a rich reservoir of such metabolic properties, these viruses are becoming challenging to regulate, and there are still relatively few drugs for the medication of viral diseases [14]. For many years viral infections have been studied as intransigent to selective anti-viral chemotherapy because the replicative cycle of the virus was assumed to be too nearly interlacing with normal cell metabolism so that any pursuit of repressing virus reproduction would be intent to kill (or severely damage) the uninfected cell as well [14, 15].

### Importance of Studying Anti-Viral Phytomedicines Instead of Conventional Drugs

There is a growing need to search for the latest compounds with anti-viral activity because the treatment of viral infections with accessible anti-viral drugs is usually [16]. Analysis for bio-prospecting of natural products is often accomplished in two ways. Firstly, the academic method comprises phytochemical factors, luck and random screening approaches. Secondly, one depends on cognitive knowledge and practices or Ethno-pharmacology, which provides a unique approach for the invention of anti-viral agents, namely the study of medicinal plants with a history of the traditional use of their bioactive components as a possible source of drugs with important biological and pharmacological

activities [17]. For the treatment of infectious disorders, natural products remain a significant source of biologically active substances such as flavones, tannins, terpenoids, alkaloids, carotenoids, organosulfur compounds, and so more. Plants possessing such bioactive precursors play a promising role against *in vitro* viral pathogens [18]. It has been proposed that the selection of plants on indigenous applications provides a better shot than screening methods of general synthetic products [19]. It has been postulated that medical usage of such pharmacologically active plants is as old as 4000-5000 B.C., according to the literature suggested [20]. However, in India, the earliest note of the use of phytomedicines appeared in Rig-Veda, which was written around 3500-1600B.C. In later days the properties and therapeutic benefits of medicinal plants were examined intimately and recorded pragmatically by the traditional therapist in Ayurveda which may be a fundamental foundation of ancient medicinal plants in India [21]. Despite natural products being utilised by civilisation from past, only in current decades there has been widening research into alternative remedies and therefore the

therapeutic use of natural products, particularly those derived from plants. As a result, various studies have been implemented on the anti-viral activity of herbal medications against different pathogenic viruses irrespective of humans and other animals altogether [22]. Traditional medicines furnish the data and thus constitute a natural source reservoir of pharmacologically active drugs. Plants synthesise many biochemical products, many of which are extractable and used for scientific investigations. These phytochemicals consist of primary and secondary metabolites that have endless benefits to humans, exploited as natural pesticides, additives, aromas, medicinal compounds, fibres and beverages. Although secondary metabolites have restricted distribution, which may be a taxonomically related group of species, primary metabolites are found everywhere under kingdom Plantae. Essential oils of remedial importance are also found in medicinal plants. Therefore, medicinal plants proved to be a crucial resort of bioactive compounds that find their use in treating diseases in many cultures [23, 24], as described in table 1.

**Table 1:** Drug derived from medicinal plant and their anti-viral effect

Virus	Medicinal Plant Used	Derived Drug	Possible Target	Mechanism of Action
Herpes simplex virus (HSV)	<i>Carissa edulis</i> Vahl	Acyclovir	Virus polymerase	Exhibits strong anti-HSV 1 and both <i>in vitro</i> and <i>in vivo</i> activities.
Hepatitis B virus	<i>Boehmeria nivea</i> L.	Interferons	Cell defence protein activation	The root extract of <i>Boehmerianivea</i> reduces HBV production in an <i>in vitro</i> and <i>in vivo</i> model.
Hepatitis C virus (HCV)	<i>Saxifraga melanocentra</i>	Interferons	Cell defence protein activation	A compound called 1,2,3,4,6-penta- <i>O</i> -galloyl-beta-d-glucoside isolated from <i>Saxifraga melanocentra</i> .
Influenza virus	<i>Geranium sanguineum</i> L.	Biflavanoids	Influenza virus sialidase	Reduces the infectivity of various influenza virus strains <i>in vitro</i> and <i>in vivo</i> .
HIV	<i>Camellia sinensis</i>	Ritonavir, Indinavir	Reverse transcriptase	EGCG inhibits HIV 1 directly and interacts with the D1 domain of CD4 and the pocket that binds gp120.
Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)	<i>Lycoris radiate</i>	Lycorine	Interferon and glycyrrhizin	Lycorine, isolated from <i>Lycoris radiate</i> , has anti-SARS-CoV.

### Mechanism of Action of Anti-Viral Phytochemicals

One of the main steps in drug discovery is to spot and validate specific molecular targets. The advance of recent day biology has enabled us to identify microbial enzymes, receptors and molecular processes that facilitate drug action against one particular kind of virus. Studies have indicated that the anti-viral activity of plant-derived products may be attributed to a variety of well-defined mechanisms. The anti-viral efficacy of some natural compounds could also be explained by more than one mechanism. However, in some cases, the mechanism of the action could also be unknown. Realising the properly roadway may guide us to breakthrough promptly with more logical drug design and future other analytical procedures [25-27].

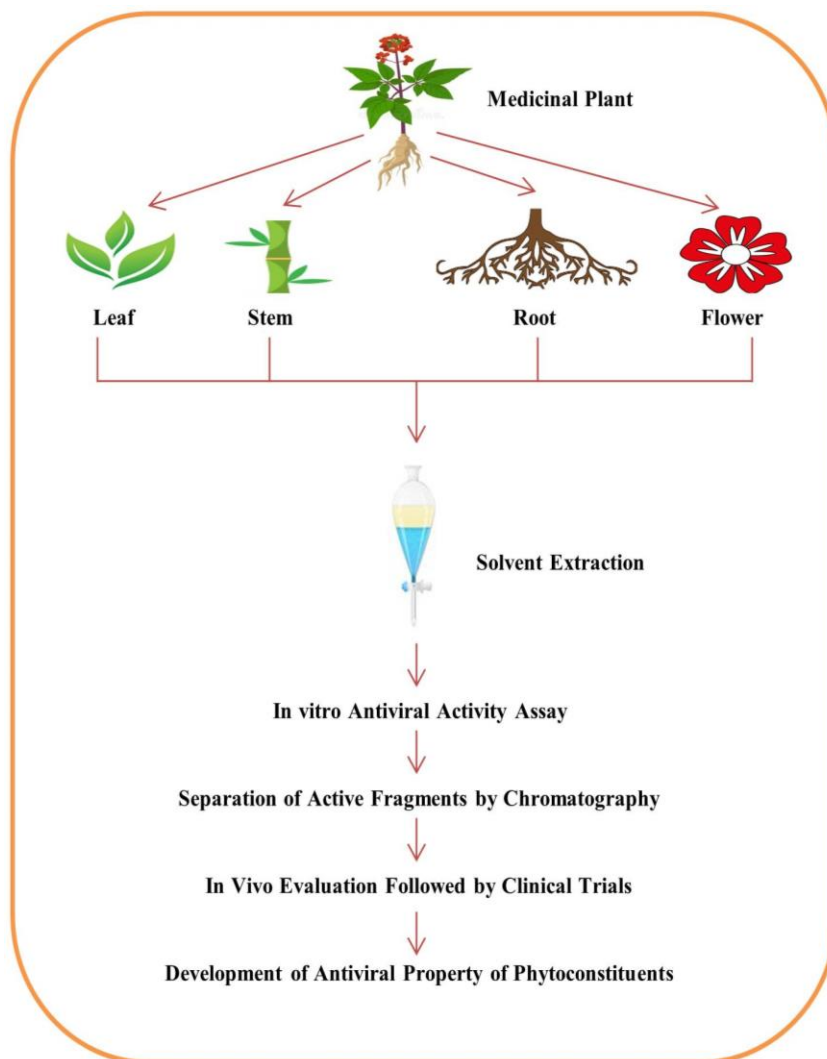
### The Conceivable Practice of Plant-Derived Phytocompounds to Prohibit the Present Pandemic Status of Covid 19 Causing Coronavirus

SARS-CoV-2 is an RNA virus with a genetic structure almost like SARS-CoV or MERS-CoV [28, 29]. The viral genome encodes a protease, which plays an essential role in the production of viral proteins and controlling the activity of the replicase complex [30, 31]. Earlier outbreaks of SARS-CoV and MERS-CoV have provided us with info about anti-viral phytochemicals with health beneficial activity [32]. This review gives us the prospect of using phytocompounds extracted from various parts of a plant using different solvents (Figure 2) and their further consideration as a source of biologically active substances, including different types of

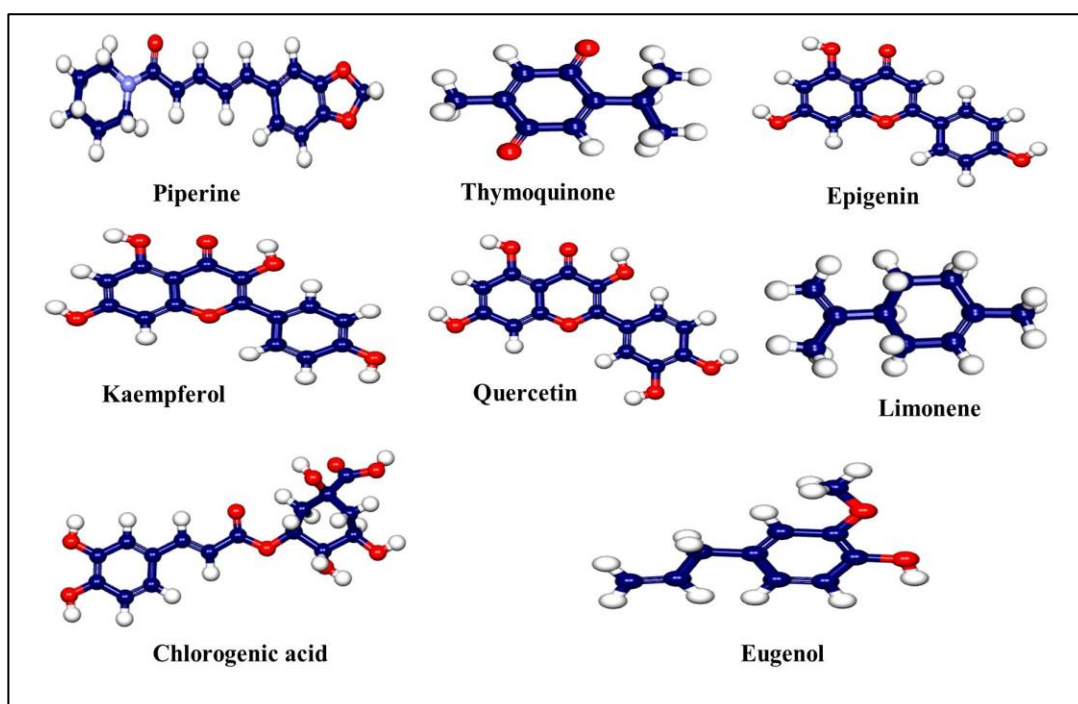
polyphenols, flavonoids and many more other bioactive constituents, which are found to be effective in inhibiting the event of Covid-19-inducing coronavirus [33] (Figure 3). The strategy of implementing such preparations is fast because the raw materials for their preparation, namely herbs and consumable plants, are approved for human consumption worldwide [34]. The shortage of Covid-19-oriented conventional therapeutic agents (vaccines, antibiotics) enforces the utilisation of broad-spectrum antibiotics, also as widely known anti-virals and corticosteroids [35]. Plant extracts are a rich source of natural products; many are incredibly bioactive. Hence, they may find applications against different ailments, including coronavirus pandemics. Application of traditional herbal extracts of some distinctive Chinese medicine plants, e.g. *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora* and *Tsuga Chinensis*, were found to hinder the SARS-CoV viral genome replication [36, 37]. There are some other well-known herbs (Table 2) present that act as a rich reservoir of antioxidants, carbohydrates, amino acids, vitamins and minerals along with anti-virals. These antibacterial phytochemicals will aid in regenerating the immune system and also help in destroying the infected viruses [38, 39]. Thus, the event of such bioactive agents that inhibit coronavirus-associated respiratory syndrome (SARS-CoV) is vital for preventing and re-emerging the disease [40]. The wide selection of natural substances present in herbal extracts, underrated in conventional medicine, may constitute an almost inexhaustible source of medicaments. The proficiency about

their salutary activities and functions has been passed on from generation to generation. The new trends in biotechnology and medicine have enabled the utilisation of natural-origin

compounds to a more significant extent than within the previous decades, mainly because the dietary supplements and Nutraceuticals [41, 42].



**Fig 2:** Phytochemicals extracted from various plant parts using different solvents.



**Fig 3:** Bioactive compounds

**Table 2:** Medicinal herbs and their bioactive compounds

Name of The Medicinal Herb	Scientific Name	Major Bioactive Compounds
Black pepper	<i>Piper nigrum</i>	Piperine, piperlylin, feroperine, pipernonaline.
Black cumin	<i>Nigella sativa</i>	Thymoquinone, $\gamma$ -terpinene, safranal, p-cymene, and $\beta$ -pinene.
Clove	<i>Syzygium aromaticum</i>	$\beta$ -pinene, limonene, farnesol, benzaldehyde, 2-heptanone and ethyl hexanoate, eugenin, kaempferol, quercetin.
Holy basil	<i>Ocimum sanctum</i>	Apigenin, Ursolic acid, luteolin, apigenin-7-O-glucuronide, luteolin-7-O-glucuronide, orientin and molludistin.
Bettle vine	<i>Piper betel</i>	$\alpha$ -Pinene, hydroxyl chavicol, allylpyrocatechol, Chlorogenic acid, Chavibetol, Eugenol, edible natural phenols,
Cinchona	<i>Cinchona officinalis</i>	Chloroquine, cupreine, cinchonine.
Giloy	<i>Tinospora cordifolia</i>	Tinosporide, Furanolactone diterpene, Furanolactone clerodane, Giloin, Tinosporan acetate, Tinosporal acetate, Tinosporidine.

### Cytotoxicity Testing and Screening of Anti-Viral Herbal Drugs

It is crucial to evaluate the cytotoxic profile of each anti-viral herbal drug. Our first and foremost concern will always be the toxicological assessment and screening of any herbal formulation to identify the adverse effects. There are various *in vitro* anti-viral assays for this purpose, the majority of which are cell-based, including cytopathic effect assay (analysis of plaque reduction) and MTT assay (cell variability measurement). However, these anti-viral assays aren't standardised and time-consuming. Thus, other new techniques are increasingly used for drug screening [43, 44]. The most common classes are anthraquinones, polyphenolic compounds and triterpenoid saponins. The high content of polyphenolic compounds and anthraquinones is responsible for the antioxidant activity associated with more potent cytotoxic activity. Therefore in the early (pre-clinical) and late (clinical) stages of drug discovery and development, this will facilitate the identification of toxicants that can be discarded or modified during the process and create an opportunity for an extensive evaluation of safer, promising alternatives [45-47].

### Limitation of Using Anti-Viral Phytochemicals

While considering this aspect of plants for treating human viral diseases, one must be careful, as most viral vaccines are constituted of attenuated or inactivated viral particles. Due to these limitations, efforts have been directed toward expressing coat proteins of different viruses, which are presumed to assemble as virus-like-particles (VLP) in plants and are antigenic. Several other issues like the appropriate processing of protein to be expressed in plants are important aspects to be considered. In addition, there are other issues to be resolved before the translational usage of medicinal plants in the developed world. One such issue is the isolation of active ingredients associated with the medicinal characteristics of a particular plant. Moreover, considering the problems faced by the developed world, such as drug resistance and failure to find an effective vaccine for deadly infectious agents such as HIV, a causative agent for deadly AIDS, phytomedicinal products may provide hope [48-50].

### Conclusion

There is a requirement for the advancement of novel anti-viral agents. Many epidemiological and animal model studies are explored for cellular and subcellular targets of those anti-virals, and promising outcomes are observed. However, further investigation is needed to reveal its potential for human usages. Therefore, each herbal drug should undergo different screening assays, including computational and bioinformatics techniques followed by anti-viral resistance, biosensor techniques using capacitance sensor arrays, and RT-

PCR technique last but not least [43, 44]. This review has revealed a varied source of therapeutic and potential targets of the many plant's extracts.

Additionally, advanced herbal principles are inherently safer, simpler, and cheaper than their synthetic counterparts, lacking the favourable side effects of pharmaceutical drugs. Within the present scenario, a variety of synthetic anti-viral drugs are accessible, which proves to be effective against viruses but in a particular manner. Again, the difficulty of anti-viral resistance makes most anti-viral medicines ineffective. Therefore, there's an immediate need for the latest formulations having effective anti-viral properties. Traditional treatments are often linked with various herbal formulations from multiple medicinal plants. The world of herbal drugs holds enormous prospects for research and development. Many countries worldwide are now counting on their research and development programs to formulate effective therapeutic drugs against various viral diseases supported by the knowledge of traditional medicines [51, 52].

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