Approaches to antiviral herbal medicine

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SUMMARY

The problem of antiviral therapy is currently of global importance. The review provides general information on viral infections, summarizes experimental and clinical data on the antiviral activity of herbal medicines. The mechanisms of the antiviral action of biologically active substances of medicinal plants are considered.

Keywords:antiviral activity, medicinal plants, viruses, bacterial biofilms, biologically active substances.

RESUME

Antiviral therapy problem is being of the global importance now. There is viral infection general awareness information in the revision, as well as experimental and clinical data on vegetable medical means antiviral effectiveness. Antiviral effect mechanisms of biologically active substances of medicinal plants are considered.

Introduction

Viruses (kingdom Virae) are strict intracellular parasites on the geneticlevel, widespread among vertebrates and invertebrates, plants, protozoa, fungi, bacteria, archaea [2]. Humanity has faced viral infections throughout its history. About 90% of human infectious pathology is caused by viruses. Only from acute viral infections in the world annually die from 10 to 14 million people [80]. According to various estimates, in Russia, each person gets sick with viral infections on average 4-6 times a year. At least 300 known viruses belonging to 51 genera of 30 families are capable of causing pandemics (influenza A, smallpox, HIV infection, poliomyelitis), epidemics (Dengue, yellow, Chikungunia, West Nile fevers), epidemic outbreaks and sporadic diseases. Thus, it is obvious that the problem of antiviral therapy is of global importance.

Modern medical practice has a relatively small number of highly specific antiviral drugs that have received international recognition. Therefore, the search for new antiviral agents is extremely urgent. Along with the search for new antiviral drugs among derivatives of aminoadamantanes, modified pyrimidine and purine bases, organophosphorus synthetic compounds, polyanions, research is being carried out for antiviral agents of plant origin. Biologically active substances (BAS) are contained in rapidly dividing plant cells (an evolutionary analogue of mammalian embryonic and stem cells) and have unique regulatory properties [3]. In the future, herbal medicine has good prospects, as people perceive drugs from medicinal plants very positively.

Antiviral activity of plants

Scientific interest in herbal antiviral agents began in Europe after World War II. In 1952, the Broot Drug Company in England (Nottingham) tested the effect of 288 plants on influenza A virus in chicken embryos. It was found that 12 of them suppress the multiplication of the virus [19]. For 25 years, screening programs have been carried out in various parts of the world in order to assess the antiviral activity of medicinal plants in experiments.in vitro and in vivo. Canadian researchers in1970 reported on the antiviral activity of grape, apple, raspberry and other fruit juices against herpes simplex virus (HSV), poliovirus type 1, Coxsackie virus B5 and echovirus type 7 [38, 39]. One hundred British Columbia medicinal plants have been screened for antiviral activity against seven viruses [50]. Twelve extracts had antiviral activity. Nutkan rose extracts (Rosa nutkana), alder irgi (Amelachier alnifolia) were veryactive against intestinal coronaviruses. Potentilla root extracts (Potentilla arguta) andextracts of branches of red elderberry trees (Sambucus racemosa) completely inhibitedrespiratory syncytial virus (RSV). Plant extractImpomopsis aggregata showed good activity against parainfluenza virus type 3. Extract from the roots of dissected lomatium (Lomatium dissectum) completely inhibited the cytopathic effectrotaviruses. Extracts from the angular core (Cardamin angulata), hydrophilic hepaticmoss (Conecephalum conicum), American lysichitum (Lysichiton americanum), fern (Polypodium glycyrrhiza) and common mullein (Verbascum thapsus) showed antiviralactivity against herpes simplex virus type 1.

Extracts from raw materials of 40 species of Australian medicinal plants used in traditional medicine were studied for antiviral activity against DNA-containing viruses of human cytomegalovirus (CMV) and two RNA-containing viruses of the Ros River virus (RRV) and poliovirus type 1 in a non-toxic concentration [73] ... The most active extracts isolated from the aerial parts of spherical pterocaulon (Pterocaulon sphacelatum)and the roots of Dianella longifolia (Dianella longifolia var. grandis) in concentration52 μg / ml and 250 μg / ml, respectively, inhibited the reproduction of poliovirus type 1. The authors concluded that milkweed extracts from southern (Euphorbia australis) and scaveola spinensis (Scaevola spinescens)(Goodeniaccae) showed the greatest antiviral activity against CMV, while extracts from Latrobe eremophilia (Eremophilia latrobei subsp. glabra) (Myoporaceae) and resin seed (Pittosporum phyllraeides var. microcarpa) exhibited antiviral activityagainst RRV.

Human rotavirus (RV), RSV and influenza A virus are susceptible to liquid extract of prickly berry root (Eleutherococcus senticosus). DNA viruses suchboth adenoviruses and herpes simplex virus type 1 are not inhibited by this plant extract [28]. The authors concluded that the antiviral activity of the extract affects the synthesis of viral RNA. It was also shown that the synthesis of RNA of the influenza virus is inhibited by water-soluble extracts of the European tree forest (Sanicula europaea) [77]. Later it was shown that the acidic fraction of the coarse extractSanicula europaca more actively suppressesreplication of parainfluenza virus type 2 in non-toxic concentration [36]. At the same time, the alcoholic extract did not have antiviral activity. A likely explanation for this fact is that the antiviral activity is not stable and may disappear upon fractionation. Another example is the plant myrcyantes cisplathensis (Myrciantes cisplatensis) showingactivity in vitro against RSV, while HSV and adenovirus 7 serotypes were insensitive to its effects [41]. In contrast to this observation, other medicinal plants, for example, blue catnip (Nepeta coerulea), catnip small (Nepeta nepetella), catnip tuberous (Nepeta tuberosa), small burnet (Sanguisorba minor), ditrichia viscosa (Ditrichia viscosa) showed antiviral activity against both DNA and RNA-containingviruses such as HSV-1, vesicular stomatitis virus (VVS) and poliovirus type 1 in case ofDitrichia viscosa [5]. It has been shown that extracts of margose leaves (Azadirachta indica) wereare active against many viruses, such as smallpox, chickenpox, poliomyelitis, and herpes viruses [60, 35]. Cactus extract prickly pear streptocant (Opuntia streptacantha) inhibitedreplication of viral DNA and RNA and inactivated intact viruses such as herpes simplex virus, equine herpes virus, vesicular stomatitis virus and influenza virus [7]. Plants incense reed (Bergenia ligulata), Indian oleander (Nerium indicum), and crowded cholera (Holoptelia integrifolia) showed significant antiviral activity against influenza virus andherpes simplex virus [59]. Table 1 shows some plants containing biologically active substances with antiviral activity.

Antiviral substances of medicinal plants

The acquisition of resistance of viruses to antiviral agents requires the search for new effective drugs against viral infections. Medicinal plant preparations are capable of inhibiting the replication of DNA and RNA-containing viruses. Various research groups in Asia, Europe and America are working in this direction. At present, some compounds with antiviral activity of plant origin have been identified. These biologically active substances, as a rule, belong to terpenes (essential oils), polyphenols, including flavonoids, peptides, polysaccharides. Below are data on the antiviral activity of these compounds.

Essential oils

Essential oils are a mixture of odorous volatile substances, the structure of which is based on the structure of isoprene. Essential oils can contain over 150 different chemicals (aldehydes, ketones, alcohols, phenols, terpenes, sesquiterpenes, esters, lactones and ethers). Therefore, essential oils have a variety of pharmacological or therapeutic properties.

Shown is the antiviral effect of Melaleuca St. John's wort (Melaleuca alternifolia) and eucalyptus oils against HSV-1 and HSV-2 viruses in cell culture [60]. Italian researchers found that insularis santolina oils (Santolina insularis) providedirect antiviral effect on herpes viruses and their transmission from cell to cell [55]. Sandalwood Oil, Sandalwood Oil Essence (Santalum album) providedose-dependent effect on the HSV-1 virus, but not on the HSV-2 virus [11]. The antiviral effect of black seed oil was shown.Nigella sativa) for cytomegalovirus(CMV) [62].

Polyphenols

Polyphenols are organic compounds of plant origin that are powerful natural antioxidants. This is a large group of chemically diverse substances of various spectrum of action, widespread in nature, both in the form of glycosides and free aglycones. All of these compounds have one or more hydroxyl groups of a phenolic nature. They are labile and easily oxidized, which is the reason for their antioxidant (and antihypoxant) properties. Polyphenols are found in vegetables, fruits, grains, seasonings, and wine, tea, coffee, and cocoa. They have a number of beneficial properties for humans: antioxidant, anti-cancer, antibacterial and anti-inflammatory.

Table 1

Plants containing substances with antiviral and antimicrobial activity *

Научное название	БАВ или группы БАВ	Класс	Активность
Лопух большой *(Arctium lappa L.)*		Полиацетилен, танины, терпеноиды	Бактерии, грибы, вирусы
Тмин обыкновенный *(Carum carvi L.)*		Кумарины	Бактерии, грибы, вирусы
Крушина Пурша, к. американская, каскара *(Rhamnus purshiana DC.)*	Таннины	Полифенолы	Вирусы, бактерии, грибы
Ромашка обыкновенная *(Matricaria chamomilla L.)*	Антемовая кислота	Кумарины	Вирусы
Эвкалипт шариковый *(Eucalyptus globulus Labill.)*	Таннин	Полифенолы Терпеноиды	Бактерии, вирусы
Чайный куст китайский *(Thea sinensis L. = Camelia sinensis (L.) O.Ktze.)*	Катехин	Флавоноиды (полифенолы)	Вирусы
Конопля посевная *(Cannabis sativa L.)*	β-резорцикловая кислота	Органические кислоты	Бактерии и вирусы
Иссоп лекарственный *(Hyssopus officinalis L.)*	Люпулон, гумулон	Терпеноиды	Вирусы
Мелисса лекарственная *(Melissa officinalis L.)*	Таннины	Полифенолы	Вирусы
Полынь эстрагон *(Artemisia dracunculus L.)*	Кофейные кислоты, танины	Терпеноиды Полифенолы	Вирусы, гельминты
Тимьян обыкновенный *(Thymus vulgaris L.)*	Кофейная кислота Тимол Танины	Терпеноид Фенольный спирт Полифенолы	Вирусы, бактерии, грибы
Ясменник душистый *(Asperula odorata L.)*	Танины	Полифенолы	Вирусы
Тысячелистник обыкновенный *(Achillea millefolium L.)*	Не известно		Вирусы, гельминты

* При составлении таблицы использованы материалы обзора Cowan M.M. [22]

It has been shown that polyphenols, in particular, proanthocyanides, extracted from the bark of witch hazel (Hamamelis virginiana), markedly inhibited HSV-1 [24] and human immunodeficiency virus (HIV-1) reverse transcriptase [85]. In general, most of the antiviral activity of polyphenols is associated with direct inactivation of the virus and / or inhibition of the binding of the virus to cells. Although polyphenols inhibit viral replicative enzymes such as HIV reverse transcriptase or influenza virus RNA polymerase, their effect is likely nonspecific. So it was shownin vitro antiviral activitypolyphenol complex isolated from blood-red geranium (Geranium sanguineum), againstherpes viruses of types 1 and 2 and influenza [68, 69]. However, the wide spectrum of antiviral activity of polyphenols shown in experimentsin vitro, was not detected in experiments in vivo [63].

Peptides

Peptides are relatively short protein molecules (on average, about 30–40 amino acids). Antimicrobial peptides are the primary measure of the body's defense against pathogens and are involved in the innate immune system.

Meliacin peptide isolated from the leaves of melia asedarah (Melia azedarach), and perhapsand present in many other plants, it has an antiviral effect [30]. The effect of meliacin was tested in mice infected with HSV-1. It has been shown that this peptide has an antiviral effect without a toxic effect on the herpes virus, which causes eye diseases [8]. The antiviral effect of meliacin on Junin hemorrhagic fever virus has been reported. Meliacin inhibits its reproduction in VERO cells treated with meliacin before infection or immediately after adsorption of the virus [18]. Meliacin also inhibits the reproduction of the FMD virus in BHK-21 cells [81]. It is assumed that this peptide acts on two events of the viral replicative cycle, which requires membrane fusion, the stripping of the virus or its disintegration in the infected cell, and budding (release of new viral particles from the cell) [18].

Polysaccharides

Polysaccharides - the general name for a class of complex high molecular weight carbohydrates, the molecules of which consist of tens, hundreds or thousands of monomers - monosaccharides. Polysaccharides are essential for the life of animals and plant organisms. They are one of the main sources of energy generated as a result of the body's metabolism. The diverse biological activity of plant polysaccharides has been established: antibiotic, antiviral, antitumor, antidote.

Human rotaviruses (RVs) cause gastroenteritis, accompanied by diarrhea in children and often fatal [82]. Anti-RV and anti-HSV-1 activity was found in aqueous extracts of bifolia (Stevia rebaudiana) and Achyrocline flaccida, respectively [26, 72]. These extracts inhibited the replication of the four serotypes of human rotavirus (HR) and HSV-1in vitro by blocking the adsorption of the virus on the cellsurface. Inhibitory components of extracts fromStevia rebaudiana and Achyrocline flaccidawere defined as heterogeneous anionic polysaccharides with different ionic charges.

Polysaccharides extracted from the leaves of the short-pointed rhizophora (Rhizophora apiculata) and rhizophora bark (Rhizophora mucronata), were tested in vitro for activityin cell culture [56, 57]. Both extracts protected MT-4 cells from HIV-induced cytopathogenicity and blocked the expression of HIV p24 antigens (viral capsid protein), preventing the binding of the virus to the cell and the formation of syncytium.

It was found that a purified preparation of polymanose from aloe barbados (Aloe barbadensis) increased the production of antibodies to the epitopes of the capsid protein of the Coxsackie B virus 3 [27]. The mechanism of this phenomenon requires further research. However, the authors suggest that this drug can be used to increase the production of antibodies against vaccine strains of other enteroviruses and poliovirus.

The action of a new domestic antiviral drug Panavir, the main substance of which is a polysaccharide (a class of hexose glycosides) from potato shoots (sprouts) (Solanum tuberosum), studied in detail in vitro and in vivo [3]. The drug inhibits the synthesis of viral proteins, has a pronounced mitogenic activity, as an immunomodulator increases the level of leukocyte interferon. Panavir is included in the State Register of Medicines of the Russian Federation in 2008; in medical practice it is recommended for the treatment of herpesvirus infections and tick-borne encephalitis. To date, extensive clinical experience has been accumulated in the use of this drug in infectious diseases caused by cytomegalovirus, human papillomavirus, and Epstein-Barr virus. The mechanisms of binding of antiviral agents to virions and the interaction of the virus with the host cell in the presence of a polysaccharide are probably related to its binding to the glycoproteins of the viral envelope, which then prevent the interaction of the virus with the cell plasma membrane [48].

Flavonoids

Flavonoids are a group of polyphenolic compounds based on the diphenylpropane skeleton. Flavonoids are very widespread throughout the plant world, accumulate in fruits, vegetables, tea, grains, bark, roots, stems and flowers, and are part of traditional food products of different peoples. The spectrum of pharmacological activity of flavonoids is very wide. Vitamin P is a plant flavonoid (rutin, catechins, quercetin, citrine, hesperidin, eriodictyol, cyanidin) with similar biological properties: they increase the strength of the walls of blood capillaries and normalize their permeability. In total, about 150 flavonoids with similar properties are known. Food flavonoids prevent the development of various diseases [52].

Initiation of studies of the antiviral activity of flavonoids extracted from medicinal plants, falls on the 70-80 years of the 20th century [10, 75]. In particular, the black tea flavonoid theaflavin, a well-known antioxidant, has been shown to neutralize bovine rotavirus and bovine coronavirus infections [21].

Flavonoids are known as specific inhibitors of picornaviruses and rhinoviruses [66]. Dianella long-leaved (Dianella longifolia) and spherical pterocaulon (Pterocaulon sphacelatum) contain flavonoids that inhibit in vitro poliovirus replication 2 and 3 types [66]. Flavonoids isolated from Barleria serrata (Barleria prionitis) and the roots of machamia yellow (Markhamia lutea), showed high antiviral activity in vitro against RSV [20, 37]. In another study, five groups of flavonoids isolated from sumac succulent (Rhus succedanea) and from Garcinia multiflora, showed antiviral effect inin relation to respiratory viruses (influenza A and B, parainfluenza type 3, RSV, measles and type 5 adenovirus) and herpes viruses (HSV-1, HSV-2, CMV, herpes zoster virus) [46].

The mechanism of the antiviral action of flavonoids is not well understood. However, viral replication is known to be inhibited by flavonoids. Basically, the aforementioned antiviral activity is characteristic of flavonoids and phenylpropanoids (rosmarinic acid, low molecular weight glycoside-forming components of chlorogenic acid, caffeic acid and their derivatives) [47].

Table 2 summarizes data on the mechanisms of action of the most active antiviral components from plants [32].

Herbal medicine and clinical trials

The use of plants to fight viral infections is based on historical experience. In traditional medicine in India and China, dried plant extracts in the form of tablets and capsules are used as antiviral agents. In China, for example, licorice root extract is used smooth (Glycyrhiza glabra). Numerous studies of antiviral actionlicorice is summarized in a review by Fiore et al. [25]. It has been shown that glycyrrhizin (glycoside) from the rootGlycyrhiza glabra and its derivatives reduce liver cell damage in chronicpatients with hepatitis B and C. Experiments on animals have shown a decrease in mortality in encephalitis caused by the herpes simplex virus, and in pneumonia caused by the influenza A virus.Phyllantus), a family of Euphorbiaceae (Euphorbiaceae).

These plants are widespread in tropical and subtropical countries and are used in folk medicine for the treatment of diabetes, diseases of the kidneys, bladder, intestinal infections, as well as various viral, bacterial and parasitic infections [16].

table 2

Mechanisms of Action of the Most Active Antiviral Components from Plants

Класс соединений	Механизм воздействия на вирус	Пример растительного источника
Фурановые соединения: фуранокумарины и фурахромоны	ДНК и РНК геномы. С помощью УФ-облучения (300–400 nm)	Некоторые представители сем. Рутовых – Rutaceae и Зонтичных (Сельдерейных) – Umbelliferae (Apiaceae)
Алкалоиды: β-карболины, фуранохинолины, камптотецин, атропин, кофеин, индолизидины, свенсонин, кастаноспермин, колхицины, винбластин	ДНК и др. полинуклеотиды и вирионые белки. Взаимодействие усиливается УФ облучением	Некоторые представители сем. Рутовых – Rutaceae; камптотека остроконечная (Camptotheca acuminate Desne), красавка белладонна (Atropa belladona L.), свансония сероватая (Swainsona canescens(Lindl.) F.Muell.), астрагал крапчатый(Astragalus lentiginosus Dougl.), каштаносемянник южный (Castanospermum australe A. Cunn.), аглая Роксбурга (Aglaia roxburghiana Miq.)
Полиацетилены (полиины)	Взаимодействие с мембранами. Для фототоксичной активности часто необходимо УФ облучение	Некоторые представители сем. Астровых – Asteraceae, Сельдерейных – Apiaceae, Колокольчиковых – Campanulaceae; женьшень настоящий (Panax ginseng (L.) C.A.Hey), череда (Bidens sp.), хризантема сибирская (Chrysanthemum sibiricum Turcz. ex DC.)
Полисахариды	Блокирование адсорбции вируса на клеточной поверхности	ахроклине фласида (Achyrocline flaccida(Weinm.) DC.), морской мох (Bostrychia montagnei W.H. Harvey.), цедрела тубифлора (Cedrela tubiflora Bertoni), черноголовка обыкновенная (Prunella vulgaris L.), склероциум глюканикум (Sclerotium glucanicum Halleck), двулистник сладкий (Stevia rebaudiana Bertoni), ризофора остроконечная (Rhizophora mucronata)
Тиофены	Взаимодействие с мембранами. Для фототоксичной активности часто необходимо УФ облучение	аспилия (Aspilia sp.), хенактис Дугласа (Chenactis douglasii(Hook.) Hook.), диссодия (тимофилла) антемидифолиа (Dyssodia anthemidifolia Benth.), эклипта белая (Eclipta alba(Linn.) Hassk.)), эриофиллум шерстистый (Eriophyllum lanatum (Pursh) Forles)
Полифенолы (в т.ч. флавоноиды): аментофлавон, теафлавин, агатисфлавон, робустафлавон, русфлавон, сукцеданфлавон, морин, галангин (3,5,7-trihydroxyflavone), байкалин, хризоспленол С; иридоиды, фенилпропаноидные гликозиды, кумарины	Блокирование синтеза РНК ВИЧ	многоколосник морщинистый (Agastache rugosa (Fish. et Mey.) O. Kuntze), молочай Гранта (Euphorbia grantii Oliv.), барлерия пильчатая (Barleria prionitis L.), калофилум колючий (Calophyllum cerasiferum Vesque), александрийский лавр (Cal. inophyllum L.), калофилум Тейсмана (Cal. teysmannii Miq.), чайный куст китайский (Camellia sinensis (L.) O.Ktze), гарциния многоцветковая (Garcinia multiflora Champ.), бессмертник золотистый (Helichrysum aureonitens Sch. Bip.), маклюра китайская (Maclura cochinchinensis(Lour.) Corner.), макхамия желтая (Markhamia lutea(Benth.) K.Schum.), монотес африканский (Monotes africanus A. DC.), птерокаулон шаровидный (Pterocaulon sphacelatum(Labill.) Benth. & Hook. f. ex F. Muell.), сумах последовательный (Rhus succedanea L.), шлемник байкальский (Scutellaria baicalensis Georgi), селягинелла китайская (Selaginella sinensis(Desv.) Spring.), софора Муркрофта (Sophora moorcroftiana Benth. ex Baker), софора войлочная (Sophora tomentosa L.), тефрозия (Tephrosia sp.)
Терпеноиды: сесквитерпены, тритерпеноиды (мороновая кислота, урсоловая кислота, маслиновая кислота)	Подавление синтеза вирусной ДНК	Некоторые представители сем. Первоцветных – Primulaceae; акокантера (Acokanthera sp)., очный цвет полевой (Anagallis arvensis L.) Конопля посевная (Cannabis sativa L.), гравилат японский (Geum japonicum Thunb., G. faueriei Lev.), солодка гладкая, лакричник (Glycyrrhiza glabra L.), глиптопеталюм сухоплодный (Glyptopetalum sclerocarpum (Kurz) M. A. Lawson), джимнема лесная (Gymnema sylvestre R.Br.), меса ланцетная (Maesa lanceolata), маслина европейская (Olea europea L.), квилайя мыльная (Quillaja saponaria Molina), сумах яванский (Rhus javanica L.), строфант великолепный (Strophanthus gratus)
Лигнаны 1. Подофиллотоксин и родственные лигнаны (циклолигнанолиды), такие как пельтатины	Блокирование вирусной репликации	аманоя облонгифолия (Amanoa oblongifolia Muell.Arg.), можжевельник обыкновенный (Juniperus communis L., джастиция лежачая (Justicia procumbens L.), подофил щитовидный (Podophyllum peltatum L.)
2. Дибензоциклооктадиеновые лигнаны такие как схизандрин В и тайванширин D (taiwanschirin D)	Блокирование репликации HBV	кадзура японская (Kadsura matsudai Hayata)
3. Ринакантин Е и ринакантин F	Блокирование репликации вируса гриппа А	ринакант носатый (Rhinacanthus nasutus (L.) Kurz)
Различные соединения фенольной природы: антрахинон хризофановая кислота, эфгениин, гиперицин, таннины (конденсированные полимеры), проантоцианидины, салицилаты и хинины (нафтохиноны, нафтохиноны и антрахиноны, в частности, алоэ-эмодин)	Ингибирование репликации вирусных РНК и ДНК	алоэ (Aloe barbadensis), астра шершавая (Aster scaber Thunb.), кассия узколистная (Cassia angustifolia Vahl.), дианелла длиннолистная (Dianella longifolia), эводия Роксбура (Euodia roxburghiana Benth.), гравилат японский (Geum japonicum Thunb. G. faueriei Lev.), гамамелис виргинский (Hamamelis virginiana L.), зверобой (Hypericum sp.), мелисса лекарственная (Melissa officinalis L.), филлантус миртолистный (Phyllanthus myrtifolius Moon), филлантус уринария (Phyllanthus urinaria L.), гранат обыкновенный (Punica granatum L.), крушина ломкая (Rhamnus frangula L.), крушина Пурша, к. американская, каскара (Rhamnus purshianus DC), ревень аптечный (Rheum officinale Baill.), ринакант носатый (Rhinacanthus nasutus (L.) Kurz), шефеірдия серебристая (Shepherdia argentea (Pursh) Nutt.), гвоздичное дерево (Syzgium aromatica (L.) Merrill et L.M. Perry)
Протеины и пептиды 1. Белки инактивирующие рибосомы	Взаимодействие с рибосомами инфицированных клеток и подавление синтеза вирусных белков	клеродендрум безколючковый (Clerodendrum Inerme (L. Gaertn.), гвоздика садовая (Dianthus caryophyllus L.), гелониум многоцветковый (Gelonium multiflorum A. Juss.), момордика, горькая тыква (Momordica charantia Linn.), фитолакка, лаконос американский (Phytolacca Americana L. s.l.), мыльнянка лекарственная (Saponaria officinalis L.), трихозант Кирилова (змеиный огурец Кирилова) (Trichosanthes kirilowii Maxim.), пшеница мягкая (Triticum aestivum Lam.)

Антивирусные протеины лаконоса (PAP) (MRK29, MAP30 и GAP31)	Инактивация инфекционного ВИЧ и ВИЧ-зараженных клеток	фитолакка, лаконос американский (Phytolacca Americana L. s.l.), момордика, горькая тыква (Momordica charantia Linn.), гелониум многоцветковый (Gelonium multiflorum A.Juss.)
Панаксагин (Panaxagin)	Ингибирование ВИЧ-1 РТ	женьшень настоящий (Panax ginseng (L.) C.A.Hey)
Альфа- и бета-противогрибковые протеины	Ингибирование ВИЧ РТ	вигна початковая (Vigna unguiculata (L.) Walp.)
2. Димерные цитотоксины	Взаимодействие с рибосомами инфицированных клеток и подавление синтеза вирусных белков	клещевина обыкновенная (Ricinus communis L.), абрус прекаторный (Abrus precatorius L.), адения дигитата (Adenia digitata (Harv.) Engl.)
3. Лектины	Мембранное взаимодействие	канавалия мечевидная (Canavalia ensiformis L.), чечевица съедобная (Lens culinaris Medik.), фасоль обыкновенная (Phaseolus vulgaris L.), пшеница мягкая (Triticum vulgare Vill.)
4. Антивирусный фактор	Механизм действия не известен	табак клейкий (Nicotiana glutinosa L.)
5. Мелиацин	Нарушение репликации вируса	мелия аседарах (Melia azedarach L.)

Important advances have been made in chemical and pharmacological studies as well as in clinical trials of some Phyllantus species. Phyllanthus bitter powder (Phyllantus amarus) to purify the blood of chroniccarriers of the surface antigen of the hepatitis B virus (HBsAg) [74]. However, in acute hepatitis B, this drug was not very effective. Perhaps this was due to insufficient concentration of the drug.

In experiments it has been shown in vitro that Phyllantus amarus powder at a concentration 1 mg / ml inhibited HBsAg secretion in 48 hours. It was also shown that the drug suppresses the transcription of mRNA of the hepatitis B virus [44]. Inactivation of the polymerase activity of the hepatitis B virus and suppression of mRNA transcription and replication caused byPhyllantus amarus, allowsconsider a preparation from this plant as an antiviral agent.

The antiviral activity of another representative of this species, phyllanthus niruri (Phyllantus niruri) [thirty]. It was shown that the extract of this plant inactivates HBsAg in positive sera of chronic carriers of the hepatitis B virus. Antiviral activity and non-toxicity of this drug were shown in experiments on mice infected with hepatitis B virus and Vero cells. It has also been shown that the extract fromPhyllantus niruri in experiments in vivoeliminates the virus from infected animals within 3–6 weeks [84]. Although the number of animal studies is insufficient to draw a definitive conclusion, it is assumed that the extract fromPhyllantus niruri can be used to treat hepatitis B for recoverystructure and function of the liver. Clinical trials of an extract fromPhyllantus niruri wereperformed on a group of patients, chronic carriers of HBsAg, who were given this drug daily for 30 days. 3 months after the course of treatment, HBsAg was not detected in 65% of patients [30]. The hepatitis C virus poses a serious threat to human health around the world. An intensive search is underway for means of combating this dangerous disease. The review by Patrick [54] reviewed the results of studies on the effectiveness of attempts to treat chronic hepatitis and liver damage using plant-based biologically active substances such as glycyrrhizin, catechin, silymarin and phytosterols, and the antioxidants N-acetylcysteine   and vitamin E.in vitro extracts from Nile acacia (Acacia nilotica), incense tree (Boswellia carterii), Schimper's embelia (Embelia schimperi), cubeb pepper (Piper cubeba), infectious oak (Quercus infectoria), azhgon (Trahyspermum ammi), clove tree), was their inhibitory activity against the hepatitis C virus protease has been shown [31].

More recently, a study was carried out on the effect of the drug Iscador Spezial (trademark of an aqueous extract of mistletoe (Viscum album)) on five patients with chronichepatitis C throughout the year. As a result of treatment, the production of the virus decreased 6–20 times in two patients, the liver function returned to normal, and the quality of life improved [78].

In the United States, the possibility of using herbal medicine to treat HIV-positive patients has been studied. Clinical trials of the activity of andrographolide, extracted from the leaves of andrographis paniculata (Andrographis paniculata), on 13 HIV-positive patients and 5 healthy volunteers [15]. After 3 weeks of treatment, an increase in the level of immunocompetent CD4 + cells was noted in all HIV-1-infected patients.

Based on these data, the authors conclude that andrographolide can inhibit cell cycle dysregulation in HIV-infected cells. The positive therapeutic effect of lemon balm (Melissa officinalis), used as a cream, noted upon infectionherpes simplex virus [42].

Many medicinal plants and herbs are prescribed in the form of composites, which is a traditional principle of herbal medicine, taking into account the need to neutralize or reduce the toxicity of the poisonous plants used. The success of the combined use of several herbal extracts is possibly due to the complementarity of the action of the individual ingredients. In this case, the restoration or activation of functions occurs in an unknown way.

Anti-influenza activity of herbal preparationsThe most common viral infections are acute respiratory infections. The leading role among them belongs to influenza. The few existing means of fighting influenza are not effective enough. Therefore, the search for new means of preventing and treating influenza continues today.

As mentioned at the beginning of the review, back in 1952, the Broot Drug Company in England tested the effect of 288 plants on influenza A virus in chicken embryos. It was found that 12 of them suppress the multiplication of the virus [19]. Korean scientists conducted studies on the inhibitory activity against influenza A virus of aqueous extracts from 101 Korean plants. 13 of them have a pronounced antiviral effect: they inhibit the attachment of the virus to the host cells. Yuzu fruit extracts (Citrus junos) (complex hybrid of citrus fruits) and from ginger rootsmedicinal (Zingiber officinale) have the most potent activity against influenza A virus,do not give a cytopathic effect and are recommended by the authors for the prevention of influenza [34].

Reviewed by Wang et al. [84] summarized recent studies of the anti-influenza activity of a number of biologically active substances (various polyphenols, flavonoids, saponins, glycosides and alkaloids) isolated from plants. Table 3 presents the results of these studies.

The highly effective drug oseltamivir (commercial name Tamiflu from Roche) inhibits neuraminidase of all subtypes of influenza A and B viruses, including the causative agent of bird flu H5N1, and a new strain of influenza A / California / 2009 virus, pathogen »Flu. The World Health Organization has recommended oseltamivir for prevention and treatment in the event of an influenza pandemic. However, the manufacture of this drug is a complex and costly multi-step process using shikimic acid as a raw material. Shikimic acid in many plants and microorganisms is an important component in the biosynthesis of aromatic amino acids phenylalanine, tyrosine and tryptophan, many alkaloids, tannins, flavonoids and lignin.Illicium verum). Canadian firmBiolyse Pharma Corporation has proposed a new solution for obtaining shikimic acid - to use the needles of unnecessary, discarded Christmas trees (pine, spruce, Canadian spruce) for its extraction. The content of shikimic acid in needles is 2-3%. Since 2006, when about 500 thousand Christmas trees were collected in Toronto, the company has significantly increased and reduced the cost of production of oseltamir [49].

Noteworthy is another antiviral drug from needles - fosprenil. This substance of a terpenoid nature, obtained by domestic scientists by special processing of wood needles [23], is approved for use in the prevention and treatment of a number of viral infections in animals, including feline flu. Experimental data have been obtained indicating the possibility of using fosprenil for the prevention of H5N1 avian influenza in combination with vaccination in poultry farms. Fosprenil increases the natural resistance and the immune response of the bird's body to the vaccine [4].

Table 3

Activity of extracts and biologically active substances of some plants against influenza viruses

Латинское название растения	Русское название растения	Часть растения	Составляющая или активный компонент	Функция
Geranium sanguineum L.	Герань кроваво-красная	Не указано	Полифенольный комплекс	Против различных вирусов гриппа
Cydonia oblonga Mill.	Айва продолговатая	Плоды	Фенолы	Против вируса гриппа А
Citrus junos Tanaka	Юнос, юзу, юдзу, юное (сложный гибрид между несколькими видами цитруса)	Плоды	Флавонон тригликозид	Против вируса гриппа А
Bupleurum Chinense DC.	Володушка китайская	Надземная часть, корни	Флавоноид, экстракты	Против вируса гриппа В. Подавляет репродукцию вируса
Polygala tenuifolia Willd.	Истод тонколистный	Корни	Сапонины	Мукозный адъювант
Pinellia ternata (Thunb.) Breit.	Пинеллия терната	Корневища	Пинелловая кислота	Мукозный адъювант
Mangifera indica L.	Манго индийское	Листья	Хинонин	Снижение инфекционности вируса гриппа А
Solanum tuberosum L.	Картофель	Корневища	Антоциан	Инактивирует вирус гриппа А и В
Uncaria rhynchophylla Jacq.	Ункария клюволистная, науклея клюволистная, «кошачий коготь»	Не указано	Индол алкалоид	Против вируса гриппа А
Thalictrum simplex L.	Василистник сложный	Не указано	Талимонин	Против вирусов А (H7N7, H7N1)
Cynanchum stauntonii (Decne.) Schltr.ex Levi	Цинанхус стентона	Корни	Эфирное масло	Против вируса A/NWS/33
Sanicula europaea L.	Подлесник европейский	Листья	Экстракт	Против вируса A/PR/8/34
Hypericum perforatum L.	Зверобой продырявленный	Надземная часть	Гиперицин	Против вирусов A/H5N1, H9N2
Mangifera indica L.	Манго индийское	Листья	Хинонин	Против вируса гриппа А
Schizonepeta tenuifolia Briq.	Схизонепета тонколистная	Колос, соцветие	Эфирное масло и экстракты	Облегчает течение пневмоинфекции
Arctium lappa L.	Лопух большой	Семена	Арктигенин	Подавляет или инактивирует вирус гриппа А
Forsythia suspensa (Thunb.) Vahl	Форзиция свисающая	Плоды	Флавоноиды Фенольные гликозиды (forsythosides)	Антивирусное действие
Mentha haplocalyx Briq.	Мята канадская	Листья	Флавоноиды	Антивирусное действие
Lonicera japonica Thunb.	Жимолость японская	Бутоны	Флавоноиды Экстракт	Антивирусное действие Против вируса А (H9N2)
Glycyrrhiza uralensis Fisch.	Солодка уральская	Корни	Лигнаноиды Экстракты Экстракты	Антивирусное действие Против вируса гриппа А Подавление IL-α
Isatis indigotica Fort	Исатис красильная	Корни, листья	Активные белки	Против вируса гриппа А
Houttuynia cordata Thunb.	Гуттуиния сердцевидная	Целое растение	Экстракты	Подавление апоптоза клеток, зараженных вирусом гриппа А (H3N2)
Toddalia asiatica Lam.	Тодалия азиатская	Корни	Экстракты	Против вируса гриппа А (H1N1)
Acacia catechu (L. f.) Willd.	Акация катеху	Стебель и листья	Экстракты	Против вируса гриппа А
Ganoderma applanatum (pers) pat.	Трутовик плоский (гриб)	Все растение (слоевище)	Экстракты	Против вируса A/FM1
Notopterygium incisum Ting ex H.T. Chang	Нотоптеригиум вырезной	Корневище и стебель	Экстракты	Против вируса A/FM/1/47
Chaenomeles speciosa (Sweet) Nakai	Айва японская	Не указано	Экстракты	Против вируса гриппа А
Zingiber officinale Rose	Имбирь лекарственный	Не указано	Экстракты	Против вируса гриппа А

In terms of preparing for an influenza pandemic, the World Health Organization, among other things, recommended the development and production of genetically engineered plant-based vaccines against influenza viruses (so-called plant vaccines) [73]. Edible or plant vaccines are produced by altering the genome of plants that begin to accumulate a protective antigen. To obtain vaccines, tobacco, tomatoes, potatoes, bananas, and rice are mainly used. The main advantages of herbal vaccines, experts say, are safety, cost-effectiveness, and the development of mass production without large investments. In addition, such a vaccine can be administered without the participation of a health worker, for example, parents can vaccinate their children at home. Recently, a group of Anglo-American researchers reported the creation of a subunit vaccine against influenza A virus [51].Nicotiana). Ferrets were immunized with purified HA antigen, followed bybeing infected with the same virus. HA produced by tobacco proved to be highly immunogenic, and antibodies to it conferred complete protection of animals against influenza.

Viruses and bacterial biofilms

Biofilm is a layer of bacterial cells enclosed in a biopolymer matrix. In natural ecosystems, microorganisms do not exist in the form of free-living cells suspended in the environment (plankton), but as a community that forms a film on various biotic and abiotic surfaces. Intercellular communication in the biofilm is carried out with the participation of a mechanism called quorum sensing (QS). The exchange of information in the microbial community occurs with the help of specialized chemical signaling molecules [6].

The formation of a biofilm located on various dense substrates, as well as on the surface of a liquid, is a complex process consisting of several stages.

The first stage is initial attachment or adhesion, the second stage is irreversible attachment, the third and fourth stages are maturation, and the fifth is dispersion, destruction of biofilm and return of cells to planktonic existence [53]. Irreversible adhesion and maturation are associated with the formation of a mucous exopolymer matrix - a waste product of the cells themselves. The main component of the matrix is exopolysaccharide. Exopolysaccharides form the surface layer of the cell membrane (glycocalyx) on the cells. When the biofilm matures, a significant amount of exopolysaccharide is produced, which unites neighboring cells and forms a matrix.

Biofilm formation is of medical importance. It has been shown that the development of a number of chronic infections is due to the ability of pathogenic microorganisms to form biofilms [17]. The colonization of tissues of a macroorganism by pathogenic microorganisms, accompanied by the formation of a biofilm, is an important stage in the development of the infectious process. Naturally formed biofilms represent a community of various microorganisms, including viruses. Polymicrobial infections are the result of complex interactions between two or more etiological agents. Polymicrobial diseases are divided into polyviral and polybacterial, infections caused by a combination of bacterial and viral pathogens, polymycosis, diseases caused by parasites, and diseases resulting from induced immunosuppression [13]. Polymicrobial diseases, including bacteria and viruses, are characteristic of the oral cavity, respiratory tract, gastrointestinal tract. It has been shown that the herpes virus plays an important role in the pathogenesis of periodontitis [13]. In diseases of the oral cavity, viruses increase sensitivity to bacterial pathogens, which ultimately contributes to the development of sinusitis, otitis media and bronchopneumonia. In turn, bacterial proteases enhance the pathogenicity of influenza A virus by cleaving viral hemagglutinin. In diseases of the gastrointestinal tract, 10 bacterial species and 9 types of viruses were isolated [13]. Viral infection in some cases promotes bacterial adhesion and invasion. In diseases of the oral cavity, viruses increase sensitivity to bacterial pathogens, which ultimately contributes to the development of sinusitis, otitis media and bronchopneumonia. In turn, bacterial proteases enhance the pathogenicity of influenza A virus by cleaving viral hemagglutinin. In diseases of the gastrointestinal tract, 10 bacterial species and 9 types of viruses were isolated [13]. Viral infection in some cases promotes bacterial adhesion and invasion. In diseases of the oral cavity, viruses increase sensitivity to bacterial pathogens, which ultimately contributes to the development of sinusitis, otitis media and bronchopneumonia. In turn, bacterial proteases enhance the pathogenicity of influenza A virus by cleaving viral hemagglutinin. In diseases of the gastrointestinal tract, 10 bacterial species and 9 types of viruses were isolated [13]. Viral infection in some cases promotes bacterial adhesion and invasion.

Viruses are associated with mixed infections. In this case, the biofilm can play an important role due to the slimy, exopolysaccharide matrix that sorbs various pathogens, including viruses. So it was shown that biofilms on dental equipment contain the following pathogens: HIV, pseudomonas (Pseudomonas species),streptococci (Streptococcus), staphylococci (Staphylococcus), non-tuberculosis mycobacteria (Nontuberculosis mycobacteria), Klebsiella pneumoniae, Mycobacterium tuberculosis (Tuberculosis) (TB), legionella (Legionella).

Viruses are present in biofilms formed on equipment in the water supply system. Viruses in such an attached state, together with bacteria, can persist for a long time and pose a threat to public health [64]. A particular problem is biofilm viruses in chronic inflammatory diseases. Thus, in the case of otitis media, biofilms formed by pneumococci were detected using confocal laser scanning microscopy.S. pneumoniae and Haemophilus influenzae (H. influenze), contaminated with viruses [33]. The following viruses were found: respiratory syncytial virus, influenza A virus, adenovirus, parainfluenza virus type 3. The viruses present in the biofilm have facilitated the multiplication of bacteria through the following mechanisms. They caused dysfunction of the Eustachian tube (edema, moisture), impaired immune defense (dysfunction of leukocytes) and promoted bacterial adhesion and colonization, destroying mucous and ciliary cells. In eye diseases, various types of bacteria, protozoa, and viruses have also been isolated [76]. It has been found that biofilms on lenses can be the cause of chronic eye diseases of mixed etiology. Diseases of the oral cavity, which have a source of biofilm of pathogenic microbes, often develop in an organism weakened by the immunodeficiency virus [43]. Respiratory viruses are detected in sputum in chronic lung disease (cystic fibrosis) caused by bacteria that form a biofilm [22]. Clinical observations indicate a viral-bacterial interaction between respiratory syncytial virus (RSV) and Ps. aeruginosa with cystic fibrosis. In experimentsin vitro RSV promoted the attachment of Ps. aeruginosa toepithelial cells IB3-1, Hep-2, and A549 [79]. It has been shown that neuraminidase Ps. aeruginosa participates in biofilm formation, modifying the epithelial cells of the respiratory tract and facilitating bacterial adhesion [70]. A similar role is played by viral neuraminidase in respiratory diseases. Viral damage to the epithelium of the respiratory tract leads to a violation of its barrier function and contributes to the addition of a bacterial infection. It has been shown that influenza virus neuraminidase unmasks receptors for pneumococci, which provides the possibility of their attachment and colonization [71]. The viral-bacterial interaction causes the destruction of ciliary cells and desquamation of the epithelium, which prevents the removal of bacterial pathogens from the respiratory tract and enables them to form a biofilm. Thus, with a viral respiratory infection, damage to the self-cleaning mechanism of the tracheobronchial tree is observed. The relationship between viruses and bacterial biofilm can be traced using the example of respiratory tract disease. Viruses can promote biofilm formation. In turn, the biofilm mechanically traps viruses. In addition, biofilm has a protective effect. Viruses in biofilm are more resistant to the action of antiviral agents. Biofilm can be viewed as a reservoir or trap for various microorganisms, including viruses. In this case, various variants of microbial-viral interaction are possible. With viral-bacterial coinfection or secondary bacterial superinfection, virus-induced immunosuppression and destruction of the epithelium are observed, which increases bacterial attachment.

From the foregoing, it follows that to combat a combined viral-bacterial infection, it is necessary to use drugs that prevent the formation of biofilms. For this purpose, various herbal products and herbal preparations can be used. At present, the effect of such drugs on various stages of film formation has been established. The creation of herbal preparations is based on the idea that plants that do not have immune defense synthesize various chemical compounds to fight microorganisms [1]. Data were obtained on the antiadhesive properties of plants and on the ability of plant extracts to suppress the sense of quorum [61].

Plants in antiadhesive therapy and in inhibition of biofilm formation

Lectins of microorganisms participate in adhesion, which selectively bind to complementary sugars on the surface of the cells of the microorganism. The resulting ligand-receptor interaction plays an important role in the adhesion process. Based on these data, an antiadhesive strategy for the prevention and treatment of infectious diseases is being built. Sugars can bind to microorganisms and thus prevent their interaction with epithelial receptors. Among plants, adhesion inhibitors have been found that act according to this principle. It has been shown that preparations from the edible hibiscus plant (Okra, Hibiscus esculentus). Okra inhibits the adhesion of Helicobacter pylori to the mucosastomach [45]. Antiadhesive properties are associated with blocking specific receptors on the surfaceHelicobacter, responsible for interacting with host cells. Anti-adhesiveactivity towards Helicobacter pylori also possesses cranberry and whitemulberry (Morus alba) [fourteen]. Cranberry effectively inhibits bacterial adhesion to host cells [83]. It turned out that cranberry prevents biofilm formation Streptococcus mutants, participating in the formation of dental plaque [40].

Plant extracts prevent biofilm formation by suppressing the sense of quorum in pathogenic bacteria. Some vegetable oils have this property. Recently, it was shown that water extracts of a number of plants: erect conocarpus (Conocarpus erectus),black olive (Bucida buceras), Callistemon viminalis (Florida), influencefor a sense of quorum Ps. aeruginosa and inhibit biofilm formation [6].

Conclusion

As follows from the above data, many plants have antiviral activity. Their components that determine the antiviral effect are coumarins, flavonoids, tannins, alcohols, terpenes and terpenoids, polysaccharides, proteins and peptides. These biologically active substances have either a direct effect on viruses (at different stages of viral reproduction), or indirectly, by activating the immune system, or both. Several of these plant compounds are promising candidates for further clinical research. However, many plant-based biologically active substances demonstrate antiviral activity onlyin vitro, but not effective in clinical trials and / or toxic in vivo.However, some of these compounds are currently undergoing either preclinical studies or clinical trials. In addition, plants can and are already being used as a vector for the creation of genetically engineered antiviral vaccines. The search for new interesting antiviral drugs among natural compounds from plants seems promising and promising.

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