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ANTIVIRAL MEDICINAL HERBS AND PHYTOCHEMICALS

CECILIA PERERA AND THOMAS EFFERTH*

Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, University of Mainz, Staudinger Weg 5, Germany.
*Corresponding Author: Email- efferth@uni-mainz.de

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Abstract- Due to the global disease burden caused by viral infections there is an urgent need for novel and more effective antiviral drugs. Medicinal herbs and their bioactive constituents came in the center of interest, since they may provide feasible treatment options for the population of developing countries, where the majority of the population cannot account for expensive chemical drugs of western medicine. This review gives an overview of some important medicinal plants with antiviral activity, their bioactive constituents and the modes of action.
Key words- antiviral, natural product, phytochemical, pharmacognosy, viruses.

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Introduction

Many viral infections are still a great danger to humans and often cause death. In the past, deadly viruses caused pandemics in the world. Nowadays, the risk of spreading viruses between continents and countries is even larger. Due to the metabolic properties of viruses, they are difficult to control and there are still relatively few drugs for treatment of viral diseases [1]. A major problem in the fight against viruses is their rapid adaptation and development of drug-resistance as well as the emergence of new hybrid viruses. Common medications are often inadequate and show a variety of side effects [2]. In the past few years, natural remedies came more and more in the center of interest [3]. The idea of herbal drugs is popular, because of easy access and good tolerability.

Viruses are obligate intracellular parasites with a viral genome (DNA or RNA) and protein envelope (capsid). Some viruses are surrounded by an additional membrane (enveloped viruses). Viruses do not have an own metabolism and are not able to independently replicate or to perform biosyntheses. To this end, they exploit and control the host cell. They are transmitted by droplet infection, contact infection, exchange of body fluids and blood-sucking insects.

The viral life cycle can be divided in various sections. During adsorption, the virus attaches to the host cell. The virus penetrates the cell and releases genetic material during uncoating. The genome of the virus reprograms the cell and takes control over it. The cell begins to synthesize virus particles. Then, new viruses are formed, and finally leave the cell. The new viruses are now able to infect other cells.

Mechanisms of action of established antiviral drugs

There are different approaches for antiviral control. To prevent viral entry into the cell, adsorption of the virus has to be avoided, *e.g.* by antibodies or specific ligands. Capsid-stabilizing agents and blocking of endosomal ion channels inhibit viral uncoating after endocytosis. DNA or RNA replication can be suppressed by inhibition of DNA- or RNA-polymerases, by endonucleases, or by nucleoside analogues.

Nucleoside analogs are derivatives of nucleosides and interfere with virus replication. As false DNA precursors, they are not incorporated into DNA by the virus-encoded DNA polymerase. Nucleoside analogs inhibit this enzym, resulting in chain termination.

Neuraminidase inhibitors bind to neuraminidase. As a consequence, the budding virus budding remains bound to the cell re-

ceptors and the release of new viruses is inhibited. This interrupts the infectious process.
Protease inhibitors prevent virus maturation and discharge. These substances are peptides that block protease substrates. This leads to suppression of maturation and interruption of the viral replication cycle.

Antiviral substances in plants
Plants contain a wide variety of diverse phytochemicals, such as alkaloids, tannins, saponins, flavonoids, terpenoids, lignans, coumarins, and many other components [4, 5]. The modes of action of the substances are multi-facetted and often not yet extensively explored. The focus of the present review is particularly on antiviral agents of plants used in traditional medicines.

Aloe emodin from *Rheum palmatum*
Aloe-emodin (1,8-dihydroxy-3-hydroxymethyl-anthraquinone) is a natural anthraquinone (Fig. 1), which among others is present in *Rheum palmatum*, a plant used in traditional Chinese medicine. Aloe-emodin showed activity against herpes simplex virus (HSV), influenza virus and human cytomegalovirus [6]. An important benefit of aloe-emodin is its low cytotoxicity.
Studies on the activity of aloe-emodin against Japanese encephalitis and enterovirus 71 in TE 671 cells showed a dose-dependent induction of interferons (IFN). Type I and II interferons play a role in non-specific host response towards viral infections. IFNγ stimulates prevents viral replication in macrophages and in the central nervous system [7]. Aloe-emodin induces the activation of interferon-stimulated response elements (ISRE). It also causes the upregulation of IFN-stimulated gene expression, such as the dsRNA-activated protein kinase and the 2' 5' oligoisoadenylate synthetase. Antiviral activities were demonstrated against the replication of Japanese encephalitis virus and enterovirus 71.
In the same study [7], the active ingredients of *Rheum palmatum*, shikonin and arecoline, also showed a dose-dependent induction of IFNa, inhibition of viral replication and effects on nitric oxide production, however, to a lesser extent than aloe-emodin.

Emodin from *Rheum officinale* and *Polygonum multiflorum*
Like aloe-emodin, emodin (6-methyl-1,3,8-trihydroxyanthraquinone) is also a non-anthraquinone (Fig. 1). Severe acute respiratory syndrome (SARS) is an infectious disease that is caused by the SARS coronavirus. An interaction between the SARS coronavirus spike protein and angiotensin-encoding enzyme 2 (ACE2) is important for attachment to the host cell. Screening of 312 Chinese medicinal plants revealed that emodin from *Rheum officinale* and *Polygonum multiflorum* inhibited the interaction between the SARS CoV spike protein and ACE2 in a dose-dependent manner without cytotoxicity on host cells [8]. 1,4-Bis-anthraquinone did not exert considerable inhibition of the S protein-ACE2 interaction, indicating that the side chain rather than the anthraquinone skeleton is essential for antiviral activity [8].
Emodin may also exert its activity by inhibition of casein kinase 2, which is commonly used by many viruses for protein phosphorylation [9]. Furthermore, emodin attacks the lipid bilayer, thereby destroying enveloped viruses. Other anthraquinone derivatives such as chrysophanic acid and hypericin also showed antiviral activity [10, 11].

Glycyrrhizinic acid from *Glycyrrhiza glabra*
Glycyrrhizic acid is an ingredient from the root of licorice (*Glycyrrhiza glabra*) (**Figure 1**). The licorice root is a well-known medicinal plant and has long been known and highly valued in European and Asian cultures. Licorice was used by the Greeks, Romans, Arabs, Scythians, and the Chinese. Glycyrrhizic acid exerts antiviral activity against Kaposi's sarcoma-associated virus by elimination of the inactive form of the virus via apoptosis. Numerous anti-viral effects have been described against DNA and RNA viruses, *e.g.* hepatitis A virus, hepatitis B virus, coronavirus, influenza virus, HIV-1 etc. [12]. Glycyrrhizic acid also inhibited the replication of SARS-associated coronavirus *in vivo* [13].
Glycyrrhizic acid treatment was associated with increased interferon-γ production. In mice inoculated with influenza virus, glycyrrhizic acid decreased mortality and morbidity. In latent HSV infections, glycyrrhizic acid induced apoptosis by downregulation of the latency-associated nuclear antigen (LANA) and upregulation of the viral cyclin expression. LANA is a repressor of the transcriptional activity of the tumor suppressor p53, which leads to inhibition of p53-induced apoptosis. This in turn favors growth of malignant tumors. LANA induces a latency stage of B-cells, which ensures viral survival. Glycyrrhizic acid reactivates p53.

Ellagic acid from *Phyllanthus urinaria*
The flavonoid ellagic acid (**Figure 1**) inhibits immunotolerance of mice against the hepatitis B virus e-antigen. Hepatitis B virus (HBV) can cause chronic and acute hepatitis. Among the four HBV viral proteins, the HBV e-antigen (HBeAg) is thought to support the chronic form of hepatitis B. HBeAg is a secretory form of HBcAg, which is not involved in virus replication [14]. Ellagic acid can also be found in strawberries, raspberries and other fruits.

Artemisinin from *Artemisia annua*
Artemisinin is a sesquiterpene and the active ingredient of *Artemisia annua* (sweet wormwood) (**Figure 1**). This plant is known in traditional Chinese medicine to treat fever and chills, and artemisinin is an important antimalarial drug. It is safe and considerable side effects in humans are rare [15].
Artemisinin is metabolized in the liver by the microsomal cytochrome P 450 monooxygenase enzymes, CYP2B6 and CYP3A4 [16]. It induces the activation of CYP2A5, CYP2A6, CYP2B1, CYP2B6, CYP2B10, CYP2B6 and CYP3A4 and activates the constitutive androstane receptor and the pregnane X receptor.
Artemisinin and its derivatives showed antiviral activity against human cytomegalovirus and other members of the Herpesviridae family (*e.g.*, herpes simplex virus type 1 and Epstein-Barr virus), hepatitis B virus, hepatitis C virus, and bovine viral diarrhea virus [17].

Specific terpenoides and lignoids with activity against SARS
There is still no efficient and safe treatment available against SARS infections. Therefore, the search among phytochemicals to identify compounds with anti-SARS activity is in the focus of researchers. In a Taiwanese study, 221 phytochemicals were examined for their activity against the SARS-associated coronavirus (SARS-CoV). Ten diterpenoids, two sesquiterpenoids, two triterpe-

noids, five lignoids and curcumin inhibited the virus at concentrations below 10 µM. Some of these phytochemicals with activity against SARS are shown in Fig. 1. Active components were isolated from the heartwood of *Chamaecyparis obtuse*, *Juniperus fomosana*, *Cryptomeria japonica* and other plants [18].

Tannins from *Castanea* and *Schinopsis* species

Tannins exert activity against HIV and HSV. Water-soluble tannins from the wood of three different varieties of chestnut (*Castanea sp*.) and quebracho (*Schinopsis sp*.) showed *in vitro* activity against avian reovirus (ARV) and avian metapneumovirus (AMPV) [18]. Infections with these viruses have considerable negative impact for the poultry industry.

Tannic acids are thought to prevent the cellular absorption of viruses. A water-soluble tannin from *Terminalia arjuna,* casuarinin, interferes with attachment and penetration of HSV [20]. Moreover, tannins interfere with HIV-1 fusion to cells by gp41, an envelope glycoprotein, which plays a role for viral entry into the cell. This observation is consistent with studies on tannins from chestnut and quebracho and their activity towards AMPV and ARV. Again, these tannins prevented viral attachment and cell penetration by their interaction with viral proteins.

***Echinacea* species**

Echinacea species were used in ancient Egypt because of their antiviral and antibacterial potential. Pharmacological studies have shown that the *Echinacea* species used by Indians in North and Middle America (*E. angustifolia* and *E. purpurea*) activate macrophages and nonspecific immune defense against viruses. The active principles are immune-stimulating polysaccharides as well as alkamides and cichoric acid (**Figure 1**), which stimulate phagocytosis. Alkamides are also antiphlogistic, because they inhibit the arachidonic acid metabolism [21, 22].

Afromomum melegueta* and *Bambusa vulgaris

Extracts of *Aframomum melegueta* and *Bambusa vulgaris* from the traditional African Medicine showed activity against yellow fever and smallpox viruses. Poliovirus was not affected by these two plant extracts [23]. The phytochemicals responsible for these effects have not been identified yet.

Antiviral agents of fruit juices

Orange juice and grape juice are reported to reduce the infectivity of the bacteriophage T4 by [24]. Cranberry juice reduced the titers of T4 bacteriophages by more than one order of magnitude. The titers of the T2 bacteriophage were even reduced to an undetectable level. The considerable antiviral effects indicate that viral replication may be inhibited at an early stage of the replication cycle. Cranberry juice also prevented the infection of host cells with rotavirus SA-11.

Oregano vulgare* and *Rosmarinus officinalis

The investigation of various herbs showed that methanol extracts of *Origanum vulgare* and *Rosmarinus officinalis* inhibit the replication of enterovirus 71. The extracts revealed greater effects than amantadine, a common antiviral agent and also showed a higher therapeutic index and greater safety [25].

Chinese herbs

A screenings of 21 Chinese plants showed that *Agrimonia pilosa, Pithecellobium clypearia* and *Punica granatum* were active against anti-HSV1. These plants contain many polyphenols and tannins. After removal of the polyphenols, the anti-HSV1 activity drastically decreased [26]. The aqueous extracts of *Blumea laciniata, Elephantopus scaber, Laggera pterodonta, Mussaenda pubescens, Schefflera octophylla,* and *Scutellaria indica* were active against the human respiratory syncytial virus (RSV) [26].

Conclusion and Perspectives

Nature developed a variety of antiviral agents during the evolution of plants. It is estimated that there are approximately 250,000 plants with bioactive compounds [27], most of which have not been analyzed for their bioactivity. In a few examples, the therapeutic potential has been illustrated, *e.g.* emodin, artemisinin, or glycyrrhizic acid etc.

Due to the global disease burden caused by viral infections nowadays and in the past, there is an urgent need to identify novel compounds with antiviral activity. Medicinal herbs might contribute to an improvement of public health especially in developing countries, since the majority of the population has not the economic power to account for expensive antiviral drugs. In the western world, the costs of the health systems tremendously increased in the past years and their collapse seems to be only a question of time.

A condition to realize the concept of evidence-based phytotherapy is to explore the scientific basis of bioactive medicinal plants. Placebo-controlled, double-blind clinical trials have to be performed to provide unambiguous evidence for the therapeutic value of medicinal plants. In addition to efficacy, the safety of phytotherapeutic approaches has to be demonstrated.

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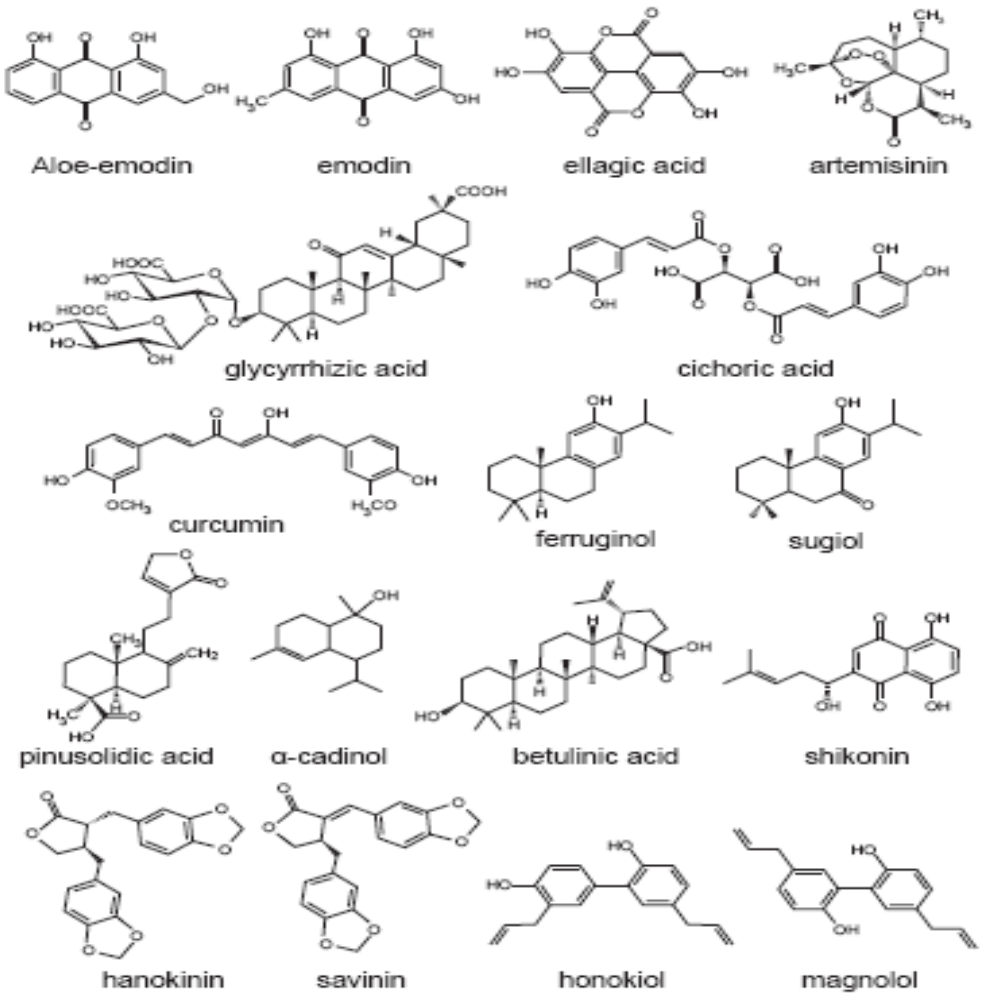

Fig. 1- Chemical structures of phytochemicals with antiviral activity