



**REVIEW ON: ANTIVIRAL AND IMMUNOMODULATORY
PROPERTIES OF MEDICINAL PLANTS**

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ABSTRACT

Several medicinal plants with potential antiviral activity used to treat a variety of infectious diseases. The antiviral activities of medicinal plants valued in Ayurvedic Rasayana have been a recent topic of scientific investigation. Nowadays a number of plant extracts and phytochemicals are used as potential sources for viral inhibitors, by showing antiviral activities against some RNA and DNA. Regarding nutraceuticals and their availability they can be used to enhance immunity by showing their effectiveness in viral infections. Many nutraceuticals can be used to enhance immunity depending on their availability. Several medicinal plants and phytochemicals responsible for immunomodulation and having antiviral properties have been compiled and published in the literature. The analyzed data is used to provide perspectives and directions for development of herbal formulations. This work will encourage researchers to carry out further study on medicinal plants with immunomodulatory and antiviral potential.

Keywords: Medicinal plants, Antiviral, Immunomodulators, Nutraceuticals

INTRODUCTION

Nowadays throughout the globe infectious viral diseases are still a major problem to public health and these viral diseases are

responsible for morbidity and mortality. Number of cases of viral diseases reported from different regions of the world. Due to

the lack of treatment for viral diseases and narrow therapeutic window of most of the drugs it causes dependence on vaccines as a preventive major. Various common drugs can be used to treat such illnesses but these drugs also have some serious side effects on patients which worsen the scenario of resistant patterns of drug. In traditional systems of medicine varieties of herbal plants have been usually used to treat various infectious and non-infectious diseases. According to the estimation, 25% of the commonly used medicines contain compounds isolated from plants. Several plants could offer a wide platform for drug discovery of infectious diseases, particularly in an era when the latest separation techniques are available but at the same time human population is challenged by a number of emerging infectious diseases on the other hand. Recent studies showing antiviral potential of plant extracts against viral infections resistant to conventional antiviral agents have challenged the modern drug discovery practices, and are gaining importance toward exploring natural antiviral components of medicinal plants. India has a rich cultural heritage in field of traditional medicines, comprising of two systems of treatments, i.e. Ayurveda and Unani systems. Ethno-pharmacological knowledge of traditional herbal medicine usage has been an important source of

information and have shown to be very efficient in the identification of bioactive compounds.

Various traditional systems of medicines all over the world have herbal formulations as their foundation. It is necessary that biological activity of medicinal plants has been ethno-botanically reported or scientifically established [1].

The molecular mechanisms related to the antiviral effects of plant extracts may vary among different viruses. In recent years, a number of studies have explored immunomodulatory properties of several medicinal plants having antiviral properties. Development in clinical and experimental studies of immunology has suggested that many infectious diseases and disorders arise because of stressful environmental conditions associated with suppression of the immune system. Naturally compounds possessing immunomodulatory properties are able to alter those mechanisms and offer further possibilities for modulating immune responses [2].

Antivirals: An Herbal Approach

Although vaccines have been very successful in controlling many viral diseases, some diseases are likely 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. Being strictly dependent on cellular metabolic processes, viruses possess only limited intrinsic enzyme systems and building blocks that may serve as specific targets for a drug. Moreover, contrary to a bacteriostatic compound, an effective antiviral drug should not only display considerable specificity in its antiviral action, but should also irreversibly block viral synthesis in order to stop cell suicide due to the viral infection and restore normal cell synthesis. In addition to this inhibition, the antiviral agent must have a broad spectrum of activity, favorable pharmacodynamics properties, and not be immunosuppressive. In the ideal situation, the antiviral drug checks the infection while the immune system prepares to destroy the last virus particles. This point is critical for those immune-compromised by illness (AIDS, cancer) or drug therapy (transplants, cancer). A frequent cause of death in these instances is from viral infections, so adjuvant antiviral chemotherapy is vital in these circumstances. Many viral infectious diseases still cause high mortality. Although antiviral chemotherapy has shown outstanding progress, antiviral agents are still required. The emergence of drug-resistant viruses during treatment

raises a potential problem for effective therapy. Furthermore, new viral pathogens may be discovered. Biologically active substances of plant origin have long been known as viral inhibitors. These antiviral compounds may be extracted from sources, such as higher plants, which have, for various reasons, been explored considerably less than the traditional ones.

A research program to detect and isolate antiviral compounds from higher plants is best carried out by a multidisciplinary team, consisting of at least a pharmacognosist and a virologist. The antiviral screening system should meet *all* requirements of any good assay, including validity, lack of ambiguity, accuracy, reproducibility, simplicity, and reasonable cost. Moreover, because we are dealing with plant extracts, the antiviral screen should be highly selective, specific, and sensitive; it is advisable to discriminate a true antiviral activity from a veridical one at this stage

Because most of the aforementioned requirements are better met by *in vitro* testing, we not only prefer *in vitro* screening of the plant extracts, but also the use of the same bioassay to guide the isolation of the virally active compounds from the plant extracts. The antiviral activity of the pure compounds then has to be confirmed in a later stage by *in vivo* assays [3].

Different methods for antiviral evaluation of herbal drugs are included in **Table 1**.

with reported anti-viral activity is given in **Table 2**.

List of plants and their active constituents

Table 1: In-vitro methods for evaluation of antiviral potential

Virus Assay Method	Specificity and Application
End point titration technique (EPTT)	<ul style="list-style-type: none"> Determination of virus titer reduction in the presence of twofold dilutions of test compounds
Virus-induced cytopathic effect inhibition (CPE)	<ul style="list-style-type: none"> For viruses that induce CPE but do not readily form plaques Determination of virus-induced CPE in monolayers, cultured in liquid medium, infected with a limited dose of virus, and treated with a nontoxic dose of the test substances
Virus yield reduction assay	<ul style="list-style-type: none"> Determination of the virus yield infected with a given amount of virus and treated with a nontoxic dose of the test substances Virus titration is carried out after virus multiplication by the plaque test or the 50% tissue culture dose end point test (TC50)
MTT assay	<ul style="list-style-type: none"> Determination of inhibition of virus infection treated with a nontoxic dose of the test substances by MTT reagent Inhibition is determined by calculating optical density (OD) in an ELISA plate reader
Plaque reduction assay	<ul style="list-style-type: none"> Only for viruses that form plaques Titration of residual virus infectivity after extracellular action of test substances Cytotoxicity should be eliminated, for example, by dilution, filtration, etc., before the titration
Assays on specialized functions and viral products	<ul style="list-style-type: none"> Determination of virus-specific parameters, e.g., hemagglutination and hem adsorption tests (myxovirus), inhibition of cell transformation (Epstein-Barr virus, EBV), immunological tests detecting antiviral antigens in cell cultures (EBV, HIV, HSV, and CMV), TZM-bl cell-based assay (HIV), CEM-green fluorescent protein cell-based assay (HIV), Hep AD38 assay (HBV), immunofluorescence assay, enzyme-linked Immunosorbent assay (ELISA) Reduction or inhibition of virus-specific polypeptides synthesis in infected cell cultures, e.g., viral nucleic acids, determination of the uptake of radioactive isotope labeled precursors or viral genome copy numbers
Other assays for antiviral activity	<ul style="list-style-type: none"> Virus inactivation assay, virus adsorption assay, virus attachment, and penetration assay

Table 2: List of plants and their active constituents with reported anti-viral activity

Viruses	Plant Species	Family	Active Constituent	Reported Activity
Human Immuno Deficiency Virus (HIV)	<i>Mallotus peltatus</i>	Euphorbiaceae	Ursolic acid	Active against HSV-1 and HSV-2 [4]
	<i>Buchenavia capitata</i>	Combretaceae	O-demethylbuchenavianine	Produces partial protection against the cytopathic effect of HIV in cultured human lymphoblastoid cells [5]
	<i>Syzygium claviflorum</i>	Myrtaceae	Betulinic acid	Potent against HIV [6]
	<i>Ancistrocladus korupensis</i>	Ancistroclada-ceae	Michellamines D and F	Exhibited in vitro HIV-inhibitory activity [7]
	<i>Schumanniphyton magnificum</i>	Rubiaceae	Schumannificine	Activity against HIV and anti-HSV [5]
	<i>Curcuma longa</i>	Zingiberaceae	Curcumin	Active against HIV [8]
	<i>Glycyrrhiza glabra</i>	Leguminosae	Licopyrano-coumarin	Inhibit giant cell formation in HIV-infected cell cultures without any observable cytotoxicity [5]
	<i>Artemisia annua</i>	Asteraceae	Artemisinin	Anti-HIV activity [9]
	<i>Berberis vulgaris</i>	Berberidaceae	Berberine	Antiviral effects against HIV-1 [10]
Herpes Simplex Virus (HSV)	<i>Securigeria securidaca</i>	Fabaceae	Kaempfero	Active against HIV-1 [11]
	<i>Actinodaphne hookeri</i>	Lauraceae	Actinophnine	Active against HSV-1 [12]
	<i>Achyranthes aspera</i>	Amarantha-ceae	Oleanolic acid	Active against HSV [13]
	<i>Pedilanthus tithymaloides</i>	Euphorbia-ceae	Luteolin	Active against HSV-2 [14]
	<i>Mallotus peltatus</i>	Euphorbia-ceae	Ursolic acid	Active against HSV-1 and HSV-2 [15]
	<i>Artocarpus lakoocha</i>	Moraceae	Oxyresveratrol	Inhibit viral replication [16]
Influenza Virus	<i>Caesalpinia sappan</i>	Fabaceae	3-Deoxysappanchalcone	Antiinfluenza, apoptosis, and antiinflammation [17]
	<i>Syzygium aromaticum</i>	Myrtaceae	Eugenol	Inhibit the activation of extracellular signal-regulated kinase, p38-mitogen-activated protein kinase, IκB kinase (IKK)/ NF-κB signal pathways [18]
	<i>Angelica keiskei</i>	Apiaceae	Xanthokeistal A	Neuraminidase inhibitor [19]
	<i>Lonicera japonica</i> Thunb	Caprifolia-ceae	Chlorogenic acid	Influenza A (H1N1/H3N2) virus [20]
	<i>Houttuynia cordata</i>	Saururaceae	Quercetin 3 rhamnoside	Inhibit replication in the initial stage of antiinfluenza A virus infection by indirect interaction with virus particles [21]
	<i>Melaleuca alternifolia</i>	Myrtaceae	Terpinen-4-ol, terpinolene	Anti-A/PR/8 virus (H1N1) [22]
Hepatitis B virus (HBV)	<i>Liriope platyphylla</i>	Asparagaceae	LPRP-Et-97543	Inhibit viral gene expression and replication. Inhibit viral promoter activity [23]
	<i>Piper longum</i> Linn.	Piperaceae	Piperine	Inhibit the secretion of HBV surface antigen [24]
	<i>Swertia macrocarpa</i>	Gentianaceae	Swermacroactones and luteoli	Inhibit secretion of HBV surface antigen [25]
	<i>Phyllanthus niruri</i> L.	Phyllantha-ceae	Nirtetralin A	Anti-HBV activities [26]
Hepatitis C virus (HCV)	<i>Ruta angustifolia</i>	Rutaceae	Chalepin and pseudane IX	Inhibited HCV at the postentry step and decreased the levels of HCV RNA replication and viral protein synthesis [27]
	<i>Syncephalastrum racemosum</i>	Syncephalastraceae	Ursolic acid	Anti-HCV activity [28]
	<i>Embelia ribes</i>	Primulaceae	Quercetin	Active against HCV [29]
	<i>Vaccinium virgatum</i> Aiton	Ericaceae	Proanthocyanidin	Inhibit HCV replication [30]
Respiratory syncytial virus (RSV)	<i>Citrus reticulata</i>	Rutaceae	Tangeretin and nobiletin	Affected the intracellular replication of RSV. Tangeretin down regulated the expression of RSV phosphoprotein (P protein) [31]
	<i>Rosmarinus officinalis</i>	Lamiaceae	Carnosic acid	Inhibit replication of RSV [32]
Dengue virus (DEN)	<i>Magnolia grandiflora</i>	Magnoliaceae	Honokiol	Inhibits dengue virus type 2 infection [33]
	<i>Scutellaria baicalensis</i>	Lamiaceae	Baicalein	Viricidal against DEN-2 [34]
Vesicular stomatitis virus (VSV)	<i>Melia azedarach</i> L.	Meliaceae	1-Cinnamoyl-3,11-dihydroxymeliacarpin (CDM)	CDM blocks VSV entry and the intracellular transport of VSV-G protein and confined it only to the Golgi apparatus [35]
	<i>G. glabra</i>	Fabaceae	Glycyrrhizin	Inhibit phosphorylation enzymes and latency of VSV [36]
	<i>Calendula arvensis</i>	Asteraceae	Oleanolic acid	Inhibit VSV multiplication [37]
Epstein-Barr virus (EBV)	<i>Glycyrrhiza radix</i>	Leguminosae	Glycyrrhizic acid	Interferes with an early step of EBV replication cycle [38]
	<i>Saururus chinensis</i>	Saururaceae	Manassantin B	Inhibitory effects toward EBV lytic replication [39]
SARS-corona virus (SARS-CoV)	<i>G. glabra</i>	Fabaceae	Glycyrrhizin	Anti-SARS-CoV [40]
Polio virus (PV)	<i>Baccharis Gaudichaudiana</i>	Compositae	Apigenin	Anti-PV type 2 [41]
	<i>Dianella longifolia</i>	Xanthorrhoeacea	Chrysophanic acid	Inhibit PV 2 and PV 3 replication [42]
	<i>Pterocaulon sphacelatum</i>	Asteraceae	Chrysosplenol C	Inhibit PV [43]
Ebola virus	<i>Aglaiia foveolata</i>	Meliaceae	Silvestrol	Active against Ebola virus [44]
	<i>C. longa</i>	Zingiberaceae	Curcumin	Active against Ebola virus [45]

Plant Based Immunomodulators:

Nowadays, the immunomodulatory properties of plants are extensively studied for disease prevention and cure, due to benefits by immune system modulation. Several medicinal plants are known for their anti-infective effects; these plants not only affect the pathogens but also stimulate natural and adaptive defense mechanisms of the host. As animal bodies are excellent places for perpetuating microbes, they are everywhere, so the significance of the immune system plays an important role for surviving in these hostile conditions. Many illnesses are responsible for weakness of the immune system. The endogenous potential of the immune system can be stimulated with immune enhancers, by creating microbial invasion and reducing the chances of infections. Herbal preparations act by modulating the immune system by functioning immunostimulation, immunosuppression, or immunoregulation effects. They can also increase the efficacy of chemotherapy for the control and prevention of infections [46].

There are three classes of nonspecific immune enhancers:

1. Synthetic chemical compounds
2. Herbal extracts
3. Derived from microbial products

The use of herbal preparations can also be an effective method to boost the immune system. Early studies on

immunomodulatory effects of medicinal plants can identify a variety of herbal compounds as immunostimulants. The immunomodulatory responses of these medicinal plants are used for treating infectious diseases like arthritis, allergy, asthma, general debility, geriatric problems, analgesic, anti-convulsive, sedative etc. Therefore, herbal plant remedies are gaining more importance by means with improved knowledge and application of immunotherapy for treating many infectious and noninfectious diseases nowadays. An immunomodulator is defined as a biological or non-biological substance that directly acts on a specific immune function or modifies one or more components of an immunoregulatory network to achieve an indirect effect on a specific immune function. The main function of the immune system is to destroy the nonself organism or foreign particle by detecting them and thus act as a defense mechanism. The system works by a complex regulation of cellular and humoral factors throughout the body. In recent time, the field of immunomodulation gaining tremendous attention from the scientific community, in view of the spreading awareness regarding the need to modulate the immune system to achieve the desirable effects of preventing an infection rather than treating it at an advanced state [47].

Methods for Testing Immunological

Factors:

The routine process for screening is to extract a single component or single distilled fraction from herbal drugs, determine its bioactivity by the traditional pharmacological methods. The whole animal model is the most classic

pharmacological screening model, it can apparently respond to the efficacy, side effect and toxicity of medicines in whole. Several in vitro and in vivo methods of pharmacological screening of medicinal plants for immunomodulatory activity are as follows [48].

Table 3: In vitro and In vivo evaluation for Immunomodulatory Potential [49]

Methods (In Vitro)	Purpose and Rationale
Inhibition of Histamine Release from Mast Cells	Hypersensitivity reactions can be elicited by various factors: either immunologically induced, i.e., allergic reactions to natural or synthetic compounds mediated by IgE, or non-immunologically induced, i.e., activation of mediator release from cells through direct contact, without the induction of, or the mediation through immune responses. Mediators responsible for hypersensitivity reactions are released from mast cells. An important preformed mediator of allergic reactions found in these cells is histamine. Specific allergens or the calcium ionophore 48/80 induce release of histamine from mast cells. The histamine concentration can be determined with the <i>o</i> -phthalaldehyde reaction.
Mitogen-Induced Lymphocyte Proliferation	Cultured lymphocytes can be stimulated to a proliferative response and to DNA synthesis by various mitogens. Measurement of DNA synthesis can be accomplished by pulse-labeling the culture with tritiated thymidine (³ H-thymidine), a nucleoside which is incorporated into the newly synthesized DNA. Immunomodulating properties can be detected either by pretreatment of the animals in vivo or by adding the test drug to the cultured lymphocytes.
Inhibition of T Cell Proliferation	Activation and/or proliferation of clonal populations of T cells are critical for the initiation of an antigen-specific immune response. Thus, inhibition of T cell activation provides a potent means for suppressing specific immune response. A number of immunosuppressive agents exhibit the ability to suppress T cell activation.
Chemiluminescence in Macrophages	The stimulation of macrophages by antigen, complement, phorbol esters, etc., leads to elaboration of O ₂ ⁻ and other oxygen metabolites. Superoxide ion (O ₂ ⁻) and other highly reactive oxygen metabolites (radicals) form the basis for an efficient microbicidal system in vivo. Yet, when these radicals are released in response to self-antigens, tissue damage is often the result. Inhibition of this process can be regarded as a measure for immunomodulating effects of compounds. The oxygen metabolites can produce light-emitting reactions (chemiluminescence), which is measurable if amplified with suitable agents, such as the cyclic hydrazide luminol.
PFC (Plaque Forming Colony) Test In Vitro	Identification of antibody-producing cells is based on the ability of the secreted IgM antibody to fix complement and thereby lyse the indicator erythrocytes. Spleen cells or peripheral blood lymphocytes, previously incubated with antigen, are mixed with sheep red blood cells (SRBC). After addition of complement and incubation, plaques (clear areas) caused by the lysis of SRBC appear in the otherwise cloudy layer. Antibody-forming cells can be detected by the appearance of plaques. The number of plaques obtained is proportional to the number of antibody-producing lymphocytes in the cell population.
Inhibition of Dihydroorotate Dehydrogenase	Dihydroorotate dehydrogenase catalyzes the fourth committed step in the de novo biosynthesis of pyrimidines. As rapidly proliferating human T cells have an exceptional requirement for de novo pyrimidine biosynthesis, small-molecule dihydroorotate dehydrogenase inhibitors constitute an attractive therapeutic approach to autoimmune diseases, immunosuppression, and cancer. The main mode of action of the immunosuppressive compound leflunomide and its active metabolites is considered to be the inhibition of the enzyme dihydroorotate dehydrogenase.
In Vivo Spontaneous Autoimmune Diseases in Animals	Several spontaneous autoimmune diseases have been reported in several inbred animal strains are as follows: New Zealand black mouse (NZB mouse), New Zealand black/white F1 (B/W) mouse, A substrain of the autoimmune-prone mouse, NZB/kl, Immunodeficient alymphoplasia mice Palmerston, Nonobese diabetic mouse (NOD mouse), North autoimmune mouse strain, BDF1 mice, Bio-breeding rat (BB rat), Obese strain chicken (OS chicken).
Acute Systemic Anaphylaxis in Rats	Rats are immunized with ovalbumin and <i>Bordetella pertussis</i> suspension as adjuvant. After 11 days, the animals are challenged by intravenous injection of ovalbumin. The shock symptoms

	can be inhibited by corticosteroids and intravenous disodium cromoglycate.
Anti-anaphylactic Activity (Schultz–Dale Reaction)	Guinea pigs are sensitized against egg albumin. Challenge after 3 weeks causes in isolated organs' release of mediators, e.g., histamine, which induce contraction in isolated ileum.
Passive Cutaneous Anaphylaxis	Passive cutaneous anaphylaxis is an immune reaction of the immediate type. By passive immunization of rats in the skin with rat anti-ovalbumin serum and a challenge 2 days later with ovalbumin at the same skin area, antigen–antibody complexes are formed in the mast cells inducing release of mediators. This results in vasodilatation, increase in permeability of the vessel walls, and leakage of plasma. To make the allergic reaction visible, Evan's blue dye is administered along with the antigen. Evan's blue dye is attached to the albumin fraction of plasma, producing a blue spot. This blue spot indicates that an anaphylactic reaction has taken place in the skin.
Arthus type Immediate Hypersensitivity	The immune complex-induced Arthus reaction comprises inflammatory factors that have been implicated in the acute responses in joints of rheumatic patients. Complement and polymorphonuclear neutrophils are activated via precipitating antigen–antibody complexes leading to an inflammatory focus characterized by edema, hemorrhage, and vasculitis. Arthus reaction of the immediate type becomes maximal 2–8 h after the challenge.
Delayed type Hypersensitivity	Delayed-type hypersensitivity is a reaction of cell-mediated immunity and becomes visible only after 16–24 h. The same methods as for testing immediate-type hypersensitivity can be used.
Reverse Passive Arthus Reaction	In the reversed passive Arthus reaction, the antigen is injected intravenously followed by a local injection – either intradermally or into the pleural space – of the respective antibody. Generation of an immune-mediated reverse passive Arthus reaction in the rat pleural cavity results in a classic acute inflammatory response. The methods are used to evaluate new anti-inflammatory agents.
Adjuvant Arthritis in Rats	Adjuvant arthritis in rats has been described by Pearson and Wood exhibiting many similarities to human rheumatoid arthritis. Injections of complete Freund's adjuvant into the rat paw induce inflammation as primary lesion with a maximum after 3–5 days. Secondary lesions occur after a delay of approximately 11–12 days which are characterized by inflammation of non-injected sites (hindleg, forepaws, ears, nose, and tail) and a decrease of weight and immune responses. The procedure has been modified by several authors in order to differentiate between anti-inflammatory and immunosuppressive activity. Anti-inflammatory compounds do not inhibit secondary lesions, which are prevented or diminished by immunosuppressive agents.
Collagen Type II-Induced Arthritis in Rats	Intradermal injection of homologous or heterologous type II collagen in incomplete Freund's adjuvant results in an inflammatory polyarthritis in rats. The demonstration of antibodies to collagen in patients with rheumatic polyarthritis suggests that autoimmunity may contribute to the pathophysiology of synovitis and joint destruction. Because of the similarities of the symptoms in rats to human disease, the test is considered to be useful to detect anti-inflammatory and immunosuppressive properties of test compounds.
Proteoglycan-Induced Progressive Polyarthritis in Mice	Proteoglycan-induced progressive arthritis and spondylitis in BALB/c mice as an animal model displaying similarities to human rheumatoid arthritis and ankylosing spondylitis as indicated by clinical assessments, immunological parameters, and histopathological studies of diarthrodial joints and spine.
Pristane-Induced Arthritis in Mice	The mineral oil 2, 6, 10, 14-tetramethylpentadecane (known as pristane) induces a chronic inflammatory arthritis in mice after intraperitoneal injection. The immunological involvement in the pathogenesis of pristane-induced arthritis was studied by several authors. Moreover, the genetic basis for the susceptibility to pristane-induced arthritis was studied. Not only in mice but also in rats arthritis could be induced by pristane injections.
Streptococcus Cell Wall-Induced Arthritis	Streptococcal cell wall (SCW)-induced arthritis is a chronic and erosive polyarthritis which may be induced in susceptible Lewis rats by a single injection of a sterile, aqueous suspension of SCW via the intraperitoneal route of administration.
Experimental Autoimmune Thyroiditis	Immunization of rats or mice with porcine thyroglobulin results in thyroiditis.
Coxsackievirus B3-Induced Myocarditis	The effects of immunosuppressant drugs can be studied in the murine model of coxsackievirus B3 myocarditis.
Experimental Allergic Encephalomyelitis	Experimental allergic encephalomyelitis was first produced in laboratory animals by Rivers <i>et al.</i> in 1933. This pathological model is an immunologic disease arising from a delayed hypersensitivity reaction to nervous tissue. In many respects, the model resembles autoimmune diseases, especially demyelinating diseases, in man, and the utility of animal models as for drug discovery and development for neurological diseases especially multiple sclerosis (MS) has been extensively reviewed.
Acute Graft-Versus-Host (GVH) in Rats	The intravenous injection of a mixture of parental splenocytes into healthy inbred F ₁ -rats results in graft-versus-host (GVH)-induced immune abnormalities. This is due to T lymphocytes in the donor inoculum that recognize the major histocompatibility alloantigens expressed by the F ₁ -animals. The host F ₁ T cells are genetically unable to recognize antigens of the parental donor as foreign; thus, the response involves only donor recognition of host

	and not host recognition of donor. The ensuing immune abnormalities lead to clinical symptoms of an acute, lethal GVH-disease (GVHD), i.e., profound immunodeficiency, anemia, hypogammaglobulinemia, and runting.
Influence on SLE-Like Disorders in (MRL/lpr) mice	Systemic lupus erythematosus (SLE) is an autoimmune disease in man that affects multiple body organs and is characterized by the development of certain types of self-antigens. Primarily, the antibodies formed against double-stranded DNA (dsDNA), the most prevalent in this ailment, complex together and, with complement, deposit in the small blood vessels, leading to widespread vasculitis. MRL Mpf lpr/lpr (MRL/lpr) mice spontaneously develop a severe disease with many symptoms very similar to human SLE, i.e., hypergammaglobulinemia and glomerulonephritis. Recent years have seen the development of numerous animal models of skin disease which have assisted the discovery of potential new drugs for clinical test which in part have allowed progression of a number of small-molecule candidate drugs.
Glomerulonephritis Induced by Antibasement Membrane Antibody in Rats	Masugi nephritis and other nephritis models of immunological origin in rats have been used for evaluation of immunosuppressive activity.
Prevention of Experimentally Induced Myasthenia Gravis in Rats	Myasthenia gravis is an organ-specific autoimmune disease in man that results in skeletal muscles' weakness. Typically, the sufferer has drooping eyelids, a blank facial expression, and weak, hesitant speech. This is due to the formation of autoantibodies against the nicotinic acetylcholine receptor (AChR). The formation of autoantibodies to acetylcholine's receptor leads to a gradual destruction of the receptors in skeletal muscles that receive nerve impulses and initiate muscle contractions. As a result, affected muscles fail to respond or react only weakly to nerve signals.
Inhibition of Allogenic Transplant Rejection	Transplantation of allogenic organs to recipients results in rejection of the transplants. This effect can be suppressed or delayed by immunosuppressive agents, and the role of B cells has been investigated in animal models suggesting a role in mechanisms of transplant tolerance. Various organs are used for allogenic transplantation in animal experiments, such as skin pieces, kidney, rat heart, rat small intestine, and corneal buttons. The immunosuppressive activity can be evaluated either by using a major histocompatibility complex variant strain combination or a strong allogenic system, and the advances and limitations of murine models have been recently described.

Table 4: Medicinal plants possessing immunomodulatory properties

Plant Species	Family	Chemical Constituents	Reported Activities
<i>Urena lobata</i> Linn.	Malvaceae	Flavanoids	Diuretic, emollient, antispasmodic [50]
<i>Heracleum persicum</i> Desf.	Apiaceae	Flavonoids, furanocoumarins	Antimicrobial [51]
<i>Abutilon indicum</i> linn.	Malvaceae	Flavonoids, triterpenoids	Diuretic, antibacterial [52]
<i>Panax ginseng</i> Wall	Araliaceae	Saponins such as ginsenosides, panaxdiol, panaxtrirole and oleanolic acid	Adaptogenic properties, antiarrhythmic [53]
<i>Achillea millefolium</i> C. Koch	Compositae	Flavonoids, alkaloids, polyacetylenes, coumarins, triterpenes	Anti-inflammatory, antispasmodic, antipyretic, diuretic [54]
<i>Aloe vera</i> Tourn.ex Linn	Liliaceae	Anthraquinone glycosides	Purgative, emmenagogue, emollient, antiinflammatory [53]
<i>Asparagus racemosus</i> Wild	Liliaceae	Saponins, sitosterols	Ulcer healing agent, nervine tonic, antigout [55]
<i>Couroupita guianensis</i> Aubl.	Lecythidaceae	Steroids, flavonoids, phenolics	Antifungal [56]
<i>Tinospora cordifolia</i> Miers	Menispermaceae	Alkaloidal constituents such as berberine, tinosporic acid	Hypoglycaemic agent, antipyretic [55]
<i>Terminalia arjuna</i> Roxb.	Combretaceae	Flavonoids, oligomeric proanthocyanidins, tannins	Cardiotonic, diuretic, prescribed for hypertension [57]
<i>Ocimum sanctum</i> Linn.	Labiataeae	Essential oils such as eugenol, cavacrol, derivatives of ursolic acid, apigenin	Carminative, stomachic, antispasmodic, antiasthmatic, hepatoprotective [55]
<i>Acacia catechu</i> Willd.	Leguminosae	Flavonoids, quercetin	Hypoglycaemic, astringent [53] [55]
<i>Hibiscus rosa sinensis</i> Linn	Malvaceae	Cyclopropanoids	Antidiarrheal, anti-inflammatory [58]

<i>Ganoderma lucidum</i>	Polyporaceae	Flavonoids, triterpenes	Antioxidant [59]
<i>Apium graveolens</i> Linn.	Apiaceae	Flavonoids, coumarins	Anti-inflammatory [60]
<i>Artemisia annua</i> Linn	Compositae	Artemisinin	Immunosuppressive [61]
<i>Actinidia macrosperma</i>	Actinidiaceae	Alkaloids, saponins	Antileprotic [62]
<i>Allium hirtifolium</i> Bois	Alliaceae	Thiosulfinates, flavonoids	Antirheumatic, anti-inflammatory [63]
<i>Calendula Officinalis</i> L.	Asteraceae	Polysaccharides, proteins, fatty acids, carotenoids, flavonoids, triterpenoids	Antitumor antiviral activity, anti-HIV properties [64]
<i>Cannabis sativa</i>	Cannabaceae	Cannabinoid	Immunomodulatory [65]
<i>Chlorophytum borivilianum</i> Sant. F	Liliaceae	Sapogenins	Antifungal [66]
<i>Euphorbia hirta</i> linn	Euphorbiaceae	Quercitol, myricitrin, gallic acid	Anti-inflammatory activity, sedative and anxiolytic activity [67]
<i>Piper longum</i> L.	Piperaceae	Alkaloids	Antioxidant [68]
<i>Viscum album</i> L.	Loranthaceae	Viscotoxins, polyphenols, polysaccharides	Antitumoral effect [69]
<i>Terminalia arjuna</i> Roxb	Combretaceae	Flavonoids, oligomeric proanthocyanidins, tannins	Cardiotonic, diuretic, prescribed for hypertension [57]
<i>Picrorhiza scrophulariiflora</i> Benth.	Scrophulariaceae	Iridoid glycosides, amphicoside	Antioxidant [70]
<i>Boswellia</i> spp	Burseraceae	Triterpenes, ursane	Hypoglycaemic [71]
<i>Randia dumetorum</i> Lamk	Rubiaceae	Saponins, triterpenes	Chlorosis, antiarthritic [72]
<i>Centella asiatica</i> Linn	Umbelliferae	Triterpenoid saponins	Immunomodulator [73]
<i>Lycium barbarum</i> Linn.	Solanaceae	Polysaccharide-protein complexes	Antioxidant [74]
<i>Lagenaria siceraria</i> Mol	Cucurbitaceae	Cucurbitacin, beta-glycosidase	Purgative, emetic [75]
<i>Heracleum persicum</i> Desf	Apiaceae	Flavonoids, furanocoumarins	Antimicrobial [76]
<i>Cissampelos pareira</i> Linn	Menispermaceae	Hayatine alkaloids	Antipyretic, analgesic, antilithic [77]
<i>Morus alba</i> Linn.	Moraceae	Flavonoids, anthocyanins	Expectorant, hypocholesterolaemic, diuretic [78]
<i>Couroupita guianensis</i> Aubl	Lecythidaceae	Steroids, flavonoids, phenolics	Antifungal [56]
<i>Crinum latifolium</i> Andr.	Amaryllidaceae	Alkaloids	Immunomodulator [79]
<i>Larrea divaricata</i> DC.	Zygophyllaceae	Lignans	Anti-inflammatory [80]
<i>Salicornia herbacea</i>	Chenopodiaceae	Polysaccharides	Immunomodulator [81]
<i>Bidens pilosa</i> L	Asteraceae	Polyacetylenes	Anti-inflammatory, immunosuppressive, antibacterial and antimalarial [82]
<i>Hyptis suaveolens</i>	Lamaceae	Lupeol, beta-sitosterol	Carminative, antispasmodic [83]
<i>Citrus natsudaoidai</i> Hayata	Rutaceae	Auraptene, flavonoids	Antioxidant [84]

CONCLUSION:

There is a great need for the findings of novel antiviral agents. A number of antiviral studies have been investigated for cellular and sub-cellular targets and promising results have been observed. This review includes many potential sources of medicinal plants extracts. As compared to the adverse side effects of pharmaceutical drugs, many herbal formulations are safer,

more effective and less expensive as compared to synthetic ones. Although many pharmaceutical immunomodulatory drugs with various mechanisms of action have been discovered and developed, they failed to be successful clinically due to their toxicity, less bioavailability, and stability problems. Research to discover natural products as drug molecules for development of immunomodulatory agents

has gained more importance as they offer safer alternatives to conventional therapies. Nutraceuticals can be defined as substances that have physiological benefits that prevent chronic diseases and have antiviral properties and immunomodulatory effects. Nowadays, nutraceuticals are gaining more interest due to potential nutritional, safety and therapeutic effects. In the present review much effort has been devoted to present new concepts about various medicinal plants possessing some antiviral and immunomodulatory properties. The field of herbal medicines is gaining more possibilities for research and development programs for formulations of effective drugs based upon knowledge of traditional systems of medicines including Ayurveda.

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